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Improving Standards of Pharmacovigilance Practice in Oncology

By

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Author's Declaration

The thesis is the result of the author's original research conducted between 2004 and 2009 under the supervision of Professor Steve Hudson, Professor D Nick Bateman and Professor Norman Lannigan. It has been composed by the author and has not been previously submitted for examination which has lead to the award of a degree.

14 June 2010

Author's signature **Date**

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List of abbreviations

AC	doxorubicin and cyclophosphamide
AE	adverse event
ADR	adverse drug reaction
ADROIT	Adverse Drug Reaction On-line Information Tracking
AERS	Adverse Event Reporting System
BONADONNA	doxorubicin/cyclophosphamide, methotrexate, and 5-fluorouracil
CHI	Community Health Index
CMF	cyclophosphamide, methotrexate, and 5-fluorouracil
BOPA	British Oncology Pharmacy Association
BSA	body surface area
C Difficile	Clostridium Difficile
COSTART	Coding Symbols for a thesaurus of Adverse Reaction Terminology
CPMP	Committee for Proprietary Medicinal Products
CSAG	Confidentiality and Security Advisory Group
CSD	Committee on Safety Drugs
CSM	Committee on Safety of Medicines
CTC	Common Toxicity Criteria
CTCAE	Common Terminology for Cancer Adverse Events
CTEP	Cancer Therapy Evaluation Program
ECC	Edinburgh Cancer Centre
EMEA	European Agency for the Evaluation of Medicinal Products (EMEA)
EPI	epirubicin
EU	European Union
EUDRACT	European Clinical Trials Database
FAC	5-fluorouracil, doxorubicin and cyclophosphamide
FDA	Food and Drug Administration
GPRD	General Practice Research Database
HLGT	Higher Level Group Term
HLT	Higher Level term
ICD	International Classification of Diseases

List of abbreviations (continued)

ICH	International Conference on Harmonisation
IFPMA	International Federation of Pharmaceutical Manufacturers and Associations
IMT	International Medical Terminology
ISD	Information Services Division
IQR	Interquartile range
JCCO	Joint Council for Clinical Oncology
LLT	Lower Level Term
LREC	Lothian Research and Ethics Committee
MCA	Medicines Control Agency
MedDRA	Medical Dictionary for Regulatory Activities
MEMO	Medicines Monitoring Unit
MHRA	Medicines and Healthcare products Regulatory Agency
NOSCAN	North of Scotland Cancer Network
NCI	National Cancer Institute
NEC	not elsewhere classified
OHPs	oncology healthcare professionals
PT	Preferred Term
SAE	serious adverse event
SCAN	Southeast Scotland Cancer Network
SOC	System Order Class
SOP	standard operating procedure
SOPPG	Scottish Oncology Pharmacy Practice Group
SSC	special search strategies
THIN	The Health Improvement Network
UKONS	United Kingdom Oncology Nursing Society
US	United States
WHO	World Health Organisation
WOSCAN	West of Scotland Cancer Network

List of accompanying materials

Some appendices have been submitted on a compact disc (CD) due to their size. These are annotated below. The CD is available at the beginning of the appendices.

List of accompanying materials (continued)

Preface

Chapter 1

This chapter gives a background to cytotoxic chemotherapy and the associated adverse effects, and presents essential terms and concepts in adverse drug reaction reporting and their monitoring.

Chapter 2

This chapter presents an overview of the National Cancer Institute Common Terminology Criteria for Adverse Events, including mapping to MedDRA terminology. The importance of this scale in grading of oncology adverse events experienced during treatment with cytotoxic chemotherapy, and the difference between severe and serious is discussed. This chapter also presents the reasons why a causal analysis must be undertaken to differentiate an adverse drug reaction from an adverse event; and how a causal analysis is undertaken.

Chapter 3

This chapter presents the findings of a retrospective survey of case notes undertaken at the Edinburgh Cancer Centre to investigate if a pharmacist-led reporting initiative could result in a sustained improvement in spontaneous ADR reporting via the Yellow Card scheme. Also evaluated during this study is the incidence of adverse events and ADRs in the study populations selected.

Chapter 4

This chapter presents the findings of one-to-one, semi-structured interviews with oncology healthcare professionals to elicit opinions, knowledge and behaviour on Yellow Card reporting of adverse drug reactions in oncology. The subsequent use of this information to design a questionnaire for circulation to the wider oncology community across Scotland is also described; along with the summary findings on opinions, knowledge and behaviour on Yellow Card reporting of adverse drug reactions in oncology obtained from this questionnaire.

Preface (continued)

Chapter 5

This chapter presents the results of a nominal group process to develop standards to classify serious ADRs experienced during administration of cytotoxic chemotherapy in oncology for spontaneous reporting via the Yellow Card scheme.

Chapter 6

This chapter presents the summary of key findings from the different studies carried out as part of this thesis, and recommendations for how to improve standards of pharmacovigilance in oncology.

Abstract

A retrospective survey of case notes was performed to determine if a pharmacist-led adverse drug reaction (ADR) reporting initiative in oncology could improve Yellow Card reporting. One-to-one interviews and a questionnaire were utilised to elicit attitudes, behaviour and knowledge of oncology healthcare professionals (OHPs) to ADR reporting. A nominal group process was undertaken to develop standards for classification and reporting of serious ADRs in oncology.

Serious ADRs occurred in 97% and 96% of the patients respectively in 2001 and 2003 but an increase of only 5 Yellow Card reports occurred. The level of awareness of the Yellow Card scheme was found to be high but the level of knowledge on what to report was a problem. The OHPs indicated that they often recognise ADRs but choose not to report as these were inevitable consequences of therapy, and the very large numbers of ADRs in oncology make reporting all impossible. The lack of guidance on which oncology ADRs to report was particularly highlighted as a reason for not reporting.

The nominal group achieved a consensus agreement of “serious” for 329 Lower Level Terms, not anticipated in oncology, to be considered for Yellow Card reporting. Nine factors were accepted as prompts for reporting: unknown, unusual or serious ADRs; newly licensed medicine or a combination regimen; hospitalisation or prolongation of hospitalisation; drug interactions; drug induced cancers; or suspension of treatment. There was agreement that any suspected ADRs with a new or older medicine that met the criteria of being serious, unknown and Grade 3 to 4 in severity level should be reported via the Yellow Card scheme.

OHPs must remain vigilant for unknown ADRs, but agreement of criteria specific to oncology seems essential to any improvements in Yellow Card reporting in this clinical speciality.

Chapter One
Introduction

In the treatment of oncology patients with cytotoxic chemotherapy it is desirable to have regimens that exhibit limited toxicity to keep the patients essentially well and able to lead a normal life. The preferred cytotoxic chemotherapy regimen would be one that guarantees survival without short-term toxicity or long-term complications, however, such a treatment does not exist. Therefore, all cytotoxic chemotherapy regimens exact a definable "cost" against which their benefits must be balanced (1). In the context of the seriousness of the disease both the clinician and the patient often accept this impact upon patient morbidity as a normal part of cytotoxic chemotherapy treatment.

In this process the importance of post-marketing spontaneous reporting of adverse effects which occur is often overlooked. Adverse drug reactions (ADRs) can have a significant impact upon cytotoxic chemotherapy, delaying treatment, causing admission to hospital and compromising quality of life. There is little information in the literature specific to oncology ADR incidence and reporting, with the exception of two studies carried out in a specialist cancer institute in France. Both studies showed that ADRs related to cytotoxic chemotherapy resulted in excess costs to the institute (2,3). Only one of the studies looked at whether the ADRs were reported via a traditional voluntary, spontaneous reporting scheme though. This study found that 313 ADRs occurred, of which 182 were classified as serious reactions. However only 15 (8.2%) of these serious reactions were reported (2).

The reasons for under-reporting of oncology ADRs is unknown but anecdotally most clinicians feel that there is no benefit in reporting adverse drug reactions that are common and anticipated with cytotoxic chemotherapy (e.g. neutropenia, septicaemia, leucopenia, thrombocytopenia, anaemia, etc), whether they are serious or not. Hence there is a need to determine the attitudes of clinicians on this issue and to explore what, if anything can be done to change attitudes where appropriate. Also there maybe a need for greater clarification of what ADRs caused by cytotoxic chemotherapy should be reported and how best this might be applied in clinical practice.

1.1 Cytotoxic chemotherapy Modalities

The three main options available for the treatment of cancer are surgery, radiotherapy or cytotoxic chemotherapy. In many types of cancer it is a combination of these that is employed. In some conditions cytotoxic chemotherapy can be curative but in other conditions patients can be unresponsive to cytotoxic chemotherapy. Traditionally early, localised disease is treated with surgery or radiotherapy, and cytotoxic chemotherapy (adjuvant or neo-adjuvant) as required (4). Endocrine therapy (such as oestrogen receptor antagonists, aromatase inhibitors, gonadorelin analogues, anti-androgens and somatostatin analogues) are also used adjunctively in certain types of cancers (oestrogen receptor positives breast cancer, neuroendocrine tumours and prostate cancer). In addition, adjuvant biological therapies, designed specifically to target particular cellular functions important to the cancer cell for survival and proliferation (5), have expanded in use since the late 1990s (Human epidermal growth receptor- 2 monoclonal antibody, tyrosine kinase inhibitors) for certain cancers.

1.1.1 Adjuvant and Neo-adjuvant

When early, localised disease is treated initially with surgery or radiotherapy tumours often reoccur due to undetectable micro metastasis. As a result cytotoxic chemotherapy is administered in certain tumour types to reduce the risk of relapse. This is referred to as adjuvant chemotherapy.

Conversely, when cytotoxic chemotherapy is administered before any other therapy it is called neo-adjuvant. Neo-adjuvant therapy is used to facilitate tumour shrinkage prior to surgery.

1.1.2 Mechanism of Action

Cancer cells grow by progressive steady expansion due to uncontrolled cell division, with the subsequent capability for metastasis and invasion of other organs. It is not surprising then that the chemotherapeutic agents that have been most successful in treating cancers are anti-proliferative agents that interfere with the cell cycle (6). Unfortunately these agents also interfere with the cell cycles of normal proliferating cells in the body and results in toxicity to healthy cells.

The adverse effects of cytotoxic chemotherapy depend upon which chemotherapy regimen patients receive but, in general, all chemotherapy regimens currently in use target cell types

with rapid growth and reproduction cycles. These cells include bone marrow, hair follicles, germinal epithelium lymphoid tissues and the lining of the gastrointestinal tract (6). These resultant toxicities of non-malignant cells include such things as myelosupression, septicaemia, haemorrhage, stomatitis, and alopecia.

Some will even argue that responders to neo-adjuvant chemotherapy in some cancers (e.g. breast cancer) can be predicted from whether or not they have significant toxicity from a cytotoxic chemotherapy regimen. It is thought that since chemotherapeutic agents act on rapidly multiplying cells then the common final pathway in tumour cell death and normal cells is believed to be apoptosis or programmed cell death, which would account for both the response to therapy and the toxic effects seen during cytotoxic chemotherapy. Absence or decreased apoptosis has been associated with cytotoxic chemotherapy resistance. Therefore responders to cytotoxic chemotherapy will have significant toxicity while non-responders will not show significant toxicity (7).

There are also some adverse effects of cytotoxic chemotherapy that are unrelated to their antiproliferative effect (e.g. tiredness, nausea, vomiting; and toxicity to heart, kidneys, bladder, lungs and brain)**.** Unlike toxicity to the rapidly dividing cells where stem cell renewal can occur, the toxicity to other organs tends to be irreversible or only partly reversible after cessation of cytotoxic chemotherapy. A clinical decision must then be made on how much of the toxicity the patient can tolerate before their well-being and quality of life are affected, weighed against the possibility of therapeutic benefit (6).

The treatment schedules in cancer are based on the ‘cell kill hypothesis’ which states that a certain chemotherapeutic agent dosage will kill a constant percentage of cells rather than a constant number of cells. Repeated doses of cytotoxic chemotherapy are, therefore, needed to reduce the total number of cells. The number of cells left after cytotoxic chemotherapy depends upon the results of the previous dose, the time between doses and the doubling time of the tumour (6). The duration, severity and course of adverse effects are also directly related to the dose and schedule of treatment (1). Often reductions in treatment doses and delays in treatment ensue, which can result in a diminished response and a diminished quality of life for the patients.

In addition to these acute adverse effects of cytotoxic chemotherapy described above, some chemotherapeutic agents result in long-term, delayed adverse effects. An example of this would be the risk of developing Acute Leukemia or bladder cancer following treatment with a regimen containing cyclophosphamide (8). Hence long after the initial use of chemotherapeutic agents ADRs can arise.

1.2 Definitions and Terminology Associated with Safety of Medicines

The World Health Organisation (WHO) International Drug Monitoring Centre agreed definitions and terminology were adopted by National Centres participating in the WHO International Drug Monitoring Programme in September 1991 after extensive consultation. Initially member countries were asked what terms they used in their work and to give working definitions. These were then collated and the compilation was used to create a composite definition of each term. These were subsequently circulated until agreement was reached about each definition**.** The definitions included were side effect, adverse event/adverse experience, signal, adverse reaction, unexpected adverse reaction, and other relating to causality assessment of ADRs (i.e. certain, probable/likely, possible, unlikely, conditional/unclassified, unassessible/unclassified) (9).

Subsequently the definitions were adopted by National Centres participating in the WHO international Drug Monitoring Programme in September 1991 (9). However since this time some debate has occurred on these initially agreed definitions. These arguments are included for completeness in the definitions.

1.2.1 Adverse Drug Reactions (ADRs)

An adverse Drug Reaction (ADR) is defined as any response to a medicine that is noxious and unintended and occurs at doses normally used for prophylaxis, diagnosis or therapy or disease, or for modification of physiological function (10). This definition includes all doses prescribed clinically, but is intended to exclude accidental or deliberate overdose.

This definition is the most widely accepted definition but in 2005 Aronson and Ferner (11) offered a slightly modified definition to account for defects they thought were present in the original WHO definition. There reasons for modifying the definition were:

- Adverse effects can occur at doses other than those described in the WHO definition (e.g. after a test dose)

- The use of the word ‘noxious’ excludes adverse effects that may be inconvenient but not harmful
- The definition excludes error as a source of adverse effects
- The definition excludes reactions due to contaminants (e.g. herbal products) or inactive excipients in product formulation

The modified definition they suggested for an ADR was ‘an appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product; adverse effects usually predict hazard from future administration and warrant prevention, or specific treatment, or alteration of the dosage regimen or withdrawal of the product’.

Aronson & Ferner further qualified this definition with these notes:

- ‘Appreciably’ rules out completely trivial effects but includes anything that the patient detects, which may be trivial to the doctor but not to the patient. It is better than ‘significantly’ since it can cause ambiguity between clinical and statistical significance.
- ‘Intervention: an adverse effect can result from the intervention rather than the medicinal product (e.g. haematoma from an intramuscular injection); and an intervention need not be deliberate.
- The omission of the word ‘medical’ removes the implication of who performs the intervention (i.e. it may not be a doctor but could be a nurse, pharmacist, herbalist, etc).
- ‘Medicinal product’ includes excipients and contaminants.
- ‘Usually predict hazard’: ‘usually’ because there are occasional exceptions (e.g. first dose hypotension with an ACE inhibitor does not necessarily predict hypotension with subsequent doses)
- ‘Alteration’ implies either a reduction or an increase in the total dose (e.g. if accept that a loss of effect of a medicine is an adverse effect, then an increase in dose might be the appropriate treatment’.
- ‘Dosage regimen’: it may be desirable to alter not the dose itself but the frequency, formulation or duration of treatment.

These qualifiers certainly help to further clarify the definition that Aronson and Ferner proposed; however, maybe with further qualifiers on the original definition it may also have been equally clarified to address these same issues. Nevertheless, Aronson and Ferners' definition and qualifiers certainly is better suited to the description of oncology ADRs.
This is due to the following:

1. Oncologists often accept some adverse effects of cytotoxic chemotherapy, such as tiredness, as less important since they expect the patient to get it. However from the patient's point of view the tiredness can be anything but trivial since it affects their quality of life. Hence qualifying the definition with 'appreciably' aids in highlighting the phenomenon of oversight of adverse effects viewed as trivial by the physician but not the patient.
2. In stating 'adverse effects usually predict hazard from future administration and warrant prevention, or specific treatment, or alteration of the dosage regimen, or withdrawal of the product' the definition can be directly applied to ADRs seen in oncology patients. That is the patients are prescribed a set dose of a regimen of cytotoxic chemotherapy, which can result in ADRs that may require treatment to alleviate the adverse effects, a dosage reduction for the next cycle of chemotherapy to prevent the same degree of the adverse effect again, or in worst case scenarios a withdrawal from the chemotherapy regimen (i.e. if ADRs are so severe that patient cannot possibly tolerate another cycle of the chemotherapy regimen).

1.2.2 Unexpected Adverse Drug reaction

An unexpected adverse drug reaction is an adverse reaction, the nature or severity of which is not consistent with domestic labelling or market authorization, or expected from characteristics of the drug. The subclassification of "unexpected" was included to facilitate understanding of the type of adverse reactions which are most important to report to drug monitoring agencies (12).

1.2.3 Adverse events

An adverse event is any untoward medical occurrence that may present during treatment with a pharmaceutical product but which does not necessarily have a causal relationship with this treatment. An adverse event can, therefore, be any unfavourable and unintended sign, symptom or disease temporally associated with the use of a medical product. When an

adverse event has been assessed and a causal relationship to a medicine has been established, it is then considered an ADR (13).

Other variations on this definition have been suggested. Such as:

a) The Committee for Proprietary Medicinal Products of the European Union defines adverse event as 'any undesirable experience occurring to a subject during a clinical trial, whether or not considered related to the investigational product(s)' (9).
b) The International Committee on Harmonization 1994 defines adverse event as 'any untoward medical occurrence in a patient treated with a pharmaceutical product which does not necessarily have a causal relationship with this treatment' (9).

Whereas these two definitions are very similar to the original WHO definition, it has been recently proposed by Aronson and Ferner (11) that the definition of the term 'adverse event' be changed to 'any abnormal sign, symptom, laboratory test, syndronic combination of such abnormalities, untoward or unplanned occurrence (e.g. an accident or unplanned pregnancy), or any unexpected deterioration in a concurrent illness'.

Regardless of which definition one chooses to use it is still true that all ADRs are adverse events but only some adverse events are ADRs. This distinction is important in clinical trials where not all events are caused by the medicine.

In clinical trials the possibility of a causal connection has not been considered for the clinical phenomena occurring during treatment with a medicine. Therefore by describing adverse outcomes in clinical trials as events rather than medicine-induced effects, it acknowledges that the adverse outcome may be due to other possibilities other than the medicine and that it is not always possible to attribute causality from the numbers involved in clinical trials.

The concept of collecting adverse events rather than ADRs in clinical trials was proposed after the failure of clinical trials to detect problems with the medicine practolol in 1975. 'Practolol Syndrome', also known as *oculomucocutaneous syndrome*, was found to be caused by practolol. This resulted in severe eye and skin problems, and sclerosing peritonitis. The collection of adverse events rather than ADRs was not implemented in the UK until the 1980's after another major drug disaster with benoxaprofen however (14).

In oncology adverse events are often referred to as ‘toxicities’ instead. This is for historical reasons, and throughout this thesis they may be referred to as such for this reason (15).

1.2.4 Adverse effect

An adverse effect refers to the same thing as an adverse drug reaction but is seen from the point of view of the medicine. Whereas an ADR is seen from the point of view of the patient (i.e. the medicine causes an effect but the patient has a reaction).

1.2.5 Side effect

A side effect is defined as any unintended effect of a pharmaceutical product occurring at doses normally used in man which is related to the pharmacological properties of the drug (12). This is an old term and is broad enough to include both positive and negative effects of a medicine apart from its main properties or indications. Some use the term as synonymous with adverse drug reaction.

However Aronson and Ferner (11) consider the WHO definition to be ambiguous because it states that a ‘side effect’ “is related to the pharmacological properties of the drug” which is not strictly the case since the effect may be due to a distinct pharmacological effect separate from the pharmacological effect whereby the therapeutic action is produced. Also some side effects can be beneficial and for this reason the drug is being used in the patient for a therapeutic benefit. Hence not all ‘side effects’ fall under the classification of ‘unintended’. Therefore, as suggested by Aronson and Ferner, it might be best not to use this term at all to avoid any potential confusion and opt for usage of ‘adverse effect’ or ‘adverse drug reaction’ instead. To date the above definition of ‘side effect’ is still endorsed by the WHO however.

1.2.6 Signal

A signal is an early indicator or warning of a potential problem (‘first alert’ of a potential problem with a medicine). The World Health Organisation defines a signal as reported information on a possible causal relationship between an adverse event and a medicine, the relationship being unknown or incompletely documented previously. Usually more than a single report is required to generate a signal, depending upon the seriousness of the event and the quality of the information (9, 13). Signal detection comprises the processes of: selection of a drug-adverse event; the preliminary assessment of the available evidence; and a follow-up of how the signal develops (16).

1.2.7 Toxicity

The term toxicity is defined as the relative potency of a toxicant, and it is one of the characteristics of a new medicine or biological product that preclinical and clinical trials attempt to measure (13). Toxicity has been used to describe either the toxicant's ability to cause harm/injury to a living organism or any adverse event of a toxicant on a living organism (13).

As stated previously, in oncology the term toxicity continues to be used for historical reasons (15). However the National Cancer Institute (NCI) prefer that the term adverse event with its attributes be used instead whenever possible though. To endorse this the NCI have renamed the Common Toxicity Criteria (CTC), which is the guidance information for grading adverse events in oncology, to Common Adverse Event Criteria (CTCAE) in 2003 (17).

1.3 Medical Terminology Dictionary

There are a great many dictionaries currently in use in the pharmacovigilance/ regulatory affairs environment. The characteristics of a dictionary exert a profound effect upon the data. A dictionary ideally should contain adequate terms to avoid compromises when coding of data to prevent details from being lost; group conditions appropriately for ease of finding in the database; not be so specific to result in splitting of reports (when no real significance in the reports exist) which could result in a reduction in the ability of the database to detect signals of a new ADR.

No attempt has been made to determine from the literature which, if any of the medical terminology dictionaries, is preferred in the pharmacovigilance community. However the medical terminology dictionary that is utilised by the MHRA in the UK is the Medical Dictionary for Regulatory Activities (MedDRA), and it is only this dictionary will be discussed.

1.3.1 Medical Dictionary for Regulatory Activities (MedDRA)

The Medical Dictionary for Regulatory Activities (MedDRA) was developed by the International Conference on Harmonisation (ICH) and is owned by the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) acting as trustee for the ICH steering committee. MedDRA was developed to improve the effectiveness and transparency of medical product regulation worldwide. The objective of MedDRA was to

produce a single, internationally acceptable, medical terminology intended for use in the pre- and post-marketing phases of the medicines regulatory process that would allow for efficient communication of ADR data between industry and regulatory agencies, and between countries.

It is used as well in pharmacovigilance and it is anticipated that it will become the preferred terminology for international electronic regulatory communications for medicines. It has already been accepted internationally within the European Union, the US and Japan. The Medicines and Healthcare Regulatory products Agency (MHRA) in the UK implemented this dictionary in 2004 for this reason. MedDRA is also utilized in the Eudravigilance safety Database held by the European Agency for the Evaluation of Medicinal Products (EMEA) and in the USA Food and Drug Administration (FDA) Adverse Event Reporting System (AERS) (18).

MedDRA contains pragmatic, clinically validated medical terminology with an emphasis on ease-of-use data entry, retrieval, analysis, and display, with a suitable balance between sensitivity and specificity, within the regulatory environment (19). The medical terminology within MedDRA covers diagnosis, symptoms and signs, ADRs, therapeutic indications, the names and qualitative results of investigations, surgical and medical procedures, and medical/social history (20).

The terms in MedDRA were derived from several sources including the WHO's adverse reaction terminology (WHO-ART), Medical Dictionary for Drug Regulatory Affairs (MEDDRA), MHRA's Adverse Drug Reaction On-line Information Tracking (ADROIT) database, Coding Symbols for a thesaurus of Adverse Reaction Terminology (COSTART), International Classification of Diseases (ICD) 9 and ICD9-CM (20). The integration of terminology from these sources should aid in overcoming limitations of existing terminologies and regulatory functional relevance. As well it could have an important effect on risk management performance and the analysis of safety data (18).

1.4 Classifications of Adverse Drug Reactions (ADRs)

There have been numerous proposals for classification schemes for ADRs from 1958 to present. These classifications are based on dose relatedness only in some, but others also factor in time course. Appendix 1 gives a summary of these classification schemes.

There is much discussion in the literature on the merits and deficiencies for each of these classification schemes but no attempt has been made to determine as to which one is most accepted in practice. A summary of the different proposed types of ADRs named alphabetically, and based on the pharmacological mechanism of action, from the literature has been done for simplicity. There are at least 7 types suggested in the literature, and they may be classified A to G:

1) Type A (augmented) - these reactions are considered predictable and dose dependent (1, 21). They result from an exaggerated but otherwise normal pharmacological action, primary or secondary, of a medicine and respond to dose reductions. Type A reactions have a high morbidity and are common (i.e. account for over 75% of ADRs) but low mortality (21). The majority of these types of ADRs are discovered before marketing of a medicine (22). An example of this would be digoxin toxicity.

2) Type B (bizarre) – These reactions are not predictable and are not dose-dependent (11, 21). They are also referred to as 'idiosyncratic' since they are responses unrelated to the conventional pharmacology of the medicine. Type B reactions are rare and usually cause low morbidity but high mortality however (21). This type of reaction only responds to withdrawal of the medicine. The majority of these types of ADRs are not discovered until post-marketing (22). An example of this would be a rash secondary to penicillin.

3) Type C (chronic or continuous) – This type of reaction is related to cumulative use of a medicine, as in chronic use. Hence it is dose and time related. An example would be NSAID induced renal failure (23).

4) Type D (delayed) – This type of reaction will only appear sometime after the use of a medicine. An example would be a patient developing endometrial cancer years after taking tamoxifen post breast cancer.

5) Type E (end of use) – This type of reaction is predictable and occurs at the end of treatment if a medicine withdrawn abruptly. The reaction will improve or disappear if the medicine is reintroduced. An example would be a patient on a SSRI, such as venlafaxine, for a period of time and then if the medicine were stopped abruptly the

patient would experience a withdrawal reaction. To prevent this type of reaction normally the dose must be tapered over a period of time.

6) Type F (failure)- This type of reaction is attributed to the lack of efficacy of a product. An example of this would be a failure to control infection or antimicrobial resistance (24).

7) Type G (genetic/genomic) – This type of reaction causes irreversible genetic damage. A number of medicines can produce genetic damage in humans. Notably, some are potentially carcinogenic or genotoxic. Also some teratogenic agents damage genetic material in the foetus (25).

However, with regard to time line of developing the ADR, the reaction time is defined as the time between the last drug exposure and the appearance of the first symptom (22). There are three classifications within this:

1) Acute (0-60 minutes)
2) Sub-acute (1-24 hours)
3) Latent (1 day – several weeks)

1.5 Adverse Event Criteria

In oncology there are numerous adverse event (toxicity) criteria in use throughout the world. These scales contain descriptive terminology that can be used for adverse event reporting and a grading (severity) scale is provided for each term. The scales are used to score the severity of adverse event experienced by patients during clinical trials, and is also used in oncology (out with clinical trials) to score patients adverse events after each cycle of treatment.

The two best known scales are:

1. World Health Organisation (WHO) Toxicity Criteria – Appendix 2
2. National Cancer Institute (NCI) Common Terminology Criteria of Adverse Events (previously known as Common Toxicity Criteria prior to 2003) - Appendix 3

A formal comparison between these two scales is not easy but a study on the reliability of the WHO and NCI showed no substantial difference between the two scales (26). However the NCI scale provides for a higher number of adverse events (more than 900 events grouped in 28 categories in the version 3.0) (17) as compared to the WHO scale (54 events in total in 17

categories) (27). The updated version 3.0 includes criteria for evaluating adverse events related to growth and development and other long-term secondary effects of cancer; late or chronic effects; surgical interventions (28). Therefore the NCI scale is a more complete and precise tool (29).

Also version 3 of the NCI CTCAE incorporates the preferred terms from the Medical Dictionary for Regulatory Activities (MedDRA). This means that all output data of adverse events for patients undergoing cytotoxic chemotherapy (being scored using version 3 of NCI CTCAE) could be captured on databases and electronically communicated to national/international regulatory bodies for pharmacovigilance purposes with no need for any additional mapping or manual input. This would create a significant advancement in oncology signal generation and chemotherapeutic agent(s) monitoring, which would greatly surpass voluntary, spontaneous reporting.

1.6 Pharmacovigilance

In order to prevent or reduce harm to patients and to improve public health a well organised, functional pharmacovigilance system must be in place (30, 31). Pharmacovigilance is defined as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine-related problem (30, 32). Initially it was only medicines that pharmacovigilance centred on but more recently the concerns of pharmacovigilance has widened to include herbal, traditional and complementary medicines, blood products, biologicals, medical devices and vaccines (31).

Other items of relevance to pharmacovigilance include substandard medicines; medication errors; lack of efficacy; use of medicines for unlicensed indications and for which there is inadequate scientific basis; case reports of acute and chronic poisoning; assessment of medicine-related mortality; abuse and misuse of medicines; adverse interactions of medicines with chemicals, other medicines, and food (31).

1.6.1 Aims of pharmacovigilance

The aims of pharmacovigilance, as set by the WHO Collaborating Centre for International Drug Monitoring, are (32):

1) To improve patient care and safety in relation to the use of medicines and all medicinal and paramedical interventions
2) To improve public health and safety in relation to the use of medicines
3) To detect problems related to the use of medicines and communicate the findings in a timely manner
4) To contribute to the assessment of benefit, harm, effectiveness, and risk of medicines, leading to the prevention of harm and maximization of benefit
5) To encourage the safe, rational and more effective (including cost-effective) use of medicines
6) To promote understanding, education and clinical training in pharmacovigilance and its effective communication to the public

1.6.2 Key Partners

The management of risks associated with the use of medicines demands close and effective collaboration between key players involved in pharmacovigilance. The key players include government, industry, hospitals & academia, medical and pharmaceutical associations, poisons and medicines information centres, health professionals, patients, consumers, the media and the World Health Organisation (30). These key players must maintain collaboration if the future challenges of pharmacovigilance are to be overcome. Constraints exist, however, for example lack of training, resources, political support, and scientific infrastructure can undermine this process, and must be addressed to ensure the future practice of pharmacovigilance.

1.6.3 International Pharmacovigilance Bodies

1.6.3.1 The International Conference on Harmonisation (ICH)

The ICH is a project that brings together regulatory authorities from the European Union, USA and Japan with experts from the pharmaceutical industry. The group discusses scientific and technical aspects of product registration, leading to recommendations that facilitate harmonisation of product registration requirements, thereby reducing the duplication of effort during the development of new medicinal products. The ICH has produced definitions and standards for both expedited and periodic reporting requirements.

Clinical drug safety-related topics and pharmacovigilance planning are also addressed at ICH meetings. Also the project has been instrumental in developing standards for electronic communication of safety data (22).

1.6.3.2 World Health Organisation (WHO)

The WHO Programme for International Drug Monitoring was established in 1968, and consists of a network of National Centres for pharmacovigilance. There are 79 member countries and 18 associate members in the programme at present (33). The member national centres submit case reports of suspected ADRs to be stored in a common database, which contains approximately 3.4 million ADR case reports (33). This source of data is used by the WHO to identify and analyse new adverse drug reaction signals.

In spite of the efforts of the WHO and the ICH, pharmacovigilance measures still lack true global vision and cooperation and the current approach is inadequate for the future (34). This is also true of oncology pharmacovigilance and much work must be done before the safety of oncology medicines and biologicals can be ensured.

1.6.4 The European Medicines Agency and Eudravigilance

The European Agency for the Evaluation of Medicinal Products (EMEA) was set up in 1995 to ensure the safe and effective use of centrally authorised medicines (i.e. those medicines which are authorised throughout the European Union) (33).

Eudravigilance is a data-processing network and database management system for the exchange, processing and evaluation of safety data relating to marketed products authorised for use in the EU used by the EMEA. It was established in December 2001to facilitate the collection of information on ADRs but a clinical trials module was introduced in 2004. Member states are mandated to submit all serious ADR reports received by their national regulatory body from any health professional or pharmaceutical company, whether for an investigational or marketed medicine, within 15 days of receiving the report (35).

Eudravigilance contains standard terminology with a focus on MedDRA and a product dictionary developed by the EMEA. Eudravigilance is seen as a significant development in exchange of electronic pharmacovigilance data which will allow for exchange of information between member states, as well as member states and the pharmaceutical industry. In

principle, it will allow the EMEA to hold a complete record of all serious adverse reactions reported in the EU and all serious, unexpected reactions from outside the EU if an EU-marketed medicine is implicated (35). However, currently, only the European Commission, the EMEA and EU authorities have full access; pharmaceutical companies have limited access; and individual health care professionals and patients do not have access. As the system develops and outstanding issues become resolved this may change (33).

1.6.5 Current Practice

The success of pharmacovigilance activity depends upon the reporting of suspected adverse drug reactions and the effective communication of these ADRs nationally and internationally. At present the main means of collecting ADR data has been via spontaneous reports from healthcare professionals, however, more recently some countries (including the UK) have recently introduced patient reporting. Although it is too soon to know of what quality or added benefit these reports will have in pharmacovigilance.

However spontaneous reporting schemes have their limitations (i.e. a series of spontaneous ADR reports provides only limited evidence of causation), besides under-reporting, and generally raise questions rather than provide answers (36). Therefore more systematic and robust epidemiological methods that take into account the limitations of spontaneous reporting are required. Such pharmacoepidemiological methods of collecting safety data includes prescription event monitoring, record linkage and case control studies. Some structured electronic databases in the UK that are utilised for pharmacovigilance are General Practice Research Database (GPRD), Tayside Medicines Monitoring Unit (MEMO), the Drug Safety Research unit's Prescription Event Monitoring, The Health Improvement Network (THIN) and QResearch (33).

There is no one pharmacovigilance method that is ideal or one hundred percent effective since all of these pharmacovigilance methods have strengths and limitations. However they all complement each other and if utilised effectively they could help achieve the goal of the safe use of medicines (37).

1.7 Reporting of Adverse Events and ADRs

1.7.1 Pre-marketing

Prior to a medicine being licensed it must be tested in animals and in clinical trials. A clinical trial is a research study to answer specific questions about medicines, and is used to determine whether new medicines or treatments are both safe and effective. Clinical trials are divided into three phases pre-marketing but there is also a phase of clinical trial which is carried out post-marketing. The phases of a clinical trial are:

1) Phase I – these are the first test of a new medicine or treatment in a small group of humans. It is the initial study to determine the metabolism and pharmacologic actions of medicines in humans, the adverse effects associated with increasing doses, and to gain early evidence of effectiveness; may include healthy participants and/or patients. Phase I trials normally are of a duration of a few weeks to a few months.
2) Phase II - expands the study to a larger group of people (approximately 100) and is a controlled clinical study conducted to evaluate the effectiveness of a medicine for a particular indication in patients with the disease or condition in question and to determine the common short-term adverse effects and risks. Phase II trails normally last for about one year.
3) Phase III - expands the study to an even larger group of people (at least several hundred) in controlled and uncontrolled trials after preliminary evidence has been obtained suggesting the effectiveness of the medicine. It is intended to gather additional information to evaluate the overall risk-benefit relationship of a medicine and to provide adequate information for labeling once marketed. Phase III trials are normally carried out over a two to three year period.
4) Phase IV - takes place after the drug or treatment has been licensed and marketed and it is used to delineate additional information including the medicines' long-term risks, benefits and optimal use. These trials involve thousands of people and are of no set duration but are normally carried out over a longer period.

Prior to 1977 recording of any suspected ADRs in clinical trials was required. However in 1977, after the failure of clinical trials to detect problems with practolol emerged, it was proposed that the value of clinical trials in detecting unwanted effects of new medicines would be enhanced if adverse events, not ADRs, would be recorded instead. The basic principle would be to collect all adverse events that appear whilst the patient is on a medicine and in the immediate period after stopping treatment, as well as any adverse events that were

present at baseline but has become worse whilst on the medicine (22). All events would be reported to the co-ordinating trial centre and analysed in treated subjects and controls in controlled studies.

Despite each phase involving increasing number of patients, by the end of the clinical trials as little as 500 patients, to a maximum of 5000 patients, may have received the medicine. Therefore, even with the added measure of recording adverse events instead of ADRs, pre-marketing trials do not have sufficient power to reliably detect rare ADRs, which may occur at rates of 1 in 10,000 or fewer exposures to the medicine (i.e. would require exposure in at least 30,000 patients before such an ADR would be detected from signal generation). Pre-marketing trials also lack the follow-up to detect ADRs that widely separated in time from the original exposure to a medicine or delayed consequences associated with long-term administration (38). Also unforeseen interactions with co-existing disease states and concomitant medicines may remain unexplored (39). Therefore the full safety profile of a medicine is not complete at the time of marketing of a medicine.

Hence reporting of adverse events to the manufacturer is an important responsibility during phase 1, 2 and 3 clinical trials in oncology. This information is used to determine if the treatment dose is acceptable, and to decide whether or not a medicine, including cytotoxic chemotherapy agent(s)/ regimen(s) will be used in the future. However due to the five too's of pre-marketing trials: too few, too simple, too narrow, too median aged and too brief (40), and the continued search for more effective cytotoxic chemotherapy regimens (i.e. using chemotherapy agents not previously used in combination or in differing dosing schedules) the need for continued pharmacovigilance should not end here.

Therefore more effort is still required post-marketing to aid in the detection of serious and rare adverse drug reactions in oncology. One study in the United States found that serious adverse drug reactions (ADRs), resulting in death or organ failure, could be discovered as long as 36 years after a cancer medication had received licensing (41). However, despite medical professionals' and patients' dependence on this data to ensure safe usage of chemotherapeutic agents, out with clinical trials this good practice often disappears.

1.7.2 Post-marketing

The post-marketing monitoring and evaluation of the safety and effectiveness of all medicines is essential. The post-marketing surveillance of a medicine begins once a medicine is licensed and enters the general market. The pharmaceutical industry and regulatory authorities have a shared responsibility in this process. In the United Kingdom, the Medicines and Healthcare products Regulatory Agency (MHRA) is the regulatory agency with this responsibility.

It is important to recognise that clinical trials and post-marketing surveillance address different issues. Post-marketing surveillance data provide new information that was unavailable in pre-marketing studies. The patterns of use, effectiveness and safety of a medicine in clinical practice may be substantially different to that in clinical trials due to differences in prescribing and patient groups. These differences include the limited number of patients in studies, restrictions in patient populations (e.g. pregnancy and nursing mothers, children, the elderly and those predisposed to develop adverse events are frequently excluded), and the limited duration of use of a medicine or period of evaluation in clinical trials (42). As a result a greater number of patients are exposed in a less controlled environment which allows for the observance of unexpected, rarer and sometimes serious adverse effects for the first time (i.e. the numbers of patients involved in clinical trials were too small to allow for the detection of these rarer side effects). In addition knowledge about the effectiveness and safety in off-label use and interactions with concomitantly used medicines remains unknown in pre-clinical trial data (42).

1.7.2.1 Spontaneous Reporting

Spontaneous reporting is a system in which case reports of suspected ADRs are submitted (voluntary or mandatory) by health care professionals, pharmaceutical companies or consumers to national regulatory bodies (32) with the primary role of signal generation of ADRs. Signal generation describes the first alert of a problem with a medicine. Usually more than a single report is required to generate a signal, depending upon the seriousness of the event and the quality of the information. By its nature a signal cannot be regarded as definitive causality but indicated the need for further enquiry or action (13).

Spontaneous reporting of ADRs may be defined as a scheme for collating individual case reports of clinical suspicions of ADRs operated for the primary purpose of detecting potential unknown serious medicine toxicity (36). The method was first developed in the 1960s in

response to a five year delay in detecting the association between thalidomide and phocomelia (43), and it was the only conceivable early warning system of future possible medicine induced disasters (44). Spontaneous reporting has since become the cornerstone of post-marketing safety monitoring of medicines around the world, making it possible to detect previously unknown adverse effects with a small number of cases.

Spontaneous reporting has limitations however. These limitations include (44):

1) The causal relationship is usually uncertain
2) Under-reporting (there is substantial variability but usually under-reporting of ADRs exists, however, it is difficult to quantify the extent)
3) Reporting bias
4) No quantitative measurement (measure of frequency not possible and the comparison of medicines is often difficult)
5) Less useful for the detection of adverse effects with a relatively high background frequency and occurring without a suggestive temporal relationship

Therefore whilst the spontaneous reporting system for ADRs is pivotal it is not without fundamental limitations.

1.7.2.1.1 Yellow Card scheme

In the United Kingdom spontaneous adverse drug reaction reporting via the Yellow Card scheme (in the form of a yellow card report to the MHRA) is the main means of post-marketing monitoring of the safety of medications throughout its marketing life, and of identifying any previously undetected adverse reactions. The success of the Yellow Card scheme in monitoring medication safety and ensuring patient safety depends upon voluntary reporting of ADRs by members of the multidisciplinary clinical team.

1.7.2.1.2 History

The Yellow Card scheme was introduced in 1964 by the Committee on Safety of Drugs (CSD) under the chairmanship of Sir Derrick Dunlop in response to the thalidomide disaster. Thalidomide, first marketed in 1958 in the UK, was a sedative/hypnotic medicine strongly promoted for use in morning sickness during the early stages of pregnancy which resulted in over 10,000 cases worldwide of congenital malformation of the limbs known as phocomelia as well as other internal malformations. Thalidomide was subsequently withdrawn from the market worldwide in between 1961 to 1962 (35).

Prior to the thalidomide disaster there was no formal system in place for the monitoring of safety of medicines in the UK or elsewhere. This disaster highlighted the immediate need for a system of licensing and monitoring of the safety of medicines worldwide. The establishment of the CSD in 1963 was the proposition of the joint sub-committee reviewing drug safety for the UK (35).

The CSD was subsequently renamed as the Committee on Safety of Medicines (CSM) under the umbrella of the Medicines Control Agency (MCA). However the MCA became known as the Medicines and Healthcare products Regulatory Agency (MHRA) in April 2003 after a merger with the Medical Devices Agency. The MHRA is now responsible for protecting and promoting public health and patient safety and it is the MHRA that assumes the responsibility of the Yellow Card scheme.

The purpose of the scheme was to gather reports of suspected ADRs to act as an early warning system of possible medicine safety issues. The fundamental principals of the scheme were:

- voluntary reporting based on the good will of reporters
- the collation of reports of ADRs without causal link needing to be established
- reporters encouraged to report without delay
- all reports are held in confidence
- data provided never to be used for disciplinary purposes or for enquiries about prescribing costs

Initially only doctors, dentists and procurator fiscals/coroners were allowed to report to the Yellow Card scheme. However, since 1999, pharmacists (both hospital and community), nurses, midwives, health visitors and patients have been added as official reporters to the Yellow Card scheme. Reports are also received directly from the pharmaceutical industry who has a legal obligation to report all serious ADRs to the MHRA.

The Yellow Card scheme is only one of several sources used to monitor licensed medicines in the UK but it is pivotal to the monitoring of the safety of medicines in the UK. In over 40 years approximately 500,000 reports have been received.

1.7.2.1.3 Criteria for Reporting

The criteria for reporting to the MHRA via the Yellow Card scheme are:

1. Report all reactions for:
    a. Black triangle medicines and vaccines. Black triangle medicines are those medicines that are new to the market and are under intensive surveillance by the MHRA.
    b. Herbal preparations

2. Report all serious reactions for all medicines and vaccines regardless of their black triangle status.

A serious adverse drug reaction is defined by the World Health Organisation (WHO) as any untoward medical occurrence that at any dose results in death, requires hospital admission or prolongation of existing hospital stay, results in persistent disability/incapacity, or is life threatening (10). The term "severe" is not synonymous with serious. "Severe" is used to describe the intensity or severity of a specific event (as in mild, moderate or severe). However the event itself may be of relatively minor medical significance (such as severe erythematous rash). Seriousness (not severity) which is based on patient/event outcome or action criteria serves as guide for defining regulatory reporting obligations.

Less than 10% of all serious reactions are reported (45), and within oncology the reporting rates are even lower due to acceptance of these reactions as being a predictable and inevitable part of the normal process of cytotoxic chemotherapy treatment (2, 46, 47). Presumptions such as this may divert attention away from an analysis of the ADRs experienced by these patients (47), which can result in ADRs being overlooked.

While a yellow card report for an ADR experienced by a patient receiving cytotoxic chemotherapy may not alter that individual patient's treatment regimen or outcome, it can aid in the production of signals on Sentenil® (Sentenil is the computer software used by the MHRA to compile all of the suspected ADRs reported via the Yellow Card scheme, HIV Reporting scheme, and from the pharmaceutical industry). This could result in safety issues being detected and lead to changes in practice for future treatment of other patients with the cytotoxic chemotherapy regimen in question.

In oncology the lack of adherence to the criteria for submitting a report to the MHRA produces a challenge to the Yellow Card scheme to function to its full capacity in this clinical area. Oncology oriented guidelines for ADR reporting, which highlight clinical relevance, need to be developed to address this issue, and greater education and training of oncology staff is required.

1.7.2.1.4 Review of the Yellow Card scheme

In July 2003 the parliamentary Under Secretary of State for Health, Lord Warner, announced that an independent review of the Yellow Card scheme would be undertaken. This was in response to increased requests for yellow card data which raised issues in relation to confidentiality of reports submitted (a fundamental principle ensured by the scheme). The MHRA wished to avoid any changes in access to yellow card data that might discourage reporters from reporting and resulting in damage to the scheme's ability to protect the public (35). It needed to be decided, therefore, what data, in what circumstances and to whom data should be made available to for the purpose of assuring public safety. Other issues considered during the review was patient reporting, how to improve the quality and frequency of ADR reporting, commitment to Eudravigilance, and implications of the Freedom of Information Act.

The review of the Yellow Card scheme was led by Dr Jeremy Metters and was completed in 2004. Amongst the findings of the report was the recommendation that it was essential that the scheme maintain its focus upon serious, previously unknown ADRs; and black triangle products but supported developing clearer guidelines for definitions of serious ADRs (35). In oncology where adverse events experienced during treatment with cytotoxic chemotherapy are scored by severity not seriousness, this is certainly of relevance. There is a need to define which adverse events (considered to be an ADR) and grades specifically should be reported.

Another finding of relevance is the need for increasing the utilisation of electronic reporting where available. This would aid in increasing the efficiency of the Yellow Card scheme by decreasing the time line of receiving a suspected ADR and it being entered into Sentenil®. This is due to the elimination of manual tasks (i.e. scanning and manual entry by a pharmacovigilance scientist at the MHRA) which would slow the process. Hence, where possible electronic reporting is preferred and should be encouraged. Most hospitals now have internet access for the majority of staff to facilitate electronic reporting on the MHRA website

(www.yellowcard.gov.uk) but, in general, uptake by staff is very poor in all clinical disciplines.

One way to facilitate electronic reporting of oncology ADRs would be via electronic capture of NCI CTCAE scores and introduction of an electronic yellow card that would be pre-populated with anonymised patient details, cytotoxic chemotherapy regimens, past medical history and any other concomitant medicines. At present in Scotland cancer centres are moving towards paperless systems, which would facilitate electronic capture of adverse events but further IT investment would be required to realise the pharmacovigilance potential of these electronic advancements.

The Scottish Oncology Pharmacy Group have a pharmaceutical care plan for cancer patients (Appendix 4) of which an electronic version was piloted that could be adapted to facilitate electronic ADR reporting (48). Unfortunately uptake of this electronic care plan did not occur after the pilot phase. This was a missed opportunity since an electronic yellow card, pre-populated with the majority of the required data-fields from the information within the patients' records, could have been integrated into the pharmaceutical care plan to help facilitate ADR reporting in oncology.

1.7.2.1.5 Reasons for Under-reporting

Under-reporting of ADRs is the main limitation to spontaneous reporting worldwide. Whilst the actual rate of under-reporting is difficult to quantify, a systematic review of 37 studies found that the median rate of under-reporting was 94% (49). The reasons for under-reporting are not been totally delineated but 'seven deadly sins' that might cause low reporting rates of ADRs among healthcare professionals have been highlighted. These included ignorance (I am not sure how to report), diffidence (I may appear foolish if I report a suspected ADR), fear (I may expose myself to legal liability if I report an ADR), lethargy (I am too busy to report), guilt (I am reluctant to admit I may have caused harm), ambition (I would rather collect cases and publish them) and complacency (only safe medicines are marketed) (33). Since then other studies have been carried out in this area and researchers have found other factors of great importance in determining if healthcare professionals will report an ADR (50 - 55). Chapter 4 gives a detailed summary of this published literature.

In oncology, however, factors that have been proposed to limit ADR reporting include the common occurrence of many ADRs, their non-life-threatening nature in the context of cancer, and possibly clinicians' perception that these reactions are of little significance (47). However, there were no published studies in the literature that specifically looked at the attitudes of healthcare professionals on oncology ADR reporting.

1.7.3 Intensive Monitoring schemes

There are many variations on the theme of spontaneous reporting, as with intensified reporting which may concentrate on selected medicines or adverse effects. This form of monitoring can be valuable to pharmacovigilance, provided the information is linked to national pharmacovigilance databases (44).

1.7.3.1 The Edinburgh Cancer Centre scheme

While there are a number of examples, Chapter 3 of this thesis is based upon the pharmacists' led ADR reporting initiative at the Edinburgh Cancer Centre (ECC). Chapter 3 gives further details of this initiative and the audit undertaken in 2002, which resulted in an 800% increase in reporting due to this pharmacist-led ADR reporting initiative in oncology (50, 56, 57, 58). This initiative is no longer promoted at the ECC due to key staff who were involved leaving. However this example of good practice could be built upon to improve oncology pharmacovigilance practice in the future if it was proven to be a sustainable effort.

1.7.4 Active Surveillance

Active surveillance seeks to ascertain completely the number of adverse events in a pre-organised process. Active surveillance can be achieved by reviewing medical records or interviewing patients and/or clinicians in a sample of sites to ensure complete and accurate data on reported adverse events. This process is most efficient for those medicines used mainly in an institutional centre. Oncology medicines would fall into this category. However this process would be labour intensive and might not be sustainable.

Other methods that can be employed under active surveillance include drug event monitoring and maintaining registries such as a disease registry or a specific drug exposure registry. In Scotland, the Information Services Division (ISD) maintains a cancer registry. The scheme has been collecting information on cancer since 1958. The data are used for a wide variety of purposes which include: public health surveillance; health needs assessment, planning and

commissioning cancer services; evaluation of the impact of interventions on incidence and survival; clinical audit and health services research; epidemiological studies; and providing information to support genetic counseling and health promotion (59).

The majority of surveillance registries are now maintained electronically, which gives potential for record-linkage with other datasets (i.e. the linkage of patient-specific information that is stored separately). In particular record-linkage can make a significant contribution to monitoring of exposure to medicines and outcomes. In Scotland there is potential for the establishment of linkage between data recorded in the cancer registry at ISD and other healthcare datasets facilitated by the widespread use of the Community Health Index (CHI) Number**.** The CHI number is a ten digit number allocated to all patients when they register with a general practitioner in Scotland, and it is unique and specific to each patient (i.e. the first six digits represents date of birth, then a three digit serial number of which the last digit indicates sex) (60).

Initially, in response to the Data Protection Act 1998, the Confidentiality and Security Advisory Group (CSAG) advised that the CHI number should not be used for other systems or agencies unless it is with patient consent. Subsequently guidance from the Information Commissioner has superseded this. Therefore although informed consent from a patient is the ideal, the Information Commissioner is not opposed to the NHS number (or CHI) being used by a non-healthcare body as a means of linking with healthcare records held by a health service body when both bodies are working together to deliver a joint service or for agreed research and statistical purposes (61).

Hence this presents the possibility of developing electronic capture of oncology adverse events and outcomes within the hospital setting throughout Scotland, and linkage to the Cancer Registry at ISD and possibly MHRA databases. This would require a great amount of investment in information technology in particular software and interfaces but the pharmacovigilance benefits would be valuable to both the MHRA and the oncology profession in obtaining information on medicines safety.

1.8 Opportunity for future development

In the future, as more and more health institutions introduce electronic records (i.e. paperless systems), the possibility of automatic capture of data from computers within the health services offers the most scope for advancement of pharmacovigilance (36). In oncology the capability of electronic capture of oncology adverse events and outcomes within the hospital setting would allow regulatory bodies to have access to a vast amount of data on oncology adverse events (and possible ADRs) not currently available via spontaneous reporting schemes. This would provide a great potential to improve oncology patient safety.

2. Research Questions

1) What is the current practice of oncology ADR reporting within Lothian?
2) What attitudes might affect oncology ADR reporting via the Yellow Card scheme?
3) Is it possible to develop standards to operationalise the classification of serious ADRs for spontaneous reporting that will aid oncology healthcare professionals to improve their current pharmacovigilance practice?

3. Aims and Objectives

Aim

To produce guidelines on serious adverse drug reaction spontaneous reporting as appropriate to cancer chemotherapy; and to derive potential recommendations for improvement in pharmacovigilance practice in oncology.

Objectives

3.1 To quantify the potential for improvement in spontaneous ADR reporting before and after a pharmacist led ADR reporting initiative by a retrospective survey of case notes.

3.2 To identify the range of attitudes of oncology healthcare professionals on the need for improving reporting of ADRs in oncology.

3.3 To develop standards for classification and reporting of serious ADRs in patients receiving cytotoxic chemotherapy.

Chapter 2

An overview of the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE)

2.1. Introduction

The National Cancer Institute's (NCI) Cancer Therapy Evaluation Program (CTEP) in the United States developed the original Common Toxicity Criteria (CTC) in 1982 in an effort to provide standard language for reporting adverse events occurring in cancer clinical trials sponsored by the NCI [15]. The CTC were widely adopted internationally and as new agents were introduced and new adverse events identified, many groups began to add supplemental criteria. This independent revision of the CTC resulted in nonstandard adverse event nomenclature and inconsistent definitions for severity.

In keeping with international harmonisation efforts, a CTC Review Committee with representation from the pharmaceutical industry, the Food and Drug Administration (FDA), the Committee for Proprietary Medicinal Products (CPMP), and major clinical trials groups in the US, Canada, Europe, and Japan was convened. The objective of the committee was to improve accuracy, precision and completeness of the CTC and to standardise reporting. As part of its commitment to the International Conference on Harmonization (ICH), the US FDA agreed to adopt an internationally agreed upon International Medical Terminology (IMT) based on the Medicines Control Agency's Adverse Drug Reaction On-line Tracking (ADROIT) Medical Dictionary for use in reporting medical information from clinical trials (62). The first discussions for a single medical dictionary to facilitate reporting of adverse drug reactions between regulatory authorities and pharmaceutical companies began in 1993 but it was March 1999 before Medical Dictionary for Drug Regulatory Reporting (MedDRA) became available for subscribers (63).

The National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) was renamed (from NCI CTC) in 2003 when version 3 was launched. Version 3 (Appendix 3) contains descriptive terminology for a high number of adverse events (more than 900 events grouped in 28 categories) (17); and includes criteria for evaluating adverse events related to growth and development and other long-term secondary effects of cancer; late or chronic effects; surgical interventions and improved coverage of paediatric issues (28, 64). A grading (severity) scale is provided for each term in the NCI CTCAE. The grading scale allows for

scoring of the severity of adverse event experienced by patients during clinical trials, and is also used in oncology (out with clinical trials) to score patients adverse events after each cycle of treatment. Version 4 of CTCAE was recently published on 28 May 2009 and the main difference from version 3 is that it is completely MedDRA version 12.0 compatible (65). The mapped MedDRA terminology for CTCAE version 3 can be seen in Appendix 5. Currently mapping of CTCAE version 4 to MedDRA version 12.0 is awaited.

The purposes of using MedDRA are (66):

- To aggregate reported terms in medically meaningful groups for the purpose of reviewing and analysing safety data.
- To facilitate identification of common data sets for evaluation of clinical and safety information.
- To facilitate consistent retrieval of specific cases or medical conditions from a database.
- To improve consistency in comparing and understanding "safety signals" and aggregated clinical data.
- To facilitate electronic interchange of clinical safety information.
- To report adverse reaction/adverse event terms via individual case reports.
- To include adverse reactions/adverse events in tables, analyses and line listings for reports
- To identify frequency of medically similar adverse reactions/adverse events.
- To capture and present product indications, investigations, medical history and social history data.

Since the preferred terms from MedDRA are incorporated into version 3 and 4 of the NCI CTCAE, this means that all output data of adverse events for patients undergoing cytotoxic chemotherapy (being scored using version 3 or 4 of NCI CTCAE) could be captured on databases and electronically communicated to national/international regulatory bodies for pharmacovigilance purposes with no need for any additional mapping or manual input. This would create a significant advancement in oncology signal generation and chemotherapeutic agent(s) monitoring, which would greatly supplement voluntary, spontaneous reporting of suspected ADRs.

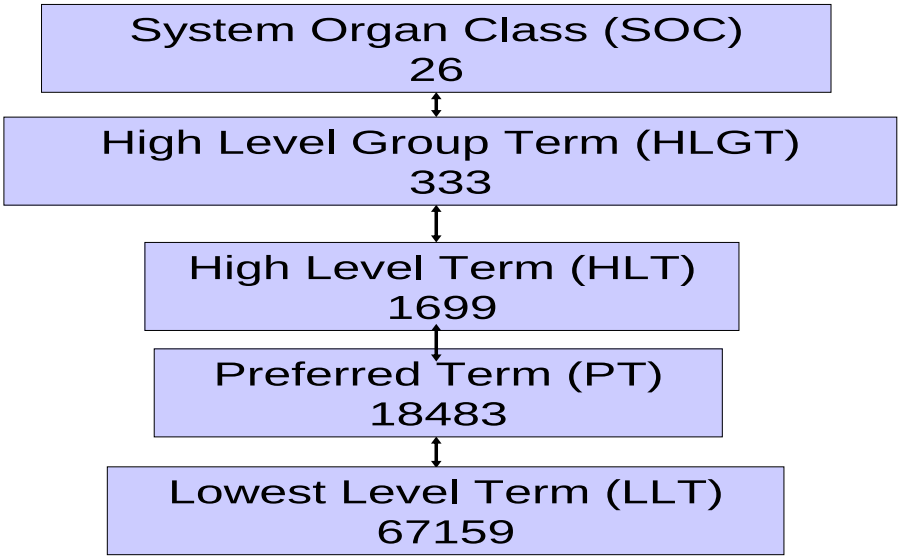
2.2. Organisation of CTCAE

CTCAE adverse event terms are grouped by MedDRA primary System Organ Classes (SOCs). Within each SOC, adverse events are listed and accompanied by description of severity (67).

2.2.1. Classification system of MedDRA

MedDRA terms are organised in five levels as can be seen in Figure 2.1 (63, 68, 69):

Figure 2.1. MedDRA Hierarchy



The number of terms in the hierarchy given in figure 2.1 is from the most recent version 12 (69).

A SOC is the highest level of the MedDRA hierarchy, which is identified by anatomical or physiological system, etiology (67). There are 26 SOCs and these are blood and lymphatic system; cardiac disorders; congenital, familial and genetic disorders; ear and labyrinth disorders; endocrine disorders; eye disorders; gastrointestinal disorders; general disorders and administration site conditions; hepatobiliary disorders; immune system disorders; infections and infestations; injury, poisoning and procedural complaints; investigations; metabolism and nutrition disorders; musculoskeletal and connective tissue disorders; neoplasms benign, malignant and unspecified; nervous system disorders; pregnancy, puerperium and postnatal disorders; psychiatric disorders; renal and urinary disorders; reproductive system and breast disorders; respiratory, thoracic and mediastinal disorders; skin and subcutaneous disorders; social circumstances; surgical and medical procedures; and vascular disorders.

The preferred synonym of an adverse event for analysis is the Preferred Term (PT). PTs are classified according to SOCs. PTs are grouped in Higher Level Terms (HLTs) and then in Higher Level Group Terms (HLGTs) in the same SOC. Although terms may belong to different SOCs, no preferred term is related to more than one HLT within a SOC. This hierarchical property ensures that terms cannot be counted twice in statistical studies, although it does not allow appropriate semantic groupings of preferred terms. Due to this problem, special search categories (SSCs), which are collections of preferred terms assembled from various SOCs, are used in MedDRA to group terms with similar meanings (68).

Lower Level Terms (LLTs) are used for data entry and can be true synonyms or may capture the healthcare professionals' verbatim term. All PTs are duplicated at the LLT level and is linked to a primary SOC but can be linked to other secondary SOCs.

Not elsewhere classified (NEC) terms have been introduced at the HLT level to indicate a group of PTs that do not fit a given category in the MedDRA hierarchy. They are provided as a set of terms that do not share common semantic features (68).

2.2.2. Grading of CTCAE

The grades of the CTCAE refer to severity of the adverse event. Grades of one through five are given (where appropriate) for all listed adverse effects within the CTCAE. There is a unique clinical description of severity for each adverse event based on the following general guidance in Table 2.1 (67):

Table 2.1. Description of CTCAE grades

Grade	Description
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
2	Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental activities of daily living (such as preparing meals, shopping, using phone, etc)
3	Severe or medically significant but not immediately life-threatening; hospitalisation or prolongation of hospitalisation indicated; disabling; limiting self-care activities of daily living (such as bathing, dressing, feeding self, using toilet, taking medications and not bedridden)
4	Life-threatening consequences; urgent intervention indicated
5	Death related to adverse event

Table 2.2 shows an example excerpt from CTCAE version 4.0 to demonstrate this grading system (67).

Table 2.2. Example excerpt from CTCAE version 4 for atrial flutter

Adverse Event	1	2	3	4	5
Atrial flutter	Asymptomatic, intervention not indicated	Non-urgent medical intervention indicated	Symptomatic and incompletely controlled medically; or controlled with device (e.g. pacemaker), or ablation	Life-threatening consequences; urgent intervention indicated	Death

Definition: a disorder characterised by a dysrhythmia with organised rhythmic atrial contractions with a rate of 200-300 beats per minute. The rhythm disturbance originates in the atrium.

Not all grades are appropriate for all adverse events so some adverse events are listed with fewer than five grades. In the situation where a grade is not applicable a single dash (-) will be seen instead within the CTCAE. For example Grade 5, death, is not appropriate for some adverse events and is therefore not an option. Table 2.3 shows an example excerpt from CTCAE version 4.0 to demonstrate this (67).

Table 2.3. Example excerpt from CTCAE version 4 for alopecia

Adverse Event	1	2	3	4	5
Alopecia	Hair loss of up to 50% of normal for that individual that is not obvious from a distance but only on close inspection; a different hair style may be required to cover hair loss but it does not require a wig or hair piece to camouflage	Hair loss of >50% normal for that individual that is readily apparent to others; a wig or hair piece is necessary if the patient desires to completely camouflage the hair loss; associated with psychological impact	-	-	-

Definition: a disorder characterised by a decrease in density of hair compared to normal for a given individual at a given age and body location.

2.3. Distinguishing between CTCAE adverse events and ADRs

While the CTCAE allow for adverse events to be identified and their severity to be graded, it does not allow determination of the cause of the adverse event (i.e. is it induced by a medicine, co-morbidity, etc) nor does it determine if a spontaneous report should be made to the post-marketing regulatory scheme (such as the Yellow Card Scheme). It is then necessary to first establish the cause of a suspected event before deciding if a CTCAE is a potential adverse drug reaction. Only then can a decision be made whether the suspected ADR should be reported via the Yellow Card Scheme.

2.3.1. Assessing causality

Pharmacovigilance has provided tools to assess the likelihood of a casual connection between a medicine and an adverse event on a case-by-case basis. These tools consider the following criteria (10, 70-72):

- Dose and duration of treatment with a medicine.
- Is the time relationship between the use of the medicine and appearance of the adverse event plausibly linked?
- Pathophysiology of the adverse event (i.e. the pattern of adverse event may fit known pharmacology or allergy pattern of a suspected medicine).
- Other diseases and medical history.
- Concomitant medicines used in the same time period.

- Results of investigations can aid diagnosis and establish baselines for organ function, and provide means for monitoring what happens after changes in treatment with medicines; but can also help rule out any alternative diagnosis.

- Response to a dechallenge such as discontinuation of the medicine or a decrease in dose of the suspected medicine (if done).

- Response to a rechallenge, if performed (i.e. reintroduction of a medicine after stopping). Normally only considered if the patient would benefit directly from the knowledge gained.

There have been 34 methods for classification of causality published worldwide. These fall into three broad categories (71):

1) Expert judgement/global introspection
2) Algorithms
3) Probabilistic methods

However there is still no method universally accepted for causality assessment of ADRs due problems with reproducibility and validity (71). In the absence of any universally accepted method, the method used in this thesis was chosen due to its simplicity and is described in Table 2.4. This table organises the criteria to gauge casual link between a medicine and an adverse event into levels of certainty (certain, probable, possible, unlikely, conditional/unclassified, or unassessable/unclassifiable) (10).

Table 2.4. Causality assessment levels of certainty

Certain

- A clinical event, including a laboratory test abnormality, that occurs in a plausible time relation to drug administration, and which cannot be explained by concurrent disease or other drugs or chemicals.
- The response to withdrawal of the drug (dechallenge) should be clinically plausible.
- The event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge procedure if necessary.

Probably/likely

- A clinical event, including laboratory test abnormality, with a reasonable time relation to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (dechallenge).
- Rechallenge information is not required to fulfil this definition.

Possible

- A clinical event, including laboratory test abnormality, with a reasonable time relation to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals.
- Information on drug withdrawal may be lacking or unclear.

Unlikely

- A clinical event, including laboratory test abnormality, with a temporal relation to administration of the drug, which makes a causal relation improbable, and in which other drugs, chemicals, or underlying disease provide plausible explanations.

Conditional/unclassified

- A clinical event, including a laboratory test abnormality, reported as an adverse reaction, about which more data are essential for a proper assessment or the additional data being examined.

Unassessable/unclassified

- A report suggesting an adverse reaction that cannot be judged, because information is insufficient or contradictory and cannot be supplemented or verified.

Table reproduced from the Lancet 2000;356: pp. 1255-1259 (10).

Post administration of a cytotoxic chemotherapy regimen each oncology patient is assessed and 'toxicities' are recorded. The oncology healthcare professional must then make an informed decision as to whether the adverse event(s) observed are attributable to the medicine(s) received before it is classified as an ADR. The simple causal assessment tool above will allow such an assessment to be undertaken. Most experienced healthcare professionals intuitively carry out this assessment without having to consult an assessment tool/algorithm or guide however. This assessment can be difficult at times though due to multiple medicines or co-morbidity. In oncology ADRs are even more particularly difficult to identify and distinguish from tumour progression sometimes (73). However it is only after

this causal assessment has been made and an ADR is suspected that a healthcare professional would consider completing a Yellow Card report.

2.3.2. Documentation versus reporting a suspected ADR in oncology

Even once a causal analysis has been made by an oncology healthcare professional and a suspected ADR has been identified there is no mandatory requirement in the UK for healthcare professionals to complete a Yellow Card report for suspected ADRs. Therefore ADRs in oncology will be documented in the patient's chart but the majority will go unreported to the Medicines and Healthcare products Regulatory Agency (MHRA). Documenting adverse drug reactions in a patient's chart is a distinctly different activity then reporting to a regulatory agency such as the MHRA. Table 2.5 summarises the difference in these activities.

Table 2.5. Comparison of documentation and reporting of adverse drug events

Events/reports	Document in patient's notes	Report to the MHRA via Yellow Card Scheme
Type of event		
Drug-related injuries	Probable of certain adverse drug reactions Life-threatening, possible adverse drug reactions Dosing ranges specific to the patient that resulted in adverse drug events Adverse drug events resulting from medication errors	All suspected reactions for newer medicines and vaccines (black triangle) Serious reactions for established medicines and vaccines (i.e. reactions resulting in death, life-threatening, involved or prolonged hospitalisation, involved persistent or significant disability or incapacity, congenital abnormality or medically significant
Properties of reports		
Goal	Prevent recurrence of an adverse drug event in a patient	Contribute to labelling changes or withdrawal of medicine recommendations
Determination of causation	Clinician determines casual link between drug and event for each case	MHRA monitors Sentenil* for similar reports and determines causation from multiple reports. Reporting clinicians may be asked for additional information to facilitate this determination
Where to report	Documented in allergy/ADR section of patient's chart, case record, drug prescription and administration record	To MHRA via the Yellow Card Scheme
Voluntary or mandatory	Required for good clinical care	Voluntary but encouraged as good practice and as part of healthcare professionals' responsibility to ensure public safety

* Sentenil is the MHRA's programme for licensing, inspection and surveillance of medicines (74).
Note. This table was modified from a table prepared by Nebeker JR et al in the US (70).

This lack of reporting to the regulatory authority is of great concern since the full ADR profile of a medicine is not known at time of marketing, especially for rarer reactions (due to small number exposed during clinical trials and/or exclusion of certain patient groups as per trial protocols), and the potential for late or delayed effects of a medicine. Serious and potentially fatal ADRs for cancer medicines emerge throughout the life cycle of a medicine. In the US one study showed that serious ADRs may be discovered as long as 36 years after FDA

approval (41). Some examples of late understanding of an ADR profile include endometrial adenocarcinoma and uterine sarcoma with tamoxifen, warning against intrathecal administration for vinblastine, and severe bone marrow suppression for thioguanine that were identified between 15 to 36 years after first approval by the FDA in the US (41).

As well, in January 2001 two new adverse reactions were added to the list of possible side effects with cyclophosphamide (Stevens Johnson syndrome and toxic epidermal necrolysis) (75), despite the medicine having been on the market for approximately 40 years (76) in many countries by then. Therefore it is not enough to just record patients' 'toxicities' in isolation in case notes, and more must be done to foster greater use of these data for pharmacovigilance purposes.

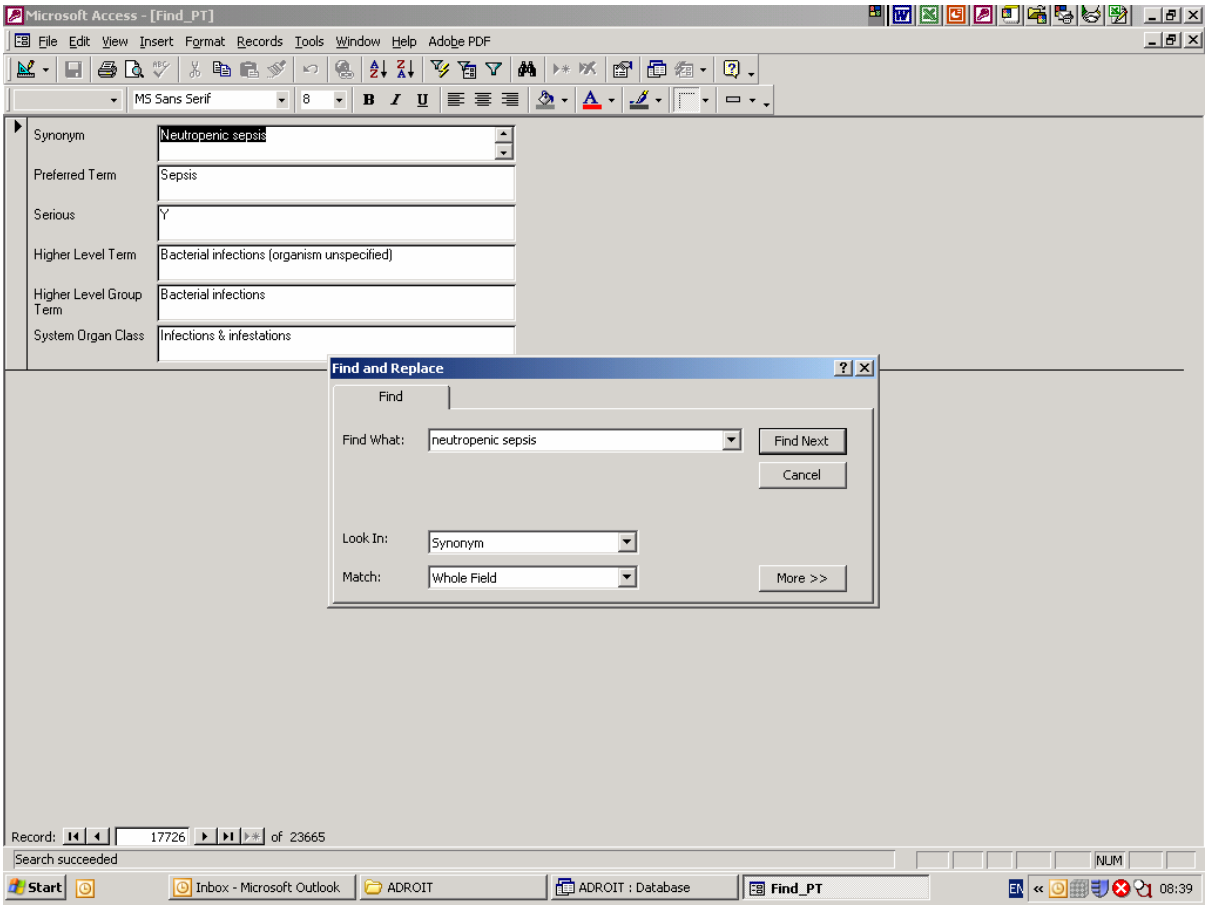
2.3.3. Serious versus severe

The difference in the meaning of the words 'serious' and 'severe' is crucial to reporting suspected ADRs via the Yellow Card Scheme. As discussed in Chapter one, the term "severe" is not synonymous with serious. A serious adverse drug reaction is defined by the World Health Organisation (WHO) as any untoward medical occurrence that at any dose results in death, requires hospital admission or prolongation of existing hospital stay, results in persistent disability/incapacity, or is life threatening (10). "Severe" is used to describe the intensity or severity of a specific event (as in mild, moderate or severe). The event itself, however, may be of relatively minor medical significance (such as severe erythematous rash). It is the severity of an adverse event that the CTCAE scale scores but, in contrast, the seriousness (not severity) serves as the criteria for reporting suspected ADRs via the Yellow Card Scheme to the MHRA. Hence the CTCAE criteria do not correlate directly to the MHRA reporting criteria. However it is possible to classify each of the mapped MedDRA terms as 'serious' or 'not serious' using the Adverse Drug Reaction On-line Tracking (ADROIT) dictionary. The ADROIT dictionary was the dictionary used by the MHRA (and its predecessor organisation the Medicines Control Agency) up until March 2004 (63) to classify suspected adverse drug reactions into the preferred medical terminology for the ADROIT database, and for classification of seriousness of the suspected ADR. In fact, the MHRA had to map all MedDRA terms to 'serious' or 'non-serious' before the transfer from ADROIT to MedDRA occurred since the MedDRA dictionary did not have these classifications pre-assigned.

2.4. Mapping the CTCAE preferred terms to classification of serious or non-serious

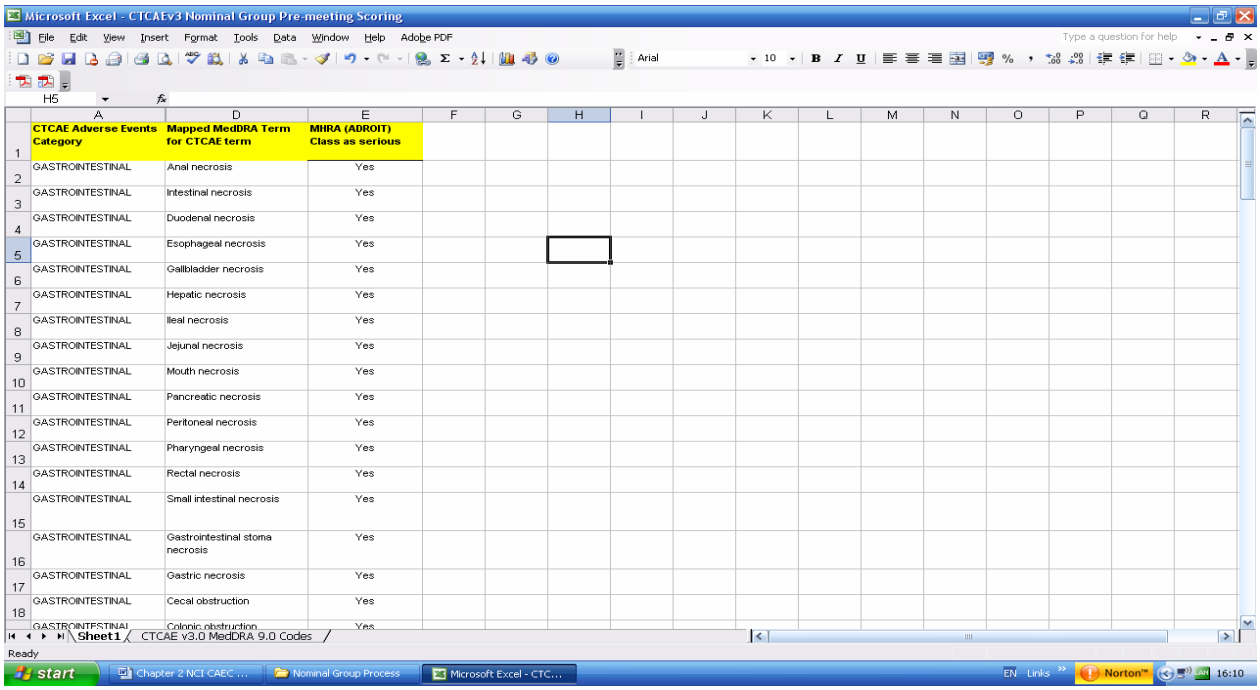
To address this deficiency in the CTCAE scale as a tool for aiding in reporting of a suspected ADR, the researcher assigned the mapped MedDRA term for each CTCAE to the classification of 'serious' or 'not serious'. The ADROIT dictionary was employed for this purpose. Each term was entered into ADROIT as can be seen in Figure 2.2 below.

Figure 2.2. ADROIT screen shot



The resultant classification was then noted in a Microsoft Excel Spreadsheet as can be seen in Figure 2.3 below:

Figure 2.3. Serious or non-serious classification of mapped MedDRA term for CTCAE term



Microsoft Excel - CTCAEv3 Nominal Group Pre-meeting Scoring

	CTCAE Adverse Events Category	Mapped MedDRA Term for CTCAE term	MHRA (ADROIT) Class as serious
2	GASTROINTESTINAL	Anal necrosis	Yes
3	GASTROINTESTINAL	Intestinal necrosis	Yes
4	GASTROINTESTINAL	Duodenal necrosis	Yes
5	GASTROINTESTINAL	Esophageal necrosis	Yes
6	GASTROINTESTINAL	Gallbladder necrosis	Yes
7	GASTROINTESTINAL	Hepatic necrosis	Yes
8	GASTROINTESTINAL	Ileal necrosis	Yes
9	GASTROINTESTINAL	Jejunal necrosis	Yes
10	GASTROINTESTINAL	Mouth necrosis	Yes
11	GASTROINTESTINAL	Pancreatic necrosis	Yes
12	GASTROINTESTINAL	Peritoneal necrosis	Yes
13	GASTROINTESTINAL	Pharyngeal necrosis	Yes
14	GASTROINTESTINAL	Rectal necrosis	Yes
15	GASTROINTESTINAL	Small intestinal necrosis	Yes
16	GASTROINTESTINAL	Gastrointestinal stoma necrosis	Yes
17	GASTROINTESTINAL	Gastric necrosis	Yes
18	GASTROINTESTINAL	Cecal obstruction	Yes
	GASTROINTESTINAL	Colonic obstruction	Yes

Sheet1 | CTCAE v3.0 MedDRA 9.0 Codes

Ready

Appendix 6 contains the completed spreadsheet of the mapped MedDRA terms for CTCAE terms with the assigned classification of 'serious' or 'non-serious'. This information will be utilised in Chapter 5 of this thesis to develop standards to operationalise the classification of serious ADRs in oncology for spontaneous ADR reporting.

2.5. Summary

The National Cancer Institute (NCI) Common Terminology Criteria of Adverse Event Criteria (CTCAE) is a more complete and precise tool than the WHO or other toxicity assessment scales (29); and incorporates the internationally agreed Medical Dictionary for Drug Regulatory Reporting (MedDRA). Considering that MedDRA is used internationally for use in reporting adverse events from clinical trials, it is then logical that the NCI CTCAE be used as a basis for deriving a list of adverse events that are classified as serious, regardless of the severity rating within CTCAE. This list could then be used by oncology healthcare professionals in conjunction with a reporting algorithm when considering reporting a suspected ADR via the Yellow Card Scheme. Alternatively the list could possibly be incorporated into the functionality of electronic patient records/prescribing systems to automatically prompt healthcare professionals to consider reporting a suspected ADR that has

a ‘serious’ classification assigned to it, once a positive causal assessment has been undertaken.

Chapter 3

A retrospective survey of case notes in adjuvant breast cancer to investigate a pharmacist led ADR reporting initiative and if it has potential for improving spontaneous ADR reporting.

3.1. Introduction

Breast cancer is the most common cancer in the United Kingdom despite this cancer being a rarely seen in men (77). Worldwide, more than a million women are diagnosed with breast cancer every year, accounting for a tenth of all new cancers and 23% of all new female cancer cases (78). Incidence rates vary considerably, with the highest rates in North America, Australia, New Zealand, Western Europe and Northern Europe and the lowest rates in Africa or Asia (78). While the incident rate has continued to increase, mortality has fallen consistently since 1989 (77). This decline is due to advances in prevention, screening and treatment; with adjuvant chemotherapy dramatically improving the outlook of patients with this disease (79). Adjuvant chemotherapy is additional cancer treatment given after the primary treatment (usually surgery) to reduce the risk of cancer recurrence or death from microscopic spread of cancer that is suspected but cannot be detected at the time of diagnosis (77). Adjuvant chemotherapy reduces the risk of breast cancer recurrence and death by about 30% and 20% respectively (77). Due to the risk of adverse effects with the cytotoxic chemotherapy regimens, adjuvant chemotherapy is usually only given to women with a significant risk of recurrence, or those who test as oestrogen receptor negative (77). The benefits of adjuvant chemotherapy to the patients must be weighed against the adverse effects that occur during treatment; with hospitalisation, dose delays, dose reductions or cessation of treatment possible outcomes. ADRs resulting from cytotoxic chemotherapy are one of the main causes of patient morbidity; and they play an important role in increasing healthcare costs associated with cancer therapy since they frequently result in hospital admissions. One study showed that more than 9% of patients with breast cancer were admitted to hospital due to adverse effects of the cytotoxic chemotherapy they received (80).

In the context of the seriousness of the disease both the clinician and the patient often accept this impact upon patient morbidity as an inevitable consequence of cytotoxic chemotherapy treatment. The importance of post-marketing reporting of adverse effects via the Yellow Card scheme is, therefore, not regarded as a high priority in the clinical

management of the patient since it does not impact directly upon the outcome of therapy. The perception is that a Yellow Card report for an ADR experienced by a patient receiving cytotoxic chemotherapy will not alter that individual patient's treatment regimen or outcome. However without reporting of oncology ADRs it is possible that safety issues could go undetected. If these had been detected then that understanding may have lead to changes in practice designed to prevent such an occurrence with future treatments involving the same cytotoxic chemotherapy regimen.

Chapter 1 discussed the merits of the success of the Yellow Card scheme for monitoring medication safety and ensuring patient safety. This depends upon voluntary reporting of ADRs by members of the multidisciplinary clinical team. The criteria for reporting to the MHRA via the Yellow Card scheme are:

3. Report all reactions for:
    a. Black triangle medicines and vaccines - those medicines that are new to the market and are under intensive surveillance by the MHRA.
    b. Herbal preparations
4. Report all serious reactions for all medicines and vaccines regardless of their black triangle status.

The term "severe" is not synonymous with serious. This is an important distinction to make in oncology where the severity of adverse events patients experience during treatment is a concern. Hence a patient may have a severe reaction but the event itself may be of relatively minor medical significance. Seriousness (not severity) serves as guide for defining regulatory reporting obligations and no report would be required in these circumstances via the Yellow Card scheme.

In oncology the lack of adherence to the criteria for submitting a report to the MHRA produces a challenge to increase reporting via the Yellow Card scheme in this clinical area. The reasons for under-reporting of oncology ADRs is unknown but experience suggests that clinicians feel that there is no benefit in reporting adverse drug that are common and anticipated with cytotoxic chemotherapy (e.g. neutropenia, septicaemia, leucopenia, thrombocytopenia, anaemia, etc), whether they are serious or not.

There is little information in the literature specific to oncology and ADR incidence and reporting rates due to cytotoxic chemotherapy. Two studies carried out in a specialist cancer institute in France showed that ADRs related to cytotoxic chemotherapy resulted in excess costs to the institute (2, 3). Only one of the studies looked at whether the ADRs were reported via a traditional voluntary, spontaneous reporting scheme. This study found that 313 ADRs occurred, of which 182 were classified as serious reactions. Only 15 (8.2%) of these serious reactions were reported (2). Another study from Australia looked at establishing a baseline incidence of ADRs in hospitalised oncology patients and they found that 9.6% of admissions were related to previous drug therapy and that 37.5% of patients admitted experienced an ADR (47). As well one study from German research assessed the incidence, predictability, preventability and severity of ADRs in hospitalised oncology patients. They found that 454 ADRs occurred during 127 admissions, with a mean ADR of 2.7 per admission (81). No assessment of reporting rates via the national ADR reporting scheme was looked at in either of the latter two studies.

Pharmacists at the Edinburgh Cancer Centre (ECC) became concerned over the deficiency in ADR reporting in their clinical practice during 2001 and in order to improve and to encourage more frequent and higher quality reporting via the Yellow Card scheme, the pharmacists developed an adverse drug reaction monitoring standard operating procedure (SOP). This SOP set the grade of the National Cancer Institute Common Adverse Event Criteria for reporting as 3 and 4 for all cytotoxic chemotherapy regimens. In addition if a patient was hospitalised due to an adverse effect or if there stay in hospital was prolonged due to an adverse effect then this was deemed within the SOP to be reportable as well. Training was given to all clinical pharmacists working within the oncology directorate in the autumn of 2001 and an audit of the Yellow Card reports was undertaken from January 2002 to January 2003. 118 yellow card reports were submitted during this period compared to 13 reports received in the previous year; which was an increase in reporting of over 800% (57, 58). Of the 118 Yellow Cards submitted, 42% (50) related to patients being treated for breast cancer, of which 35 were admitted to hospital with neutropenic sepsis (57, 58). An ADR reporting rate of 1.8 per cycle was estimated (57, 58) but the true incidence of ADRs in patients receiving cytotoxic chemotherapy at the ECC during this period was not known; nor was the number of these ADRs which would have met the MHRA criteria for reporting. This audit did demonstrate the degree of under-reporting of

ADRs which exists in oncology; and showed that a pharmacist-led reporting initiative was effective during the audit period, however, it is unknown if it is a sustainable project.

The purpose of this study is to determine whether intensive monitoring of oncology ADRs results in an improvement in ADR reporting via the Yellow Card scheme in the long-term. The primary objective is to quantify the potential for improvement in spontaneous ADR reporting before and after a pharmacist led ADR reporting initiative by a retrospective survey of case notes.

3.2. Methods

A non-experimental design of a retrospective case-note review survey was chosen for this study. The main criticism of this type of study design is that the quality of the data derived from case-notes review is dependant upon the quality of the information that is recorded.

3.2.1. Identification of Patient Groups

For the retrospective survey a cohort of patients with breast cancer who were treated with adjuvant chemotherapy at the ECC during 2001 and 2003 was chosen. This patient group was chosen taking into consideration that 42% of the patients from whom ADR reports were completed during the audit performed at ECC in 2002 were patients with breast cancer, of which the majority received adjuvant chemotherapy regimens. The years of 2001 and 2003 were chosen for the retrospective study to allow comparison of ADR reporting in these years compared to the audit year. In 2001 there was no adverse drug reaction reporting initiative in place since this was not initiated until 2002; and in 2003 the pharmacists' led adverse drug reaction audit had completed but the practice of pharmacists' reporting of oncology adverse drug reactions continued as routine. In addition, the standard cytotoxic chemotherapy regimens for treating these patients had not changed from 2001 to 2003. The study design allowed for comparison of spontaneous adverse drug reaction reporting rates via the Yellow Card scheme before and after the implementation of the pharmacists' led adverse drug reaction monitoring in 2002. The study was also designed to measure any benefit resulting from the pharmacist-led adverse drug reaction intensive monitoring initiative.

Patients were excluded from the study if they were enrolled in commercial adjuvant chemotherapy clinical trials at the time. This is because adverse reactions experienced

during phase III commercial clinical trials do not get reported spontaneously to the MHRA via a Yellow Card but are reported directly to the sponsor company who then pass the data to the MHRA. Any non-commercial clinical trial patients were included in the study since these adverse drug reactions were not captured by industry and were reportable via the Yellow Card scheme to the MHRA prior to the issue of the new Medicines for Human Use (Clinical Trials) Regulations being issued in 2004.

Patients were grouped into two groups. Group 1 included all patients treated in the year 2001. Group 2 included all patients treated in the year 2003.

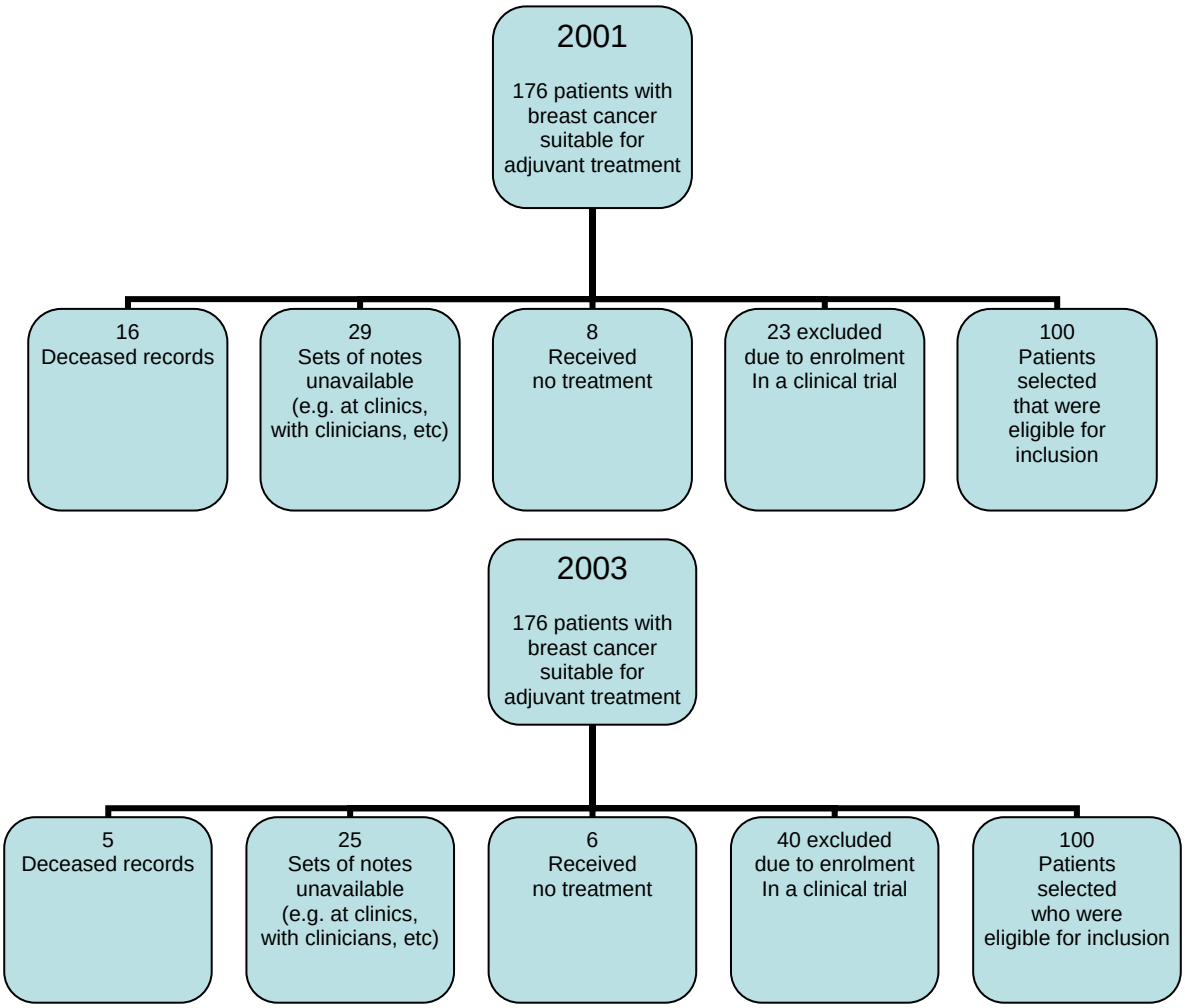
3.2.2. Sample Size

It was estimated that approximately 200 patients with breast cancer were treated each year with adjuvant chemotherapy at the ECC under the care of two oncologists in 2001 and 2003. To explore the actual incident rate of reportable ADRs, a sample of 96 patients would be required (assuming 6.7% ADR reporting rate and a margin of error of 5%, 90% power and 95% confidence) for both Group 1 and Group 2. Therefore each group contained a sample population of 100 patients.

3.2.3. Collection of Data from Patients' Case Notes

Review of the patients' case notes was undertaken in the breast cancer unit at the ECC over a 2 week period during November 2004. A complete list of patients treated in each year was obtained and the researcher started at the top of the list and worked ascending down the list until a sample of 100 eligible patients' had been obtained for each year. Figure 3.1 describes the sample selection for each year.

Figure 3.1. Study sample selection for patients with breast cancer receiving adjuvant chemotherapy in 2001 and 2003



Each patient's case notes were reviewed including the progress notes, laboratory results and treatment charts (which record the NCI CAEC scores prior to each cytotoxic chemotherapy administration). The data to be collected from the patients' notes included:

- Patient initials
- Patient age
- Tumour type
- Tumour grade
- Number of nodes involved
- Oestrogen receptor status
- Menopausal status
- Smoking status
- Any known allergies

- Cytotoxic chemotherapy regimen
- Dose of cytotoxic chemotherapy received
- Number of cycles
- Adverse events and NCI CAEC scores
- Number of admissions to hospital or prolongation of hospital stay that occurred due to adverse event
- Number of days admitted to hospital
- Patient outcome after each cycle of cytotoxic chemotherapy (i.e. recovered with no dose reduction; dose reduction; chemotherapy regimen changed; treatment stopped)
- Concurrent medications
- Any annotation that a Yellow Card had been submitted or copy of a yellow card that had been submitted

All adverse events experienced by the patients were recorded in the appropriate fields of the data collection form (Appendix 7).

3.2.4. Black triangle status assessment

The adjuvant chemotherapy regimens were reviewed to see if any medicines with a black triangle status were used in 2001 and 2003. The Intensive Monitoring list prepared by the MHRA for these years was used to determine if any of the medicines in question had a black triangle status during the corresponding years. This was necessary since all ADRs experienced by the patients', regardless of grade or seriousness, would be deemed as reportable under the criteria of "black triangle status" set out by the MHRA.

3.2.5. Classification of Adverse Events

At the Edinburgh Cancer Centre (ECC) the NCI CTCAE Scores are assessed by nursing or medical staff and recorded on the standard forms located on the back of each cytotoxic chemotherapy regimen prescription sheet (Appendix 8). The adverse event grades of 1 to 4 for each criteria listed are scored subjectively or objectively as appropriate by the assessor. Any additional adverse events experienced by the patients are also annotated. These adverse event scores are not linked directly to MHRA criteria for reporting.

None of the medicines contained within the cytotoxic chemotherapy regimens in these years had a black triangle status so it was only necessary to consider those adverse events that were classed as 'serious' for reporting purposes. Therefore it was necessary to assign each adverse event to the classification of 'serious' or 'not serious' before a decision could be made on whether the adverse event met the criteria for reporting via the Yellow Card scheme. The ADROIT dictionary was used to classify each adverse event recorded for the patients as either "serious" or "non-serious". The ADROIT dictionary was the dictionary used by the MHRA up until the end of 2004 to classify suspected adverse drug reactions into the preferred medical terminology for the ADROIT database, and for classification of seriousness of the suspected ADR.

3.2.6. Designation as ADR

At the ECC, after the nurse scores the adverse event no formal assessment of causality is performed to determine whether the adverse effect in question is due to the cytotoxic chemotherapy. Therefore a causal analysis had to be carried out for each patient by the researcher to determine if the serious adverse event(s) documented could be attributed to the medicines used in the cytotoxic chemotherapy regimens or supportive therapies given. The adverse event was only classed as an ADR if a positive association was found.

All haematological adverse events, which have a serious classification, were given the classification of ADR if any decrease in the patient's baseline haematological values occurred during cytotoxic chemotherapy treatment. All other serious, non-haematological ADRs had a causal analysis carried out by the researcher using the nomogram seen in Table 2.3 in Chapter 2, and were assigned a probability of certain, probable, possible, unlikely, unclassified or unclassifiable. If the serious, non-haematological adverse event was considered to be certain, possibly or probably due to the cytotoxic chemotherapy or supportive therapy given then it was too classed as an ADR.

The summarised information on haematological and other serious adverse events (classed as an ADR by the researcher) was independently reviewed separately by a pharmacist and two doctors to validate the decision made to classify an adverse event as an ADR.

3.2.7. Yellow Card Reports

Yellow Card data from Lothian for 2001 and 2003 was used to obtain the list of adverse drug reaction reports received for cytotoxic chemotherapy agents. This was achieved through the following methods:

a) For 2001 a search of the ADROIT yellow card data for the year 2001 was carried out to compile the list of adverse drug reaction reports for cytotoxic chemotherapy regimens/medicines received from the postcode "EH4 2XU". Once the list was compiled the reports were cross-referenced by Group 1 patients' initials, age, date of reaction and adverse drug reaction(s) experienced. Any reports that matched were confirmed as a positive yellow card report having been submitted.
b) For 2003, a search of the Yellow Card Centre Scotland (previously known as CSM Scotland) database for the year 2003, including direct yellow card reports and bypass reports, was carried out to compile a list of all reports for oncology medicines received from the Western General Hospital (hospital code "LT2" on the database). Once the list was compiled the reports were cross-referenced by Group 2 patients' initials, age, date of reaction and adverse drug reaction(s) experienced. Any reports that matched were confirmed as a positive yellow card report having been submitted.

A separate method was employed for obtaining the data in 2001 than in 2003, since the 2001 data set was not available within the Yellow Card Centre database that did not open until October of 2002. Once all yellow card reports had been matched and entered into the Microsoft Access® database, the reporting rate for 2001 and 2003 was established.

3.2.8. Database

A Microsoft Excel® database was designed for compilation of the data. The data fields included audit number, patient initials, age, tumour type, nodes, tumour grade, estrogen receptor status, cytotoxic chemotherapy regimen, body surface area, number of cycles, serious ADR experienced, admitted to hospital due to ADR, admission prolonged due to ADR, number of admissions, number of days admitted, patient outcome, dose delays, other medicines, smoking status, menopausal status, ejection fraction, known allergies, adverse events experienced, classed as an ADR, and additional comments. From this database information on patient demographics, cytotoxic chemotherapy regimens, adverse events, outcomes and ADRs were summarised for both Group 1 and Group 2.

3.2.9. Statistical Analysis

Data was analysed using Minitab statistical package (version 15). Descriptive statistics were used to describe the demographics of the adjuvant breast cancer patients sampled in both years. The Fisher's Exact test was used to test the Null hypothesis. This was necessary due to one of the cells containing less than 5.

3.2.10. Ethics

The Lothian Research and Ethics Committee (LREC) were provided with a protocol and flow chart (Appendix 9) for the retrospective case note survey to see if LREC approval was required. They advised that ethics approval was not required. A copy of the reply received can be seen in Appendix 10.

3.3. Analysis

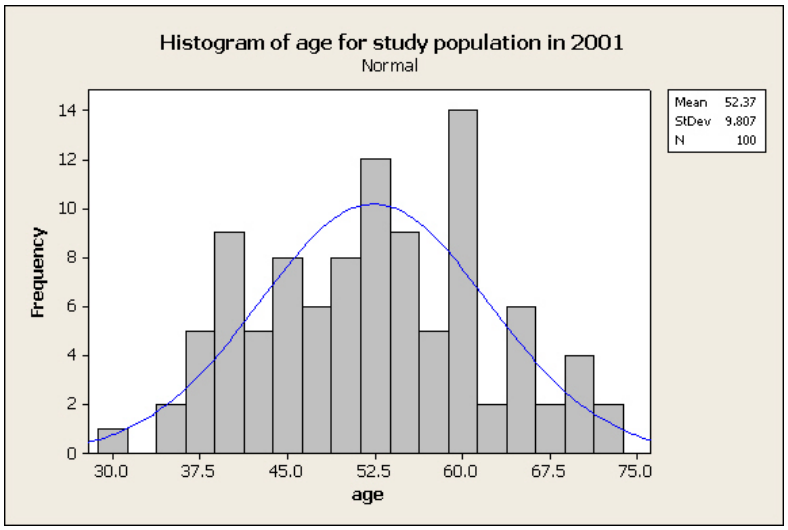
3.3.1. Patient Demographics

A total of 100 patients' case notes with breast cancer receiving adjuvant chemotherapy were reviewed for 2001 and 2003. Table 3.1 summarises the demographics of the sample population from 2001 and 2003. Figures 3.2 to 3.7 illustrate the distribution and spread of the age, body surface area (BSA) and number of cycles given within these sampled populations.

Table 3.1. Summary of patient characteristics

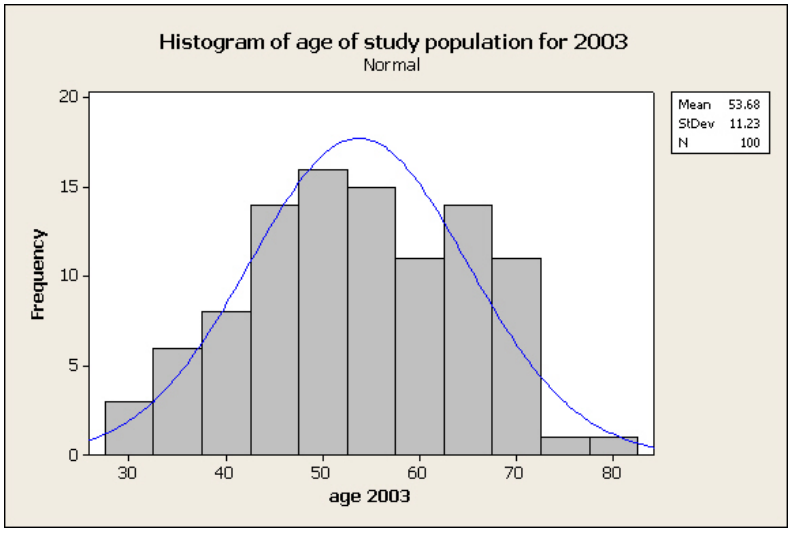
	2001	2003
Number patients case notes reviewed	100	100
Mean (SD) age	52	54
Mean (SD) number cycles given	7.2	7.8
Mean (SD) body surface area	1.7 m^2	1.7m^2
ER Status		
ER Positive	76	84
ER Negative	24	16
Tumour Grade		
3	68	58
2	21	39
1	3	2
Not recorded/Unknown	8	1
Tumour Type		
Ductal	64	77
Lobular	1	2
Not recorded/Unknown	35	21
Nodes		
0	61	84
1-3	33	13
4-9	4	1
>10	2	2
Menopausal status		
Pre	29	30
Peri	6	8
Post	45	45
Unknown	20	17

Figure 3.2.



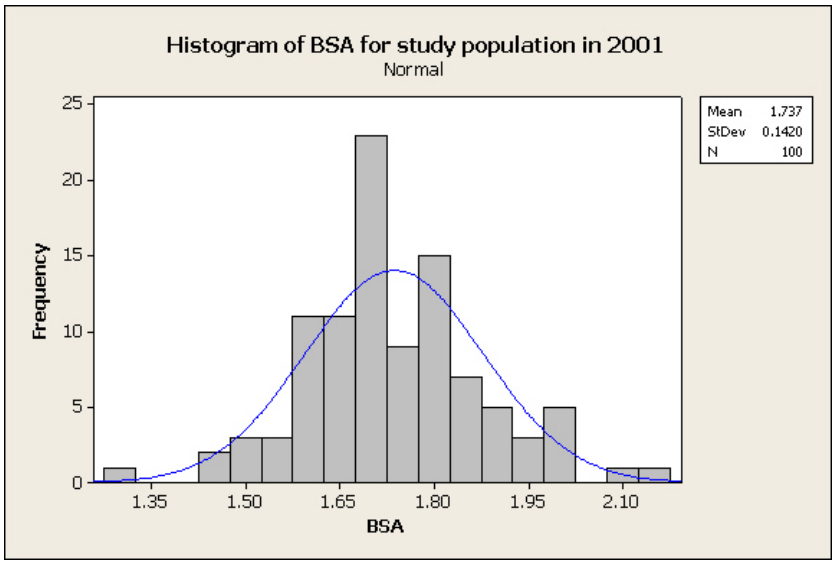
The age of the sample population in 2001 ranged from 30-73 years of age, with a mean of 52.

Figure 3.3.



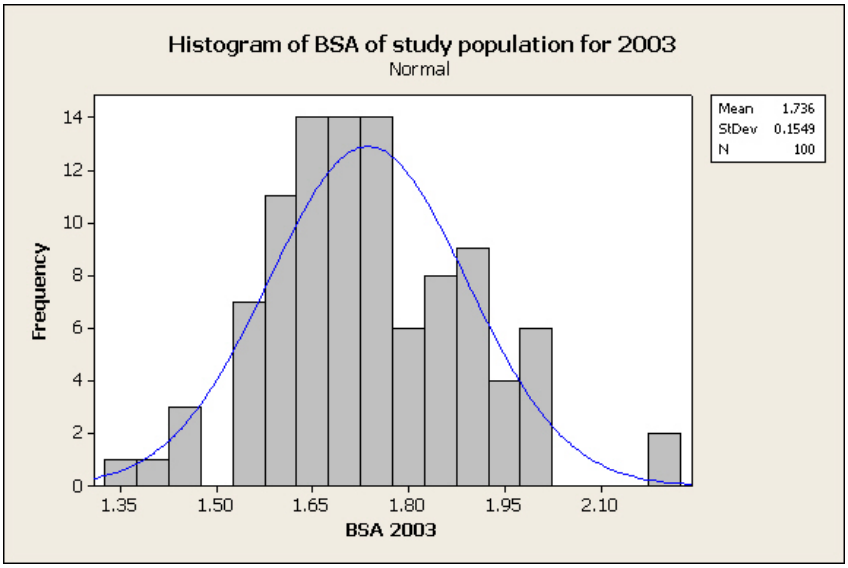
The age of the sample population in 2003 ranged from 29-79 years of age, with a mean of 54.

Figure 3.4.



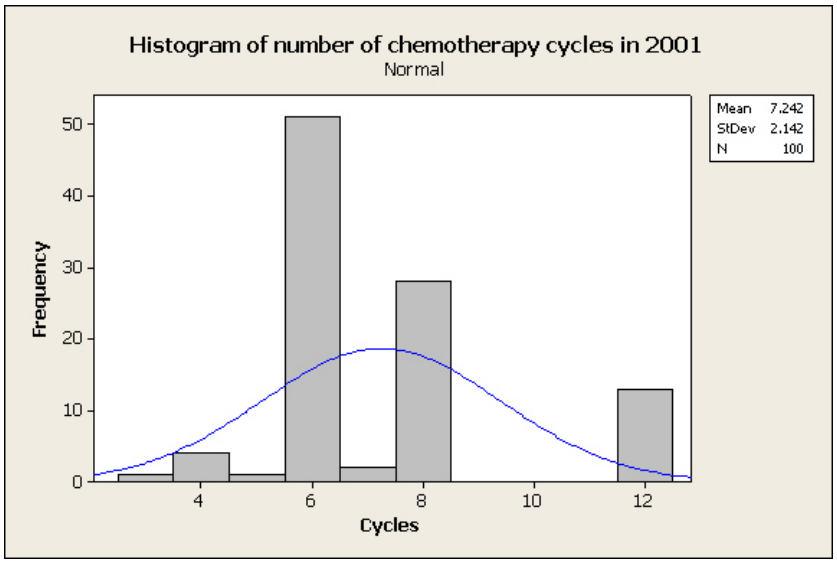
The body surface area for the sample population in 2001 ranged from 1.3 to 2.13 m^2, with a mean of 1.7m^2.

Figure 3.5.



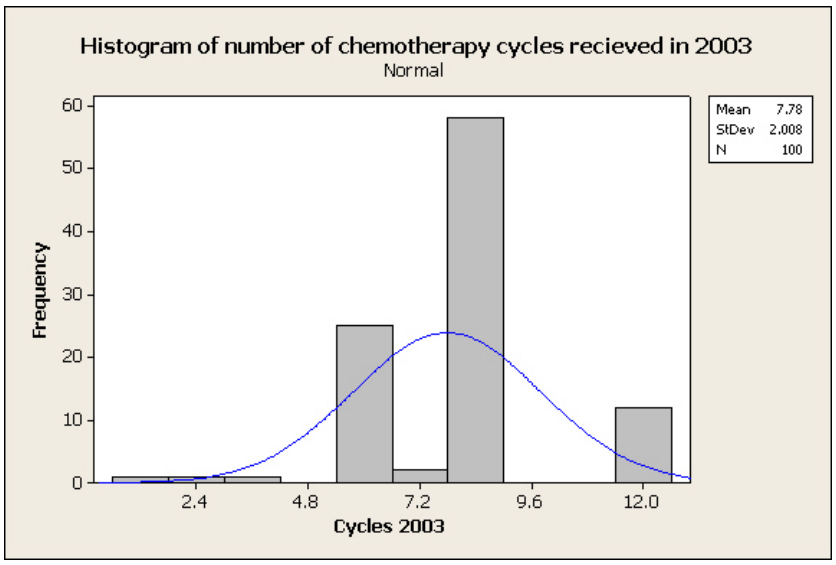
The body surface area for the sample population in 2003 ranged from 1.35 to 2.18 m^2, with a mean of 1.7m^2.

Figure 3.6.



The number of cycles received by the sample population in 2001 ranged from 3 to 12, with a mean of 7.2.

Figure 3.7.



The number of cycles received by the sample population in 2003 ranged from 1 to 12, with a mean of 7.8.

The cytotoxic chemotherapy regimens that were used in the adjuvant breast cancer sample patient population in 2001 and 2003 were:

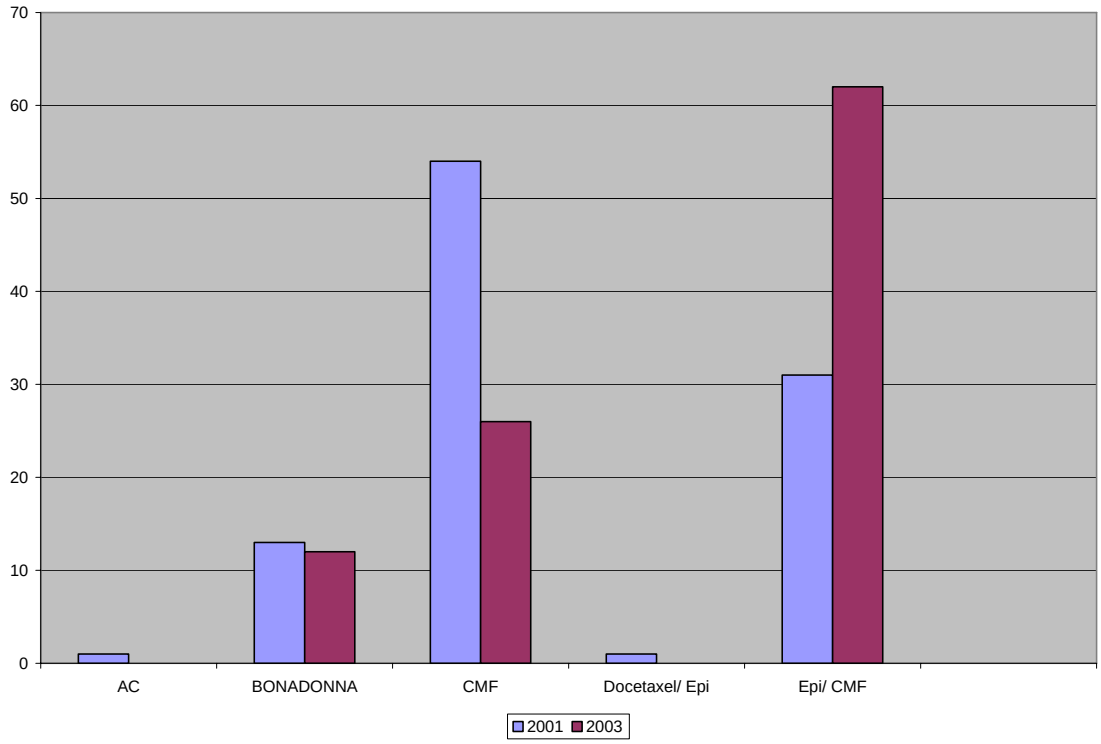
- AC (doxorubicin and cyclophosphamide)
- BONADONNA (doxorubicin /cyclophosphamide, methotrexate, and 5-fluorouracil)
- CMF (cyclophosphamide, methotrexate and 5-fluorouracil)
- Docetaxel/Epi (docetaxel /epirubicin)
- Epi/CMF (epirubicin/ cyclophosphomide, methotrexate and 5-fluorouracil)

Table 3.2 and Figure 3.8 show a summary of the number of patients receiving each cytotoxic chemotherapy regimen in 2001 and 2003. None of these cytotoxic chemotherapy regimens contained a medicine with a black triangle status.

Table 3.2. Summary of number of patients receiving each cytotoxic chemotherapy regimen in 2001 and 2003.

	2001	2003
AC	1	0
BONADONNA	13	12
CMF	54	26
Docetaxel/ Epi	1	0
Epi/ CMF	31	62
Total	**100**	**100**

Figure 3.8. Comparison of cytotoxic chemotherapy regimens received in 2001 and 2003



3.3.2 Adverse Events

In 2001 a total of 1,811 adverse events were recorded from the patient records from 717 cycles of chemotherapy administered (average 2.5 adverse events per cycle). In 2003 a total of 2,213 adverse events were recorded from the patient records from 778 cycles of

chemotherapy administered (average 2.8 adverse events per cycle). These adverse events were reviewed by the researcher and those that were classified as serious were selected for possible classification as an ADR. It was not necessary to analyse the non-serious adverse events any further for the purpose of this study since none of the cytotoxic chemotherapy regimens in either year contained any black triangle medicines, and the Yellow Card scheme does not require non-serious suspected reactions for older medicines to be submitted.

3.3.2.1 Serious adverse drug reactions

The researcher selected 917 serious adverse events from 2001, and 1134 serious adverse events from 2003 for a causal analysis. The serious ADRs selected by the researcher were independently validated separately by a pharmacist and two doctors. There were only two adverse events (neurofibromatosis and hypokalaemia) from two patients that were excluded from the original list compiled by researcher after independent validation. This gave a confirmed total of 911 and 1133 serious ADRs in 2001 and 2003 respectively. Hence, an average of 1.3 and 1.5 ADRs per cycle was observed in 2001 and 2003 respectively.

From the 100 patients sampled from 2001 and 2003 there was no noticeable difference in the percentage of patients with breast cancer receiving adjuvant chemotherapy that experienced a serious adverse drug reaction (97% versus 96% respectively). Table 3.3 summarises this information.

Table 3.3. Number of patients experiencing a serious adverse drug reaction during cytotoxic chemotherapy treatment

	2001	**2003**
Serious adverse drug reaction experienced by patient *	97	96
No serious adverse drug reaction experienced by patient *	3	4
Total Patients	**100**	**100**

*Serious as defined by MHRA criteria [10].

Figures 3.9 and 3.10 show percentage contributed by each cytotoxic chemotherapy regimen in 2001 and 2003 respectively. The main difference was a significant increase observed in the

percentage of ADRs due to Epi/CMF in 2003 compared to 2001 (61% versus 30%) but a significant decrease in the percentage of ADRs due to CMF (20% versus 43%).

Figure 3.9.

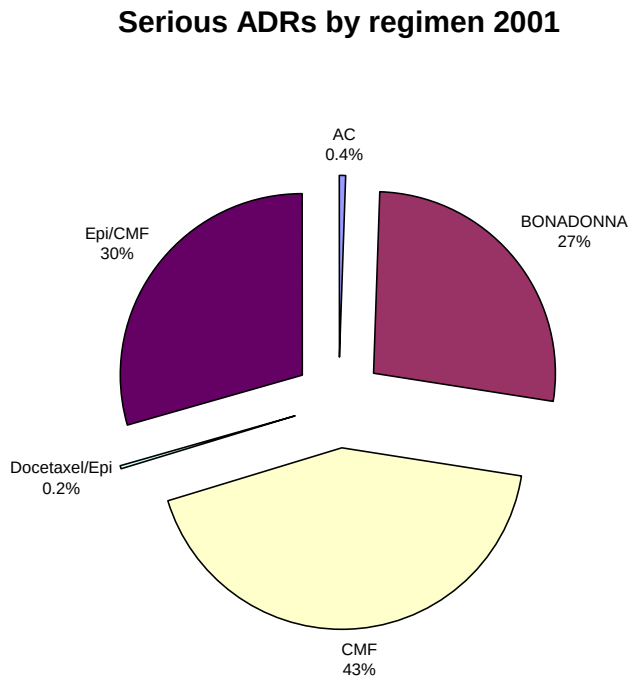
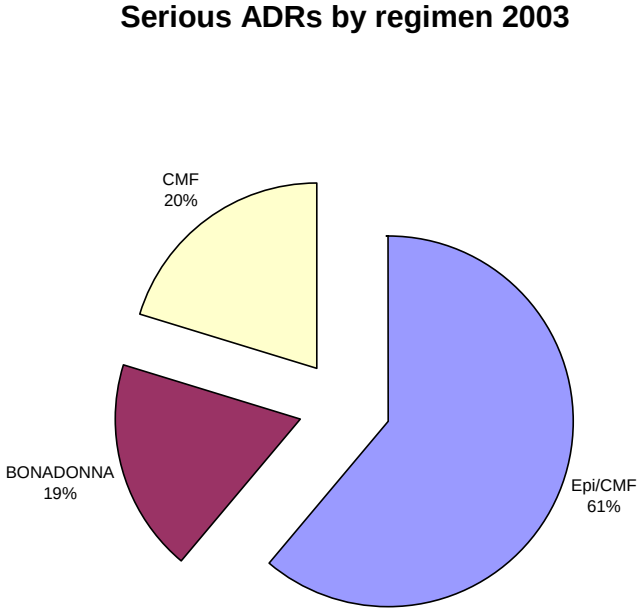


Figure 3.10.



Of the total serious ADRs, 668 (73%) and 818 (72%) were serious haematological ADRs in 2001 and 2003 respectively. Table 3.4 summarises the number and CTCAE grade of all serious haematological adverse drug reactions experienced by the patients in 2001 and 2003.

Table 3.4. Summary of serious haematological adverse drug reactions and CTCAE grade

	2001 (% of total)	**2003 (% of total)**
Grade 4 neutropenia	16	29
Grade 4 leucopenia	3	5
Grade 4 anaemia	0	0
Grade 4 thrombocytopenia	0	1
Total Grade 4	**19 (3%)**	**35 (4%)**
Grade 3 neutropenia	57	64
Grade 3 leucopenia	11	23
Grade 3 anaemia	1	0
Grade 3 thrombocytopenia	1	0
Total Grade 3	**70 (10%)**	**87 (11%)**
Grade 2 neutropenia	129	166
Grade 2 leucopenia	83	126
Grade 2 anaemia	14	12
Grade 2 thrombocytopenia	0	0
Total Grade 2	**227 (34%)**	**304 (37%)**
Grade 1 neutropenia	125	117
Grade 1 leucopenia	163	163
Grade 1 anaemia	60	111
Grade 1 thrombocytopenia	4	1
Total Grade 1	**352 (53%)**	**392 (48%)**
Total number	**668**	**818**

Grade 3 and 4 haematological ADRs accounted for only 13% (89 of the 668) and 15% (122 of the 818) of the serious haematological adverse drug reactions respectively in 2001 and 2003. Neutropenia accounted for the highest proportion of grade 3 and 4 haematological ADRs for both years (82% and 76% in 2001 and 2003 respectively).

Serious, non-haematological ADRs accounted for 27% (243 and 304 respectively in 2001 and 2003) of the total ADRs in both years. The serious, non-haematological adverse events that were experienced by patients in 2001 and 2003 can be seen in Table 3.5.

Table 3.5. Comparison of serious non-haematological adverse drug reactions

	2001	**2003**
Conjunctivitis (not otherwise specified)	161	223
Chest infection (not otherwise specified)	19	11
Depression	16	4
Neutropenic sepsis	6	19
Anxiety	6	3
Hypokalaemia	1	0
Pulmonary embolism	1	3
Allergic reaction	1	3
Haematemesis	0	1
Decrease in renal function	1	2
Cellulitis	3	3
Dysphagia	3	3
Facial oedema	0	2
Cellulitis with septicaemia	0	1
Pneumonia	2	3
Laryngitis	0	1
Atrial fibrillation	1	1
Pulmonary oedema	0	1
Cholangitis aggravated	0	1
Jaundiced	0	1
Panic attacks	0	1
Mood swings	2	1
Vasovagal and syncope	0	1
Venous thrombophlebitis	0	3
Alteration in visual acuity	1	2
Arthralgia	6	2
Bacterial infection nos	0	1
Painful swallowing	0	1
C Difficile diarrhoea	0	1
Increase in blood glucose	3	1
Epistaxis	0	1

Table 3.5 continued. Comparison of serious non-haematological adverse drug reactions

	2001	2003
Heart flutter	0	1
Blood clot in Hickman line	0	1
Indigestion (resulting in hospital admission)	0	1
Shingles	4	0
Hypomagnesaemia	1	0
DVT	1	0
Cholangitis	1	0
Liver function abnormal	2	0
Anorexia	1	0
Rash (resulting in hospital admission)	1	0
Total	**243**	**304**

Table 3.6 shows a summary of serious, non-haematological ADRs by system organ class in 2001 and 2003. The main system organ class the non-haematological serious ADRs belonged to was the eye, accounting for 67% and 74% in the respective years.

Table 3.6. Summary of serious, non-haematological ADRs by system organ class in 2001 and 2003

	Total number of ADRs for System Class 2001	Total number of ADRs for System Class 2003
Eye	162 (67%)	225 (74%)
Infections	34 (14%)	40 (13%)
Psychiatric	24 (10%)	9 (3%)
Immune	1 (<1%)	5 (2%)
Gastrointestinal	3 (1%)	7 (2%)
Hepatobiliary	3 (1%)	2 (<1%)
Renal	1 (<1%)	2 (<1%)
Cardiac	1 (<1%)	3 (1%)
Skin	1 (<1%)	0
Vascular	1 (<1%)	7 (2%)
Musculoskeletal	6 (2%)	2 (<1%)
Neurological	0	1 (<1%)
Respiratory	1 (<1%)	0
Investigations	5 (2%)	1 (<1%)

Table 3.7 provides a summary of the total number of haematological and non-haematological adverse drug reactions in 2001 and 2003. There were 222 more serious adverse drug reactions in 2003 than in 2001 (1133 versus 911 respectively) but there was no difference in the percentage in each year when serious haematological was excluded (approximately 27% in

both years); or when Grade 1 and 2 haematological ADRs were excluded (36% and 39% respectively for 2001 and 2003).

Table 3.7. Summary of total haematological and non-haematological adverse drug reactions in 2001 and 2003

	2001 (% total)	2003 (% total)
Total adverse drug reactions classified as serious (including haematological)	911	1133
Total adverse drug reactions classified as serious (excluding haematological)	243 (26.7%)	304 (26.8%)
Total adverse drug reactions classified as serious (excluding grade 1&2 haematological)	332 (36.4%)	437 (38.5%)

3.3.3 Hospital admissions and outcomes

There was almost twice as many patients admitted to hospital in 2003 than in 2001 due to an ADR (24% versus 13%); and proportionality twice as many admissions to hospital in 2003 than in 2001 due to an ADR (34% versus 17%). There was little difference in the number of admissions prolonged due to an ADR (2% versus 1%). Table 3.8 shows the number of patients admitted to hospital or had their hospital stay prolonged due to an ADR in 2001 and 2003; as well as total days admitted and the number of dose delays that resulted in these patients.

Table 3.8. Comparison of hospital admissions in 2001 and 2003

	2001	2003
Number of patients admitted to hospital due to ADR	13	24
Total number of admissions	17	34
Total number of days admitted	87	226
Admission prolonged due to ADR	1	2

The cytotoxic chemotherapy regimes that the patients received who were hospitalised with an ADR in 2001 included CMF (7 patients with a total resultant inpatient stay of 29 days), EPI/CMF (5 patients with a total resultant inpatient stay of 40 days) and BONADONNA (1

patient with a resultant inpatient stay of 7 days). The reasons for the 13 admissions to hospital in 2001 included neutropenic sepsis, pneumonia (but not neutropenic), chest infection (grade 1 neutropenia), infected dental abscess, shingles, cellulitis (not neutropenic), oesophageal candidiasis with spasm, DVT and PE.

The cytotoxic chemotherapy regimes that the patients were receiving who were hospitalised with an ADR in 2003 included CMF (4 patients with a total resultant inpatient stay of 45 days), EPI/CMF (17 patients with a total resultant inpatient stay of 166 days) and BONADONNA (3 patients with a total resultant inpatient stay of 15 days). The reasons for the 24 admissions in 2003 included cellulitis, cellulites with septicaemia, indigestion, heart flutter, C Difficile diarrhoea, chest infection, bacterial infection (not otherwise specified), pneumonia, dysphagia, haematemesis, pulmonary embolism, hypokalaemia, atrial fibrillation, pulmonary oedema, aggravated cholangitis and neutropenic sepsis.

In 2003 the percentage of admissions to hospital with an ADR with Epi/CMF was almost double that of 2001 (71% versus 38%). The total number of patients in 2003 receiving Epi/CMF, however, was double that of 2001 (62 versus 31). Table 3.9 compares the patient admissions in 2001 and 2003 by cytotoxic chemotherapy regimen.

Table 3.9. Comparison of hospital admissions in 2001 and 2003 by cytotoxic chemotherapy regimens

	2001		**2003**	
	Total patients admitted with ADR (% of total)	Percentage of patients receiving this regimen in the year (% of total)	Total patients admitted with ADR (% of total)	Percentage of patients receiving this regimen in the year (% of total)
CMF	7 (54%)	54 (13%)	4 (17%)	26 (15%)
Epi/CMF	5 (38%)	31 (16%)	17 (71%)	62 (27%)
BONADONNA	1 (8%)	13 (8%)	3 (13%)	12 (25%)
Total	**13**		**24**	

There were also proportionally more occupied bed days as a result of an ADR in 2003 than in 2001. The cytotoxic chemotherapy regimen responsible for this increase was mainly Epi/CMF. Table 3.10 shows a comparison of hospital beds days due to cytotoxic chemotherapy regimens in 2001 and 2003.

Table 3.10. Comparison of number of hospital bed days by cytotoxic chemotherapy regimen in 2001 and 2003

	2001 Number of hospital bed days (% of total)	**2003 Number of hospital bed days (% of total)**
CMF	33 (38%)	45 (20%)
Epi/CMF	46 (53%)	165 (73%)
BONADONNA	8 (9%)	16 (7%)
Total	**87**	**226**

Table 3.11 shows the patient outcomes after cytotoxic chemotherapy in 2001 and 2003 with regard to dose reductions, regimen changes, or treatment cessation.

Table 3.11. Comparison of patient treatment outcomes in 2001 and 2003

Patient outcome after treatment	**2001**	**2003**
Dose delays	78	66
Dose reduction	6	12
Chemo regimen changed	1	2
Patient recovered and no dose reduction required	89	81
Treatment stopped	4	5

There was very little difference observed between the two years for dose delays, regimen changes, treatment cessation, or patients recovering between treatment cycles requiring no dose change. However there was over twice as many dose reductions before the next cycle of treatment in 2003 than in 2001. 83% (10 of 12) of these dose reductions in 2003 was in patients who were hospitalised due to an ADR; compared to 50% (3 of 6) in 2001. As well, 60% (3 of 5) of the treatments being stopped in 2003 were for patients who were hospitalised with an ADR; compared to 25% (1 of 4) in 2001.

Figure 3.11 and 3.12 show treatment outcomes by cytotoxic chemotherapy regimens in 2001 and 2003. The main differences noted in the treatment outcomes between the different cytotoxic chemotherapy regimens in 2001 and 2003, was that there was a slight increase in the percentage of dose reduction with Epi/CMF in 2003 compared to 2001; and a decrease in the number of dose delays with CMF.

Figure 3.11.

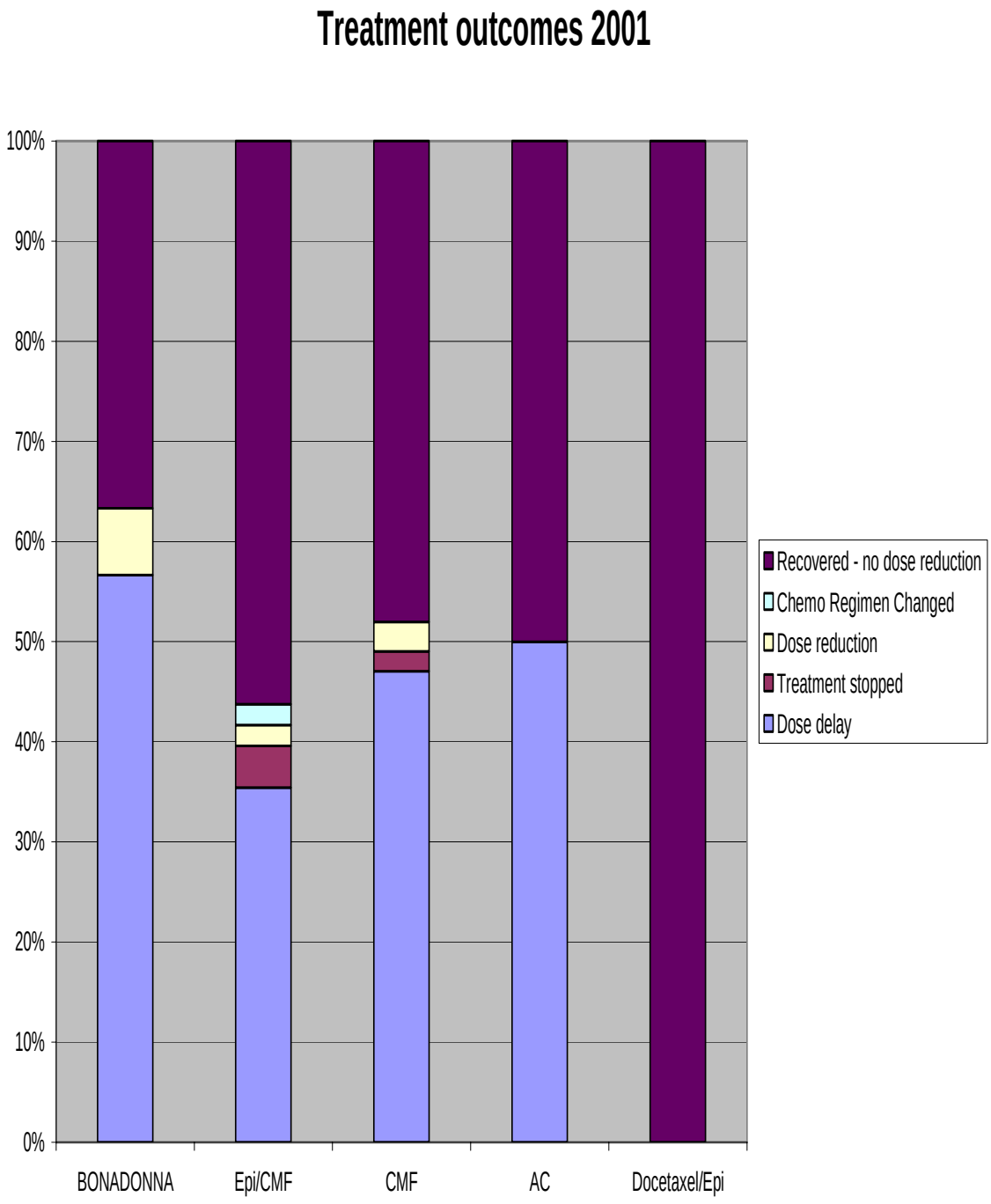
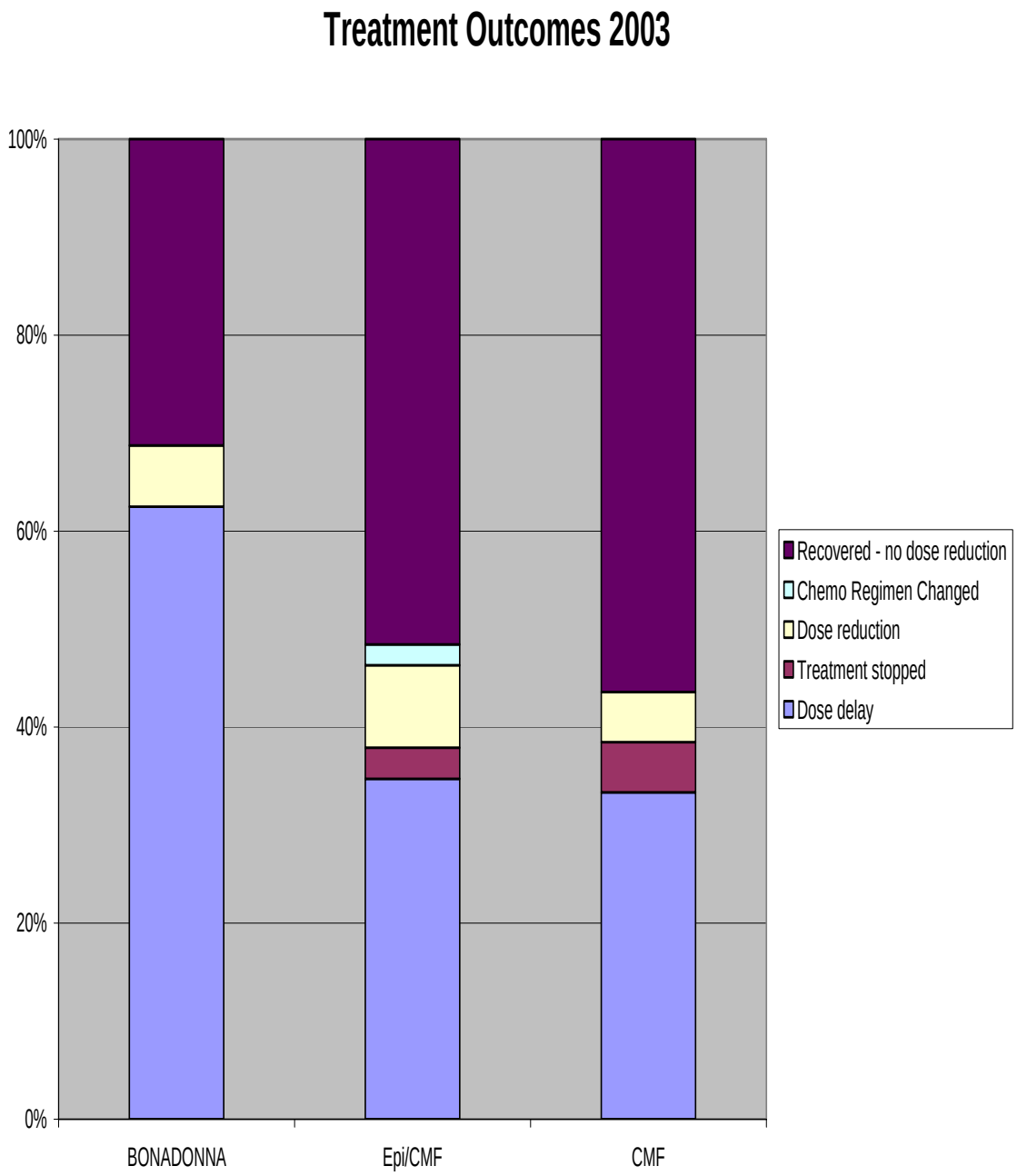


Figure 3.12.



3.3.1 Yellow card reports

Table 3.12 shows the number of patients who were identified to have had a serious ADR in 2001 and 2003; as well as the number of these identified ADRs that were reported via the Yellow Card scheme in these two years.

Table 3.12. Comparison of patients who experienced a serious ADR and the number of these ADRs that a Yellow Card report was submitted for in 2001 and 2003

	2001	2003
Number of patients who experienced a serious ADR	97	96
Number yellow card reports submitted to the MHRA	1	6
Report origin	Hospital pharmacist	Hospital Pharmacist

There was little change observed in reporting rate with a reporting rate of 1 % (i.e. 1 out of the 97 patients who experienced any serious ADR was reported via the Yellow Card scheme) in 2001 and reporting rate of 6.3% (i.e. 6 of the 96 patients who experienced a serious AE was reported via the Yellow Card scheme) in 2003. There was no statistically significant difference observed in the reporting rates between the two years (p=0.12). Pharmacists were the only oncology healthcare professional group who submitted reports for these sample populations in 2001 and 2003.

3.4 Discussion

3.4.1 Principal findings

3.4.1.1 Cytotoxic chemotherapy regimens

The cytotoxic chemotherapy regimens that were used in the adjuvant breast cancer sample population in 2001 and 2003 were AC (doxorubicin and cyclophosphamide), BONADONNA (doxorubicin /cyclophosphamide, methotrexate, and 5-fluorouracil), CMF (cyclophosphamide, methotrexate and 5-fluorouracil), docetaxel/Epi (docetaxel /epirubicin), and Epi/CMF (epirubicin/ cyclophosphamide, methotrexate and 5-fluorouracil). The only noticeable difference between the two years was the shift from using CMF in 2001 to using more Epi/CMF in 2003. None of the regimens contained any black triangle medicines.

In both 2001 and 2002, CMF, Epi/CMF, and BONADONNA resulted in admissions to hospital due to an ADR. There were twice as many patients admitted to hospital in 2003 than in 2001 due to an ADR as observed in the study populations (24% versus 13%). In 2003, the percentage of admissions to hospital with an ADR following treatment with Epi/CMF was almost double that observed in 2001 (71% versus 38%). There were also proportionally more occupied bed days as a result of an ADR in 2003 than in 2001 with a total of 226 and 87 inpatient bed days in 2003 and 2001 respectively. This increase was mainly due to Epi/CMF but it must be noted that the total number of patients in 2003 receiving Epi/CMF was double

that of 2001 (62 versus 31). In 2001 the unit cost for medical inpatient care was £359.00 per day in Scotland (82), it can be calculated therefore, that a total cost of approximately £112,000 (£81,000 for 2003 and £31,000 in 2001) was the result of ADRs in the study populations for 2001 and 2003.

There was very little observed difference between the two years for consequences from ADRs that included dose delays, regimen changes, treatment cessation, or patients recovering between treatment cycles requiring no dose change. There was, however, over twice as many dose reductions before the next cycle of treatment in 2003 than in 2001, which can be mainly attributed to Epi/CMF. This data is in contrast to the National Epirubicin Adjuvant Trial (NEAT) that showed that the excess treatment-related adverse effects with EPI/CMF did not affect delivered-dose intensity (83). 83% (10 of 12) of these dose reductions in 2003 was required in patients who were hospitalised due to an ADR; compared to 50% (3 of 6) in 2001.

It should be noted that 60% of the treatments which were stopped in 2003 were observed in patients who were hospitalised with an ADR; compared to only 25% in 2001. This suggested that more severe adverse events and intolerance to treatment were prevalent in the 2003 patient population.

3.4.1.2 Incidence rate of serious ADRs

A total of 911 serious ADRs spread over 717 cycles occurred in 97% of the patients in 2001; and 1133 serious ADRs spread over 778 cycles occurred in 96% of the patients in 2003. This gave an average incident rate of 1.3 and 1.5 ADRs per cycle in 2001 and 2003 respectively. Epi/CMF caused 61% of these serious ADRs in 2003 but only contributed 30% in 2001. Again the doubling in number of patients receiving this regimen in 2003 from 2001 gave a proportionate increase in observed serious ADRs. This observation is in agreement with the NEAT trial, which showed that the overall incidence of adverse effects was significantly higher for epirubicin plus CMF than with CMF alone (83).

3.4.1.2.1 Haematological

Serious haematological ADRs accounted for 73% and 72% of the total observed ADRs in 2001 and 2003 respectively. Grade 3 and 4 haematological ADRs accounted for only 13% and 15% of the serious haematological adverse drug reactions respectively in 2001 and 2003. Oncology healthcare professionals anticipate these haematological ADRs since they are

known side effects with all the adjuvant chemotherapy regimens. It is usually only grade 3 or grade 4 ADRs that oncologists would be concerned with during treatment since patients' levels of haemoglobin, neutrophils, platelets and WBCs must recover sufficiently before a subsequent cycle of chemotherapy can be given. Further considerations of haematological parameters dictate dose delays, dose reductions or cessation of treatment. Grade 1 ADRs normally require no treatment and grade 2 ADRs normally require support care only and do not carry the same consequences for treatment outcomes.

3.4.1.2.2 Non-haematological

Serious, non-haematological ADRs accounted for 27% of the total ADRs in both 2001 and 2003. The system organ classes (SOCs) involved included 14 of the 25 SOCs (eye disorders, infections, psychiatric disorders, immune system disorders, gastrointestinal disorders, hepatobiliary disorders, renal disorders, cardiac disorders, skin disorders, vascular disorders, musculoskeletal disorders, neurological disorders, respiratory disorders and investigations. The top three SOCs were eye disorders, infections and psychiatric disorders.

The main system organ class the non-haematological serious ADRs belonged to was eye disorders (67% and 74% in 2001 and 2003 respectively). This was due to the high number of incidences of conjunctivitis seen in the patients receiving 5-fluoruracil. This is an anticipated side effect that is seen with treatment and patients are managed with symptomatic care.

Infections accounted for 14% and 13% of the total non-haematological serious ADRs in 2001 and 2003 respectively. Neutropenic sepsis, specifically, accounted for a very small percentage of the total non-haematological serious ADRs seen in 2001 and 2003 (2% and 6% respectively). This was surprising considering that in the audit conducted in 2002 at ECC, 77 (44%) of the adverse reactions reports were due to neutropenic sepsis; with 35 (80%) of these reports being observed in patients with breast cancer (58). Therefore the incident rate for neutropenic sepsis in the 2001 and 2003 study populations appears to be lower than estimated from previous audit.

Psychiatric ADRs (including depression, mood swings, and anxiety) accounted for 10% and 3% of the total non-haematological serious ADRs seen in 2001 and 2003. Psychological stress is frequently seen in cancer patients. There is evidence published in the literature from a multivariate analysis to suggest that a past history of major depressive disorder and

helplessness/hopelessness were significantly associated risk factors with psychiatric disorders in patients with breast cancer. However various other factors are considered to be associated with, and are intricately related to, psychiatric disorders during cancer treatment. These include physical variables such as pain, fatigue, other symptom burdens (such as nausea and vomiting) and poor performance status. Further studies are needed to clarify causal links between QOL and psychiatric disorders (84, 85). All of the latter factors are directly attributable to cytotoxic chemotherapy, so psychiatric adverse events will continue to be considered an outcome of the medicine and deemed a possible ADR until future evidence suggests otherwise.

3.4.1.3 Yellow Card reporting rate

There was an increase of 5 Yellow Card reports from 2001 to 2003 with pharmacists being the only oncology healthcare professional group submitting all of these reports. The Fisher's Exact test found no statistically significant difference in the reporting rates between 2001 and 2003 (1% versus 6.3%). The reporting rate for serious ADRs in this study for both years is less than that observed in a French study at a cancer institute, which found a reporting rate of 8.2% for serious ADRs due to cytotoxic chemotherapy (2).

3.4.2 Strengths and weaknesses of study

During the data collection period, building work was ongoing in the area of the hospital where all deceased patient records were kept. As a result the researcher was not able to access any of these patients' notes. These patients who had an end result of mortality may have had more serious adverse events and could have contributed to a higher incident rate of serious ADRs. Therefore the possibility of a bias having been introduced as a result cannot be ruled out.

With all retrospective case note review surveys, the quality of the data obtained is dependent upon the quality of the recording of data in the notes. While a standard 'toxicity' assessment sheet is used by all nurses there is likely to be variation in the recording observed toxicities. The grading of adverse events is subjective in nature so internal validity of the grading instrument will be a confounding factor. It was noted by the researcher that, in some case notes, that nurses either did not record toxicities or graded lower than that recorded in the patient progress notes by the oncologist. As a result it is possible that some adverse events/ADRs will have been missed.

It has been shown that structured case note review, when carried out by a trained professional, results in reliable detection of adverse events (86). The researcher in this case was an experienced pharmacist with expertise in ADR detection and reporting who had worked in the oncology speciality before.

Data should be gathered by the same observer whenever possible to ensure that the results will be free from bias resulting from differences between observers (87). The same researcher reviewed all 200 sets of notes, recorded the data on the recording form and entered the data into a Microsoft Excel spreadsheet, which eliminated any bias due to differences in observers. There was no validation of the recording of the adverse events by the researcher from the case notes or of the entry into the database due to practicality of resource constraints.

There was no independent review undertaken after the researcher assigned the serious classification according to ADROIT. The researcher, later, undertook a causal analysis on all serious ADRs and assigned the likelihood of whether it was an ADR, and independent assessment of the assignments was undertaken by three others to validate these assignments however.

3.4.3 Strengths and weaknesses in comparison to other studies

This study used a retrospective case note review as the study design and the target population selection came from a complete list of all patients treated from the oncology database at ECC. The possibility of interpreter bias exists with this study design, both for nurses (assessing adverse events at each cycle of treatment) and for the researcher (recording relevant information from the notes). ICD-9 codes were utilised to identify potential patients in Lapeyre-Mestre et al and Couffignal et al studies (2, 3) this was not as accurate a means of identifying a target population since it is dependent upon a correct code being assigned to following discharge from hospital. Poole et al (47) used a prospective study design to collect their data that depended upon pharmacists identifying patients who had experienced an ADR, which introduced the possibility that some patients would not have been identified. Lau et al utilised interviews and review of case notes to gather their data. The quality of the information obtained from the interviews depends on the questions asked and answers received (81). The potential for interviewer bias, therefore, was likely to exist in this study.

No independent validation of causal analysis occurred in the studies carried out by Poole et al or Lau et al; and Lapeyre-Mestre et al or Couffignal et al did not undertake any further causal analysis since the information had come from ICD-9 codes for potential ADRs of concern (2, 3, 47, 81).

3.4.4 Implications of findings

Oncology healthcare professionals often anticipate the majority of haematological ADRs seen in oncology; and best supportive care is given to prevent or treat (such as G-CSF to treat neutropenia; or erythopoieses-stimulating agents or blood transfusions to treat anaemia) (88). These treatments are not without risks in some patient groups (such as risk of thromboembolism and decreased survival outcomes with erythopoieses-stimulating agents) (89-91) or financial implications (89); so patients selected to receive these therapies are done so taking into consideration the risks and benefits. In this study haematological ADRs (which are classed as serious by MHRA definition) accounted for over 70% of the total ADRs seen in both study populations. Considering that all haematological ADRs were known and expected it is highly unlikely that the oncology healthcare professionals would consider reporting these ADRs via the Yellow Card scheme, even though they do meet the Yellow Card criteria for reporting. Also considering the volume of haematological ADRs (which are all classed as serious) seen in routine clinical practice, it does then bring into question whether the current Yellow Card criteria are realistic or achievable in oncology.

Similarly with non-haematological serious ADRs, the majority seen in the patient populations in 2001 and 2003 are those that would be anticipated (infections secondary to immunosuppression, eye problems with 5-fluorouracil regimens, and psychiatric related ADRs). Additionally, oncologists are aware that allergic reactions are a possibility; particularly those associated with infusion of with cytotoxic chemotherapy regimens. As a result patients are either pre-medicated with dexamethasone and an antihistamine or are treated as per treatment protocol when they do occur. Reporting of any of these expected ADRs with cytotoxic chemotherapy regimens are unlikely to be considered for reporting via the Yellow Card scheme.

Since this case review was conducted the Gold Standard for treatment of adjuvant breast cancer has changed with BONADONNA and single agent CMF no longer being used. Anthracycline-based regimens (epirubicin or doxorubicin) are now the current standard (77).

These standard regimens include EPI/CMF (83); or AC (doxorubicin and cyclophosphamide) or FAC (5-fluorouracil, doxorubicin and cyclophosphamide) with the addition of a taxane (paclitaxel or docetaxel) sequentially or concomitantly (5). Docetaxel and paclitaxel can cause serious ADRs such as febrile neutropenia (especially with docetaxel regimen) (92-94), arthralgia, myalgia, peripheral neuropathy, significant hypersensitivity infusion reactions and cardiotoxicity (95, 96). Hence the adverse event profile and subsequent serious ADRs will change from the one observed and reported in this case review. Other changing practices in adjuvant chemotherapy that may also affect the adverse effects profile observed in a patient population are:

1) Concurrent use of trastuzumab in Her-2 positive patients (5), which can cause serious ADRs such as arthralgia, myalgia, supraventricular tachyarrhythmia, hypotension, heart failure, cardiomyopathy, palpitations, and hypersensitivity reactions (97).
2) The addition of other medicines to anthracycline or taxane-based chemotherapy, such as gemcitabine and paclitaxel (5, 93). Gemcitabine can cause serious ADRs such as myocardial infarct, cardiac insufficiency, arrhythmia (predominantly supraventricular in nature), interstitial pneumonitis together with pulmonary infiltrates, serious hepatotoxicity, haemolytic uraemic syndrome and renal failure, febrile neutropenia and thrombocythaemia (98).

Therefore the likelihood is that patients with breast cancer receiving adjuvant chemotherapy may experience even a greater number of serious ADRs. Proportionately there is likely to be an increase in the number of ADRs that remain unreported via the Yellow Card scheme unless other initiatives are taken to attempt to facilitate reporting and to improve reporting rates. The pharmacist-led ADR reporting initiative showed no significant increase in reporting rate after the initial launch of the initiative during 2002 was complete. This suggests that long-term sustainability of increased ADR reporting is problematic with this initiative.

Oncology oriented guidelines for ADR reporting, which highlight clinical relevance, need to be developed to address under-reporting of ADRs. Greater education and training to support ADR reporting by oncology healthcare professionals is required to highlight the importance of the Yellow Card scheme and post-marketing monitoring of medicines. The review of the Yellow Card scheme, which was led by Jeremy Metters, was completed in 2004. Amongst the findings of the report was the recommendation that it was essential that the scheme

maintain its focus upon serious, previously unknown ADRs and black triangle products but the report supported the development of clearer guidelines for definitions of serious ADRs (35). In oncology practice this is certainly of relevance since it is usually the severity of adverse events, grade 3 and grade 4, that are considered of concern oncology healthcare professionals. However, even after a positive causal analysis for an ADR is made in these situations, these high-grade adverse events do not always correspond to a serious ADR that would constitute reporting to the MHRA. Hence there is a need to define which adverse events (considered to be an ADR) and grades specifically that should be reported. The simplest and easiest means of achieving this may be through mapping of the NCI CTCAE criteria to either serious or non-serious. This information could then be incorporated into patient electronic records for recording oncology patients' adverse events; and could act as a prompt for reporting those adverse events considered to be an ADR to regulatory agencies such as the MHRA.

3.4.5 Unanswered questions and future research

This study has raised a few questions that require further study. These include:

1) What are the knowledge, behaviour and attitudes of oncology healthcare professionals regarding reporting of oncology ADRs via the Yellow Card scheme?
2) What would define the adverse events (considered to be an ADR) and NCI CTCAE grades that should be reported via the Yellow Card scheme to help increase the ADR reporting rate in oncology?

3.5 Conclusions

The pharmacist-led ADR reporting initiative resulted in only a non-significant 5% absolute increase in reporting in the year after the audit finished compared to the year before the audit. Therefore the substantial increase in reporting that was seen during the audit year in 2002 was proven not to be sustainable. As a result, even though this initiative encourages good reporting practice and highlights Yellow Card reporting in oncology it cannot be adopted as a means for sustaining increased ADR reporting in oncology via the Yellow Card scheme. In addition, only pharmacists contributed the reports so there is a greater need to ensure that all oncology healthcare professionals report ADRs. Hence other means of improving oncology ADR reporting must be pursued in addition to this model of good practice to improve pharmacovigilance in oncology.

Chapter 4

Knowledge, behaviour and attitudes of oncology healthcare professionals in Scotland on adverse drug reaction reporting via the Yellow Card scheme

4.1. Introduction

Oncology practice has experienced a great increase in new drug approvals since the late 1980s. Fewer than a dozen agents were commonly employed in the treatment of patients with cancer 25 years ago (99). While these new medicines may offer therapeutic benefit, leading to improved outcomes, survival and possibly quality of life for some cancer patients, adverse effects continue to be a problem. Adverse effects from oncology medicines may occur following administration anytime from immediately to more than three decades after administration (99). Oncology healthcare professionals are well versed in management of most common adverse effects experienced by patients during cytotoxic chemotherapy; however, the newer targeted medicines (such as trastuzumab and imatinib) have introduced new adverse reaction experiences to contend with.

Some of these rarer adverse drug reactions may not have been apparent during clinical trials because the number of patients involved in these trials usually do not allow for detection of ADRs that occur infrequently (less than 1 in 10,000). Also due to exclusion of certain patient populations (such as those with concomitant disease states, renal or liver dysfunction, children, pregnancy and lactation) from clinical trials that subsequently go on to receive the medicines after marketing, the full ADR profile in these populations is unknown. Hence, the detection of unknown suspected ADRs depends upon rigorous post-marketing surveillance of medicines.

In the UK, the Yellow Card scheme is the post-marketing, voluntary ADR reporting scheme; and all healthcare professionals are encouraged to report all serious expected ADRs for all medicines and all suspected ADRs for newer medicines (black triangle) that are under intensive monitoring during the initial period of use in the non-trial clinical environment. A black triangle status can be reapplied to a medicine at any point in its lifespan, however, if a new safety concern arises and more intensive monitoring is required.

All reports received via the Yellow Card scheme are reviewed and analysed to generate 'signals' but by increasing the number of reports received it can increase the number of 'signals' produced and decrease the time to detect any public health problems. It is estimated that less than 10% of all serious ADRs and 2-4% of non-serious ADRs are reported via the Yellow Card scheme (45, 100, 101). This has obvious implications in the generation of signals and detection of possible problems. It is unknown whether under-reporting is any worse in the oncology speciality when compared with other clinical specialities but a review of the literature identified that under-reporting of low-grade and recurrent events and inconsistent or incomplete reporting of high-grade or significant adverse events in oncology was a problem (99, 102, 103).

Without adequate support and participation of oncology healthcare professionals in voluntary reporting of suspected ADRs then post-marketing surveillance of oncology medicines will be inadequate. It is possible, therefore, that possible short- and long-term adverse effects of these medicines may go undetected. The reasons why healthcare professionals do not report ADRs have been studied extensively and reported in the literature, looking at various reporter groups. Survey questionnaires have been the main assessment tool employed but focus groups were also employed. The original 'seven deadly sins' proposed by Inman (33) is assessed in the majority of these questionnaires [ignorance, diffidence, fear, lethargy, guilt, ambition and complacency]. There is commonality in the findings of the majority of studies but some variation of specific reasons is observed. These reasons include:

- Uncertainty as to whether the reaction was caused by a drug (52, 53, 55, 104-107).
- ADR being trivial or already well known (52, 104, 106, 107).
- Did not feel reporting serious, established reactions was necessary (54, 55, 100).
- Severity of the reaction (106).
- Not aware of the need to report ADRs (54, 104).
- Did not know how to report an ADR (104, 107-109).
- Did not know or unclear what to report (104, 106, 110, 111).
- Not enough time to report (54, 104-106, 108-110, 112).
- Lack of access to reporting forms (105, 108, 109, 112).
- Forget to report (106).
- Took to long to complete a report (prefer easier way) (52, 53, 110, 113)

- Thought reporting too bureaucratic (104)
- Lack of knowledge of the purpose of the ADR reporting scheme, such as the Yellow Card scheme (53, 54, 105, 111)
- Misconception that had to be 100% certain a medicine caused an ADR (52, 55, 112)
- Underestimate the true incidence of adverse ADRs (54)
- Lack of access to information and resources for searching for evidence of ADR (105)
- Lack of information or feedback on ADRs (52, 105)
- Legal liability and judicial claims (105)
- Belief that one report not enough to make a difference (52, 53)
- Lack of contact details of reporting agency (108)

The items identified that would have a positive impact upon participation in the Yellow Card scheme were:

- Education and training (40, 49, 55, 110, 114)
- Define priorities for reporting – types of medicines, severity of ADR, unexpected ADR (105)
- More feedback on the reports (105, 110)
- Reminders and increased awareness (110)
- Increased accessibility of Yellow Cards, including on-line access and telephone based reporting (110)
- Local initiatives (to promote ADR reporting) (110)
- Information and support for reporting (105)

There is a lack of studies reported that have looked specifically at why oncology healthcare professionals do not report ADRs, despite seeing them routinely in their clinical practice. The study reported here was designed to obtain more insight into the knowledge, behaviour and attitudes of oncology healthcare professionals with regard to ADR reporting via the Yellow Card scheme.

4.2. Methods

4.2.1. Development of survey questionnaire

In the absence of identification of a published validated questionnaire, a questionnaire for eliciting the attitudes, behaviour and knowledge of oncology healthcare professionals to

adverse drug reaction reporting one was developed. As part of the work, one-to-one semi-structured interviews were carried out to obtain necessary background information on attitudes, behaviour and knowledge to the Yellow Card scheme and adverse drug reaction reporting in general within oncology. This information was then used to help structure the content for the final questionnaire in combination with other key findings that had been derived from previous questionnaires, which are highlighted above. The questionnaire on ADR reporting attitudes, opinions and knowledge used by Bateman DN et al (54) was used as a basis for general layout of the questionnaire.

This questionnaire was subsequently developed within on-line software for survey development "Survey Monkey" (available at www.surveymonkey.com) into an electronic format by the researcher for dissemination and self-completion via a webpage.

4.2.1.1. Semi-structured one-to-one interviews

Six oncology healthcare professionals from the South East of Scotland Cancer Network (SCAN) (2 pharmacists, 2 nurses and 2 doctors) were selected to participate in in-depth, one-to-one, semi-structured interviews to be carried out by the researcher to obtain a range of attitudes to oncology adverse drug reactions. Purposive sampling was employed to identify these six oncology healthcare professionals. Purposive sampling is a deliberate non-random method of sampling, which aims to sample a group of people or setting with a particular characteristic (115). In this case, the characteristic required was equal representation of oncology nurses, doctors and pharmacists.

Interviews are one of the main methods of data collection for qualitative research. Depth interviews are unstructured or only have a minimum structure of topics in the interview schedule. The pre-determined structure of semi-structured interviews provides the interviewer with a deliberately focused schedule using mainly fixed questions to work from (but with no, or few, response codes). The questions may be used flexibly to allow the interviewer to probe issues raised by the interviewees or to enable interviewees to raise other relevant issues not covered by the interview (115-119). Prior to the interviews in this study a standardised set of questions was compiled to act as a rough guide for the interview. A copy of these questions can be seen in appendix 11.

To arrange the in-depth interviews a letter of invitation was sent to the proposed subjects, which detailed the background to the research, aim of the study, the method, the use of the data, and how the confidentiality of the information that they might provide if they choose to participate would be maintained. This letter can be seen in appendix 12. Six letters of invitation were sent and five positive replies were received (2 doctors, 2 pharmacists and 1 nurse). Another letter was subsequently sent to an alternate nurse and a positive response was received, which gave the required 2 pharmacists, 2 nurses and 2 doctors. Once a positive response was received from participants an interview date, time and place of their convenience was arranged.

One-to-one semi-structured interviews provide a flexible and adaptable way of gathering information based on one person's experiences and opinions but it is essential that the researcher develops a rapport with the interviewee early in the interview in order to develop a positive relationship. This ensures the interviewee has a comfortable environment for sharing their personal views and experiences (119). To facilitate this, the interviews took place with each participant in a quiet office space (either their own office or a meeting room), to promote minimal (if any) interruptions. All interviewees were given standard introductory information prior to the interview beginning, including a requirement for verbal consent to audio-record the interview (appendix 13). All of the interviews were audio-recorded with the interviewee's verbal consent. The interviews were of 30 minutes approximate duration each.

After each of the interviews, the subject was given a post-interview comments sheet and was requested to complete and return the document via post in a pre-addressed envelope to the researcher. A post interview comments sheet was used to obtain feedback from subjects about his or her feelings on the interview (impression of how the interview went, time taken, rapport with interviewer, any disruptions). A copy of this comments sheet can be seen in appendix 14.

Post-interview a verbatim transcript was produced. Four were transcribed by researcher and two were transcribed by a secretary. The researcher reviewed the audio-recording and transcription of the two transcriptions carried out by a secretary to ensure accuracy. Copies of these verbatim transcripts can be seen in Appendix 15.

The researcher analysed the transcripts and assigned codes according to developing themes. Coding involves relating sections of the interview data to categories that the researcher has either predetermined or developed as the data is collected (115, 120). This coding ensures that all related themes of information obtained from the subjects during an interview can be placed into mutually exclusive categories for subsequent aggregate and analysis. This method of analysis allows for easier handling of the qualitative information received. In this study the coding process was carried out initially by the researcher. A summary of the coded themes can be seen in appendix 16. The categories identified from the coded transcripts were then check-coded by an individual experienced in coding qualitative data to ensure validity of the themes (115, 119). There was agreement in coding and the validated themes and concepts from these in-depth, one-to-one, semi-structured interviews were therefore able to be used to develop a questionnaire designed to elicit the attitudes, behaviour and knowledge of a wider group oncology healthcare professionals across Scotland.

4.2.1.2. Designing questionnaire

Questionnaires are useful research tools for collecting information about people's knowledge, beliefs, attitudes and behaviour, and are commonly used to collect data from a large sample group (121). To obtain reliable and valid data, questionnaires must be designed to ensure questions are clear and meaningful with a low likelihood of being misinterpreted. The themes and ideas selected from those identified in the one-to-one interviews were converted into closed questions. Closed questions are questions where the researcher has defined the possible responses and can vary from "yes," "no" or "don't know" to scales or tick box answers (122). Recognising that there is a risk of forcing respondents into inappropriate categories by using this format (115), closed questions with pre-coded responses were used to make the data easier to analyse (115). Using the "Survey Monkey" tool, summary tables of the data can be produced directly without the need for further manipulation.

It is recommended that the same response scale should not be used too frequently throughout the questionnaire, as this can lead to a response set (a tendency to answer all the questions in a specific direction regardless of their content) (115). The closed questions in this questionnaire used a mixture of pre-coded answers appropriate to the question (age ranges, percentages, etc), yes/no/not sure, and scaled (strongly agree, agree,

disagree or strongly disagree). The latter used a four point Likert Scale (115, 123) for a series of opinion statements, in which the respondent must indicate their level of agreement or disagreement. A four point scale was used rather than the usual 5 point scale, which contains a neutral ground option such as undecided, in order to require the respondent to make a decision. The respondents were given the opportunity at the end of each set of questions to record any other comments they wished to make however.

All questionnaires require informal pre-testing, initially concentrating on individual questions before deciding upon a final draft of questionnaire (123). The content for each question for the questionnaire was initially written in a "Microsoft Word" document by researcher then peer reviewed by project supervisors and an individual experienced in qualitative research, including questionnaire design. After this the final draft content was decided and the questionnaire was produced on "Survey Monkey" prior to piloting of final draft or electronic circulation.

4.2.1.3. Pilot of survey questionnaire

It is recommended that questionnaires should always be piloted involving participants representative of the sample group being analysed (123). This procedure may then lead to questions being re-phrased and will increase the quality of responses. It is during this formal pilot that acceptability, validity and reliability of the measure is tested (124). A questionnaire is said to be valid if it examines the full scope of the research question in a balanced way (it measures what it aims to measure) (124). In this case criterion validity (comparing against gold standard) was not possible since no questionnaire specific to oncology was available. Instead tested scales and questions from other generalist areas were used (52-55, 100, 104- 111, 113, 114). Face validity was carried out during the pilot phase though to check if the questions were relevant, reasonable, unambiguous and clear (115, 123). The participants in the pilot phase were asked to provide specifically any comments on these items. To test reliability (reproducibility and consistency of an instrument), test-retest and internal consistency should be evaluated (124). In this case a test-retest was not performed but internal consistency was confirmed by asking a question in more than one way during the questionnaire (124). For example, in this questionnaire the final item in question 15 ('If grade of adverse event is a factor in your decision to submit a Yellow Card, which grades?') was cross-checked for internal consistency from answers given in question 13 ('Which of the following oncology adverse events do you

think you would report?') that presents all possible grades and reporting criteria scenarios. In the 10 questionnaires which formed the pilot there was 100% internal consistency confirmed. To test acceptability the pilot study subjects should be asked to feedback comments (in writing or verbally). The time taken to complete should be asked, which can then be used in the cover letter to accompany questionnaire) (124).

The final draft questionnaire was initially piloted by testing on 10 pharmacists at the Royal Infirmary of Edinburgh. All but two of these colleagues had either previously worked in oncology or had completed clinical MSc placements within this speciality. The two colleagues with no prior experience in oncology had prior experience with questionnaire design and/or adverse drug reaction reporting and it was considered that their input would be beneficial. Comments from the pilot subjects on the following were requested within a 10-day period:

- How long did the questionnaire take to complete?
- Were questions relevant? If not why?
- Were questions and instructions clear? If not why?
- Was lay-out attractive?
- Any other comments?

After receipt of feedback the required changes were made and questionnaire layout and content finalised within "Survey Monkey". A copy of the final questionnaire can be seen in appendix 17.

4.2.2. Distribution of questionnaire

The questionnaire was to be circulated electronically for self-completion to a sample of 125 oncology healthcare professionals working within Scotland. This number was determined following assumption of a minimum of a 30% response rate and acceptance of a 5% margin of error and 95% confidence level. Only oncology healthcare professionals caring for patients with solid tumour disease were to be selected for this sample. Non-solid tumour (such as haematopoiesis) disease was intentionally excluded since in these patients the intent of cytotoxic chemotherapy is mainly to ablate the patients' own bone marrow to eliminate underlying disease prior to allowing for restoration of healthy bone marrow (125). Hence the haematological side effects observed are intended and considered beneficial in clinical haematology.

The e-mail addresses for about half of the healthcare professionals were provided directly to the researcher but some areas within one cancer network preferred not to give e-mail contact details directly to the researcher but agreed to disseminate the questionnaires at the request of the researcher. As a result of these distribution methods the survey questionnaire was circulated to 150 healthcare professionals in total. The sample population was drawn from Southeast Scotland Cancer Network (SCAN, which covers NHS Borders, NHS Dumfries & Galloway, NHS Fife and NHS Lothian) and West of Scotland Cancer Network (WOSCAN, which covers NHS Ayrshire and Arran, NHS Forth Valley, NHS Greater Glasgow & Clyde and NHS Lanarkshire). No questionnaires were distributed within North of Scotland Cancer Network (NOSCAN, which incorporates NHS Tayside, NHS Highland, NHS Grampian, NHS Western Isles, NHS Orkney and NHS Shetland) due to lack of response from contacts.

A standard letter was written to invite oncology healthcare professionals to complete the questionnaire by logging on to the webpage assigned within "Survey Monkey" that, in turn, allowed collation of responses. A copy of this letter can be seen in Appendix 18. This letter was sent via e-mail, either by the researcher directly (for those e-mail addresses that had been provided by Scottish Oncology Pharmacy Group contacts) or indirectly by an appointed contact person (for onward circulation within their local teams).

A response was requested within three weeks of sending the e-mail. If a reply was not received within 3 weeks a reminder e-mail was sent. After 6 weeks the questionnaire was closed.

4.2.3. Statistical Analysis

Analysis of the responses to the questionnaire was carried out using Minitab statistical package (Version 15). Descriptive statistics was used to describe the demographics of the oncology healthcare professionals who responded to the questionnaire. Chi-square test was calculated using expected versus observed frequencies for one question within Question 18 and 19 of the questionnaire, all with cell sizes greater than 5. In all other questions there was limited use of this test when comparing responses by oncology healthcare professionals due to the majority of the questions having at least one cell with less than 5. Even for those cells with greater than 5 responses the potential for introducing a Type 1 error bias from performing multiple Chi-square calculations for multiple answers within

each question was considered very great. This is because when more than one test of significance is performed to evaluate a single overall 'Null hypothesis' the probability increases that an apparently significant difference will be found due to only random sampling variation when there really is no difference (126). Although the probability of a type 1 error is held at $p \leq 0.05$ for individual tests of significance, when multiple tests are used to evaluate the same hypothesis, the overall type 1 error rate accumulates to an unacceptably high level (126).

Binary Logistic Regression was used to determine if any association between covariant and the decision to submit a Yellow Card report from scenarios given in question 13 of the questionnaire. Binary (or binomial) logistic regression is a form of regression which is used when the dependent variable is a dichotomy and the independent variables are of any type (127). Logistic regression can be used to predict a dependent variable on the basis of continuous and/or categorical independents and to determine the percent of variance in the dependent variable explained by the independents; to rank the relative importance of independents; to assess interaction effects; and to understand the impact of covariate control variables. The impact of predictor variables is usually expressed in terms of odds ratios and the 95% confidence interval (127).

4.2.4. Ethics

An e-mail with a copy of the protocol and a flowchart (appendix 19) was sent to the research ethical approval body, A-Rec, to enquire whether ethics approval was required for the one-to-one interviews or the survey questionnaire. A response was received confirming that an ethics application was not required for either process (see appendix 20).

4.3. Analysis of results

4.3.1. Development of questionnaire

4.3.1.1. Semi-structured, one-to-one, in-depth interviews

A summary of the answers for all twelve standardised questions that the interviewees were asked is provided below. In addition, a summary of any other comments made by the interviewees are detailed.

Are you familiar with the Yellow Card scheme for spontaneous reporting of ADRs? How does it work?

All interviewees reported that they were aware of the Yellow Card scheme. Six of the subjects interviewed appeared to know how the scheme is designed to operate, although there was some confusion with the Green Card Reporting scheme (the UK system for reporting any incidents of extravasation with parenteral medicines (128) among nurses. Some gave details of how the scheme operated in their own workplace, rather than describing the general underlying principles. Four of the six subjects interviewed were aware that an electronic system of reporting is available, but no-one used it.

When asked who can use the scheme to report an ADR there was uncertainty among participants. All but one suggested that doctors, nurses and pharmacists can do this, and two added that perhaps patients can also do so.

In relation to the criteria for reporting an ADR, interviewees' knowledge was variable. Nurses, generally, were unaware of the criteria; pharmacists showed awareness although one believed that the criteria for reporting are different in oncology. One doctor demonstrated knowledge of the criteria while the other did not. Both pharmacists and one doctor mentioned newly licensed drugs listed with a black triangle in the BNF as one of the criteria, and three of the six interviewees suggested that 'serious' ADRs should be reported.

No interviewee was aware of any areas of specific interest, and both nurses suggested that they were confused about the difference between a side-effect and an ADR.

Some illustrative quotations:

- 'I am aware that there is a scheme for reporting adverse drug reactions'
- 'You fill in a yellow card and send it off if you suspect something is an ADR'
- 'In practice here if the patient comes into the ward they fill it in and send it down to us….'
- 'Nurses who are treating patients should complete the details (of an ADR) and pass it to pharmacy, who send it away and then you get a reply back'
- 'Nurses, doctors and pharmacists I presume [can use the scheme]. I presume there is some kind of mechanism for patients to report ADRs but I'm not sure.'

- ‘Anything that is supposedly a rare side effect of the drug [can be reported], or if it is a black triangle drug in the BNF’
- ‘Any type of ADR [can be reported] because you’re interested in whatever drugs are doing to the majority of patients.’
- ‘…apart from in oncology, when I have worked as a clinical pharmacist I tended to report anything that was very rare or a side effect that is not often seen…..’
- ‘..I know that with some chemotherapy drugs…one of the known side effects of that is actually anaphylaxis but I wouldn’t class that as an adverse drug reaction if you see what I mean…’
- ‘…you see so many you think of it more as a recognised side effect rather than as an ADR. It probably is an ADR as much as it is a side effect though, isn’t it?’

What purpose do you think this scheme serves?

All participants indicated that the scheme gathers information and four suggested that it serves to identify potentially serious ADRs that may be too rare to show up in clinical trials. Two interviewees mentioned that the scheme serves to increase safety of medicines; one suggested that it can help to show up differences between patient groups in their reaction to drugs; and one mentioned that it detects drugs that are not safe for use and should be withdrawn. No interviewee mentioned that the purpose of the Yellow Card scheme was to help protect patients.

Some illustrative quotations:

- ‘So at least you can get some information on the drug when it is actually being used in the population since previously to that it will have been used in a small select population in trials..’
- ‘I think there are certain drugs where ADRs tend to be serious but not common enough to be picked up in clinical trials…and separate to that there are drug interactions which might not be seen in clinical trials’
- ‘…build up a better safety profile of the drug.’
- ‘It is to get information on safety of using the drugs…’
- ‘If a reaction were happening all over the country…that maybe the drug wasn’t safe… whether it should be withdrawn’

- '…you do see different reactions in different groups of patients. So different ethnic groups can have different reactions to different groups of drugs; depending upon their background'

Do you think it is beneficial to public safety?

All interviewees agreed that the scheme is beneficial or potentially beneficial to public safety. Supporting comments included that the scheme monitors drug problems, gives a fuller picture, and can detect unexpected ADRs. Only one interviewee noted that the scheme aids in detecting drug interactions. Three interviewees qualified their answer: one pointed out that the system depends on an adverse effect being recognised; one suggested that it is important to distinguish between established side effects and ADRs; and the third emphasised that the healthcare professionals need to take the scheme seriously and to report anything that might be an ADR. Two people, however, added that there is no benefit of collecting ADRs that are already known or suspected in oncology.

Some illustrative quotations:

- 'Oh yes…because we're keeping a close eye on the drugs.'
- 'It can be helpful…the difficulty with the scheme is that it relies on someone considering something an adverse effect.'
- 'Yes, I'm sure it is. I know on several occasions drugs that have had new or unexpected side effects have been detected through the system.
- 'If people are a bit complacent about it then you won't get the details that you need from the report.'
- '…drug interactions which might not well been seen in clinical trials. Often patients in clinical trials are pre-selected for limited co-morbidity and therefore limited concomitant medications.'
- '…we already know that is an established side effect and I think that we should rather be filling in yellow cards for patients with unexpected…'
- 'There is a great danger of being swamped with expected toxicities particularly for oncology drugs where if we reported every expected event we see.'

Have you ever reported a suspected ADR via the Yellow Card scheme? Was it easy to do? Any suggestions for improvements?

All pharmacists and doctors interviewed reported that they had used the Yellow Card scheme, and it was regarded as being easy to use. Neither of the nurses had reported previously via the Yellow Card scheme. For suggested improvements to the Yellow Card scheme, one interviewee felt that the scheme should be restricted to unexpected events that have not been described in the Summary of Product Characteristics (SPC) that is required as part of marketing authorization; while two others felt that there was inadequate space to write on the paper card. Some illustrative quotations:

- 'In my view it should be restricted to those events that are unexpected …[this] might focus the system on identifying those rare events that only become evident in the post-marketing phase when large numbers are exposed.'
- '…the space to record the drug at the top, especially if chemotherapy regimen, there are often not enough lines….and also the drug history, the concurrent drug therapy section is fairly small…'
- 'I think the card is quite congested'

Have you ever reported an oncology-related ADR via the Yellow Card scheme? What types would you report?

All of the pharmacists and doctors, but the neither of the nurses, interviewed said that they had reported oncology-related ADRs.

The types of ADR that interviewees specifically mentioned that they would report were:

- Problems with IV antibiotics
- Problems with Morphine
- Problems with Steroids
- Skin eruptions
- Hypersensitivities to paclitaxol and herceptin (trastuzumab)
- Laryngeal spasms with oxalaplatins
- Hand and foot reactions with capecitabine. This is also known as acral erythema, palmoplantar erythema, or Burgdorf reaction, which is a swelling and numbness of the hands and feet**.** The patient first experiences tingling and/or numbness of the palms and soles that evolves into painful, symmetric, and well-demarcated swelling and red plaques. This is followed by peeling of the skin and resolution of the symptoms (129).

- Diarrhoea with capecitabine
- Hepatic problems
- Renal failure
- Osteonecrosis of the jaw
- Significant GI symptoms
- Severe respiratory reactions
- Neutropenic sepsis
- Grade 4 stomatitis

The interviewees were given a list of ADRs and asked whether they think they should be reported. A summary of these responses can be seen below:

- **Neutropenic sepsis** Two said that they would report, two said no, and two replied that they would not if this were an expected side effect of the particular drug.
- **Grade 4 stomatitis** Four replied that they would report, one said sometimes, and one said no.
- **Grade 2 thrombocytopenia** None of the interviewees said that they would report this.
- **DVT or PE** Three people said that they would report if they though this was caused by the drug rather than the condition. Three thought that they would not.
- **Anaphylaxis post chemo infusion** Three interviewees said yes, two said only if it was an unexpected side effect, and one replied that it would depend on the severity.

Some illustrative quotations given by the interviewees:

- '…we do see quite a lot so it becomes second nature to staff, and there is a protocol in place to follow….It is kind of almost expecting it and pre-empting it.'
- 'I probably wouldn't report that as an ADR because especially in oncology it's more likely to be related to the malignancy than rather than an actual drug.'
- 'Depends upon what the drug is. So if it's a chemotherapy drug that has been on the market for a while and it's in the datasheet as a side effect that's well reported, then no.'

- ‘if we are filling in one (yellow card) for every neutropenic patient who comes in to oncology, we already know that is an established side effect and I think that we should rather be filling in yellow cards for patients maybe have deceased from neutropenic sepsis or something like that as opposed to every single patient who have had neutropenia with chemotherapy.’
- ‘Neutropenic sepsis - Depends upon what the drug is. .. so if it is a chemotherapy drug that has been on the market for a while and it is in the datasheet as a side effect that is well reported then no. But if I had someone on imatinib admitted to hospital with neutropenic sepsis then I would because my impression is that neutropenic sepsis is not an anticipated side effect’

Are oncology ADRs underreported in your opinion?

Five of those interviewed felt that oncology ADRs are probably underreported, while one person did not. Some illustrative quotations:

- ‘I know for neutropenic sepsis we are all told to fill out yellow cards….with the newer drugs. I think we are more aware of side effects expected and they are all black triangle so we know to report anything serious…’
- ‘You know we see a lot of the same things; we see dozens of ADRs with taxanes in a month so I suppose we become a bit used to it and don’t see it as an ADR.’
- ‘I don’t know if there should be certain guidelines there that should be telling about chemotherapy ADRs, which ones we should be highlighting on the yellow card.’

Would more specific guidance from the MHRA on the types and grades of oncology and adverse events (toxicities) to be reported help you in recognising what types of oncology ADRs to report?

Every subject interviewed agreed that more guidance from the MHRA would encourage people to use the Yellow Card scheme. Some illustrative quotations given by interviewees:

- ‘I think that would absolutely be beneficial. I think it would be good across Scotland to actually ensure that everyone was doing the same thing.’
- ‘Maybe if we knew what they wanted’

- ‘Yes, particularly if it was more focused and more targeted. In other words we weren’t expected to report every event we have already described to our patients as an expected event.’
- ‘Yes, probably if you are given more specific guidelines it raises your awareness and you’re more likely to do that.’
- ‘I think it is quite good just now but I think that if we had more guidance we would probably pick up things we are not reporting that should be reported from an education point of view.’

There is a separate reporting scheme for HIV ADRs. Do you think there would be any advantage of having a separate one for oncology ADRs?

Three interviewees answered that there would be no advantage, while three thought that there might be. Some illustrative quotations given:

- ‘I think that all drugs should go through the same regulatory reporting mechanism.
- ‘It seems to me the major issue is that many of the oncology drugs are being exposed to say four or five thousand patients before they come to the market but they need to be exposed to tens of thousands of patients before the rarer…events are detected.’
- ‘I think it probably would be useful to know how common a specific ADR is...’
- ‘I suppose you would want to know side effects of new drugs on the market…a lot of these [oncology] drugs are still being used on a trial basis so [side effects] are reported through the trials so they probably don’t reach the MHRA.’

Have you reported NCI common toxicity grades to industry via sponsored trials or via EUDRACT? What is the purpose/benefit of this? Would a continuation of such intensive monitoring be beneficial?

Four subjects said that they had had some level of involvement in trials. Sponsored trials and the European Clinical Trials Database (EUDRACT) were seen to provide valuable information on the frequency of common events and latent effects and to build a bigger picture on cost implications and patient safety to aid prescribing decisions. They were also thought to provide a means of comparing treatments. Some illustrative quotations given:

- ‘I think it gives you an idea of what to expect…and what monitoring is required.’

- ‘You can see more side effects and build up the bigger picture...’
- ‘...if you’re comparing treatments of relatively similar efficacy... then the toxicity profile might be important.’

In general, participants acknowledged the value of intensive monitoring during the clinical trial period but recognised that there are logistical problems about continuing at such a level post-marketing. The time of staff and patients is a factor, and some felt that most side effects would have been identified during the trials. Some illustrative quotations:

- ‘A drug that is … in everyday use… has been through all these trials and will hopefully have ironed out the problems.’
- ‘I think probably in the climate at work we wouldn’t have the time…’
- ‘...time issues about it, and who would follow it up, whose responsibility would it be?’
- ‘I think that once the trial has run for a year and a half ...you already have that experience of use with the drug…’
- ‘Often clinical trials are not robust enough to give us the information but you can’t monitor all drugs like that forever.

Do you think electronic prescribing and capture of NCI toxicity grades in clinical practice would be beneficial?

All of those interviewed replied that electronic prescribing and recording of NCI toxicity grades would be beneficial; five people appeared to be wholly positive about this idea, suggesting that it could reduce variability in interpreting the criteria, lessen the chance of missing a toxicity, collate data and allow easier access to it, and avoid the problem of missing case notes. One interviewee qualified their comments with concerns that such a system would cause an increased workload, and also that there would be a serious problem if the electronic system crashed. Some illustrative quotations given:

- ‘An electronic system would have the possibility of a pop-up flag to remind you of what each grade means.’
- ‘Ideally we would have an electronic prescribing system that would link in with pharmacy…and the whole record would be there.’

- ‘I think we’ll have to do the paper recording and the electronic recording, it will be double the work. [And] what will it be like when [the computer system] goes down!’

Would a nationwide anonymised aggregate of these data be of benefit?

Potential benefits of aggregated data were suggested as monitoring toxicities, gathering national data and identifying trends, and helping doctors decide what drug to use. All 6 interviewees said that they would be willing to contribute data to such a database, although two were concerned that this might increase the workload. Most people thought that it would be feasible to develop such a database in Scotland, but it was pointed out that this would need to be resourced adequately. Some illustrative quotations given included:

- ‘For newer drugs it would be quite good to, across the UK say, be able to see what has been experienced elsewhere and build up a more complete picture’
- ‘I think we already have a programme for filling in near misses and incidents. So you are filling in that and you’re filling in the patient’s notes and you have to do a yellow card, it is a lot of paperwork plus your care plan.’
- ‘[It] would be an advantage of electronic prescribing when it can be linked directly to the capture of data nationwide, on deaths for example or major morbid events; because I think we do not know that kind of data.’
- [To develop such a database in Scotland] is absolutely essential to the future in my view…at present in general we have poor follow-up data on our patients…’
- ‘..I suspect we are already halfway there.’
- ‘..People with the worst toxicities do not attend for any more chemo... so there could be gaps in the dataset. And they don’t always come back to oncology either so the gaps will be with the patients with the most problems…’

Do you think that patient reporting of ADRs in oncology would be of any value?

Five of the interviewees were generally fairly positive about the idea of patient reporting of ADRs. One disagreed, seeing it as a problem that patients are not trained to identify ADRs; other reservations expressed were whether the quality of the data might vary and whether patients would under-report. Some illustrative quotations given by interviewees:

- ‘I suspect that three-quarters of patients could quite easily input data directly themselves, and we would get it much more frequently. But the concern… is what to do with the patients with toxicities who have not contacted you.’
- ‘… there will always be some groups of patients who will be more willing to report than others.’
- ‘…the problem might be grading. …they are not trained people …and accuracy is even difficult with trained staff.’
- ‘…they would also need to be educated and not to report, you know, nausea for example, it’s not a severe adverse effect.’
- ‘I think patients tend to downplay things.’

4.3.1.2. Feedback from Post Interview Comment Sheets

All six healthcare professionals that were interviewed returned the Post Interview Comment Sheet (100% response rate). The interviewees were asked to respond to nine questions with either ‘strongly agree’, ‘agree’, ‘undecided’, ‘disagree’ or ‘strongly disagree’. All were in agreement that:

- The interview went well
- The interview finished within 30 minutes
- They felt at ease with the interviewer and could express their opinions freely on posed questions
- The interviewer gave them adequate time to answers questions
- The interviews took place in a room free from disruptions or distractions
- They enjoyed the interview and felt it was worthwhile.

There was only one question that there was a difference in the response from all interviewees. This question asked ‘Were there any questions you were asked that you did not understand?’. Four of the six (67%) interviewees disagreed. However one interviewee agreed stating that there were a few points that had to be clarified, and one interviewee was undecided. These two interviewees were nurses.

Some additional comments received included:

- Good project

- Good to get some background on the whole Yellow Card scheme and where it is going for future developments

4.3.1.3. Selection of themes/questions for use in survey questionnaire

The themes or items that were selected for inclusion in the questionnaire were coded with a lettering sequence from 'A to Z and AA to FF'. This gave a total of 32 items from the interviews that were incorporated into questions within the questionnaire. This corresponding coding can be seen on the Coding of Analysis of Semi-structured Interview for Use in Questionnaire Document (appendix 21) and the Draft Questionnaire Document (appendix 22).

These items covered the following themes and items:

a) Reporting behaviour
    i. Examples of adverse events they may or may not consider reporting
b) Reporter knowledge
    i. Pharmacovigilance terminology
    ii. Purpose of the Yellow Card scheme
c) Reporter attitudes and opinions
    i. Which types of oncology ADRs should be reported
    ii. Reasons for not reporting
    iii. How oncology ADR reporting can possibly be improved via the Yellow Card scheme
    iv. How electronic recording of adverse event criteria might benefit monitoring of oncology adverse events in Scotland
    v. The possible benefit of patient reporting of ADRs in oncology

These items were then transformed into closed questions for inclusion in the draft questionnaire.

The final draft questionnaire tested in a pilot contained 19 questions (Appendix 23), with one filter question (if they answered that they had never completed a Yellow Card Report previously then it skipped the participant from question 7 to question 11 since questions 8 to 10 were specific to their Yellow Card reporting experience and preferences). These questions dealt with demographics of sample population, ADR reporting behaviour,

knowledge of oncology adverse events, knowledge of the Yellow Card scheme, opinions and attitudes on Yellow Card reporting of oncology ADRs, opinions on patient reporting of ADRs in oncology, and opinions on electronic capture of Common Terminology of Cancer Adverse Events.

4.3.2. Pilot of questionnaire

The 10 pharmacists to whom the questionnaire was sent in the pilot study said that it took between 10 to 15 minutes to complete the questionnaire. The questionnaire was seen by the pharmacists to be easy to understand and complete, for even those without any prior oncology background. The following suggestions for change were made:

- Insert 'direct' into question 4 to make question clearer (i.e. How much of your job is devoted to direct patient care in oncology) since one of the pharmacist said that other wise the definition of patient care would be open to interpretation.
- One spelling error on a medicine's name in one question 13.
- Rephrasing of question 14 to make clearer that a response was required for each statement given below in the question.
- Spell out total name for acronym NCI CTCAE in question 19

These changes were made to the questionnaire within the "Survey Monkey" tool and it was ready for distribution.

4.3.3. Survey questionnaire

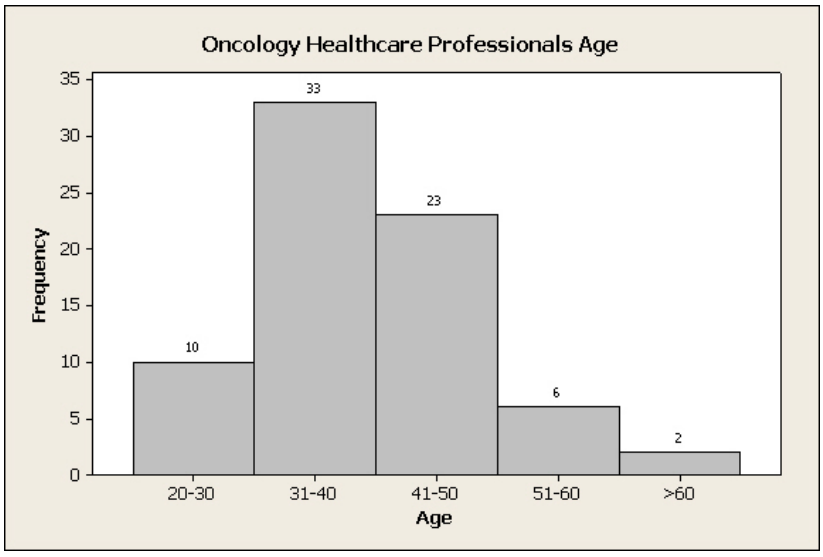
4.3.3.1.Demographics

150 invitations to respond to the questionnaire were extended, a total of 75 responses were received (50% response rate). Table 4.1 summarises the demographics of the oncology healthcare professionals from within Scotland from whom responses were received. Figures 4.1, 4.2, 4.3, 4.4, 4.5 and 4.6 further illustrate the distribution and central tendency of these variables in the sampled population for the healthcare professional groups.

Table 4.1. Comparison of demographics of oncology healthcare professionals who replied to questionnaire

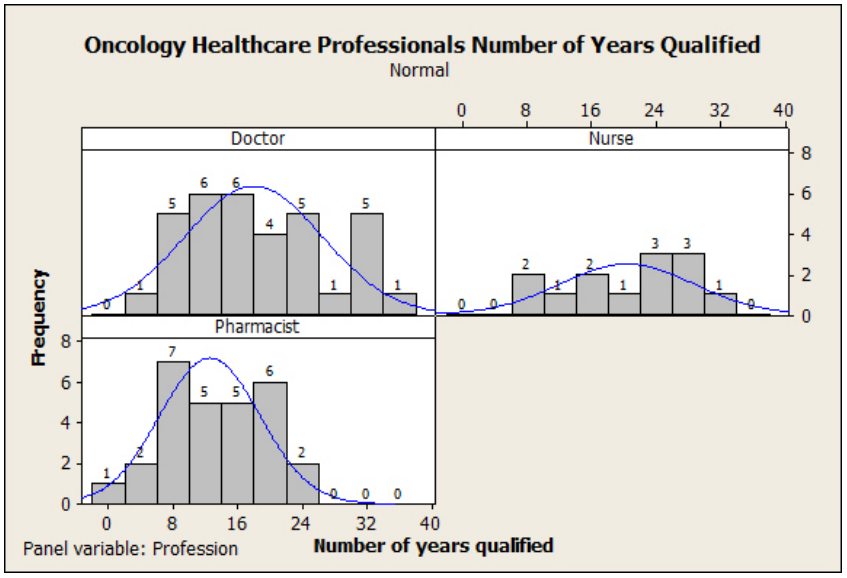
	Doctor	Pharmacist	Nurse
Returned Questionnaire (% response totals)	34 (45%)	28 (37%)	13 (17%)
Gender Ratio M:F	1:1	1:5	0:1
Age (%)			
20-30	2 (6%)	6 (21%)	2 (15%)
31-40	16 (48%)	14 (50%)	3 (23%)
41-50	9 (27%)	8 (29%)	6 (46%)
51-60	4 (12%)	0	2 (15%)
>60	2 (6%)	0	0
Median number of years qualified	17	12	28
Median number of years working in oncology	12	5	15
Percentage time devoted to direct patient care in oncology			
<25%	3 (9%)	3 (11%)	1 (8%)
25-50%	0	7 (25%)	1 (8%)
51-75%	7 (21%)	5 (18%)	4 (30%)
>75%	24 (70%)	13 (46%)	7 (54%)

Figure 4.1. Histogram of age ranges for oncology Healthcare professionals



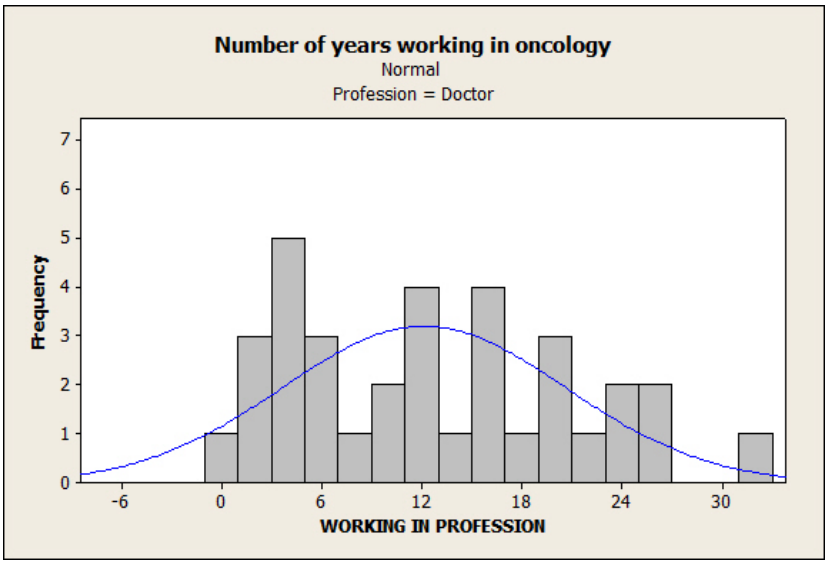
The mode for age of the healthcare professional was 31-40, with a range from 20 to >60.

Figure 4.2. Histogram of number of years qualified for each healthcare professional group.



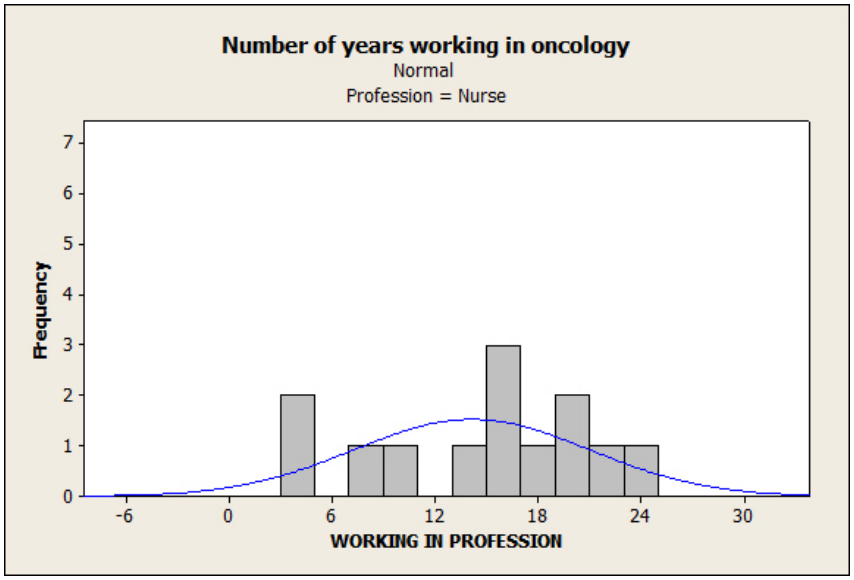
The median number of years qualified for doctors was 17 with an IQR of 13; the median number of years qualified for nurses was 28 with an IQR of 15; and the median number of years qualified for pharmacists was 12 with an IQR of 10.

Figure 4.3. Histogram of number of years working in oncology for doctors.



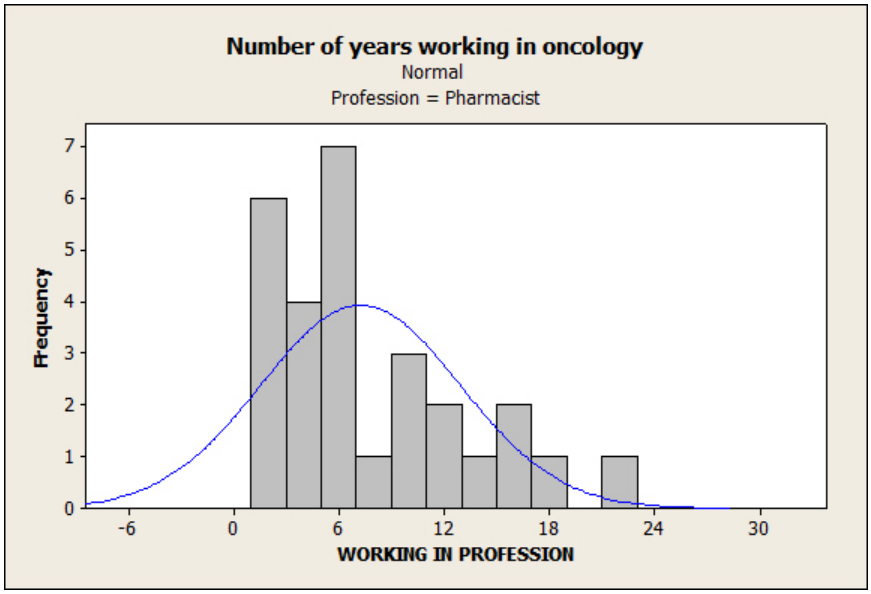
The median number of years working in oncology for doctors was 12, with an interquartile range of 16.

Figure 4.4. Histogram of number of years working in oncology for nurses.



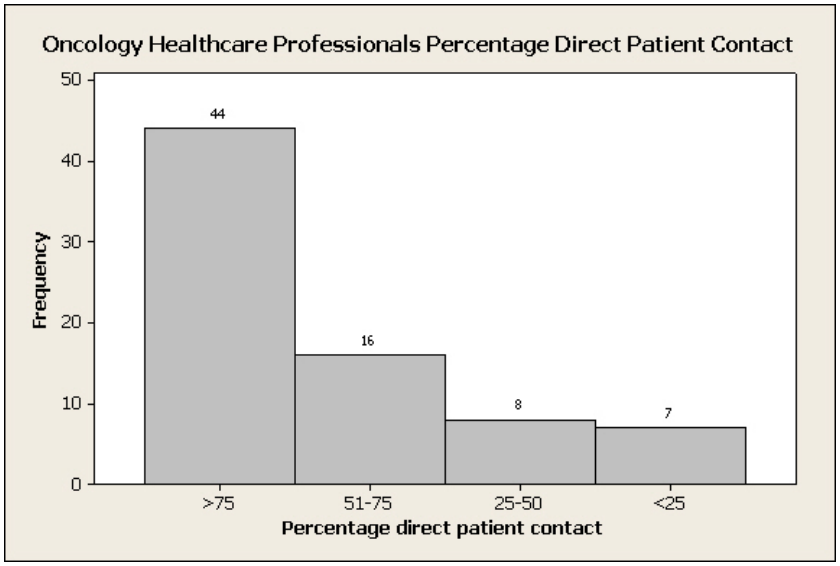
The median number of years working in oncology for nurses was 15, with an interquartile range of 12.

Figure 4.5. Histogram of number of years working in oncology for pharmacists.



The median number of years working in oncology for pharmacists was 5, with an interquartile range of 8.5.

Figure 4.6. Histogram of direct patient contact for all oncology Healthcare professionals.



The mode for direct patient contact for all the healthcare professionals was >75%, with a range of <25 to >75.

4.3.3.2.Reporting Behaviour

Respondents were asked how many times, if ever they had completed a Yellow Card during their career; and how many of these reports were in oncology. 19 (26%) of the studied oncology healthcare professionals had never completed a Yellow Card report with nurses accounting for 8 (44%) of this group. The majority of oncology healthcare professionals, comprising of 43 (59%) of the respondents, had submitted between 1 and 10 Yellow Card reports during their career. Only 11 (15%) of the oncology healthcare professionals reported more than 10 reports. Table 4.2 shows the number of Yellow Card reports completed during their career by the healthcare profession.

Table 4.2. Comparison of oncology Healthcare Professionals who completed a Yellow Card report during their career

Completed a Yellow Card Report	Doctor (n=33)	Pharmacist (n=27)	Nurse (n=13)
Never	9 (27%)	2 (7%)	8 (62%)
1-5 times	13 (39%)	15 (56%)	4 (33%)
6-10 times	6 (18%)	4 (15%)	1 (8%)
11-20 times	1 (3%)	3 (11%)	0
>20 times	4 (12%)	3 (11%)	0

Of the oncology healthcare professionals that had previously completed a Yellow Card report, 8 (15%) of the respondents (7 doctors, 1 pharmacist) indicated that none of the reports had been for oncology related adverse drug reactions or patients. None of the nurses had completed ADR reports for anything other than oncology.

Of those reporters who had previously reported 26 (48%) did not have any strong preference for reporting method (paper or electronic). 16 (30%) said they preferred to complete Yellow Cards electronically, some reasons they gave for this preference are:

- can be stored easily
- more confidential
- easier to access
- do not have to remember to post

The group who preferred to submit Yellow Card reports electronically comprised 10/25 (40%) of the pharmacists, 5/24 (21%) of the doctors and 1/5 (20%) of the nurses.

12 (22%) of reporters preferred paper Yellow Cards, some reasons they gave for this preference are:

- easier to find and complete
- easier to attach additional information (for example laboratory test results)
- when completing on the ward access to a computer can be a problem
- electronic completion takes longer
- Habit/familiarity since only have used paper Yellow Cards

The group who preferred to submit paper Yellow Card reports comprised 6/25 (24%) of the pharmacists, 5/24 (21%) of the doctors and 1/5 (20%) of the nurses.

The area of preference in which the oncology healthcare professionals normally completed the Yellow Card reports included the office (n=21, 40%), the pharmacy department (n=16, 30%), the ward area (n=10, 19%), the outpatient area (n=3, 6%), or near clinical area (n=3, 5%). 15/23 (65%) of the doctors completed them in their office; 13/25 (52%) of the pharmacists completed them in the pharmacy department; and 2/5 (40%) of the nurses completed the Yellow Cards in the outpatient area.

4.3.3.3. Deterrents to Yellow Card Reporting

The oncology healthcare professionals were asked to specify if any of a set of five statements applied to them regarding Yellow Card reporting. 30 (41%) of the respondents identified that they often recognised ADRs in patients receiving cytotoxic chemotherapy

but choose not to report believing that they are an inevitable consequence of therapy and little relevance for reporting; 23 (32%) replied that they had seen ADRs in clinical oncology practice but were not sure which ones the MHRA wanted them to report; 10 (14%) had completed a Yellow Card report for a suspected ADR but did not send it; 7 (10%) had wanted to report an ADR but could not find a Yellow Card; and 4 (6%) had wanted to report an ADR but was unable to gain access to the electronic Yellow Card. In contrast 33 (45%) of the respondents replied that none of the statements applied to them. Table 4.3 summarises the responses to these statements by healthcare professional group.

Table 4.3. Deterrents to reporting via the Yellow Card scheme by oncology healthcare professionals

	Doctor n=33	**Pharmacist** n= 27	**Nurse** n= 13
I have wanted to report an ADR but was unable to find a yellow card	5 (15%)	1 (4%)	1 (8%)
I have wanted to report an ADR but was unable to obtain access to the electronic Yellow Card	1 (3%)	3 (11%)	0
I have seen ADRs in clinical oncology practice but I am not sure which ones the MHRA want me to report	11 (33%)	11 (41%)	1 (8%)
I have completed a Yellow Card for an ADR but did not send it	4 (12%)	6 (22%)	0
I often recognise ADRs in patients receiving chemotherapy but choose not to report believing that they are inevitable consequence of therapy and little relevance for reporting	14 (42%)	16 (59%)	0
None of the above	14 (42%)	8 (30%)	11 (85%)

4.3.3.4.Perception

One of the questions asked in th**e** questionnaire was designed to understand the oncology healthcare professionals' perception of what proportion of their patients experience an adverse event (toxicity); and what proportion of their patients have serious adverse event (toxicity). The majority of the respondents (n=29, 43%) estimated that greater than 75% of their oncology patients receiving chemotherapy experienced any kind of adverse event during treatment; 27% (n=18) estimated less than 75%; 13% (n=9) estimated less than 50%; 7.5% (n=5) estimated less than 25%, and 9% (n=6) estimated less than 10%. However 69% (n=46) the respondents estimated that less than 10% of the patients experienced a serious adverse event during treatment with 15% (n=10) of these

estimating that less than 1% of their patients actually experienced a serious adverse event during cytotoxic chemotherapy. Another 22% (n=15) estimated that less than 25% of the patients experienced a serious adverse event during treatment; and 9% (n=6) estimated that less than 50%. None of the respondents thought that more than 50% of the patients experienced serious adverse events during treatment with cytotoxic chemotherapy.

The responses by individual health care profession to this question can be seen in Table 4.4 and Table 4.5.

Table 4.4. Estimate of proportion of oncology patients who experience any adverse events during treatment with chemotherapy.

Estimate of percentage of patients who experience any type of adverse event	**Doctor** N=30	**Pharmacist** n= 26	**Nurse** n= 11
>75%	12 (40%)	12 (46%)	5 (45%)
<75%	11 (37%)	4 (15%)	3 (27%)
<50%	3 (10%)	5 (19%)	1 (9%)
<25%	2 (7%)	2 (8%)	1 (9%)
<10%	2 (7%)	3 (12%)	1 (9%)
<5%	0	0	0
<1%	0	0	0

Table 4.5. Estimate of proportion of oncology patients who experience serious adverse events during treatment with chemotherapy.

Estimate of percentage of patients who experience serious 'toxicity'	Doctor n=30	Pharmacist n= 26	Nurse n= 11
>75%	0	0	0
<75%	0	0	0
<50%	3 (10%)	3 (12%)	0
<25%	6 (20%)	8 (31%)	1 (9%)
<10%	12 (40%)	4 (15%)	4 (36%)
<5%	7 (23%)	6 (23%)	3 (27%)
<1%	2 (7%)	5 (19%)	3 (27%)

4.3.3.5.Reporting Knowledge

4.3.3.5.1. Criteria for submitting Yellow Card reports

One of the questions was designed to evaluate the respondents' knowledge of what oncology ADRs they would report in everyday practice. The questions were chosen to ensure that all reporting scenarios were covered (see Appendix 24 for the matrix, corresponding question and the desired answer by Yellow Card reporting criteria). The questionnaire asked for responses of 'yes', 'not sure' or 'no' to the questions. A summary table of the responses for all of the oncology healthcare professionals can be seen in Table 4.6.

Table 4.6. Summary of responses from oncology healthcare professionals to questions on what they would report

	Oncology healthcare professionals that would report		
Criteria of Questions	**Yes**	**Not Sure**	**No**
Black triangle status Serious Known side effect of medicine CTCAE Grade 1-2	15 (22%)	14 (21%)	38 (57%)
Black triangle status Not serious Known side effect of medicine CTCAE Grade 1-2	23 (34%)	20 (30%)	24 (36%)
Black triangle status Serious Not a known side effect of medicine CTCAE Grade 3-4	48 (73%)	17 (26%)	1 (2%)
Black triangle and non-black triangle combination Not serious Known side effect of medicine(s)	0	8 (12%)	59 (88%)
Black triangle status Serious Known side effect of medicine CTCAE Grade 3-4	14 (21%)	16 (24%)	36 (55%)
Black triangle status Serious Not a known side effect of medicine CTCAE Grade 1-2	25 (37%)	18 (27%)	24 (36%)
Black triangle status Not serious Not a known side effect of medicine CTCAE Grade 3-4	18 (27%)	31 (46%)	18 (27%)
Non-black triangle status Serious Known side effect of medicine Grade 1-2	13 (19%)	11 (16%)	43 (64%)
Black triangle status Not serious Known side effect of medicine CTCAE Grade 3-4	5 (8%)	10 (15%)	51 (77%)

Table 4.6 continued.
Summary of responses from oncology healthcare professionals to questions on what they would report

	Oncology healthcare professionals that would report		
Criteria of Questions	**Yes**	**Not Sure**	**No**
Non-black triangle status Not serious Known side effect of medicine Grade 1-2	1 (1%)	7 (11%)	58 (88%)
Non-black triangle status Serious Not a known side effect of medicine Grade 1-2	12 (18%)	20 (30%)	35 (52%)
Non-black triangle status Serious Known side effect of medicine Grade 3-4	17 (25%)	16 (24%)	34 (51%)
Non-black triangle status Not serious Known side effect of medicine Grade 3-4	3 (5%)	9 (13%)	55 (82%)
Non-black triangle status Serious Not known side effect of medicine Grade 3-4	40 (60%)	12 (18%)	15 (22%)
Non-black triangle status Not serious Not known side effect of medicine Grade 3-4	5 (8%)	22 (33%)	39 (59%)

The classification of 'serious' is as per the MHRA criteria [10]; and 'known' encompasses any side effects of a medicines currently listed on the Summary of Product Characteristics (SPC).

Of the answers received only 5 of the 17 questions (29%) received a correct response from the majority of the oncology healthcare professionals. A summary table of the percentage correct answers as per Yellow Card reporting criteria for each individual oncology healthcare professional group can be seen in Table 4.7. If respondents answered 'not sure' then it was considered to be an incorrect response.

Table 4.7. Summary of correct answers (as per Yellow Card reporting criteria) to questions for each individual oncology healthcare professional group

	Number (percentage) of each healthcare professional group who gave correct answer (as per Yellow Card criteria)		
Criteria of Questions	**Doctor**	**Pharmacist**	**Nurse**
Black triangle status Serious Known side effect of medicine CTCAE Grade 1-2	4 (13%)	6 (23%)	5 (45%)
Black triangle status Not serious Known side effect of medicine CTCAE Grade 1-2	7 (23%)	10 (39%)	6 (55%)
Black triangle status Serious Not a known side effect of medicine CTCAE Grade 3-4	19 (63%)	21 (84%)	8 (73%)
Black triangle and non-black triangle combination Not serious Known side effect of medicine(s)	0	0	0
Black triangle status Serious Known side effect of medicine CTCAE Grade 3-4	4 (14%)	6 (23%)	4 (36%)
Black triangle status Not serious Known side effect of medicine CTCAE Grade 3-4	0	3 (12%)	2 (18%)
Black triangle status Not serious Not a known side effect of medicine CTCAE Grade 3-4	5 (17%)	11 (42%)	2 (18%)
Non-black triangle status Serious Known side effect of medicine Grade 1-2	5 (17%)	1 (4%)	7 (64%)

Table 4.7 continued.
Summary of correct answers (as per Yellow Card reporting criteria) to questions for each individual oncology healthcare professional group

	Number (percentage) of each healthcare professional group who gave correct answer (as per Yellow Card criteria)		
Criteria of Questions	**Doctor**	**Pharmacist**	**Nurse**
Non-black triangle status Not serious Known side effect of medicine Grade 1-2	26 (87%)	24 (92%)	8 (80%)
Non-black triangle status Serious Not a known side effect of medicine Grade 1-2	4 (13%)	6 (23%)	2 (18%)
Non-black triangle status Serious Known side effect of medicine Grade 3-4	6 (20%)	8 (31%)	3 (27%)
Non-black triangle status Not serious Known side effect of medicine Grade 3-4	24 (80%)	26 (100%)	5 (45%)
Non-black triangle status Serious Not known side effect of medicine Grade 3-4	16 (53%)	15 (58%)	9 (82%)
Non-black triangle status Not serious Not known side effect of medicine Grade 3-4	21 (72%)	16 (62%)	2 (18%)

Please note that the classification of 'serious' is as per the MHRA criteria [10]; and 'known' encompasses any side effects of a medicines currently listed on the Summary of Product Characteristics.

Binary Logistic Regression was performed on the responses to this question to determine if there was any association between the co-variants and the likelihood of a respondent to submit a Yellow Card report for a given scenario. The co-variants evaluated included the profession, grade of toxicity, seriousness of the reaction, black triangle status or whether the reaction is a known (expected) side effect of a medicine. The odds ratio and the 95% confidence intervals can be seen in Table 4.8.

Table 4.8. The likelihood of profession, grade of toxicity, seriousness of the reaction, black triangle status or whether the reaction is a known (expected) side effect of a medicine to be associated with any increased likelihood to a respondent's decision to submit a Yellow Card report.

Variable	Odds Ratio	95% Confidence Interval
Doctor	1.00	
Pharmacist	3.79	2.73-5.28
Nurse	0.50	0.27-0.92
Grade 1-2	1.00	
Grade 3-4	1.01	0.73-1.40
Black triangle	1.00	
non-black triangle	1.04	0.76-1.41
Non-serious	1.00	
Serious	1.01	0.73-1.40
Known side effect	1.00	
Unknown side effect	0.99	0.72-1.37

The only co-variant that showed an increased likelihood for reporting was profession, with pharmacists being over three and a half times more likely to report than doctors and nurses half as likely as doctors to report.

4.3.3.5.2. Roles of the Yellow Card scheme

One of the questions posed in the questionnaire sought opinions from the oncology healthcare professionals on roles of the Yellow Card scheme from a list of six possible roles. The respondents were asked to answer 'yes, not sure or no' in response to the proposed roles. 89% (n=59) of the respondents agreed that one of the roles was to ensure public safety; 97% (n=65) agreed that one of the roles was to identify potentially serious ADRs that were too rare to be picked up during clinical trials; 81% (n=54) agreed that one of the roles was to identify factors that might predispose to toxicity/ADRs; 75% (n= 49) agreed that one of the roles was to enable ADRs of medicines in similar classes to be compared; 99% (n=65) agreed that one of the roles was to identify any previously unknown reactions to a medicine; and 94% (n=63) agreed that one of the roles was to monitor the safety of the medicines throughout its life. A summary table of the responses by each of the oncology healthcare professionals groups can be seen in Table 4.9 below.

Table 4.9. Summary of oncology healthcare professionals' opinions on the roles of the Yellow Card scheme.

Possible Role	Number (percentage) of oncology healthcare professionals' group that said 'Yes'		
	Doctor	Pharmacist	Nurse
To ensure public safety	27 (93%)	22 (85%)	9 (82%)
To identify potentially serious ADRs that were too rare to be picked up during clinical trials	30 (100%)	25 (96%)	9 (82%)
To identify factors that might predispose to toxicity/ADRs	24 (80%)	21 (81%)	8 (73%)
To enable ADRs of medicines in similar therapeutic classes to be compared	20 (69%)	20 (80%)	8 (73%)
To identify any previously unknown reactions to a medicine (i.e. not listed in the Summary of Product Characteristics of a medicine)	30 (100%)	25 (100%)	9 (82%)
To monitor the safety of a medicine throughout its life	28 (93%)	26 (100%)	8 (73%)

4.3.3.6. Factors which influence an oncology healthcare professionals' decision to make a Yellow Card report

Two questions within the survey were designed to ascertain what, if any, factors influenced an oncology healthcare professionals' decision to complete a Yellow Card report. The first group of questions looked at factors around the ADRs or grades of adverse event; the direct consequences of an ADR; and the relative newness of a medicine and the known side effect profile in oncology. The second group of questions looked at other external factors. In the first set of questions the respondents were asked to reply using 'yes, not sure or no'. In the second set of questions the respondents were asked to reply using a Likert scale of 'Strongly Agree', 'Agree', 'Disagree', 'Strongly Disagree'.

4.3.3.6.1. Types of ADRs/Adverse events, consequences and known oncology side effect profile

Of the factors that were listed in this question, the ones that received the higher level of agreement from all of the respondents that affected their decision to make a Yellow Card report were:

- Seriousness of a reaction - 59 (94%) said 'Yes', 4 (6%) said 'Not sure' and 0% said 'No'.
- Unusual ADRs not normally seen in oncology – 58 (92%) said 'Yes', 5 (8%) said 'Not sure' and 0% said 'No'.
- A newly licensed medicine - 59 (94%) said 'Yes', 2 (3%) said 'Not sure' and 2 (3%) said 'No'.
- ADR not listed as a known side effect in the SPC – 54 (86%) said 'Yes', 6 (10%) said 'Not sure' and 3 (5%) said 'No'.
- Significant drug interactions – 47 (75%) said 'Yes', 10 (16%) said 'Not sure' and 6 (10%) said 'No'.

The factors that received a medium level of agreement from all respondents that contributed to their decision to make a Yellow Card report but 25% or more of the respondents who were 'Not sure' were:

- Patient hospitalised or hospitalisation prolonged because of ADR – 37 (59%) said 'Yes', 18 (29%) said 'Not sure' and 8 (13%) said 'No'.
- Latent drug induced cancers – 37 (59%) said 'Yes', 18 (29%) said 'Not sure' and 8 (13%) said 'No'.
- A new chemotherapy regimen (not necessarily containing a new medicine) – 35 (56%) said 'Yes', 16 (25%) said 'Not sure' and 12 (19%) said 'No'.

The factors that received a higher level of agreement from all respondents that did not contribute to their decision to make a Yellow Card report were:

- Suspension of chemotherapy due to an adverse event – 10 (16%) said 'Yes', 23 (37%) said 'Not sure', and 30 (48%) said 'No'.
- Adverse event resulting in dose delays to chemotherapy – 6 (10%) said 'Yes', 18 (29%) said 'Not sure' and 39 (62%) said 'No'.

The factor where there was a most obvious variable opinion between 'Yes', 'Not Sure' and 'No' was with the grade of adverse event (toxicity), where 20 (32%) said 'Yes', 22 (35%) said 'Not sure and 21 (33%) said 'No'. Of those respondents (n=20) who indicated that grade of adverse event would be a determining factor in their decision to send a Yellow Card report for an oncology ADR, the following are the summary of the CTCAE grade that they would consider reporting:

- Grade 3 and Grade 4 (n=11, 55%)

- Grade 4 only (n=5, 25%)
- Some Grade 3 but mostly Grade 4 (n=2, 10%)
- Unexpected Grade 3 or above (n=1, 5%)
- Grade 2 or above (n=1, 5%)

One respondent also indicated that the decision to make a Yellow Card report based on the factor of grade of CTCAE would be dependant upon what toxicity it was and the expected incidence within oncology.

A summary of the responses on whether the factors types of ADRs/Adverse events, consequences or known oncology side effect profile influence an oncology healthcare professionals' decision to make a Yellow Card report by the oncology healthcare professional groups can be seen below in Table 4.10.

Table 4.10. Summary of responses on whether the factors types of ADRs/Adverse events, consequences or known oncology side effect profile influence an oncology healthcare professionals' decision to make a Yellow Card report by oncology healthcare professional group.

Factor	Response	Number (percentage) of the oncology healthcare professional group		
		Doctor	Pharmacist	Nurse
Seriousness of the reaction	Yes	25 (89%)	25 (100%)	9 (90%)
	Not Sure	3 (11%)	0	1 (10%)
	No	0	0	0
Unusual ADR not normally seen in oncology	Yes	26 (93%)	23 (92%)	9 (90%)
	Not Sure	2 (7%)	2 (8%)	1 (10%)
	No	0	0	0
ADR not listed as a known side effect in the SPC	Yes	25 (89%)	21 (84%)	8 (80%)
	Not Sure	2 (7%)	2 (8%)	2 (20%)
	No	1 (4%)	2 (8%)	0
A newly licensed medicine	Yes	26 (93%)	25 (100%)	8 (80%)
	Not Sure	1 (4%)	0	1 (10%)
	No	1 (4%)	0	1 (10%)
A new combination Chemotherapy regimen (not necessarily containing a new medicine)	Yes	16 (57%)	15 (60%)	4 (40%)
	Not Sure	6 (21%)	6 (24%)	4 (40%)
	No	6 (21%)	4 (16%)	2 (20%)
Patient hospitalised or hospitalisation prolonged because of an ADR	Yes	13 (47%)	18 (72%)	6 (60%)
	Not Sure	8 (29%)	7 (28%)	3 (30%)
	No	7 (25%)	0	1 (10%)
Significant drug interaction	Yes	20 (71%)	20 (80%)	7 (70%)
	Not Sure	5 (18%)	3 (12%)	2 (20%)
	No	3 (11%)	2 (8%)	1 (10%)
Latent drug induced cancers	Yes	17 (61%)	14 (56%)	6 (60%)
	Not Sure	6 (21%)	9 (36%)	3 (30%)
	No	5 (18%)	2 (8%)	10 (10%)
Adverse events resulting in dose delays	Yes	2 (7%)	4 (16%)	0
	Not Sure	6 (21%)	7 (28%)	5 (50%)
	No	20 (71%)	14 (56%)	5 (50%)
A suspension of chemotherapy due to an adverse event (toxicity)	Yes	4 (14%)	5 (20%)	1 (10%)
	Not Sure	8 (29%)	12 (48%)	3 (30%)
	No	16 (57%)	8 (32%)	6 (60%)
Grade of adverse event (toxicity)	Yes	11 (39%)	8 (32%)	1 (10%)
	Not Sure	7 (25%)	11 (44%)	4 (40%)
	No	10 (36%)	6 (24%)	5 (50%)

4.3.3.6.2. Other external factors

Question 16 sought opinions from respondents on possible reasons why oncology healthcare professional do not make Yellow Card reports. The respondents were asked to give their level or agreement or disagreement to 20 statements using a scaled response (strongly agree, agree, disagree or strongly disagree). Of the factors that were listed in this question as possible reasons why healthcare professionals do not make Yellow Card reports, the majority of the respondent oncology healthcare professionals were in disagreement with the following:

- Really serious ADRs are well documented by the time the medicine is marketed so do not see any point in reporting.
- A single report is not enough to add to medical knowledge
- Lack of professional obligation to report
- Feeling of being personally liable for ADR
- The Yellow Card form is too congested
- People prefer to report directly to the pharmaceutical company instead of via the Yellow Card scheme
- Do not know how the information reported in Yellow Cards is utilised
- Fear that if I report an ADR via the Yellow Card I will be badgered to provide more information
- Fear of looking stupid to other members of the patient care team (if they were to see a copy of the report)

Of the factors that were listed in this question as possible reasons why healthcare professionals did not make Yellow Card reports, the majority of the respondent oncology healthcare professionals agreed with the following:

- Not certain of the causality of an ADR with a specific medicine
- Inadequate information sources on ADRs to aid in determining which drug could be causing an ADR
- Not a high priority in everyday clinical practice
- Do not know what types of ADRs that should be reported via the Yellow Card scheme
- Sheer volume of ADRs seen in oncology make it impossible to report them all
- Reporting is too time-consuming

- Do not see benefit in reporting well recognised ADRs which are seen routinely in everyday clinical practice
- Do not view oncology adverse events (toxicities) as an ADR (i.e. expect to see them and know how to prevent them or reduce their severity with pre-medication)
- Lack of specific guidance on the types and grades of oncology ADRs to report via the Yellow Card scheme

Of the factors that were listed in this question as possible reasons why healthcare professionals do not make Yellow Card reports; there was variability between the respondent oncology healthcare professionals with approximately 50% of respondents agreeing and 50% disagreeing with the following:

- Inadequate information sources on ADRs to aid in determining which drug could be causing an ADR
- Lack of feedback on reports received via the Yellow Card scheme
- Lack of adequate access to advice on ADR reporting or the Yellow Card scheme

Table 4.11 shows the agreement with statements given by oncology healthcare professional group.

Table 4.11. Oncology healthcare professionals groups' agreement on possible reasons why healthcare professionals do not make Yellow Card reports.

Possible reasons	Number (percentage) in agreement with statement from each healthcare group		
	Doctor	**Pharmacist**	**Nurse**
Really serious ADRs are well documented by the time the medicine is marketed so do not see any point in reporting	12 (46%) (n=26)	7 (28%) (n=25)	2 (25%) (n=8)
Not certain of the causality of an ADR with a specific medicine	20 (74%) (n=27)	20 (80%) (n=25)	6 (67%) (n=9)
Inadequate information sources on ADRs to aid in determining which drug could be causing an ADR	13 (52%) (n=25)	12 (48%) (n=25)	6 (67%) (n=9)
Not a high priority in everyday clinical practice	15 (58%) (n=26)	13 (52%) (n=25)	5 (56%) (n=9)

Table 4.11 continued. Oncology healthcare professionals groups' agreement on possible reasons why healthcare professionals do not make Yellow Card reports.

Possible reasons	Number (percentage) in agreement with statement from each healthcare group		
	Doctor	Pharmacist	Nurse
Do not know what types of ADRs that should be reported via the Yellow Card scheme	16 (59%) (n=27)	17 (68%) (n=25)	7 (78%) (n=9)
Sheer volume of ADRs seen in oncology make it impossible to report them all	18 (69%) (n=26)	22 (88%) (n=25)	5 (56%) (n=9)
A single report is not enough to add to medical knowledge	3 (11%) (n=27)	2 (8%) (n=25)	1 (11%) (n=9)
Reporting is too time-consuming	13 (48%) (n=27)	18 (75%) (n=24)	4 (44%) (n=9)
Lack of professional obligation to report	6 (22%) (n=27)	8 (32%) (n=25)	2 (22%) (n=9)
Feeling of being personally liable for ADR	3 (11%) (n=27)	1 (4%) (n=25)	0 (n=9)
Do not see benefit in reporting well recognised ADRs which are seen routinely in everyday clinical practice	22 (81%) (n=27)	24 (96%) (n=25)	5 (56%) (n=9)
Do not view oncology adverse events (toxicities) as an ADR (i.e. expect to see them and know how to prevent them or reduce their severity with pre-medication)	20 (74%) (n=27)	23 (92%) (n=25)	6 (67%) (n=9)
Lack of specific guidance on the types and grades of oncology ADRs to report via the Yellow Card scheme	22 (81%) (n=27)	24 (96%) (n=25)	7 (78%) (n=9)

4.3.3.7.Attitudes and opinions on oncology adverse drug reaction reporting

4.3.3.7.1. Under-reporting of oncology ADRs

Question 17 examined the attitudes of the respondent oncology healthcare professionals to under-reporting of ADRs. 92% (n= 56) of the respondents were in agreement that oncology ADRs were under reported, however, only 53% (n=30) were in agreement that the reporting rate for oncology ADRs was not any less than in other clinical areas. It is interesting to note that the 54% (n=13) of the respondent oncology pharmacists were in disagreement that the reporting rate of oncology ADRs is not any less than in other clinical areas; whereas 54% (n=13) oncology doctors and 75% (n=8) nurses were in agreement with this statement.

80% (n= 48) of the respondents were in agreement that a reporting form that took less time to complete might help increase reporting in oncology. These forms could utilise more tick

boxes; less free-format text; pre-populated fields on an electronic report such as patient details, medicines, past medical history, etc.

There were additional comments given in this question as well. These included: I think mandatory completion of a Yellow Card with summaries at the completion of chemotherapy regimens (or death) would help.

- 'Probably do not think about reporting if I know it is an expected adverse event.'
- 'Don't know very much about the Yellow Card scheme – was not aware of its existence.'
- 'I have been waiting for ages for someone to re-evaluate the way the Yellow Card scheme is used! When I started in this hospital, I was very surprised to see that we reported neutropenic sepsis events on Yellow Cards. I feel this is unnecessary as neutropenic sepsis is a well recognised and well documented side effect of chemotherapy. Completing cards for this puts staff off completing for genuine ADRs which occur.'
- 'There is also the issue of the deluge of information which follows after reporting an ADR and this puts me off completing a Yellow Card. It is particularly bad if you report an ADR directly to the company as they require information forms to be completed which is time-consuming.'
- 'Another major obstacle to staff reporting on-line is that websites outwith the hospital intranet are blocked. Could we set up a direct link to the electronic Yellow Card and send a hospital wide e-mail to publicise it better.'
- 'It should form part of the doctors training plan when they come into hospital, especially in oncology.'
- 'The forms are time consuming and unfortunately a low priority on a busy ward.'
- 'If there was a quick 'highlight' method to get someone else to follow-up, it would catch more patients. We sometimes report possible adverse effects to our ward pharmacist to follow up.'
- 'Oncologists are so use to having to deal with toxicity that they think of their drugs in a different way to other normal drugs.'
- 'Main difficulty will always be conflicting requirements for time. Can be time consuming filling in reports and undoubtedly filling in reports for all toxicities for

all patients could be all-consuming and hence impossible. One, therefore, has to be selective and choose unusual, serious, unexpected ones.'

- 'We have to report adverse events (AE) and serious adverse events (SAE) in clinical trials patients; if the MHRA want every AE and SAE on every oncology patient we can provide, but I don't think they will cope.'
- 'More specific guidance for oncology specific ADRs and which to report required.'
- 'More information on what is done with the information received.'
- 'Although time to complete is important, I believe the key issues in oncology is separating the 'expected' from the unexpected and being able to report by regimen rather than by suspected drugs.'

4.3.3.7.2. Patient reporting of oncology ADRs

In question 18 there were four statements that asked respondent oncology healthcare professionals their opinions on patient reporting of oncology ADRs. The respondents were asked to indicate their level of agreement or disagreement by selecting either 'strongly agree', 'agree', 'disagree', or 'strongly disagree' in response to the statements. 79% (n=46) of the healthcare professionals were in agreement that patient reporting of ADRs in oncology would be beneficial. 77% (n=47) were in agreement that patients are not adequately trained to detect ADRs so accuracy of grading might be a problem. 77% (n=46) also were in agreement that patients would not be able to distinguish what ADR was serious enough to report without education. Also 68% (n=39) were in agreement that patients might under-report ADRs (i.e. downplay toxicities to avoid having treatment delays). The latter was the only statement that there was a deviation in opinions between the three healthcare professional groups. In this case 58% (n=15) of the doctors were in disagreement that patients might under-report ADRs (i.e. downplay toxicities to avoid having treatment delays), while the greater majority of the pharmacists (88%, n=22) and nurses (75%, n= 6) were in agreement. However this difference was not statistically significant (p=0.075).

The following additional comments were also received in response to this question:

- 'I think a patient report corroborated by managing personnel would be ideal.'
- 'Patient reports would have to be followed up by professional to assess the grade of the ADR and likely causative drug.'

- ‘Patients would need simple language and probably need confirmed by the doctor.’
- ‘Some patients would report a lot of minor, well-recognised stuff (may be dozens of cards), whilst severe reactions would probably not (largely because they may be too ill to do so).’
- ‘Patient reporting might bring to light some less serious side effects that the doctors don’t detect and that the patient may not feel is necessary to report to his/her doctor. The downside is that it could become a litigants charter triggering all sorts of potentially spurious claims.’
- ‘Would empower the patient and help identify what the real issues are for the patients. If in a format that was not linked to treating team then they would not worry about impact on their care so may be more honest report.’
- ‘A lot of patients are receiving day care, homecare and are receiving therapies for a longer period and thus they may be at home more for longer periods without seeing a specialist to whom they could report ADRs. The use of oral therapies is also increasing which is also an issue.’

4.3.3.7.3. Electronic capture of NCI CTCAE data

The final question in the questionnaire sought the opinions and attitudes of respondent oncology healthcare professionals on statements pertaining to electronic capture of adverse events from electronic prescribing systems in oncology across Scotland. The respondents were asked to indicate their level of agreement or disagreement by selecting either ‘strongly agree’, ‘agree’, ‘disagree’, or ‘strongly disagree’ in response to the statements. From the responses received from the oncology healthcare professionals there was a very high agreement with the statements. That is 98% (n=59) were in agreement that electronic capture of NCI CTCAE grades in clinical practice will be beneficial. 97% (n=59) were in agreement that anonymised, aggregate data resulting from electronic capture of NCI CTCAE grades would be beneficial in monitoring oncology adverse events Scotland wide; and 95% (n=58) were in agreement that it would be helpful to doctors if the anonymised, aggregate data could identify adverse event trends (possibly help in making decisions on which medicines or regimens to use). As well 95% (n=58) were in agreement that they would be interested in any adverse event trends (if they became available) from aggregate data in oncology; and 93% (n=55) were in agreement that they would be happy to contribute their patients’ anonymised NCI CTCAE data for electronic linkage for this purpose. There was not any deviation or

statistically difference in opinions between the three healthcare professional groups (p=1, p=0.914, p=0.914, and p=0.920 respectively).

Some additional comments also received in response to this question included:

- 'This could be most helpful in determining place in therapy of cancer drugs where there are several that may be used e.g. for 2nd line treatment.'
- 'This is the way forward!'
- 'Good idea and better way of seeing trends in ADRs as nurses would be toxicity assessing patients anyway and this would save repetition.'
- 'Dependent upon how easy to enter data. If linked into an electronic prescribing system would not be any additional work.'
- 'Electronic capture will only be of value if it does not require additional input time from doctors since if it did, I suspect it would not get done.'
- 'Again the problem will be the volume of data, especially the analysis linking in age, PS, smoking habit, tumour stage and treatment, concomitant medicines, deprivation category, etc that would be necessary to make sense of the data.'
- 'While I agree in principle, I think it is unlikely that the resources will be available to contribute data for electronic linkage, unless it was done automatically through current electronic prescribing systems.'

4.4. Discussion

4.4.1. Principle findings

4.4.1.1. Knowledge and awareness of the Yellow Card scheme

In both the one-to-one interviews and the survey questionnaire awareness of the Yellow Card scheme and its roles was found to be high. Results from the survey questionnaire showed that 89% of the respondents agreed that one of the roles was to ensure public safety; 97% agreed that one of the roles was to identify potentially serious ADRs that were too rare to be picked up during clinical trails; 81% agreed that one of the roles was to identify factors that might predispose to toxicity/ADRs; 75% agreed that one of the roles was to enable ADRs of medicines in similar classes to be compared; 99% agreed that one of the roles was to identify any previously unknown reactions to a medicine; and 94% agreed that one of the roles was to monitor the safety of the medicines throughout its life. This result is in contrast to some

previous studies that found a lack of knowledge of the purpose of the ADR reporting scheme (53, 54, 105, 111).

The level of knowledge about what ADRs to report was identified as a problem, with 66% of the oncology healthcare professionals indicating that they did not know what types of ADRs that should be reported via the Yellow Card scheme. In addition 32% of oncology healthcare professionals admitted to having seen ADRs in clinical practice but were not sure which ones the MHRA wanted them to report. Further only 30% of the respondents to the survey questionnaire were able to correctly identify which oncology ADR scenarios met the criteria for reporting via the Yellow Card scheme.

4.4.1.2.Difference in Yellow Card reporting behaviour of the oncology healthcare professionals

26% of the oncology healthcare professionals had never completed a Yellow Card report previously in their career, with nurses accounting for 58% of this group. This is not surprising since nurses were one of the last healthcare professional groups to be added as official reporters to the Yellow Card scheme in 2002. The lack of reporting by nurses is of concern, considering the vital role that nurses provide in the continuum of care of patients and in the monitoring of adverse events during cytotoxic chemotherapy. Of those oncology healthcare professionals who had reported, 70% had submitted between 1 and 10 Yellow Card reports during their career (with pharmacists and doctors accounting for 47% and 40% respectively of this group). Considering the number of adverse events that are seen daily in oncology, this indicates a very low Yellow Card reporting rate.

4.4.1.3.Preference for type of Yellow Card to complete

Almost half of the oncology healthcare professionals did not have any strong preference for reporting method (paper or electronic). However approximately a third of the oncology healthcare professionals said that they preferred to complete Yellow Cards electronically (with pharmacists accounting for almost two-thirds of this group) and one-fifth of the reporters indicated preference for paper Yellow Cards (doctors and nurses accounted for 54% and 34% respectively of this group).

The reasons given for a preference for submitting Yellow Card paper reports included that they found them easier to find and complete; easier to attach additional information (lab

results); electronic completion takes longer and when completing on the ward access to a computer can be a problem; and habit/familiarity since only have used paper Yellow Cards. The reasons given for the electronic Yellow Card reporting preference included that the Yellow Card can be stored easily; it was more confidential; easier to access; and do not have to remember to post.

It was, however, noted by one respondent that access to the electronic Yellow Card was an obstacle to submitting suspected ADRs electronically since websites out with the hospital intranet was blocked. It is unknown how widespread this problem is but is an issue that must be kept in mind when assessing preferences for types of Yellow Card.

4.4.1.4.Perception of incidence of adverse events in oncology

Greater than 40% of the oncology healthcare professionals estimated that over 75% of their patients experience any type of adverse event during treatment with cytotoxic chemotherapy, and an additional 27% of the oncology healthcare professionals estimated that between 50-75% of their patients experience any type of adverse event. Conversely 78% of the oncology healthcare professional estimated that only 5-25% of their patients experienced a serious adverse event during cytotoxic chemotherapy treatment. However 15% of the oncology healthcare professionals estimated that less than 1% of their patients experienced a serious adverse event during cytotoxic chemotherapy treatment. It is difficult to give a definitive number to the incident rate of serious adverse events during cytotoxic chemotherapy since it varies greatly with tumour types and cytotoxic chemotherapy regimens given, however, from the retrospective case review (in chapter 3 of this thesis) the incident rate for serious adverse events was 97% and 96% in 2001 and 2003 respectively for adjuvant, breast cancer patients. Another study from France found that 58% of patients experienced serious adverse events during treatment with cytotoxic chemotherapy within their cancer centre. This suggests that the oncology healthcare professionals' perception of the incidence of serious adverse effects during cytotoxic chemotherapy is biased towards a major underestimate.

4.4.1.5.Perception on under reporting of ADRs

92% of the healthcare professionals were in agreement that oncology adverse drug reactions were under-reported but 53% were in agreement that the reporting rate for oncology adverse drug reactions was not less than that of any other clinical area. In chapter 3 of this thesis, it was demonstrated that an estimated 1% reporting rate existed at the Edinburgh Cancer Centre

(ECC) for adjuvant, breast cancer patients in 2001 but improved to 6.3% in 2003 after a pharmacist-led intensive monitoring initiative in 2002. While the Yellow Card reporting rate in 2003 was closer to the reporting rate of 6.5% (observed in a recent study for two acute hospitals in Liverpool) (130), it was much less than the unsustainable 800% increase in reporting seen in 2002 during the pharmacist-led initiative at ECC.

80% of the respondents were in agreement that a reporting form that took less time to complete might help increase reporting in oncology. These forms could utilise more tick boxes; less free-format text; pre-populated fields on an electronic report such as patient details, medicines, past medical history, etc. The electronic Yellow Card addresses the issue of more tick boxes and having to enter free-format text since there is a drop down menu to select from for suspected reactions and suspected medicine(s) or concurrent medicines. However more work is required to develop interfaces between all UK electronic patient/prescribing records and the electronic Yellow Card to allow for patient-specific pre-populated fields.

4.4.1.6. Criteria for ADRs that oncology healthcare professionals would consider reporting

It has always been anecdotally known that oncology healthcare professionals see little benefit in reporting ADRs that are inevitable consequence of cytotoxic chemotherapy. In the responses to the survey questionnaire 42% of the oncology healthcare professionals indicated that they often recognise ADRs in patients receiving cytotoxic chemotherapy but choose not to report believing that they are inevitable consequence of therapy and little relevance for reporting.

When the oncology healthcare professionals were given examples of possible ADRs that met the MHRA criteria for to submit a Yellow Card report, only 30% of the examples were selected as ones that they would report to the MHRA. A possible reason for this low level of agreement with reporting a ADR could possibly be attributed to the fact that 80% of the oncology healthcare professionals did not view oncology adverse events (toxicities) as an ADR (i.e. expect to see them and know how to prevent them or reduce their severity with pre-medication)

The two situations that the oncology healthcare professionals were in agreement that they would consider completing a Yellow Card report for were: 1) Black triangle status, serious, not a known side effect of medicine CTCAE Grade 3-4 and 2) Non-black triangle status, serious, not known side effect of medicine, grade 3-4. However there was no association between a healthcare professionals' decision to submit a Yellow Card report and the black triangle status, the seriousness of an ADR, the grade of toxicity or whether an ADR was known (expected). The only covariant factor that was associated with an increase in the decision to report via the Yellow Card scheme was reporter group, with pharmacists being over three and a half times likely to report then doctor; and nurses half as likely as doctors to report.

4.4.1.7.Factors that influence a decision to make a Yellow Card report in oncology

All oncology healthcare professionals indicated agreement that there were factors of high, medium and low level of importance that had an impact upon their decision to complete a Yellow Card report. The factors of high importance included seriousness of the reaction; unusual ADRs not normally seen in oncology; a newly licensed medicine; an ADR not listed as a known side effect in the SPC for the product; and significant drug interactions. The factors seen of medium importance included patients being hospitalised or hospitalisation prolonged because of an ADR; latent drug induced cancers; and any new chemotherapy regimen(s). The factors deemed to be of low importance were suspension of chemotherapy due to an adverse event; and any adverse event resulting in dose delays to chemotherapy.
There was no consensus observed from the oncology healthcare professionals on whether the grade of NCI CTCAE would be of high, medium or low importance in their decision to make a Yellow Card report since there was a relatively even distribution of responses (32% said 'Yes', 35% said 'Not sure and 33% said 'No'). For those individuals that said it was important, 55% indicated that Grades 3 and 4 should be considered for reporting.

As with previous results from other survey questionnaires reported in the literature (33, 52-55, 100, 104-107, 110, 111, 113), the oncology healthcare professionals were in agreement that the following were factors influenced their decision to report an ADR:

- Not certain of the causality of an ADR with a specific medicine.
- Inadequate information sources on ADRs to aid in determining which drug could be causing an ADR.

- Do not know what types of ADRs that should be reported via the Yellow Card scheme. 32% of oncology healthcare professionals admitted to having seen ADRs in clinical practice but were not sure which ones the MHRA wanted them to report.
- Too time-consuming.
- Do not see benefit in reporting well recognised ADRs which are seen routinely in everyday clinical practice.

Other factors identified in this study by oncology healthcare professionals that influenced their decision to report an ADR, and which have not previously been described in the literature, included:

- The volume of ADRs seen in oncology makes it impossible to report them all.
- Lack of specific guidance on the types and grades of oncology ADRs to report via the Yellow Card scheme.
- Submitting Yellow Card reports are not a high priority in everyday clinical practice.

In contrast to previous results from other survey questionnaires described in the literature (33, 52, 53), the majority of the oncology healthcare professionals disagreed that the following factors influenced their decision to report an ADR:

- A single report is not enough to add to medical knowledge
- Lack of professional obligation to report
- Feeling of being personally liable for ADR
- The Yellow Card form is too congested

Another factor that was identified previously as not impacting upon a healthcare professions decision to report (113), and replicated by the results from this survey is that serious ADRs are well documented by the time the medicine is marketed so oncology healthcare professionals do not see any point in reporting.

Other factors identified by the oncology healthcare professionals factors that did not influence their decision to report an ADR, and not previously described in the literature, included:

- Do not know how the information reported in Yellow Cards is utilised. This factor has been previously suggested in the literature as a reason for not reporting an ADR (52, 105) but was not seen as important by oncology healthcare professionals in their decision to submit a Yellow Card report in this study.
- Fear that if they report an ADR via the Yellow Card they will be badgered to provide more information.
- Prefer to report directly to the pharmaceutical company instead of via the Yellow Card scheme.

The last two factors have not been evaluated previously in the literature but have been speculated as possible reasons for low-reporting rates via the Yellow Card scheme. The results from this questionnaire suggest that this may not be valid.

4.4.1.8.Patient reporting of oncology ADRs

More than 75% of the oncology healthcare professionals were in agreement that patient reporting of ADRs in oncology would be beneficial but accuracy in grading might be a problem since patients are not adequately trained to detect ADRs, and they would not be able to distinguish what ADRs were serious enough to report without appropriate education. 68% of the oncology healthcare professionals, however, were in agreement that patients might under report ADRs (minimise toxicities to avoid treatment delays). Despite these concerns, the need for patients to be able to report an adverse event directly is increasing in importance due to the increasing number of patients receiving cytotoxic chemotherapy treatments at home; and the use of oral therapies, which could mean that patients could go for a much longer time before seeing a healthcare professional to detect and report an ADR.

4.4.1.9.Electronic capture of NCI CTCAE grades

In Scotland investment has been given to purchasing a paperless, electronic chemotherapy programme for all of Scotland. AEs will be recorded within these electronic patient records. Other than the obvious benefits of a paperless patient record, there is a pharmacovigilance potential that is undeveloped at present. The suggested potential benefits of aggregate data from these electronic patient records included monitoring of ‘toxicities’, gathering national data and identifying trends, and helping doctors decide which chemotherapeutic medicines or regimens to use.

Greater than 95% of the oncology healthcare professionals were in agreement that capture of CTCAE grades in clinical practice would be beneficial; and that anonymised, aggregate data of these CTCAE would be beneficial in monitoring oncology AEs in Scotland (possibly inform decision making on which medicines and regimens to use). Also almost all of the oncology healthcare professionals surveyed would be happy to contribute their patients' anonymised CTCAE grade data for electronic linkage, and would be interested in any results from aggregate data on oncology AE trends (if it became available). It was the opinion of those surveyed that, while it would be feasible to develop such a database in Scotland, it would only be of value if it did not involve additional input time from healthcare professionals and it was adequately resourced to ensure quality.

4.4.2. Strengths and weaknesses of the study

Different qualitative methods (one-to-one semi-structures, and in-depth interviews) were used to collect the data within this study. This increases the validity of the study and reduces the chance of not identifying or obtaining important and relevant information.

The researcher had no previous experience in conducting one-to-one semi-structured, in-depth interviews. To minimize the effect of this the questions and schedules were peer reviewed by the research supervisors and collaborators within the project. The oncology healthcare professionals were aware that the researcher worked within the Centre for Adverse Reactions to Drugs (Scotland)/Yellow Card Centre Scotland, introducing a potential bias in the answers given. An independent researcher may have avoided this bias but may also have had limited knowledge of oncology adverse events or the Yellow Card scheme and, therefore, would not have been able to use this experience in interviewing to probe further or stimulate debate.

The interviews were all conducted at the Edinburgh Conference Centre. Different or more varied responses may have been obtained if a wider geographical spread of oncology healthcare professionals had been interviewed. However, in interviewing doctors, pharmacists and nurses the perspective of each profession about oncology adverse events and reporting of ADRs, a multidisciplinary view was obtained.

The researcher was a specialist in pharmacovigilance with prior experience of working as a clinical pharmacist in oncology. This aided in identification of themes during the coding process of the one-to-one semi-structured, in-depth interviews. The independent investigator

who carried out the validity testing was experienced in coding previous research projects but had no prior knowledge of oncology. It may have been useful to have had a second validity check from another individual with an oncology background but resource restrictions did not allow for this.

The researcher had no previous experience in the design of survey questionnaires but had attended two, one-day research modules on qualitative methods and questionnaire design hosted by the Wellcome Trust Clinical Research Facility. The content for each question was derived from themes/items derived from the one-to-one interviews or previous ADR reporting questionnaires in the literature. The final questions were peer reviewed by the project supervisors and another researcher experienced in questionnaire design.

The piloting of the questionnaire was carried out using clinical pharmacists at the base hospital of the researcher. None of these pharmacists were specialist in oncology so the critique of the questionnaire may not have highlighted some issues that a specialist in oncology may have. However, eight of the ten pharmacists had previously worked in oncology or had undertaken a placement in oncology during their MSc in Clinical Pharmacy so were not naïve to oncology adverse events/ADR issues.

Criterion validity, comparing against a Gold Standard, was not possible since no questionnaire on obtaining information on attitudes, behaviour and knowledge of ADR reporting and adverse events specific to oncology was identified in the published literature. There were, however, a number of questionnaires described in the published literature from non-oncology generalist areas that was utilized where possible. Face validity was carried out on the questionnaire, as well as internal consistency during the pilot phase. Internal consistency was confirmed at 100%. Test-retest reliability was not carried out, however, due to time and resource restraints.

The study population that the questionnaire was circulated to for self-completion involved doctors, nurses and pharmacists from two of the cancer networks in Scotland (SCAN and WOSCAN) but not to the third (NOSCAN) due to lack of response from contacts in that network. It would have been better to have had a geographical spread across the whole of Scotland but without the co-operation of the contact in NoSCAN this was not possible to achieve.

Within SCAN and WOSCAN, the researcher had to rely on independent, external individuals to distribute questionnaire (with the exception of Lothian). As a result the total number of each profession that the questionnaire was sent to is unknown since researcher was only given the total number from each independent contact. Therefore it was not possible to calculate response rate by profession. Hence while the nurses only accounted for 17% of the respondents, it is unknown what the response rate was for this group. It would have been desirable to have more replies from this healthcare professional group. The response rate overall was 50% (75 of the 150) after two mailings, which is acceptable. It is unknown if a better response rate could have been obtained if the questionnaire had been distributed directly by researcher.

4.4.3. Strengths and weaknesses in comparison to other studies

No other studies were found that evaluated the knowledge, behaviour and attitudes of oncology healthcare professionals on adverse drug reaction reporting via the Yellow Card scheme. From the published generalist studies that were carried out using survey questionnaires the same four areas (demographics, knowledge, attitudes and behaviour) were assessed in some (54, 104, 113); and two mailings were undertaken (54, 104, 106, 108, 110, 112, 113). The most noteworthy differences were:

- Direct distribution of questionnaire to sample population (104, 106, 108, 109, 110, 112); with one study completing the second follow-up via telephone or in person (54).
- The sample size was bigger for some studies (54, 104, 106, 108, 110, 112, 113) . This was dependent upon the population being studied.
- Response rate was lower (37%) (113) for some but higher for others (73-74%) after two mailings (54, 104).

4.4.4. Implications of findings

The level of awareness of the Yellow Card scheme and its roles was found to be high in oncology healthcare professionals; however, the level of knowledge on what ADRs to report was found to be a problem. It was agreed by the oncology healthcare professionals that they did not know what types of ADRs they should report via the Yellow Card scheme in oncology; and the lack of specific guidance on the types and grades of oncology ADRs to report via the Yellow Card scheme was a contributing factor to reasons why they did not make Yellow Card reports.

This study has highlighted, in common with previous work reported in the literature, that the conflicting priorities for a healthcare professionals' time will always be a factor in preventing suspected ADRs to be reported via the Yellow Card scheme. The majority view is that it can be time consuming to complete a Yellow Card report so it is not surprising that it was not viewed to be a high priority in everyday clinical practice. In addition, the consensus from oncology healthcare professionals who participated in this study is that the large numbers of ADRs seen in oncology make it impossible to report them all. The view is that if the oncology healthcare professionals attempted to report all suspected ADRs in oncology that meet the Yellow Card criteria for reporting (all suspected reactions for black triangle medicines and all serious, suspected ADRs for all other medicines), it would be an unachievable goal for the healthcare professionals; and not necessarily desirable for the MHRA (possibility of 'noise'). 'Noise' in spontaneous reporting databases includes non-serious and/or incidental adverse events, which detract from the ability of assessors to detect new potential serious ADR signals (131). As one of the interviewees stated in the one-to-one interviews, 'There is a great danger of being swamped with expected toxicities particularly for oncology drugs, where if we reported every expected event we see'. Therefore more guidance from the MHRA would be beneficial to avoid this problem; and possibly aid an improvement in reporting rates.

The oncology healthcare professionals identified that not being certain of the causality of an ADR with a specific medicine; and inadequate access to information sources about ADRs that would aid in determining which drug could be causing an ADR were possible reasons why they did not make Yellow Card reports. It is, therefore, important that healthcare professionals make best use of simple causality assessment nomograms in trying to decide if a medicine could possibly be implicated in a suspected ADR. In addition, they need to be aware of (and make best use of) both paper and electronic sources of information available to them during this process. It must be made clear to healthcare professionals, however, that there is no need to be 100% certain that an adverse event has been caused by a medicine to make a Yellow Card report (a suspicion is all that is required).

The only two ADR situations that the majority of the oncology healthcare professionals would consider completing a Yellow Card report for were: 1) Black triangle status, serious, not a known side effect of medicine CTCAE Grade 3-4 and 2) Non-black triangle status, serious, not known side effect of medicine, grade 3-4. These results from the survey questionnaire were reinforced by the factors seen to be of high importance by oncology

healthcare professionals in determining whether to submit a Yellow Card report. These included the seriousness of the reaction; unusual ADRs not normally seen in oncology; a newly licensed medicine (black triangle); an ADR not listed as a known side effect in the SPC for the product. The only additionally factor of high importance, not covered within these two scenarios, was significant drug interactions.

The only covariant factor that was associated with an increase in the decision to report via the Yellow Card scheme was reporter group, with pharmacists being over three and a half times likely to report then doctors; and nurses half as likely as doctors to report. None of the factors that were assessed in the survey questionnaire on why healthcare professionals do not report ADRs via the Yellow Card scheme showed any noticeable variance in opinion between the healthcare professional groups to account for this increased tendency for pharmacists to report. Then the question remains what influences this trend and is it transferable to other healthcare professional groups.

The key questions that must be addressed before any recommendations can be made to aid reporting of oncology ADRs are:

1) Is it acceptable to report only ADRs that are not listed as known side effects in the Summary of Product Characteristics for an oncology medicine, even for medicines with a black triangle status?
2) Is it acceptable that only certain grades of NCI CTCAE (such as Grades 3 and 4) of oncology ADRs should be considered for reporting?

If both healthcare professionals and the MHRA would support such recommendations then it is possible that steps can be made to improve reporting of ADRs in oncology via the Yellow Card scheme.

If the ability to electronically capture output data of adverse events for patients undergoing chemotherapy for pharmacovigilance purposes were achieved in Scotland this could lead to a significant advancement in oncology signal generation and chemotherapeutic agent(s) monitoring. The updated CTCAE version 3.0 incorporates the preferred terms from MedDRA, which means that selected adverse effects could be electronically communicated to the MHRA (who use the same common terminology for classification of suspected ADRs in their surveillance database “Sentenil”) if this facility were written into the functionality of the software. Before this recommendation can be implemented, more work is required to ensure

that an interface is developed to allow patient-specific pre-populated fields to the electronic Yellow Card. In addition, the potential for all output data of adverse events for patients undergoing chemotherapy to be anonymised and captured Scotland wide for other pharmacovigilance purposes would be a definite benefit. Before the full potential of these datasets can be realised, data linkage between health boards must be pursued. The potential use for this anonymised dataset is largely undefined at present, however, possible applications include:

1) Individual oncology units could use this data for prospective computerised surveillance of adverse events rather than relying on the traditional 'voluntary' reporting systems, which are potentially cumbersome and less effective (132).
2) Cross-linkage to computerised registries such as the Scottish Cancer registry. This would allow for a more robust means of evaluating the impact of cytotoxic chemotherapy interventions on cancer outcomes and survival in Scotland.
3) Data mining algorithms (DMAs) to this dataset could be a possibility for supplementing post-marketing information on oncology medicines from the Yellow Card scheme. DMAs have been studied in hopes of enhancing the ability to screen large databases of adverse events with oncology medicines or other medicines with similar features (i.e. medicines that may be approved on an accelerated basis, are known to have serious toxicity, are administered to patients with substantial and complicated co-morbidity illness, are not available to the general medical community, and may have a high frequency of use out with the terms of a medicine's market authorisation or "off-label" use) (133).

One problem with the process of anonymisation, even after obvious identifying data items (name, address, postcode, date of birth) are removed from datasets, is the risk of 'indirect' identification and the data must be handled securely. In NHS Scotland the debate over the use and safeguarding of personal information is ongoing. Consensus is arising but doubt remains over the clarity of professional guidance and how to achieve consensus over its interpretation; how to inform patients and what to tell them; how to regulate disease and other registries; whether it is possible to anonymise data in ways which retain their usefulness (134). This creates a challenge and a definitive answer must be reached before anonymisation of adverse events in oncology for pharmacovigilance/epidemiological purposes can be pursued. However if this were pursued through the Information and Statistics Division (ISD), who are

responsible for collating and holding health-related data across Scotland including the Scottish Cancer registry, then this is less likely to be an obstacle.

While patient reporting of adverse events in oncology is supported by the healthcare professionals for the most part, some concerns over a patient's ability to accurately report 'toxicities' remain. Nevertheless Patient reporting must be developed in oncology to better facilitate monitoring of symptoms during cytotoxic chemotherapy, especially with the increased uptake of treatment in the home setting. Patients have been officially able to make Yellow Card reports directly to the MHRA since February 2008. This should be encouraged by healthcare professionals. However, there is a need to develop an on-line self-reporting of 'toxicities' during cytotoxic chemotherapy for completion by patients in the home setting (in real-time), which will allow doctors to have assess to this information in secondary care for review and intervention. At present most patients either keep a mental or paper diary of things they experienced during the chemotherapy cycle (or recall from memory retrospectively if they have not forgotten) to advise the nurse during assessment prior to receiving the next cycle of chemotherapy. The reliability of the information is variable, especially if being recalled from memory, and having a third-party to interpret the information provided. In symptom research, patients' reports are the gold standard for assessing symptoms, with studies consistently showing that doctors and nurses underestimate (or occasionally overestimate) symptom frequency and severity in comparison to patients (135-139); and a need for a tool for collecting patient reported adverse event data in chemotherapy was concluded (135). Hence a prospective means of capturing 'toxicities' during treatment would be beneficial and would eliminate third-party reporting biases. One such web-based system has been developed (known as STAR) that allows patients to enter and track their own symptoms based on CTCAE, which generates longitudinal reports that can be available to staff (140). This is not only beneficial in tracking all symptoms a patient may have during a given cycle but may also provide early warnings about potentially concerning symptoms to improve doctor response time in dealing with. The patients who piloted the self-reporting of symptoms via the internet found it easy to use; and believed it improved discussion and communication with their doctors (140). Therefore 'real-time' collection of 'toxicities', from patients undergoing cytotoxic chemotherapy, is not an unrealistic goal since prior work has been done in this area. An investment of time and money would be required to achieve a similar system in Scotland however.

4.4.5. Unanswered questions and future research

This study has raised questions that indicate further research is required. These include:

1) What ADR reports do we really want from oncology? What is considered desirable or practical? If criteria were developed specific to oncology (as indicated by the respondents in the survey questionnaire) that would deviate from the current Yellow Card Criteria, would it be endorsed by the oncology profession and the MHRA? How can oncology healthcare professionals and the MHRA be assured that deviating from the current Yellow Card criteria would not have an impact upon patient safety?
2) Patient reporting via the Yellow Card scheme has been official since February 2008 but no work has been done to date on evaluating information via patient reporting of ADRs in oncology in comparison to reports received from healthcare professionals. It would be beneficial to undertake this work.
3) Electronic prospective recording of adverse events by patients is a development that may be worth taking forward in order to evaluate patient understanding of NCI CTCAE; ease/difficulty to do; and comparison to adverse events recorded by healthcare professionals.
4) If collection and collation of anonymised data from electronic prescribing systems in oncology in Scotland is achieved, how would the data be utilised and what pharmacovigilance benefit would be derived?
5) Does incorporating ADR training into an oncology doctor's induction training plan affect reporting rates of oncology ADRs?

4.5. Conclusion

Awareness of the roles of the Yellow Card scheme in pharmacovigilance is not a problem but there is still a need for greater training to ensure all oncology healthcare professionals are aware of which ADRs meet the Yellow Card criteria for reporting . The greatest obstacle to oncology healthcare professionals is the large volume of ADRs that would require reporting if the current Yellow Card criteria were adhered to and the resulting time pressures required to undertake this reporting. Oncology healthcare professionals have indicated that the current Yellow Card reporting criteria need to be adapted in oncology to provide 'fit-for-purpose' reporting criteria. The question remains, however, who will develop 'fit-for-purpose' criteria for oncology ADRs; and how will it be developed. At present, in the absence of greater guidance on which suspected oncology ADRs should be reported to the MHRA, it is left to

the judgement of each oncology healthcare professional as to which ADRs they elect to report. Hence under-reporting is very likely to continue.

With the investment in electronic patient records across Scotland in oncology comes the unique opportunity to develop a cohesive pharmacovigilance system in oncology. The potential for the dataset in monitoring and preventing adverse events is largely undefined at present but limitless with ingenuity. Before such a benefit realisation can be achieved, more investment of resources and collaboration between health boards, cancer centres, the Information Services Division and the MHRA is required.

Chapter 5

Classifying serious ADRs in oncology and developing standards for reporting via the Yellow Card scheme.

5.1 Introduction

The main function of the post-marketing surveillance of medicines is to identify any unknown adverse effects from medicines not previously detected during the clinical trial period. The lack of detection of these ADRs during the clinical trial period may be due to: i) a lower incident rate which results from the low number of patients exposed to the medicines during clinical trials; ii) exclusion of specific patient populations; or iii) effects appearing after long-term use. Medicines regulatory bodies depend upon spontaneous reporting to aid the detection of these previously undetected ADRs. To encourage submission of these quality reports, the criteria for reporting to the Yellow Card scheme includes a request to report all serious ADRs observed with any medicines to be reported, and all suspected ADRs for black triangle medicines.

In 2004, a review of the Yellow Card scheme was undertaken. One of the findings of the review was that it was essential that the scheme maintain its focus upon previously unknown ADRs that were serious and black triangle products. In addition the review supported developing clearer guidelines for the definition of serious ADRs (35). To date no new guidelines of this nature have been issued by the MHRA. No reference could be found to any work to develop such guidance by any professional body or research group either.

In Chapter 4, there is discussion of the fact that the large number of ADRs experienced in oncology practice makes it very challenging to report them all. Even by limiting reporting to serious ADRs (as defined by the Yellow Card scheme), the large number of serious ADRs involved and the conflicting requirements on the oncology healthcare professionals' time make it an almost impossible goal to report them all. Hence there is a need to define a subgroup of serious ADRs in oncology which should be considered for reporting via the Yellow Card scheme.

In oncology practice, patients' response to cytotoxic chemotherapy is assessed by the severity of an adverse event on the National Cancer Institute (NCI) Common Terminology

Criteria for Adverse Events (CTCAE) scale; and it is generally only those events of grade 3 or grade 4 that are of concern to clinicians. In contrast, it is the seriousness (not severity) that serves as the criterion for reporting suspected ADRs via the Yellow Card scheme. As a result, there is no direct correlation between CTCAEs and the MHRA reporting criteria. In Chapter 2, the researcher assigned the preferred terms to the classification of 'serious' or 'not serious' using the ADROIT dictionary (Appendix 6). These assignments do not necessarily reflect the opinion of oncology healthcare professionals as to what they would class as serious in the context of treating oncology patients. The results from the questionnaire in Chapter 4 showed that the oncology healthcare professionals (surveyed in Scotland) did not see any benefit to reporting ADRs that are anticipated and well known to be associated with cytotoxic chemotherapy regimens (e.g. haematological, infusion related allergic reactions, neutropenic sepsis, etc). Consequently there is likely to be variation in the definition and selection of serious ADRs for reporting that would be adopted by oncology healthcare practitioners in their practice.

Furthermore, the results from the questionnaire survey previously reported in Chapter 4 indicated that the oncology healthcare professionals would only consider reporting those ADRs via the Yellow Card scheme that were serious, unknown and of grade 3-4 severity for any cytotoxic chemotherapeutic agent/regimen or suspected drug interaction. It was, therefore, necessary to understand if there was any consensus agreement within a sample of oncology healthcare professionals on the definition of criteria they consider important for reporting via the Yellow Card scheme.

The purpose of this study was to develop standards for classification and reporting of serious ADRs in patients receiving cytotoxic chemotherapy. With the primary objective of obtaining a list of NCI CTCAEs (mapped to MedDRA Lower Level Terms) that should be recommended to oncology healthcare professionals as those ADRs which should always be reported via the Yellow Card scheme. A secondary objective was to define potential factors and criteria to assist oncology healthcare professionals to identify situations when serious ADRs should be reported via the Yellow Card scheme.

5.2 Methods

5.2.1. Nominal group process

To develop a consensus on the standards for classification and reporting of serious adverse drug reactions in oncology a nominal group process was utilised. The nominal group process is also known as the 'expert panel' method. Within this methodology, experts who participate in the process are asked to form an independent view before the meeting. Using a nominal group process participants are normally asked to rank or to form opinions on given items. Options do not always have to be ranked, but may be evaluated more subjectively. The results from the nominal group process are summarised and presented to the participants at a subsequent meeting, sometimes with a review of the relevant literature (if applicable). At the meeting the participants discuss the rankings and their differences. They are asked to re-rank the issues in the light of the group's discussion. A final analysis of the re-ranking is fed back to the participants. A facilitator is engaged to conduct the meeting (115).

A letter contained details of the academic background to the research, aim of the study, the method, the use of the data, and confidentiality of any information received was written (appendix 25). The letter was sent via e-mail to invite oncology healthcare professionals (3 medical oncologists, 3 pharmacists and 3 nurses) from NHS Lothian to participate in the nominal group process. Positive responses to an invitation to participate in a nominal group were received from 1 medical oncologist, 2 pharmacists and 2 nurses. After the replies from participants were received a date for the meeting was determined. Two sets of different dates covering a 2 month period were distributed to obtain a common date suitable to all participants. Due to workload commitments it was only possible for 1 medical oncologist, 2 pharmacists and 2 nurses to participate in the arranged nominal group process meeting. Three weeks before the meeting was due to take place 1 nurse and 2 pharmacists advised that they would not be able to participate on the set date (due to conflicting time demands at work). At this juncture it was too late to delay the meeting any longer; but finding alternate participants was problematic. The researcher contacted 2 alternate pharmacists with oncology expertise who agreed to participate at late notice; however, an alternate nurse participant was not obtained. The final nominal group panel consisted of 2 pharmacists and the researcher due to absence at short notice of the other two participants. The pre-nominal group assessment of criteria and standards from

those participants unable to make the meeting was also included in the summary of information presented at the nominal group meeting for discussion however.

Each participant in the nominal group process was sent items via post to assess prior to the meeting. These items included: i) a list of criteria for Yellow Card reporting, resultant from the outcome of the questionnaire in Chapter 4, for ranking using the Likert scale prior to the nominal group process meeting (Appendix 26) ii) a complete list of NCI CTCAE mapped to MedDRA Lower Level Terms (LLTs) for participant assessment of seriousness in oncology and if the term should be considered as for reporting via the Yellow Card scheme (Appendix 27); iii) cover letter (Appendix 28); and iv) an excerpt of information contained in Chapter 2 to give essential background to the proposed nominal group process. The ADROIT classification of seriousness was deliberately not provided to avoid influencing the participants' decision on each LLT.

These completed forms were requested to be returned one week before the meeting for preparation of a summary. The summarised results were presented to the participants at the subsequent meeting by the researcher, who also acted as the facilitator for the nominal group process meeting. The agreement and differences on rankings and assessment of NCI CTCAE mapped MedDRA terms for seriousness in oncology was discussed. At the end of the process the participants were asked to review the prior assigned rankings and to re-assess the issues for which there was no prior consensus, taking into consideration the group discussion.

A final analysis of the reviewed ranking and assessments was summarised by the researcher after the meeting. Those LLTs that received a consensus agreement as 'serious; were accepted as those adverse events that should be considered for reporting by oncology healthcare professionals if a positive causal analysis is found with a medicine or cytotoxic chemotherapy regimen in oncology. In addition, those factors and situational criteria achieving consensus agreement for when oncology healthcare professionals should submit a Yellow Card report were adopted. These findings were communicated back to the participants.

5.2.2. Statistical Analysis

The purpose of using a nominal group process is to establish a prioritisation of ideas and issues, and the use of numerical voting can assist with this. It is important to avoid the tendency to over-interpret or to attach greater meaning to the numbers derived from the nominal group process; and the use of more sophisticated quantitative analysis should be avoided (141). In this case this was especially true as a result of the small number of participants involved. No statistical analysis was possible for classification of LLTs. The median value and inter-quartile range (IQR) would normally be presented for each of the questions scored using a Likert scale by the nominal group meeting, however, since there were only four participants in the nominal group process this statistical analysis was not feasible. A narrative description is provided instead.

5.2.3. Ethics

The Lothian Research and Ethics Committee (LREC) were provided with a protocol and flow chart (Appendix 29) of the intended study to see if LREC approval was required. The committee advised that ethics approval was not required. A copy of the reply received is documented in Appendix 30.

5.3 Narrative analysis of results

5.3.1. Demographics of participants

Three pharmacists and one nurse (all females) returned the pre-nominal group assessments. Three of these participants had an age range of 31 to 40 years and one participant had an age range of 41 to 50. The number of years that the participants had been practising within the oncology speciality was 4, 8, 14 and 16 (median 11 years with an interquartile range of 11).

5.3.2. Pre-nominal group assessment results

A total of 764 MedDRA LLTs (mapped from 1018 NCI CTCAE in version 3) covering 26 System Order Classes (SOC) were circulated for pre-assessment by the participants. Of these 764, 191 (25%) achieved a consensus agreement that the LLTs were classed as not serious in patients with cancer receiving cytotoxic chemotherapy and, therefore, should not be considered for reporting via the Yellow Card scheme; and 174 (23%) were classed as serious in patients with cancer receiving cytotoxic chemotherapy and, therefore, should be considered for reporting via the Yellow Card scheme. A copy of these lists of LLTs can be

seen in appendix 31. Another 30/764 (4%) were classed as serious in patients with cancer receiving cytotoxic chemotherapy but no consensus on whether the LLT should be considered for reporting via the Yellow Card scheme was achieved. The remaining 369/764 (48%) had no consensus agreement on whether the LLT should be considered serious in oncology or if the term should be considered for reporting via the Yellow Card scheme. Those LLTs not receiving consensus in the pre-nominal group assessments can be seen in appendix 32.

The participants were asked to score on a Likert scale from 1 to 9 there level of agreement with factors that should prompt an oncology healthcare professional to submit a Yellow Card report; and to score situation criteria which should prompt a Yellow Card report to be submitted. The participants' Likert scale rankings for the two questions from the pre-nominal group questionnaire can be seen below in tables 5.1 and 5.2. These results show that there were only one factor (adverse events resulting in dose delays) that 3 of the 4 nominal group participants disagreed or strongly disagreed with (score of 5 or below). There were two factors that 1 of the 4 nominal group participants disagreed (score of 3) but all other participants either agreed or strongly agreed with the factor (score of 7 or greater). All other factors achieved received a consensus agreement from all 4 participants in support. Both situational criteria also achieved a consensus agreement from all 4 participants in support.

Table 5.1. Consensus ratings of factors which should prompt an oncology healthcare professional to consider submitting a Yellow Card report

	Grading on Likert Scale of 1 to 9			
	Participant 1	**Participant 2**	**Participant 3**	**Participant 4**
An ADR not listed as a known side effect in the SPC	8	9	7	9
Unusual ADRs not normally seen in oncology	8	9	6	9
An ADR considered serious	9	5	5	9
A newly licensed medicine	8	9	8	9
A new combination regimen (not necessarily containing a new medicine)	8	9	8	8
Patient hospitalised or hospitalisation prolonged because of an ADR	9	5	7	9
Significant drug interactions	8	9	6	6
Latent drug induced cancers	3	9	9	8
Adverse events resulting in dose delays	1	3	5	7
A suspension of chemotherapy due to an adverse event (toxicity)	8	3	7	7

Table 5.2.
Consensus rating on which situation criteria should prompt an oncology healthcare professional to submit a Yellow Card report

	Grading on Likert scale of 1 to 9			
	Participant 1	**Participant 2**	**Participant 3**	**Participant 4**
Black triangle status medicine, serious reaction, not a known side effect of the medicine and a Grade 3-4 toxicity	8	9	9	9
Non-black triangle status medicine, serious reaction, not a known side effect of the medicine and a Grade 3-4 toxicity	8	9	9	8

5.3.3. Nominal group meeting results

At the nominal group meeting only the 399 LLTs that did not receive a consensus decision from the pre-nominal group assessments were discussed (see appendix 32). The LLTs which had achieved consensus on seriousness and consideration for reporting in the pre-nominal group assessments were accepted. The participants were supplied with a summary list of their pre-nominal assessments for the LLTs which had not achieved a consensus agreement prior to the meeting, along with a summary list of these LLTs that showed the ADROIT classification of serious for each term.

Each LLT was discussed in turn from the list of those which had not achieved consensus and a decision was then made by the group whether the term should be classed as serious and whether it should be considered for reporting via the Yellow Card scheme. Of the 399 terms discussed, 230 (58%) were classed as not serious in patients with cancer receiving cytotoxic chemotherapy and should, therefore, not be considered for reporting via the Yellow Card scheme; 155 (39%) were classed as serious in patients with cancer receiving cytotoxic chemotherapy and, therefore, should be considered for reporting via the Yellow Card scheme; and 14 (4%) were classed as serious in patients with cancer receiving cytotoxic chemotherapy but should not be considered for reporting via the Yellow Card scheme. These summary lists of LLTs can be seen in appendix 33.

During the meeting the summary results from the pre-meeting rankings on factors which should prompt reporting via the Yellow Card scheme and the situational criteria which should prompt reporting in oncology were also discussed. After the discussion the participants present were asked to rescore the criteria. From the two of the initial four participants present, the only differences in their re-rankings for the questions are listed below:

1) Participant 3 revised their pre-meeting scoring of 8 to 9 for 'a newly licensed medicine'; from a scoring of 6 to 7 for 'significant drug interactions'; and from 5 to 6 for 'adverse events resulting in dose delays.
2) Participant 4 revised their pre-meeting scoring from 8 to 7 for 'latent drug induced cancers'.

These revised scores have an insignificant impact upon their original scores and had no affect upon consensus being achieved for the three outstanding factors.

5.3.4. Final consensus on serious classification and consideration for reporting via the Yellow Card scheme

Table 5.3 shows the final number of LLTs that received a consensus of serious or not serious and whether the term should be considered for reporting via the Yellow Card scheme.

Table 5.3.
Final number of LLTs that received a consensus of serious or not serious and whether the term should be considered for reporting via the Yellow Card scheme

	Number of LLTs that received consensus during pre-nominal group meeting scoring	Number of LLTs that received consensus after nominal group meeting (% of total)
Not serious and do not report	**191**	**421 (55%)**
Serious and consider for reporting via Yellow Card scheme	**174**	**329 (43%)**
Serious but do not report via Yellow Card scheme	**0**	**14 (2%)**
Total number	**365**	**764**

The compiled lists of LLTs for each of the above categories can be seen in Tables 5.4, 5.5 and 5.6. As discussed in Chapter 2, these LLTs are used for coding adverse events into aggregate reported terms and will not exactly match all of the NCI CTCAE term that would be used by a healthcare professional for reporting. Appendix 34 shows the 329 LLTs and the corresponding 353 NCI CTCAE term(s) for those LLTs that received a consensus agreement of serious and to consider for reporting via the Yellow Card.

Table 5.4.
Lower Level Terms classed as serious and should be considered for reporting via the Yellow Card scheme

Autoimmune disorder	Colonic perforation	Muscle weakness right-sided
Serum sickness	Duodenal perforation	Musculoskeletal deformity[#]
Vasculitis	Esophageal perforation	Osteonecrosis
Hearing loss	Gallbladder perforation	Abdominal soft tissue necrosis[#]
Hemolysis	Ileal perforation	Soft tissue necrosis lower limb[#]
Myelodysplasia	Jejunal perforation	Soft tissue necrosis upper limb[#]
Spleen disorder[#]	Rectal perforation	Head soft tissue necrosis[#]
Arrhythmia	Small intestinal perforation	Neck soft tissue necrosis[#]
Atrioventricular block first degree	Gastric perforation	Pelvic soft tissue necrosis[#]
Mobitz type I	Anal stenosis	Chest wall necrosis[#]
Mobitz (type) II atrioventricular block	Bile duct stenosis	Arachnoiditis
Atrioventricular block complete	Intestinal stenosis	Ataxia
Asystole	Colonic stenosis	Ischemia cerebrovascular
Conduction disorder	Duodenal stenosis	Central nervous system necrosis
Sick sinus syndrome	Esophageal stenosis	Encephalopathy
Stokes-Adams syndrome	Ileal stenosis	Hydrocephalus
Wolff-Parkinson-White syndrome	Jejunal stenosis	Recurrent laryngeal nerve palsy
Visceral arterial ischemia	Pancreatic duct stenosis	Cerebrospinal fluid leakage
Electrocardiogram QTc interval prolonged	Pharynx stricture/stenosis	Leukoencephalopathy
Atrial fibrillation	Rectal stenosis	Neurological disorder NOS[#]
Atrial tachycardia	Small intestinal stenosis	Optic nerve disorder
Nodal arrhythmia	Stenosis of gastrointestinal stoma	Oculomotor nerve disorder
Sinus arrhythmia	Gastric stenosis	Vagus nerve disorder
Arrhythmia supraventricular	Typhlitis	Accessory nerve disorder
Supraventricular extrasystoles	Anal ulcer	Phrenic nerve paralysis
Supraventricular tachycardia	Cecal ulcer	Psychosis
Ventricular bigeminy	Colonic ulcer	Pyramidal tract syndrome
Rhythm idioventricular	Duodenal ulcer	Seizure
Torsade de pointes	Esophageal ulcer	Depressed level of consciousness
Ventricular trigeminy	Ileal ulcer	Speech disorder
Ventricular arrhythmia	Jejunal ulcer	Optic nerve edema
Ventricular fibrillation	Rectal ulcer	Retinal detachment
Ventricular flutter	Small intestine ulcer	Retinopathy
Ventricular tachycardia	Stomal ulcer	Vitreous hemorrhage
Myocardial ischemia	Gastric ulcer	Cardiac pain[#]
Cardiac troponin I increased	Bone development abnormal	Chest pain[#]
Cardiac troponin T increased	Slipped femoral epiphysis[#]	Adult respiratory distress syndrome

Table 5.4 continued.
Lower Level Terms classed as serious and should be considered for reporting via the Yellow Card scheme

Cardiopulmonary arrest	Unequal limb length	Chylothorax
Hypertension	Kyphosis[#]	Bronchial fistula
Hypotension	Developmental disturbance	Laryngeal fistula
Left ventricular failure	Developmental delay	Pulmonary fistula
Myocarditis	Delayed puberty[#]	Oral cavity fistula
Pericardial effusion	Precocious puberty	Pharyngeal fistula
Pericarditis	Short stature	Pleural fistula
Pulmonary hypertension	Intracranial hemorrhage	Tracheal fistula
Restrictive cardiomyopathy	Intra-abdominal hemorrhage	Laryngeal obstruction
Cor pulmonale	Anal hemorrhage	Pharyngeal stenosis
Cardiac valve disease	Hemorrhage in bile duct	Tracheal obstruction
Coagulopathy	Cecal hemorrhage	Pneumonitis
Disseminated intravascular coagulation	Colonic hemorrhage	Pneumothorax
Adrenal insufficiency	Pancreatic hemorrhage	Uterine fistula
Hypoparathyroidism	Peritoneal hemorrhage	Vaginal fistula
Hyperthyroidism	Rectal hemorrhage	Bladder obstruction
Hypothyroidism	Gastric hemorrhage	Fallopian tube obstruction
Ascites	Upper gastrointestinal hemorrhage	Prostatic obstruction[#]
Colitis	Esophageal varices hemorrhage	Spermatic cord obstruction
Gastro-intestinal fistula	Bladder hemorrhage	Urostomy obstruction
Anal fistula	Hematosalpinx	Testicular obstruction
Biliary fistula	Renal hemorrhage	Ureteric obstruction
Colonic fistula	Ovarian hemorrhage	Urethral obstruction[#]
Duodenal fistula	Prostatic hemorrhage	Uterine obstruction
Acquired tracheo-oesophageal fistula	Retroperitoneal hemorrhage	Vaginal obstruction
Gallbladder fistula	Spermatic cord hemorrhage	Vas deferens obstruction
Ileal fistula	Testicular hemorrhage	Bladder perforation[#]
Jejunal fistula	Ureteric hemorrhage	Fallopian tube perforation
Oral cavity fistula	Urethral hemorrhage	Kidney perforation
Pancreatic fistula	Hemorrhage urinary tract	Ovarian rupture
Fistula, Pharynx	Uterine hemorrhage	Prostatic perforation
Rectal fistula	Vaginal hemorrhage	Spermatic cord perforation
Salivary gland fistula	Vas deferens hemorrhage	Urostomy perforation
Fistula of small intestine	Bronchopulmonary hemorrhage	Testicular perforation
Gastic fistula	Bronchial hemorrhage	Ureteric perforation
Ileus	Laryngeal hemorrhage	Urethral perforation
Anal necrosis	Pulmonary hemorrhage	Uterine perforation
Intestinal necrosis	Mediastinal hemorrhage	Vaginal perforation
Duodenal necrosis	Hemorrhage nasal	Vas deferens perforation
Esophageal necrosis	Pharyngeal hemorrhage	Renal failure
Gallbladder necrosis	Pleural hemorrhage	Bladder stenosis
Hepatic necrosis	Respiratory tract hemorrhage	Fallopian tube stenosis
Ileal necrosis	Tracheal hemorrhage	Spermatic cord stenosis
Jejunal necrosis	Hemorrhage	Urostomy stenosis
Mouth necrosis	Hepatobiliary disease	Testicular stricture/stenosis
Pancreatic necrosis	Hepatic failure	Ureteric stenosis
Peritoneal necrosis	Pancreatitis	Urethral stricture[#]
Pharyngeal necrosis	Arteritis infective	Uterine stenosis
Rectal necrosis	Bone infection[#]	Vaginal stricture
Small intestinal necrosis	Encephalitis infection	Vas deferens stenosis
Gastrointestinal stoma necrosis	Encephalomyelitis infection	Treatment related 2^{o} malignancy
Gastric necrosis	Infectious colitis	Vaginal atresia

Table 5.4 continued.
Lower Level Terms classed as serious and should be considered for reporting via the Yellow Card scheme

Cecal obstruction	Endocarditis infective	Retinoic acid syndrome
Colonic obstruction	Joint infection#	Cytokine release syndrome
Duodenal obstruction	Eye infection intraocular	Tumor lysis syndrome
Esophageal obstruction	Infectious meningitis	Capillary leak syndrome
Gallbladder obstruction	Cranial nerve infection	Portal hypertension
Ileal obstruction	Peripheral nerve infection	Thrombosis
Jejunal obstruction	Spinal cord infection	Aortic injury
Rectal obstruction	Viral hepatitis	Injury to carotid artery
Small intestinal obstruction	Visceral edema	Injury to inferior vena cava
Intestinal stoma obstruction	Arthritis	Injury to jugular vein
Obstruction gastric	Scoliosis#	Venous injury
Joint range of motion decreased lumbar spine	Joint range of motion decreased cervical spine	Injury to superior vena cava
Perforation bile duct	Fibrosis deep connective tissue#	Venous injury - Viscera
Cecum perforation	Muscle weakness left-sided	
Appendicitis perforated#		

These LLTs were classed as 'not serious' by ADROIT but 'serious' by nominal group consensus.

It should be noted that 26 of these 329 (8%) LLTs that the nominal group consensus agreed were serious had a 'not serious' classification from ADROIT.

Table 5.5.
Lower Level Terms classified as not serious and should not be considered for reporting via the Yellow Card scheme

Hypersensitivity	Corneal infection*	Peripheral sensory neuropathy*
Allergic rhinitis	Tooth infection	Personality change
Immune system disorder*	Duodenal infection	Syncope*
Ear disorder	Esophageal infection	Tremor
Hearing test abnormal*	Otitis externa	Cataract*
External ear inflammation	Eye infection*	Dry eye syndrome*
Middle ear inflammation	Salpingitis infection	Eyelid function disorder
Tinnitus	Device related infection	Glaucoma*
Bone marrow hypocellular*	Gallbladder infection	Keratitis*
CD4 lymphocytes decreased*	Ileal infection	Night blindness*
Hemoglobin decreased*	Jejunal infection	Nystagmus
Atrial flutter*	Kidney infection*	Conjunctival disorder
Sinus bradycardia*	Laryngitis	Eye disorder*
Sinus tachycardia*	Lip infection	Diplopia
Syncope vasovagal*	Hepatic infection*	Proptosis
Premature ventricular contractions*	Pneumonia*	Scleral disorder
Cardiac disorder*	Lymph gland infection	Uveitis*
Diastolic dysfunction*	Mediastinal infection*	Vision blurred
Fibrinogen decreased	Otitis media	Flashing vision
INR increased*	Mucosal infection	Photophobia
Activated partial thromboplastin time prolonged*	Infective myositis*	Watering eyes
Thrombotic microangiopathy*	Infection	Abdominal pain
Fatigue	Rhinitis infective	Anal pain
Fever	Gingival infection	Back pain
Hypothermia*	Pancreas infection*	Bladder pain

Table 5.5 continued.
Lower Level Terms classified as not serious and should not be considered for reporting via the Yellow Card scheme

Insomnia	Paranasal sinus infection	Bone pain
Obesity	Pelvic infection	Breast pain
Body odor	Penile infection	Buttock pain
Chills	Stoma site infection	Chest wall pain
Sweating	Peritoneal infection*	Toothache
Weight gain	Pharyngitis	Esophageal pain*
Weight loss	Pleural infection*	External ear pain
Atrophy skin	Prostate infection	Pain in extremity
Fat atrophy	Anorectal infection	Eye pain
Bruising*	Salivary gland infection	Facial pain
Cheilitis	Scrotal infection	Gallbladder pain
Skin disorder	Sinusitis	Headache
Dry skin	Skin infection	Gastrointestinal pain*
Flushing	Small intestine infection	Joint pain*
Alopecia	Soft tissue infection	Kidney pain*
Skin hyperpigmentation	Splenic infection*	Laryngeal pain
Skin hypopigmentation	Gastric infection	Lip pain
Skin induration	Tracheitis	Hepatic pain
Injection site reaction	Nail infection	Lymph node pain
Nail disorder	Upper aerodigestive tract infection	Ear pain
Photosensitivity*	Upper respiratory infection	Myalgia*
Pruritus	Ureteritis	Neck pain
Rash desquamating	Urethral infection	Neuralgia
Acne	Urinary tract infection	Oral pain
Radiation recall reaction (dermatologic)	Uterine infection	Gingival pain
Dermatitis radiation	Vaginal infection	Ovulation pain
Decubitus ulcer	Phlebitis infective	Pain
Skin striae	Vulval infection	Pelvic pain
Telangiectasia	Wound infection	Penile pain
Urticaria	Vulvitis	Pericardial pain
Wound dehiscence	Opportunistic infection	Perineal pain
Cushingoid*	Lymph leakage	Peritoneal pain
Endocrine disorder	Lymphedema	Phantom pain
Feminization*	Localized edema	Pleuritic pain
Hot flashes	Edema limbs	Prostatic pain
Masculinization*	Palpitations	Rectal pain
Blood gonadotrophin abnormal	Lymphatic disorder	Scalp pain
Growth hormone abnormal*	Fibrosis	Scrotal pain
Blood prolactin abnormal	Lymphocele	Sinus pain
ACTH decreased	Lymphangitic streak	Pain of skin
ADH abnormal	Alanine aminotransferase increased	Stomach pain
Glucose intolerance*	Aspartate aminotransferase increased	Testicular pain
Anorexia	Acidosis*	Pharyngolaryngeal pain
Constipation	Hypoalbuminemia*	Tumor pain
Dehydration	Alkaline phosphatase increased	Urethral pain
Dental prosthesis user	Alkalosis*	Uterine pain
Periodontal disease	Amylase increased	Vaginal pain
Tooth disorder	Blood bicarbonate decreased	Aspiration*
Tooth development disorder*	Hyperbilirubinemia	Atelectasis
Diarrhea	Creatine phosphokinase increased*	Bronchospasm*

Table 5.5 continued.
Lower Level Terms classified as not serious and should not be considered for reporting via the Yellow Card scheme

Abdominal distension	Hypercalcemia*	Carbon monoxide diffusing capacity decreased*
Dry mouth	Hypocalcemia*	Cough
Dysphagia*	Hypercholesterolemia	Dyspnea
Enteritis	Creatinine increased	Laryngeal edema*
Esophagitis	Gamma-glutamyltransferase increased	Forced expiratory volume decreased
Flatulence	Glomerular filtration rate decreased	Hiccough
Gastritis	Hyperglycemia*	Hypoxia*
Gastrointestinal disorder	Hypoglycemia*	Nasal congestion
Dyspepsia	Hemoglobinuria*	Bronchial obstruction
Hemorrhoids	Lipase increased	Pleural effusion*
Fecal incontinence*	Hypermagnesemia*	Postoperative thoracic procedure complication
Biliary anastomotic leak	Hypomagnesemia*	Prolonged intubation after pulmonary resection (>24 hrs after surgery)
Esophageal anastomotic leak	Laboratory test abnormal	Respiratory disorder
Large intestinal anastomotic leak	Hypophosphatemia	Vital capacity decreased
Anastomotic leak	Hyperkalemia*	Voice alteration
Pancreatic anastomotic leak	Hypokalemia*	Bladder spasm*
Pharyngeal anastomotic leak	Proteinuria*	Cystitis
Rectal anastomotic leak	Hypernatremia*	Urinary incontinence*
Small intestinal anastomotic leak	Hyponatremia*	Bladder anastomotic leak
Intestinal stoma leak	Hypertriglyceridemia	Fallopian tube anastomotic leak
Gastric anastomotic leak	Hyperuricemia	Kidney anastomotic leak
Malabsorption*	Exostosis	Spermatic cord anastomotic leak
Anal exam abnormal	Gait abnormal*	Urostomy leak
Oesophagoscopy abnormal	Upper extremity dysfunction	Ureteric anastomotic leak
Endoscopy large bowel abnormal	Superficial soft tissue fibrosis	Urethral anastomotic leak
Laryngoscopy abnormal	Fracture	Uterine anastomotic leak
Ear, nose and throat examination abnormal	Joint effusion*	Vaginal anastomotic leak
Pharyngeal examination abnormal	Joint disorder	Vas deferens anastomotic leak
Proctoscopy abnormal	Device complication	
Endoscopy small intestine abnormal	Extraocular muscle disorder*	Prolapse of urostomy
Gastroscopy abnormal	Muscle weakness lower limb*	Urogenital disorder
Tracheoscopy abnormal	Muscle weakness upper limb*	Prostatic disorder
Esophageal mucositis	Facial muscle weakness*	Renal tubular disorder*
Mucositis oral	Eye muscle weakness*	Urinary frequency
Pharyngeal mucositis	Pelvic floor muscle weakness*	Urinary retention
Rectal mucositis	Muscle weakness trunk*	Urine discoloration
Small intestinal mucositis	Muscle weakness*	Lactation disorder
Gastric mucositis	Musculoskeletal disorder	Nipple deformity
Tracheal mucositis	Myositis*	Breast hypoplasia
Nausea	Osteoporosis*	Ejaculation disorder
Proctitis	Seroma*	Erectile dysfunction
Prolapse of intestinal stoma	Trismus*	Gynecomastia
Salivary gland disorder	Apnea*	Infertility*
Taste alteration	Radiculitis brachial*	Irregular menstruation
Vomiting	Cognitive disturbance*	Libido decreased
Hematoma*	Confusion*	Orgasm abnormal
Oral hemorrhage*	Dizziness	Reproductive tract disorder
Intestinal stoma site bleeding	Extrapyramidal disorder*	Vaginal discharge

Table 5.5 continued.
Lower Level Terms classified as not serious and should not be considered for reporting via the Yellow Card scheme

Hemorrhoidal hemorrhage*	Irritability	Vaginal dryness
Urostomy site bleeding	Memory impairment*	Vaginal mucositis
Tracheostomy site bleeding	Mental status changes*	Vaginal inflammation
Postoperative hemorrhage*	Agitation	Alcohol intolerance*
Petechiae	Anxiety	Flu-like symptoms
Cholecystitis*	Depression*	Ill-defined disorder
Pancreatic enzymes decreased	Euphoria*	Tumor flare*
Abdominal infection*	Myelitis*	Peripheral ischemia
Anal infection*	Olfactory nerve disorder	Phlebitis superficial*
Appendicitis	IVth nerve disorder	Vascular access complication
Biliary tract infection*	Glossopharyngeal nerve disorder	Vascular disorder*
Bladder infection	Trigeminal nerve disorder	Arterial injury - Extremity-lower*
Bronchitis*	Abducens nerve disorder*	Arterial injury - Extremity-upper*
Catheter related infection	Facial nerve disorder*	Arterial injury*
Cecal infection	Acoustic nerve disorder NOS*	Arterial injury – Visceral*
Cervicitis	Hypoglossal nerve disorder*	Venous injury - Extremity-lower*
Conjunctivitis infective*	Peripheral motor neuropathy*	Venous injury - Extremity-upper*

* These LLTs were given classification of serious by ADROIT but not serious by nominal group consensus

126 of the 421 (30%) of the LLTs that were classified as not serious by the nominal group and, therefore, not for reporting via the Yellow Card scheme had an ADROIT classification of 'serious'. The other 295 (70%) LLTs classified by the nominal group were in agreement with the ADROIT classification of 'not serious'.

Some of the reasons stated for classifying these LLTs accordingly included:

1) 'Terms ending in "disorder" are too general of a term to classify'.
2) 'Anticipate infection due to immunosupression and have treatment protocols to deal with so not viewed as serious and would not report'.
3) 'Arterial injury most likely to be an adverse event due to mechanical intervention not due to the effect of a medicine'.
4) 'Hypersensitivity reactions and associated symptoms are anticipated with some chemo regimens and would not report'.
5) 'With the psychosomatic type adverse events would be difficult to tell if due to disease state or the medicine so would not report'.
6) 'Would not report laboratory test or investigation results in isolation without signs, symptoms or a formal diagnosis.

Table 5.6.
Lower Level Terms classed as serious but should not be considered for reporting via The Yellow Card scheme

Blood disorder	Lymphopenia	Large intestinal mucositis**
Haptoglobin decreased	Neutrophil count decreased	Laryngeal mucositis**
Iron increased**	Platelet count decreased	Colitis, infectious (e.g. Clostridium difficile)
Leukopenia	Disease progression	Febrile neutropenia
	Anal mucositis**	Sepsis

** These LLTs were given classification of 'not serious' by ADROIT but serious by nominal group consensus.

The reasons given for not reporting these LLTs, even though they are considered serious in patients receiving cytotoxic chemotherapy, were:

1) Blood disorder (not otherwise specified) the participants agreed could possibly be serious but it is too general a term to consider for reporting via the Yellow Card scheme.
2) In the case of leucopenia, lymphopenia, neutrophil count decreased, and platelet count decreased these are anticipated and common in patients receiving cytotoxic chemotherapy and, whilst viewed as serious consequences with cytotoxic chemotherapy, oncology healthcare professionals would not report.
3) In the case of haptoglobin increased, the participants would not report this test result in isolation but would have to be accompanied by clinical signs and symptoms (such as jaundice, dark coloured urine) or a diagnosis of hemolytic anaemia.
4) In the case of febrile neutropenia and sepsis these are known consequences of cytotoxic chemotherapy secondary to the immunosuppression caused and the participants felt that oncology healthcare professionals would not report these as ADRs.
5) In the case of laryngeal mucositis, anal mucositis, large intestinal mucositis or infectious colitis, while considered serious ADRs in patients receiving cytotoxic chemotherapy, the participants felt that oncology healthcare professionals would not report as they are not unexpected ADRs.
6) In the case of disease progression the participants agreed that this is considered very serious in patients being treated for cancer, however, the lack of response to treatment is an adverse event more regarded as a treatment failure but unlikely to ever be considered an adverse drug reaction.

It should be noted that 4 of these 14 LLTs classified as serious but do not report via the Yellow Card scheme by the nominal group consensus were classed as 'not serious' by ADROIT.

5.4 Discussion

5.4.1. Principal findings

5.4.1.1. Consensus on classification of serious for MedDRA Lower Level terms

In total there was agreement with 78% (597/764) of the ADROIT classification of 'serious/not serious' for the MedDRA LLTs by the nominal group. Of the 764 possible LLTs, the nominal group participants considered 343 (45%) to be serious in patients receiving cytotoxic chemotherapy; of which 9% (31/343) were actually classed as 'not serious' by ADOIT. There were, however, 126 additional LLTs that were classed as 'serious' by ADROIT that did not receive a consensus of 'serious' by the nominal group.

The terms that received consensus agreement as being 'serious' were those adverse effects that would not commonly be anticipated with cytotoxic chemotherapy. The LLTs mainly included autoimmune disorders; auditory impairment disorders; cardiac conduction disorders; endocrine related disorders; neurological disorders; developmental problems; speech impairment; conditions due to fistula, perforation, rupture, stenosis, ulceration or necrosis of organs; sight-threatening eye disorders; haemorrhagic conditions; hepatobiliary disease; joint/motion disorders; gastro-intestinal disorders; secondary malignancy; and some infections, respiratory disorders and blood disorders. Mucositis (anal, large intestinal and laryngeal) were considered serious by the nominal group but were not classified as such by ADROIT. These terms were considered serious with higher grades (3 and 4) since patients would not be able to hydrate or receive nutrition orally; or could impair respiration in the case of laryngeal mucositis.

A total of 421 LLTs received consensus agreement as being 'not serious'. Of these 30% (126/421) were classed as serious by ADROIT. These exceptions from the ADROIT classification of 'serious' included:

1) Those LLTs which were considered too general of a term to classify.

2) Biochemical or investigative test results. These were viewed by the nominal group as clinically not important or 'serious' in isolation without any other accompanying signs, symptoms or diagnosis of disease.
3) Any LLTs that were more likely to be an adverse event which were due to mechanical intervention or disease instead of a result of the effect of a medicine (such as arterial injury, pleural effusion and postoperative haemorrhage).
4) Expected reactions in patients receiving cytotoxic chemotherapy:
    a. Hypersensitivity reactions and associated sequelae such as bronchospasm, syncope. Acute hypersensitivity reactions are associated with a number of cytotoxic chemotherapy regimens. The time to onset of the reaction can occur anytime from the start of the infusion (alemtuzumab, carboplatin, cetuximab, docetaxel, paclitaxel, etoposide, asparginase) to the entire duration of the infusion (oxaliplatin and trastuzumab) (142). As a result guidelines for preventing and managing these ADRs when they do occur are the norm in oncology; and are regarded as part of the treatment.
    b. Some eye disorders such keratitis and infective conjunctivitis which are seen as treatable conditions and not clinically severe.
    c. Some haematopoietic disorders such as bone marrow hypocellular and haemoglobin decreased. Myelosuppression is a common and anticipated adverse effect of cytotoxic chemotherapy, which is routinely managed by G-CSF administration or blood transfusions if required (88).
    d. Tumour flare – this is often anticipated in certain types of cancers when hormonal therapy is commenced such as in prostate cancer when a GnRH agonist or a LHRH agonist is commenced and an anti-androgen must be given in the first few weeks of treatment to prevent (143-145); or in breast cancer when patients are initially started on an oestrogen receptor antagonist such as tamoxifen (145).
    e. The majority of the LLTs pertaining to infections because infections secondary to immunosuppression are expected consequences of cytotoxic chemotherapy and, as such, patients are given supportive treatment to help prevent and treat infection.
    f. Dysphagia.
    g. Photosensitivity.
    h. Skin reactions such as phlebitis.

5) Unexpected but viewed as ‘not serious’ from a clinical perspective
    a. Some types of muscle weakness and neurological disorders including neuropathy.
    b. Some cardiac disorders such as bradycardia and tachycardia.
    c. Urinary and faecal incontinence.
    d. Malabsorption.
    e. Psychological related disorders such as depression, euphoria, confusion, mental status changes and memory impairment.
    f. Pain.
    g. Infertility, masculisation and feminisation.

However the majority of these unexpected adverse effects, as well as some of the expected adverse effects, classified as ‘not serious’ would impact greatly upon a patient’s quality of life (QoL). The four factors known to contribute the most to a patient’s QoL include physical and occupational function (strength, energy, ability to carry on expected normal activities); psychological state (depression, anxiety, fear, wellbeing, cognition); social interaction; and somatic sensations (symptoms due to the disease or the treatment toxicity) (146). In one quality of life study patients with lung cancer the most frequently reported general symptoms that impacted upon QoL included fatigue, pain, appetite loss, sleep disturbance and pain (147). There is then an obvious difference in what is perceived to be serious from a patient and healthcare perspective. Recognition and understanding of this discrepancy that exists between clinically serious and patient-perceived seriousness of ADRs would then suggest that these LLTs that received consensus in agreement from the nominal group has being ‘not serious’ would not be applicable to patient reporting of ADRs in oncology via the Yellow Card scheme.

5.4.1.2. Consensus on reporting of serious of MedDRA Lower Level terms

All 421 LLTs that received a consensus agreement of a ‘not serious’ classification from the nominal group were also achieved agreement that they should not be considered for reporting via the Yellow Card scheme. 30% (126/421) of these LLTs would have been considered serious by ADROIT and would normally be considered for reporting via the Yellow Card scheme. From the 343 LLTs that achieved a consensus agreement of a ‘serious’ classification from the nominal group all except 14 (4%) of these were achieved

agreement that they should be considered for reporting via the Yellow Card scheme. These LLTs and reasons for not reporting included:

1) Febrile neutropenia, leucopenia, lymphopenia, neutrophil count decreased, platelet count decreased and sepsis. These are clinically important in the treatment of patients receiving cytotoxic chemotherapy but they should not be considered for reporting via the Yellow Card scheme since they are such common and expected adverse effects.
2) Blood disorder (not otherwise specified), which the participants agreed could possibly be serious but it is too general a term to consider for reporting via the Yellow Card scheme.
3) Haptoglobin increased, which the participants would not report in isolation without clinical signs and symptoms (such as jaundice, dark coloured urine) or a diagnosis of hemolytic anaemia.
4) Laryngeal mucositis, anal mucositis, large intestinal mucositis or infectious colitis, which the nominal group considered serious ADRs in patients receiving cytotoxic chemotherapy but felt that oncology healthcare professionals would not report.
5) Disease progression, which the participants agreed is considered very serious in patients being treated for cancer but the lack of response to treatment is an adverse event and unlikely to ever be considered an adverse drug reaction.

Therefore, in total, 34% less of the LLTs would be considered for reporting via the Yellow Card scheme than by ADROIT criteria for serious alone.

5.4.1.3.Consensus on factors that should prompt an oncology healthcare professional to consider submitting a Yellow Card report

A consensus agreement, either unanimous or unanimity minus one, was achieved in favour of all factors presented that should act as a prompt for oncology healthcare professionals to consider submitting a Yellow Card report with the exception of one. These factors included:

1) An ADR not listed as a known side effect in the Summary of Product Characteristics.
2) Unusual ADRs not normally seen in oncology.
3) An ADR considered serious
4) A newly licensed medicine
5) A new combination regimen (not necessarily containing a new medicine)
6) A patient hospitalised or hospitalisation prolonged due to an ADR.

7) Significant drug interactions.
8) Latent drug induced cancers.
9) A suspension of chemotherapy due to an adverse event (toxicity).

The only factor that a consensus was not reached on was that of adverse events resulting in dose delays.

5.4.1.4. Consensus on situation criteria when an oncology healthcare professional should submit a Yellow Card report

There was a very high level of agreement that any suspected adverse effect with a new or older medicine (or cytotoxic chemotherapy regimen) that met the criteria of being serious, unknown and Grade 3 to 4 in severity level should be reported via the Yellow Card scheme by oncology healthcare professionals. This would be the minimal acceptable level of reporting in oncology to aid in the detection of any potential safety issues with a cytotoxic chemotherapy agent or regimen.

5.4.2. Strengths and weaknesses of study

All consensus methods can have problems with selection bias (115) (those experts willing to participate may not be representative of the total population targeted). This is especially of concern in this study since two participants came from the Edinburgh Cancer Centre, where a previous pharmacist-led ADR reporting initiative and standard operating procedure for reporting of serious ADRs via the Yellow Card scheme had been employed. In addition, only 4 oncology healthcare professionals were involved in the pre-nominal group process; and only 2 oncology healthcare professionals participated in the nominal group meeting and subsequent rescoring and re-assessments. Therefore the number involved would be too small to except the criteria and standards for serious ADRs to report via the Yellow Card scheme without further validation from the wider oncology healthcare community.

The nominal group process (otherwise known as the expert panel) had representation from pharmacists and a nurse but there was no representation from medical oncologists or an ‘expert’ in adverse drug reaction reporting. The facilitator had seven years experience in ADR reporting but acted as an independent facilitator during this process and took no part in influencing the consensus discussions. One of the pharmacists who participated (in both

the nominal group pre-assessment and the meeting) had worked in pharmacovigilance within the pharmaceutical industry prior to their current post and had also gained oncology expertise.

5.4.3. Strengths and weaknesses in comparison to other studies

No other published studies could be found on developing standards for 'serious' ADRs in general or in specific clinical specialities and no comparison is possible.

5.4.4. Implications of findings

The resultant NCI CTCAEs for the mapped LLTs that obtained consensus from the nominal group as 'serious' for consideration for reporting via the Yellow Card scheme mainly includes adverse effects that would not commonly be anticipated with cytotoxic chemotherapy with approximately one-third less possible terms eligible for reporting. None of the common and expected ADRs associated with chemotherapy regimens would be considered for reporting. This would then provide a more focused approach to Yellow Card reporting; and would allow oncology healthcare professionals to concentrate on adverse events that would be unexpected or unknown with a chemotherapy agent or regimen. If a positive causal analysis of the adverse event for the medicine(s) in question was obtained then it could be considered for reporting via the Yellow Card scheme. Limiting the focus of reporting via the Yellow Card scheme in oncology could also have a positive impact on the demands for time on oncology healthcare professionals since there would be fewer ADRs expected to be reported.

The factors that received consensus agreement in thus study that should act as a prompts for oncology healthcare professionals may also be beneficial in helping them decide whether a Yellow Card report should be made for a possible serious ADR. This may assist in reducing indecision for reporting ADRs. The very high consensus level for the situational criteria indicate that all oncology healthcare professionals should report any suspected serious, unknown ADRs that are Grade 3 to 4 in severity for any cytotoxic chemotherapy agents or regimens, regardless if it contains a new or established medicine. This could provide a good practice guide for oncology healthcare professionals as to the minimum acceptable level of reporting that is expected from. These results reiterate the results obtained from the questionnaire reported in Chapter 4 of this thesis.

5.4.5. Unanswered questions and future research

The areas of further research that may be a beneficial follow up to this study are:

1) Wider consultation with oncology healthcare professionals across the UK to obtain their level of agreement with the serious ADRs which require spontaneous ADR reporting in oncology patients receiving cytotoxic chemotherapy and the criteria agreed by this nominal group could be used to validate these results.
2) It is recommended that the summary classifications of LLTs that received consensus agreement during this nominal group process are reviewed by the Medicines and Healthcare products Regulatory Agency (MHRA) to ensure that the terms selected for as 'serious' and 'not serious' or reportability would be considered acceptable. The agreed LLTs classified as serious in oncology and to consider for reporting via the Yellow Card scheme could then be circulated to the wider oncology healthcare professional population. This consultation could include the Scottish Oncology Pharmacy Practice Group (SOPPG), British Oncology Pharmacy Association (BOPA), United Kingdom Oncology Nursing Society (UKONS) and the Joint Council for Clinical Oncology (JCCO).
3) If these standards were supported and implemented in oncology it would be important to evaluate whether they helped to facilitate an increase in the ADR reporting rate in oncology.

5.5 Conclusions

The results from this study provide a list of factors that should prompt oncology healthcare professionals to consider reporting ADRs via a Yellow Card report; and provide a minimum standard for when an ADR should be reported via the Yellow Card scheme. Further validation and support from the Medicines and Healthcare products Regulatory Agency and the professional oncology associations across the UK for the agreed 'serious' terms and reporting criteria is required before any recommendations for changes to current practice of reporting of serious adverse drug reactions can be made. Ultimately it is hoped that this work may act as a platform for progressing further work on deriving a definitive list of serious ADRs in patients receiving cytotoxic chemotherapy; and agreement of any subsequent standards/criteria for reporting via the Yellow Card scheme.

Chapter 6
Key findings and recommendations

6.1 Summary of key findings

The aim of this work was to produce guidelines to support reporting of serious adverse drug reactions as appropriate to cancer chemotherapy; and to derive recommendations for improvements in pharmacovigilance practice in oncology. Specific objectives were to:

i) Quantify the potential for improvement in spontaneous ADR reporting before and after a pharmacist led ADR reporting initiative by a retrospective survey of case notes.

ii) Examine attitudes of oncology healthcare professionals on the need for improving reporting of ADRs in oncology.

iii) Develop standards for classification and reporting of serious ADRs in patients receiving cytotoxic chemotherapy based on NCI CTCAE.

In the process of carrying out these studies a number of key findings were identified which are described in section 6.1.1 to 6.1.8.

6.1.1 Incidence of adverse drug reactions in oncology

In the retrospective case note review of patients receiving adjuvant chemotherapy for breast cancer, a total of 911 serious ADRs spread over 717 cycles occurred in 97% of the patients in 2001; and 1133 serious ADRs spread over 778 cycles occurred in 96% of the patients in 2003. This gave an average incident rate of 1.3 and 1.5 ADRs per cycle in 2001 and 2003 respectively. The Epi/CMF chemotherapy regimen caused 61% of these serious ADRs in 2003 but only contributed 30% in 2001, however, the doubling in number of patients receiving this regimen in 2003 from 2001 may account for this proportionate increase in observed serious ADRs. This observation is in agreement with the NEAT trial, which showed that the overall incidence of adverse effects was significantly higher for epirubicin plus CMF than with CMF alone (83).

Serious haematological ADRs accounted for 73% and 72% of the total observed ADRs in the study populations in 2001 and 2003 respectively. Grade 3 and 4 haematological ADRs accounted for only 13% and 15% of the serious haematological adverse drug reactions respectively in 2001 and 2003.

Serious, non-haematological ADRs accounted for 27% of the total ADRs in both 2001 and 2003. Oncology healthcare professionals often anticipate the majority of haematological ADRs seen in oncology; and best supportive care is given to prevent or treat (such as G-CSF to treat neutropenia; or erythopoiesis-stimulating agents or blood transfusions to treat anaemia) (88). The main system organ class to which the non-haematological serious ADRs belonged was eye disorders (67% and 74% in 2001 and 2003 respectively) due to the high number of episodes of conjunctivitis seen in the patients receiving 5-fluorouracil. Conjunctivitis is an anticipated side effect of treatment and patients are managed with symptomatic care. Infections accounted for 14% and 13% of the total non-haematological serious ADRs in 2001 and 2003 respectively. Neutropenic sepsis, specifically, accounted for a very small percentage of the total non-haematological serious ADRs seen in 2001 and 2003 (2% and 6% respectively).

Psychiatric ADRs (including depression, mood swings, and anxiety) accounted for 10% and 3% of the total non-haematological serious ADRs seen in 2001 and 2003. Psychological stress is frequently seen in cancer patients and factors such as pain, fatigue, nausea, vomiting and poor performance status are considered to be associated with, and intricately related to psychiatric disorders during cancer treatment. All of these factors are directly attributable to chemotherapy. Further studies, however, are needed to clarify causal links between QOL and psychiatric disorders (84, 85).

6.1.2 Hospitalisation in patients with breast cancer due to ADRs from cytotoxic chemotherapy

There were twice as many patients admitted to hospital in the study populations in 2003 than in 2001 due to an ADR as observed from the retrospective case review (24% versus 13%). In 2003, the percentage of admissions to hospital with an ADR following treatment with Epi/CMF was almost double that observed in 2001 (71% versus 38%). There were also proportionally more occupied bed days as a result of an ADR in 2003 than in 2001 with a total of 226 and 87 inpatient bed days in 2003 and 2001 respectively. This increase was mainly due to Epi/CMF but the total number of patients in 2003 receiving Epi/CMF was double that of 2001 (62 versus 31). In 2001 the unit cost for medical inpatient care was £359.00 per day in Scotland (82), it can be calculated therefore, that a total cost of approximately £112,000 (£81,000 for 2003 and £31,000 in 2001) was the result of ADRs in the study populations for 2001 and 2003.

6.1.3 Consequence to chemotherapy treatment regimen due to ADRs

There was very little observed difference between the study populations in 2001 and 2003 in the retrospective case note review for consequences from ADRs, which included dose delays, regimen changes, treatment cessation, or patients recovering between treatment cycles requiring no dose change. There were, however, over twice as many dose reductions before the next cycle of treatment in 2003 than in 2001, which can be mainly attributed to Epi/CMF. This data is in contrast to the National Epirubicin Adjuvant Trial (NEAT) that showed that the excess treatment-related adverse effects with EPI/CMF did not affect delivered-dose intensity (83). 83% (10 of 12) of these required dose reductions in 2003 in patients who were hospitalised due to an ADR, compared to 50% (3 of 6) in 2001.

It should be noted, however, that 60% of the treatments which were stopped in 2003 were observed in patients who were hospitalised with an ADR; compared to only 25% in 2001. This suggested that more severe adverse events and intolerance to treatment were prevalent in the 2003 patient population due to more aggressive treatment.

6.1.4 Pharmacist-led intensive monitoring initiative in oncology

The retrospective case note review showed that there was only an increase of 5 Yellow Card reports (1 versus 6) from 2001 to 2003, which was statistically non-significant. Therefore the substantial increase in the number of Yellow Cards (13 versus 118) submitted during the audit year in 2002 compared to 2001 at the Edinburgh Cancer Centre was not sustainable. As a result, even though this initiative encouraged good reporting practice, and shows the potential of Yellow Card reporting in oncology it cannot be adopted as a means for sustaining increased ADR reporting in oncology via the Yellow Card scheme; and other non-labour intensive means of improving oncology ADR reporting must be pursued in addition to this model of good practice to improve pharmacovigilance in oncology.

It must be noted that pharmacists were the only oncology healthcare professional group submitting these reports in both 2001 and 2003. In addition it was found from analysis of the questionnaire responses that the only covariant factor that was associated with an increase in the decision to report via the Yellow Card scheme was reporter group, with

pharmacists being over three and a half times more likely to report then doctors; and nurses were half as likely as doctors to report. None of the factors that were assessed in the survey questionnaire on why healthcare professionals do not report ADRs via the Yellow Card scheme showed any noticeable variance in opinion between the healthcare professional groups to account for this increased tendency for pharmacists to report more. So the question remains what influences this trend and could it be transferable to other healthcare professional groups.

6.1.5 Knowledge, attitude and opinions of oncology healthcare professionals to spontaneous reporting of oncology ADRs via the Yellow Card Scheme

The level of awareness of the Yellow Card scheme and its roles was found to be high in oncology healthcare professionals in both the one-to-one interviews and the survey questionnaire. The level of knowledge on what ADRs to report was found to be a problem with two-thirds of the oncology healthcare professionals responding to the questionnaire indicating that they were unsure of what types of ADRs that should be reported via the Yellow Card; and reporting that the lack of specific guidance on the types and grades of oncology ADRs to report was a contributing factor to reasons why they did not make more Yellow Card reports. In addition one third of oncology healthcare professionals admitted to having seen ADRs in clinical practice but were not sure which ones the MHRA wanted them to report.

Approximately one quarter of the oncology healthcare professionals had never completed a Yellow Card report previously in their career, with nurses accounting for 58% of this group. The lack of reporting by nurses is of concern, considering the vital role that nurses provide in the continuum of care of patients and in the monitoring of adverse events during chemotherapy. Of those oncology healthcare professionals who had reported, 70% had submitted between 1 and 10 Yellow Card reports during their career (with pharmacists and doctors accounting for 47% and 40% respectively of this group). Considering the number of adverse events that are seen daily in oncology, this indicates a very low Yellow Card reporting rate. From the questionnaire 92% of the healthcare professionals were in agreement that oncology adverse drug reactions were under-reported via the Yellow Card scheme but 53% were in agreement in perceiving that the reporting rate for oncology adverse drug reactions was not less than that in any other clinical specialty.

When the oncology healthcare professionals were given examples in the questionnaire of possible ADRs that met the MHRA criteria for to submit a Yellow Card report, only 30% of the examples were selected as ones that they would report to the MHRA. A possible reason for this low level of agreement with reporting a ADR could possibly be attributed to the fact that 80% of the oncology healthcare professionals did not view oncology adverse events (toxicities) as an ADR (i.e. they expect to see them and know how to prevent them or reduce their severity with pre-medication and, therefore, management of ADRs are regarded as part of the treatment process). In addition, 42% of the oncology healthcare professionals in the questionnaire indicated that they often recognise ADRs in patients receiving chemotherapy but choose not to report believing that they are an inevitable consequence of therapy and of little relevance for reporting.

In the study populations in 2001 and 2003, all the haematological ADRs seen were known and expected. These attitudes and opinions reflected in the questionnaire possibly account for why the oncology healthcare professionals would not consider reporting these ADRs via the Yellow Card scheme, even though they do meet the Yellow Card criteria for reporting. Similarly with non-haematological serious ADRs, the majority of those ADRs seen in the patient populations in 2001 and 2003 are those that would be anticipated (infections secondary to immunosuppression, eye problems with 5-fluorouracil regimens, allergic reactions and psychiatric related ADRs). Patients are either pre-medicated or are treated as per treatment protocol when they do occur. As a result, reporting of any of these expected ADRs with chemotherapy regimens is unlikely to be considered by oncology healthcare professionals for reporting via the Yellow Card scheme.

The questionnaire also highlighted, in common with previous work reported in the literature, that the conflicting priorities for healthcare professionals' time will always be a factor in reducing suspected ADRs reporting via the Yellow Card scheme. The majority view is that it can be time consuming to complete a Yellow Card report in everyday clinical practice so it is not surprising that it was not perceived to be a high priority. To compound this, the consensus from oncology healthcare professionals who participated in this study is that the large numbers of ADRs seen in oncology make it impossible to report them all and, therefore, there is a degree of tolerance probably not seen in other clinical specialities. The consensus view is that if the oncology healthcare professionals attempted to report all suspected ADRs in oncology that meet the Yellow Card criteria for reporting (all suspected

reactions for black triangle medicines and all serious, suspected ADRs for all other medicines), it would be an unachievable goal for the healthcare professionals; and not necessarily desirable for the MHRA (possibility of 'noise'). 'Noise' in spontaneous reporting databases includes non-serious and/or incidental adverse events, which detract from the ability of assessors to detect new potentially serious ADR signals (131). As one of the interviewees observed in the one-to-one interviews, 'There is a great danger of being swamped with expected toxicities particularly for oncology drugs, where if we reported every expected event we see'. Therefore it does then bring into question whether the current Yellow Card criteria are realistic or achievable in oncology practice. The need then exists for oncology oriented guidelines for ADR reporting, which highlight clinical relevance, to be developed to address this issue.

The oncology healthcare professionals responding to the questionnaire identified that not being certain of the causality of an ADR with a specific medicine; and inadequate access to information sources about ADRs that would aid in determining which drug could be causing an ADR were possible reasons why they did not make Yellow Card reports.

All oncology healthcare professionals responding to the questionnaire indicated agreement that there were factors of high, medium and low level of importance that had an impact upon their decision to complete a Yellow Card report. The factors of high importance included seriousness of the reaction; unusual ADRs not normally seen in oncology; a newly licensed medicine; an ADR not listed as a known side effect in the SPC for the product; and significant drug interactions. The factors seen of medium importance included patients being hospitalised or hospitalisation prolonged because of an ADR; latent drug induced cancers; and any new chemotherapy regimen(s). The factors deemed to be of low importance were suspension of chemotherapy due to an adverse event; and any adverse event resulting in dose delays to chemotherapy. There was no consensus observed from the oncology healthcare professionals on whether the grade of NCI CTCAE would be of high, medium or low importance in their decision to make a Yellow Card report since there was a relatively even distribution of responses (32% said 'Yes', 35% said 'Not sure and 33% said 'No'). For those individuals that said it was important, 55% indicated that Grades 3 and 4 should be considered for reporting.

As with previous results from other survey questionnaires reported in the literature (33, 52-55, 100, 104-107, 110, 111, 113), the oncology healthcare professionals were in agreement that the following were factors influencing their decision to report an ADR:

- Not certain of the causality of an ADR with a specific medicine.
- Inadequate information sources on ADRs to aid in determining which drug could be causing an ADR.
- Do not know what types of ADRs that should be reported via the Yellow Card scheme. 32% of oncology healthcare professionals admitted to having seen ADRs in clinical practice but were not sure which ones the MHRA wanted them to report.
- Too time-consuming.
- Do not see benefit in reporting well recognised ADRs which are seen routinely in everyday clinical practice.

Other factors identified in this study by oncology healthcare professionals that influenced their decision to report an ADR, and which have not previously been described in the literature, included:

- The volume of ADRs seen in oncology makes it impossible to report them all.
- Lack of specific guidance on the types and grades of oncology ADRs to report via the Yellow Card Scheme.
- Submitting Yellow Card reports are not a high priority in everyday clinical practice.

In contrast to previous results from other survey questionnaires described in the literature (33, 52, 53), the majority of the oncology healthcare professionals disagreed that the following factors influenced their decision to report an ADR:

- A single report is not enough to add to medical knowledge
- Lack of professional obligation to report
- Feeling of being personally liable for ADR
- The Yellow Card form is too congested

Another factor that was identified previously as not impacting upon a healthcare professional's decision to report (113), and replicated by the results from this survey is that

serious ADRs are well documented by the time the medicine is marketed so oncology healthcare professionals do not see any point in reporting.

Other factors that have previously been shown to affect ADR reporting in other professional groups but not identified by the oncology healthcare professionals as factors that influenced their decision to report an ADR, and have not previously been well described in the literature included:

- Do not know how the information reported in Yellow Cards is utilised. This factor has been previously suggested in the literature as a reason for not reporting an ADR (52, 105) but was not seen as important by oncology healthcare professionals in their decision to submit a Yellow Card report in this study.

- Fear that if they report an ADR via the Yellow Card they will be pressurised to provide more information.

- Prefer to report directly to the pharmaceutical company instead of via the Yellow Card scheme.

The last two factors have not been formally evaluated previously in the literature but have been speculated as possible reasons for low-reporting rates via the Yellow Card scheme. The results from this questionnaire suggest that these conclusions may not apply to oncology healthcare professionals.

Almost half of the oncology healthcare professionals did not have any strong preference for reporting method (paper or electronic). However approximately a third of the oncology healthcare professionals said that they preferred to complete Yellow Cards electronically (with pharmacists accounting for almost two-thirds of this group) and one-fifth of the reporters indicated preference for paper Yellow Cards (doctors and nurses accounted for 54% and 34% respectively of this group). Some 80% of the respondents were in agreement that a reporting form that took less time to complete might help increase reporting in oncology. These forms could utilise more tick boxes; less free-format text; pre-populated fields on an electronic report such as patient details, medicines, past medical history, etc. The electronic Yellow Card addresses the issue of more tick boxes and having to enter free-format text since there is a drop down menu to select from for suspected reactions and suspected medicine(s) or concurrent medicines. It was, however, noted that access to the electronic Yellow Card was an obstacle to submitting suspected ADRs electronically since websites out with the hospital intranet was blocked. It is unknown how widespread this problem is but is an issue which may be important and worth resolving.

6.1.6 Developing standards for reporting of serious ADRs in oncology

In total there was a consensus agreement with 78% (597/764) of the ADROIT classification of 'serious/not serious' for the MedDRA Lower Level Terms (mapped from the NCI CTCAE scale) by the nominal group. Of the 764 possible LLTs, the nominal group participants considered 343 (45%) to be serious in patients receiving cytotoxic chemotherapy; of which 9% (31/343) were actually classed as 'not serious' by ADOIT. There were, however, 126 additional LLTs that were classed as 'serious' by ADROIT that did not receive a consensus of 'serious' by the nominal group.

The terms that received consensus agreement as being 'serious' were those adverse effects that would not commonly be anticipated with cytotoxic chemotherapy. The LLTs mainly included autoimmune disorders, auditory impairment disorders, cardiac conduction disorders, endocrine related disorders, neurological disorders, developmental problems, speech impairment, conditions due to fistula/ perforation/ rupture/ stenosis/ ulceration or necrosis of organs, sight-threatening eye disorders, haemorrhagic conditions, hepatobiliary disease, joint/motion disorders, gastro-intestinal disorders, secondary malignancy; and some infections, respiratory disorders and blood disorders. Interestingly mucositis (anal, large intestinal and laryngeal) were considered serious by the nominal group but were not classified as such by ADROIT. These terms were considered serious with higher grades of toxicity (Grades 3 and 4) since patients would not be able to hydrate or receive nutrition orally; or could impair respiration in the case of laryngeal mucositis.

A total of 421 LLTs received consensus agreement as being 'not serious'. Of these 30% (126/421) were classed as serious by ADROIT. These exceptions from the ADROIT classification of 'serious' included:

i) Those LLTs which were too general of a term to classify.

ii) Biochemical or investigative test results that were viewed by the nominal group as clinically not important or 'serious' in isolation without any other accompanying signs, symptoms or diagnosis of disease.

iii) Any LLTs that were more likely to be an adverse event due to mechanical intervention or disease instead of the result of an effect of a medicine (such as arterial injury, pleural effusion and postoperative haemorrhage); iv) expected reactions in patients receiving cytotoxic chemotherapy (such as hypersensitivity reactions,

infective conjunctivitis, some haematopoietic disorders, tumour flare, dysphagia, skin reactions and the majority of the LLTs pertaining to infections).

v) those not viewed as serious from a clinical perspective (such as neuropathy, bradycardia, tachycardia, incontinence, malabsorption, pain, infertility, masculisation, feminisation, and psychological related disorders).

The majority of these unexpected adverse effects, as well as some of the expected adverse effects, classified as 'not serious' may impact greatly upon a patient's quality of life (QoL). The four factors known to contribute the most to a patient's QoL include physical and occupational function (strength, energy, ability to carry on expected normal activities), psychological state (depression, anxiety, fear, wellbeing, cognition), social interaction and somatic sensations (symptoms due to the disease or the treatment toxicity) (146). Recognition and understanding of this discrepancy that exists between clinically serious and patient-perceived seriousness of ADRs would then suggest that these LLTs that received consensus in agreement from the nominal group has being 'not serious' would not be applicable to patient reporting of ADRs in oncology via the Yellow Card Scheme.

All 421 LLTs that received a consensus agreement of a 'not serious' classification from the nominal group were also those which were agreed that should not be considered for reporting via the Yellow Card Scheme. 30% (126/421) of these LLTs would have been considered serious by ADROIT and, otherwise, would normally be considered for reporting via the Yellow Card Scheme. From the 343 LLTs that received a consensus agreement of a 'serious' classification from the nominal group all except 14 (4%) of these were agreed that they should be considered for reporting via the Yellow Card scheme. These LLTs and reasons for not reporting included:

- Febrile neutropenia, leucopenia, lymphopenia, neutrophil count decreased, platelet count decreased and sepsis, which are clinically important in the treatment of patients receiving cytotoxic chemotherapy but should not be considered for reporting via the Yellow Card scheme since they are such common and expected adverse effects.

- Blood disorder (not otherwise specified), which the participants agreed could possibly be serious but it is too general a term to consider for reporting via the Yellow Card scheme.

- Haptoglobin increased, which the participants would not report in isolation without clinical signs and symptoms (such as jaundice, dark coloured urine) or a diagnosis of hemolytic anaemia.

- Laryngeal mucositis, anal mucositis, large intestinal mucositis or infectious colitis, which the nominal group considered serious ADRs in patients receiving cytotoxic chemotherapy but felt that oncology healthcare professionals would not report.

- Disease progression, which the participants agreed is considered very serious in patients being treated for cancer but the lack of response to treatment is an adverse event and unlikely to ever be considered an adverse drug reaction.

Therefore, in total, 34% less of the LLTs would be considered for reporting via the Yellow Card scheme than by ADROIT criteria for serious alone.

The results from the survey questionnaire for factors seen to be of high or medium importance by oncology healthcare professionals in determining whether to submit a Yellow Card report included:

- The seriousness of the reaction.
- Unusual ADRs not normally seen in oncology.
- A newly licensed medicine (black triangle); an ADR not listed as a known side effect in the SPC for the product.
- Significant drug interactions.
- Patient hospitalised or hospitalisation prolonged due to an ADR
- Latent drug induced cancers.
- A new chemotherapy regimen (not necessarily containing a new medicine).

As well, the respondents to the questionnaire indicated that two factors that did not affect their decision to submit a Yellow Card included the suspension of treatment due to an ADR and adverse events resulting in dose delays to chemotherapy treatment.

The nominal group were also asked to indicate their level of agreement in support of these findings for factors that should act as a prompt for oncology healthcare professionals to consider submitting a Yellow Card report. A consensus agreement was achieved in favour of all factors posed with the exception of three. These factors included:

- An ADR not listed as a known side effect in the Summary of Product Characteristics.
- Unusual ADRs not normally seen in oncology.
- An ADR considered serious

- A newly licensed medicine
- A new combination regimen (not necessarily containing a new medicine)
- A patient hospitalised or hospitalisation prolonged due to an ADR.
- Significant drug interactions.
- Latent drug induced cancers.
- A suspension of chemotherapy due to an adverse event (toxicity).

The only factor that a nominal group consensus was not reached on was that of adverse events resulting in dose delays.

The results from the questionnaire indicated that there are only two ADR situations that the majority of the oncology healthcare professionals would always consider completing a Yellow Card report for were: 1) Black triangle status, serious, not a known side effect of medicine CTCAE Grade 3-4 and 2) Non-black triangle status, serious, not known side effect of medicine, grade 3-4. These results were supported by a very high nominal group consensus level for these situational criteria. This would be considered to be the minimal acceptable level of reporting in oncology to aid in the detection of any potential safety issues with a cytotoxic chemotherapy agent or regimen.

The key questions that must be addressed before any recommendations can be made to aid reporting of oncology ADRs are:

- Is it acceptable to report only ADRs that are not listed as known side effects in the Summary of Product Characteristics for an oncology medicine, even for medicines with a black triangle status?

- Is it acceptable that only certain grades of NCI CTCAE (such as Grades 3 and 4) of oncology ADRs should be considered for reporting?

If both healthcare professionals and the MHRA would support such recommendations then it is possible that steps can be taken to improve reporting of ADRs in oncology via the Yellow Card scheme.

6.1.7 Patient reporting of adverse events/ADRs in oncology

More than 75% of the oncology healthcare professionals were in agreement that patient reporting of ADRs in oncology would be beneficial but accuracy in grading might be a

problem since patients are not adequately informed to detect ADRs, and they would not be able to distinguish what ADRs were serious enough to report without appropriate education. 68% of the oncology healthcare professionals, however, were in agreement that patients might under report ADRs (minimise toxicities to avoid treatment delays). Despite these concerns, the need for patients to be able to report an adverse event directly is increasing in importance due to the increasing number of patients receiving chemotherapy treatments at home; and the use of oral therapies, which could mean that patients could go for a much longer time before seeing a healthcare professional to detect and report an ADR.

There is also a need to develop an on-line self-reporting of 'toxicities' during chemotherapy for completion by patients in the home setting (in real-time), which will allow doctors to have access to this information in secondary care for review and intervention. At present most patients either keep a mental or paper diary of events they have experienced during the chemotherapy cycle (or recall from memory retrospectively if they have not forgotten) to advise the nurse during assessment prior to receiving the next cycle of chemotherapy. The reliability of the information is variable, especially if being recalled from memory, and having a third-party to interpret the information provided. In symptom research, patients' reports are the gold standard for assessing symptoms, with studies consistently showing that doctors and nurses underestimate (or occasionally overestimate) symptom frequency and severity in comparison to patients (135-139); and a need for a tool for collecting patient reported adverse event data in chemotherapy was concluded (135). A prospective means of capturing 'toxicities' during treatment may be beneficial and would eliminate third-party reporting biases.

6.1.8 Active surveillance

In Scotland investment has been given to purchasing a paperless, electronic chemotherapy management system for all of Scotland. Adverse events will be recorded within these electronic patient records. Other than the obvious benefits of a paperless patient record, there is a pharmacovigilance potential that is under developed at present. The suggested potential benefits of aggregate data from these electronic patient records included monitoring of 'toxicities', gathering national data and identifying trends, and helping doctors decide which cytotoxic chemotherapeutic medicines or regimens to use based on their clinical effectiveness and safety profile. Greater than 95% of the oncology healthcare professionals were in agreement that capture of CTCAE grades in clinical practice would

be beneficial; and that anonymised, aggregate data of these CTCAE would be beneficial in monitoring oncology adverse events in Scotland (possibly inform decision making on which medicines and regimens to use). Almost all of the oncology healthcare professionals surveyed would be happy to contribute their patients' anonymised CTCAE grade data for electronic linkage, and would be interested in any results from aggregate data on oncology adverse event trends. It was the opinion of those surveyed that, while it would be feasible to develop such a database in Scotland, it would only be of value if it did not involve additional input time from healthcare professionals and it was adequately resourced to ensure quality and reliability.

6.2 Recommendations

In the 41 years since the WHO committed to developing the necessary scientific and clinical infrastructure to provide for surveillance and monitoring of the safety of medicines (or pharmacovigilance as the discipline as come to be known) much has been achieved (32). There is, however, room for improvement and much work on encouraging continued vigilance in the post-marketing monitoring of the safety of medicines exists. Based on the results of the studies presented in this thesis, the following recommendations specific to oncology (where patients receive cytotoxic chemotherapy) are made with the aim to improve pharmacovigilance practice in oncology:

1) Engage oncology healthcare professionals in the process

The success or failure of any spontaneous reporting system depends upon active participation of reporters (31). It is then essential that oncology healthcare professionals become engaged in the process; and the MHRA should foster this relationship by providing feedback on ADRs received and by specifying the subgroups of the ones they would particularly like to receive; and encouraging feedback in return from this reporter group.

2) Education and training

Greater education and training to support ADR reporting by oncology healthcare professionals is required to highlight the importance of the Yellow Card Scheme and post-marketing monitoring of medicines. It is also important that healthcare professionals make best use of simple causality assessment nomograms and be aware of (and make best use of) both paper and electronic sources of information available to them in trying to decide if a medicine could possibly be implicated in a suspected ADR.

It must also be made clear to healthcare professionals that there is no need to be 100% certain that an adverse event has been caused by a medicine in order to make a Yellow Card report; and that a suspicion is all that is required.

3) Encourage pharmacists good practice ADR reporting example

Oncology pharmacists are the professional group in oncology that are more likely to report via the Yellow Card and this good practice should continue to be encouraged. At present the reason for this increased tendency of pharmacist to report via the Yellow Card scheme is undefined but should be explored.

4) Suggestions for change to definition of 'serious' ADR reporting criteria in Oncology

The greatest obstacle to oncology healthcare professionals is the large volume of ADRs that would require reporting if the current Yellow Card criteria were adhered to and the resulting time pressures required to undertake this reporting. Oncology healthcare professionals have developed a tolerance to ADRs that are anticipated and managed as part of the treatment protocol of cytotoxic chemotherapy regimens; and have indicated that the current Yellow Card reporting criteria need to be adapted in oncology to provide 'fit-for-purpose' reporting criteria.

The resultant MedDRA Lower Level Terms that obtained consensus from the nominal group as 'serious' for consideration for reporting via the Yellow Card Scheme is an attempt to address this issue. The LLTs mainly include adverse effects that would not commonly be anticipated with cytotoxic chemotherapy with approximately one-third less possible terms eligible for reporting. None of the common and expected ADRs associated with chemotherapy regimens would be considered for reporting. This would then provide a more focused approach to Yellow Card reporting; and would allow oncology healthcare professionals to concentrate on adverse events that would be unexpected or unknown with a chemotherapy agent or regimen. If a positive causal analysis of the adverse event for the medicine(s) in question was obtained then it could be considered for reporting via the Yellow Card Scheme. Limiting the focus of reporting via the Yellow Card Scheme in oncology could also have a positive impact on the demands for time on oncology healthcare professionals since there would be fewer ADRs expected to be reported.

It is essential that the summary classifications of LLTs that received consensus agreement during this nominal group process are validated and accepted by the Medicines and Healthcare products Regulatory Agency (MHRA) and the wider oncology healthcare community before any adoption of these classifications derived during the nominal group process can occur. The MHRA must first assess to ensure that the terms selected for as 'serious' and 'not serious' or reportability would be considered acceptable. The agreed LLTs classified as serious in oncology and to consider for reporting via the Yellow Card Scheme could then be circulated to the wider oncology healthcare professional population for consultation. This consultation should include, as a minimum, the Scottish Oncology Pharmacy Practice Group (SOPPG), British Oncology Pharmacy Association (BOPA), United Kingdom Oncology Nursing Society (UKONS) and the Joint Council for Clinical Oncology (JCCO).

Any sharpening of the reporting criteria to exclude those common ADRs that are anticipated in oncology might increase reporting and should be encouraged. It is, however, necessary that oncology healthcare professionals continue to have a high threshold of suspicion for any ADRs that would be unexpected regardless if included in the list of serious LLTs. The list of factors in number 4 below would be essential prompts to aid oncology healthcare professionals in this process.

5) Factors that should prompt oncology healthcare professionals to consider submitting a Yellow Card report

The factors that received consensus agreement in this study that should be considered as prompts for oncology healthcare professionals in helping them decide whether a Yellow Card report should be made for a possible serious ADR. This would aid in taking indecision out of the reporting process. These factors included:

i) An ADR not listed as a known side effect in the Summary of Product Characteristics.
ii) Unusual ADRs not normally seen in oncology.
iii) An ADR considered serious.
iv) A newly licensed medicine.
v) A new combination regimen (not necessarily containing a new medicine).
vi) A patient hospitalised or hospitalisation prolonged due to an ADR.
vii) Significant drug interactions.

viii) Latent drug induced cancers.

ix) A suspension of chemotherapy due to an adverse event (toxicity).

6) Minimum acceptable level of reporting via the Yellow Card Scheme

All oncology healthcare professionals should be expected to report any suspected serious, unknown ADRs that are Grade 3 to 4 in severity for any chemotherapy agents or regimens, regardless if a new or old medicine as the minimum acceptable level of reporting that is expected from an oncology healthcare professional.

7) Develop and encourage patient reporting of adverse effects during treatment with cytotoxic chemotherapy

Patients may be in a better position than healthcare professionals to assess the actual benefit and harm of a medicine taken. Observations and reports made by healthcare professionals will be an interpretation of a description provided by a patient, together with objective measurements sometimes. Some believe that direct patient participation in ADR reporting will increase the efficiency of a pharmacovigilance system by compensating for some of the shortcomings of healthcare professionals' reporting (31). Patient reporting of ADRs must be developed in oncology to better facilitate monitoring of symptoms during chemotherapy, especially with the increased uptake of treatment in the home setting. Patients have been officially able to make Yellow Card reports directly to the MHRA since February 2008. This should be encouraged by oncology healthcare professionals.

8) Access to electronic Yellow Card within all hospitals

To facilitate electronic ADR reporting via the Yellow Card Scheme all healthcare professionals should have access to the internet. At present this does not appear to be the standard or hospital IT firewalls actively block access.

9) Develop interfaces between all UK electronic patient/prescribing records and the electronic Yellow Card to allow for patient-specific pre-populated fields

The updated CTCAE version 3.0 incorporates the preferred terms from MedDRA, which means that selected adverse effects could possibly be electronically communicated to the MHRA (who use the same common terminology for classification of suspected ADRs in their surveillance database "Sentenil") if this facility were written into the functionality of the software. Work is currently ongoing between the MHRA and providers of GP electronic paperless systems to achieve this interface of computer systems in primary care, however,

more work is required to develop interfaces between all secondary electronic patient/prescribing records and the electronic Yellow Card to allow for patient-specific pre-populated fields.

10) Invest in and develop the active surveillance potential available in Scotland

However much spontaneous reporting can be improved, it is unlikely to identify all important, unrecognised safety issues with medicines so alternative methods for capturing possible ADRs should be pursued to provide more systematic data collection methods (36). With the investment in electronic patient records across Scotland in oncology comes the unique opportunity to develop a cohesive pharmacovigilance system in oncology. The potential use for this anonymised dataset is largely undefined at present, however, possible applications include:

- Individual oncology units could use this data for prospective computerised surveillance of adverse events rather than relying on the traditional 'voluntary' reporting systems, which are potentially cumbersome and less effective (132).

- Cross-linkage to computerised registries such as the Scottish Cancer registry. This would allow for a more robust means of evaluating the impact of chemotherapy interventions on cancer outcomes and survival in Scotland.

- Signal generation and monitoring of chemotherapeutic agent(s)/regimens. By applying data mining algorithms (DMAs) to this dataset there could be a possibility for supplementing post-marketing information on oncology medicines from the Yellow Card Scheme. DMAs have been studied in hopes of enhancing the ability to screen large databases of adverse events with oncology medicines or other medicines with similar features (i.e. medicines that may be approved on an accelerated basis, are known to have serious toxicity, are administered to patients with substantial and complicated co-morbidity illness, are not available to the general medical community, and may have a high frequency of use out with the terms of a medicine's market authorisation or "off-label" use) (133).

Before such a benefit realisation can be achieved, more investment of resources and collaboration between health boards, cancer centres, the Information Services Division and the MHRA is required. In addition the following problems would need to be addressed:

i) In NHS Scotland the debate over the use and safeguarding of personal information is ongoing. Consensus is arising but doubt remains over the clarity of professional guidance and how to achieve consensus over its interpretation; how to inform patients and what to tell them; how to regulate disease and other registries; whether it is possible to anonymise data in ways which retain their usefulness (134). This creates a challenge and a definitive answer must be reached before anonymisation of adverse events in oncology for

pharmacovigilance/epidemiological purposes can be pursued. If this were pursued through the Information and Statistics Division (ISD), who are responsible for collating and holding health-related data across Scotland including the Scottish Cancer registry, then this is less likely to be an obstacle.

iii) Data linkage between health boards needs to be pursued.

In conclusion, in a clinical speciality that has a high threshold of acceptance for ADRs, it is necessary to agree reporting criteria specific to oncology that can lead to improvements in voluntary reporting of adverse drug reactions via the Yellow Card scheme to ensure that safety concerns with cytotoxic chemotherapeutic agents do not go undetected in the future. As Cluff wrote in 1971 (148) but still remains true today:

> 'Voluntary reporting of adverse drug reactions usually reveals only the "tip of the iceberg" rather than the full dimension of the problem. However, the ship captain navigating waters where icebergs are known to exist must rely upon lookouts to watch for them. Without more sophisticated devices, such as radar, reports of visual detection of floating ice are essential to avoid catastrophe. Once a sighting has been made, further investigation may be necessary to determine the size of the berg. Similarly, lacking more sophisticated devices than are available, spontaneous reports of suspected adverse drug reactions are required as the initial step in identifying potentially serious problems. Recognition of errors and inadequacies in spontaneous reporting does not justify abandoning the method. Spontaneous reporting programmes, not as an ends in themselves, or the only system of study, increase the probability of detecting hazards requiring further study and needing characterisation by detailed investigation. Perhaps the day will come when more certain methods will replace spontaneous reporting of adverse reactions. Until then, we have no meaningful substitute.'

So until the potential for electronic, active surveillance of ADRs in oncology within Scotland can be realised and shared with the MHRA, oncology healthcare professionals must continue to have a high degree of suspicion for unknown ADRs; and consciously make every attempt to utilise the Yellow Card to report any safety concerns.

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Appendix 1

Appendix 1

The history of classifications of adverse drug reactions based on dose relatedness and time course.

Author, Date	*Dose Relatedness*	*Time Course*
Wayne, 1958	Distinguishes predictable effects ("toxic effects… related to the main action of the drug or its side effects") and unpredictable effects ("not related to the main or subsidiary pharmacological action of a drug")	
Levine, 1973	Distinguishes dose-related ('toxic and idiosyncratic') reactions from non-dose-related ('allergic') reactions	Distinguishes acute, subacute and chronic toxic reactions
Wade and Beeley, 1976	Distinguishes dose-related and non-dose related effects	Distinguishes long-term and teratogenic effects
Rawlins and Thompson, 1977	Proposes two types of reactions: type A and type B	
Rawlins and Thompson, 1981	Add a mnemonic: type A = augmented, type B = bizarre	
Grahame-Smith and Aronson, 1984	Classifies type A and B as dose related and non-dose related reactions	Add two time-related categories: long-term and delayed
Hoigné et al, 1990		Distinguishes acute, subacute, and latent allergic reactions
Park et al, 1992		Label the categories of Grahame-Smith and Aronson (1984) as: C (long-term) and D (delayed)
Laurence and Bennett, 1992		Split type C into two types: type C (continuous) and type E (end of use)
Ferner and Mann, 1997		Distinguishes five different patterns of time course that are useful in diagnosing adverse reactions
Hartigan-Go and Wong, 2000	Add a sixth category: F for failure	
Aronson, 2002	Add a seventh category: G for genetic/genomic	
Aronson and Ferner, 2003	Distinguishes three types of dose related reactions: toxic, collateral and hypersusceptibility reactions	Distinguishes time-dependent and time-independent reactions, with important subtypes

Reproduced from Aronson & Ferner, Drug Safety 2005 [MPhil Ref 21]

Appendix 2

Appendix: **WHO TOXICITY GRADING SCALE FOR DETERMINING THE SEVERITY OF ADVERSE EVENTS**

WHO Toxicity Grading Scale for Determining The Severity of Adverse Events

ITEM	Grade 1 Toxicity	Grade 2 Toxicity	Grade 3 Toxicity	Grade 4 Toxicity
HEMATOLOGY				
Hemoglobin	9.5 - 10.5 gm/Dl	8.0 - 9.4 gm/Dl	6.5 - 7.9 gm/Dl	< 6.5 gm/Dl
Absolute Neutrophil Count	1000-1500/mm^3	750-999/mm^3	500-749/mm^3	<500/mm^3
Platelets	75000-99000/mm^3	50000-74999/mm^3	20000-49000/mm^3	<20000/mm^3
Prothrombin Time (PT)	1.01 - 1.25 x ULN	1.26-1.5 x ULN	1.51 -3.0 x ULN	>3 x ULN
Activated Partial Thromboplastin (APPT)	1.01 -1.66 x ULN	1.67 - 2.33 x ULN	2.34 - 3 x ULN	> 3 x ULN
Fibrinogen	0.75 - 0.99 X LLN	0.50 - 0.74 x LLN	0.25 - 0.49 x LLN	< 0.25 x LLN
Fibrin Split Product	20-40 mcg/ml	41-50 mcg/ml	51-60 mcg/ml	> 60 mcg/ml
Methemoglobin	5 - 9.9 %	10.0 - 14.9 %	15.0 - 19.9%	> 20 %
LIVER ENZYMES				
AST (SGOT)	1.25 - 2.5 x ULN	2.6 - 5 x ULN	5.1 - 10 x ULN	> 10 x ULN
ALT (SGPT)	1.25 - 2.5 x ULN	2.6 - 5 x ULN	5.1 - 10 x ULN	> 10 x ULN
GGT	1.25 -2.5 x ULN	1.6 - 5 x ULN	5.1 - 10 x ULN	> 10 x ULN
Alkaline Phosphatase	1.25 - 2. 5 x ULN	1.6 - 5 x ULN	5.1 - 10 x ULN	> 10 x ULN
Amylase	1.1 - 1.5 x ULN	1.6 - 2.0 x ULN	2.1 - 5.0 x ULN	> 5.1 x ULN
CHEMISTRIES				
Hyponatremia	130-135 mEq/L	123-129 mEq/L	116-122 mEq/L	< 116 or mental status changes or seizures
Hypernatremia	146-150 mEq/L	151-157 mEq/L	158-165 mEq/L	> 165 mEq/L or mental status changes or seizures
Hypokalemia	3.0 - 3.4 mEq/L	2.5 - 2.9 mEq/L	2.0 - 2.4 mEq/L or intensive replacement Rx required or hospitalization required.	< 2.0 mEq/L or paresis or ileus or life-threatening arrhythmia
Hyperkalemia	5.6 - 6.0 mEq/L	6.1 - 6.5 mEq/L	6.6 - 7.0 mEq/l	> 7.0 mEq/L or life-threatening arrhythmia
Hypoglycemia	55-64 mg/dL	40-54 mg/dL	30-39 mg/dL	<30 mg/dL or mental status changes or coma

Appendix: **WHO TOXICITY GRADING SCALE FOR DETERMINING THE SEVERITY OF ADVERSE EVENTS**

CHEMISTRIES (continued)				
Hyperglycemia (note if fasting)	116 - 160 mg/dL	161- 250 mg/dL	251 - 500 mg/dL	> 500 mg/dL or ketoacidosis or seizures
Hypocalcemia (corrected for albumin)	8.4 - 7.8 mg/dL	7.7 - 7.0 mg/dL	6.9 - 6.1 mg/dL	< 6.1 mg/dL or life threatening arrhythmia or tetany
Hypercalcemia (correct for albumin)	10.6 - 11.5 mg/dL	11.6 - 12.5 mg/dL	12.6 - 13.5 mg/dL	> 13.5 mg/dL life-threatening arrhythmia
Hypomagnesemia	1.4 - 1.2 mEq/L	1.1 - 0.9 mEq/L	0.8 - 0.6 mEq/L	< 0.6 mEq/L or life-threatening arrhythmia
Hypophosphatemia	2.0 - 2.4 mg/dL	1.5 -1.9 mg/dL or replacement Rx required	1.0 -1.4 mg/dL intensive Rx or hospitalization required	< 1.0 mg/dL or life-threatening arrhythmia
Hyperbilirubinemia	1.1 - 1.5 x ULN	1.6 - 2.5 x ULN	2.6 - 5 x ULN	> 5 x ULN
BUN	1.25 - 2.5 x ULN	2.6 - 5 x ULN	5.1 - 10 x ULN	> 10 x ULN
Creatinine	1.1 x 1.5 x ULN	1.6 - 3.0 x ULN	3.1 - 6 x ULN	> 6 x ULN or required dialysis
URINALYSIS				
Proteinuria	1+ or < 0.3% or <3g/L or 200 mg - 1 gm loss/day	2 -3 + or 0.3 - 1.0% or 3-10 g/L 1- 2 gm loss/day	4+ or > 1.0% or > 10 g/L 2-3.5 gm loss/day	nephrotic syndrome or > 3.5 gm loss/day
Hematuria	microscopic only	gross, no clots	gross+ clots	obstructive or required transfusion
CARDIAC DYSFUNCTION				
Cardiac Rhythm		asymptomatic, transient signs, no Rx required	recurrent/persistent; No Rx required	requires treatment
Hypertension	transient inc. > 20 mm; no Rx	recurrent, chronic, > 20 mm, Rx required	requires acute Rx; No hospitalization	requires hospitalization
Hypotension	transient orthostatic hypotension, No Rx	symptoms correctable with oral fluids Rx	requires IV fluids; no hospitalization required	requires hospitalization
Pericarditis	minimal effusion	mild/moderate asymptomatic effusion, no Rx	symptomatic effusion; pain; EKG changes	tamponade; pericardiocentesis or surgery required
Hemorrhage, Blood Loss	microscopic/occult	mild, no transfusion	gross blood loss; 1-2 units transfused	massive blood loss; > 3 units transfused

Appendix: **WHO TOXICITY GRADING SCALE FOR DETERMINING THE SEVERITY OF ADVERSE EVENTS**

RESPIRATORY				
Cough	transient- no Rx	treatment associated cough local Rx	uncontrolled	
Bronchospasm, Acute	transient; no Rx < 80% - 70% FEV_1 (or peak flow)	requires Rx normalizes with bronchodilator; FEV_1 50% - 70% (or peak Flow)	no normalization with bronchodilator; FEV_1 25% - 50% (or peak flow retractions)	cyanosis: FEV_1 < 25% (or peak flow) or intubated
GASTROINTESTINAL				
Stomatitis	mild discomfort; no limits on activity	some limits on eating/drinking	eating/talking very limited	requires IV fluids
Nausea	mild discomfort; maintains reasonable intake	moderate discomfort; intake decreased significantly; some activity limited	severe discomfort; no significant intake; activities limited	minimal fluid intake
Vomiting	transient emesis	occasional/moderate vomiting	orthostatic hypotension or IV fluids required	hypotensive shock or hospitalization required for IV fluid therapy
Constipation	mild	moderate	severe	distensions w/vomiting
Diarrhea	transient 3-4 loose stools/day	5-7 loose stools/day	orthostatic hypotension or > 7 loose stools/day or required IV fluids	hypotensive shock or hospitalization for IV fluid therapy required
NEURO & NEUROMUSCULAR				
Neuro-Cerebellar	slight incoordination dysdiadochokinesis	intention tremor, dysmetria, slurred speech; nystagmus	locomotor ataxia	incapacitated
Mood	mild anxiety or depression	moderate anxiety or depression and therapy required	severe anxiety or depression or mania; needs assistance	acute psychosis; incapacitated, requires hospitalization
Neuro Control (ADL = activities of daily living)	mild difficulty concentrating; no Rx; mild confusion/agitation; ADL unaffected	moderate confusion/agitation some limitation of ADL; minimal Rx	severe confusion/agitation needs assistance for ADL; therapy required	toxic psychosis; hospitalization
Muscle Strength	subjective weakness no objective symptoms/ signs	mild objective signs/symptoms no decrease in function	objective weakness function limited	paralysis

Appendix: **WHO TOXICITY GRADING SCALE FOR DETERMINING THE SEVERITY OF ADVERSE EVENTS**

OTHER PARAMETERS				
Fever: oral, > 12 hours	37.7 - 38.5 C or 100.0 - 101.5 F	38.6 - 39.5 C or 101.6 - 102.9 F	39.6 - 40.5 C or 103 - 105 F	> 40 C or > 105 F
Headache	mild, no Rx therapy	transient, moderate; Rx required	severe; responds to initial narcotic therapy	intractable; required repeated narcotic therapy
Fatigue	no decrease in ADL	normal activity decreased 25- 50%	normal activity decreased > 50% can't work	unable to care for self
Allergic Reaction	pruritus without rash	localized urticaria	generalized urticaria; angioedema	anaphylaxis
Local Reaction	tenderness or erythema	induration < 10 cm or phlebitis or inflammation	induration > 10 cm or ulceration	necrosis
Mucocutaneous	erythema; pruritus	diffuse, maculo papular rash, dry desquamation	vesiculation, moist desquamation, or ulceration	exfoliative dermatitis, mucous membrane involvement or erythema, multiforme or suspected Stevens-Johnson or necrosis requiring surgery

Appendix 3

Common Terminology Criteria for Adverse Events v3.0 (CTCAE)

Publish Date: August 9, 2006

Quick Reference

The NCI Common Terminology Criteria for Adverse Events v3.0 is a descriptive terminology which can be utilized for Adverse Event (AE) reporting. A grading (severity) scale is provided for each AE term.

Components and Organization

CATEGORY

A CATEGORY is a broad classification of AEs based on anatomy and/or pathophysiology. Within each CATEGORY, AEs are listed accompanied by their descriptions of severity (Grade).

Adverse Event Terms

An AE is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure that may or may *not* be considered related to the medical treatment or procedure. An AE is a term that is a unique representation of a specific event used for medical documentation and scientific analyses. Each AE term is mapped to a MedDRA term and code. AEs are listed alphabetically within CATEGORIES.

Short AE Name

The 'SHORT NAME' column is new and it is used to simplify documentation of AE names on Case Report Forms.

Supra-ordinate Terms

A supra-ordinate term is located within a CATEGORY and is a grouping term based on disease process, signs, symptoms, or diagnosis. A supra-ordinate term is followed by the word *'Select'* and is accompanied by specific AEs that are all related to the supra-ordinate term. Supra-ordinate terms provide clustering and consistent representation of Grade for related AEs. Supra-ordinate terms are not AEs, are not mapped to a MedDRA term and code, cannot be graded and cannot be used for reporting.

REMARK

A 'REMARK' is a clarification of an AE.

ALSO CONSIDER

An 'ALSO CONSIDER' indicates additional AEs that are to be graded if they are clinically significant.

NAVIGATION NOTE

A 'NAVIGATION NOTE' indicates the location of an AE term within the CTCAE document. It lists signs/symptoms alphabetically and the CTCAE term will appear in the same CATEGORY unless the 'NAVIGATION NOTE' states differently.

Grades

Grade refers to the severity of the AE. The CTCAE v3.0 displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline:

Grade 1	Mild AE
Grade 2	Moderate AE
Grade 3	Severe AE
Grade 4	Life-threatening or disabling AE
Grade 5	Death related to AE

A Semi-colon indicates 'or' within the description of the grade.

An 'Em dash' (—) indicates a grade not available.

Not all Grades are appropriate for all AEs. Therefore, some AEs are listed with fewer than five options for Grade selection.

Grade 5

Grade 5 (Death) is not appropriate for some AEs and therefore is not an option.

The DEATH CATEGORY is new. Only one Supra-ordinate term is listed in this CATEGORY: 'Death not associated with CTCAE term – *Select*' with 4 AE options: Death NOS; Disease progression NOS; Multi-organ failure; Sudden death.

Important:

- Grade 5 is the only appropriate Grade
- This AE is to be used in the situation where a death
  1. cannot be reported using a CTCAE v3.0 term associated with Grade 5, or
  2. cannot be reported within a CTCAE CATEGORY as 'Other (Specify)'

Contents

ALLERGY/IMMUNOLOGY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Allergic reaction/ hypersensitivity (including drug fever)	Allergic reaction	Transient flushing or rash; drug fever <38°C (<100.4°F)	Rash; flushing; urticaria; dyspnea; drug fever ≥38°C (≥100.4°F)	Symptomatic bronchospasm, with or without urticaria; parenteral medication(s) indicated; allergy-related edema/angioedema; hypotension	Anaphylaxis	Death
REMARK: Urticaria with manifestations of allergic or hypersensitivity reaction is graded as Allergic reaction/hypersensitivity (including drug fever). ALSO CONSIDER: Cytokine release syndrome/acute infusion reaction.						
Allergic rhinitis (including sneezing, nasal stuffiness, postnasal drip)	Rhinitis	Mild, intervention not indicated	Moderate, intervention indicated	—	—	—
REMARK: Rhinitis associated with obstruction or stenosis is graded as Obstruction/stenosis of airway – *Select* in the PULMONARY/UPPER RESPIRATORY CATEGORY.						
Autoimmune reaction	Autoimmune reaction	Asymptomatic and serologic or other evidence of autoimmune reaction, with normal organ function and intervention not indicated	Evidence of autoimmune reaction involving a non-essential organ or function (e.g., hypothyroidism)	Reversible autoimmune reaction involving function of a major organ or other adverse event (e.g., transient colitis or anemia)	Autoimmune reaction with life-threatening consequences	Death
ALSO CONSIDER: Colitis; Hemoglobin; Hemolysis (e.g., immune hemolytic anemia, drug-related hemolysis); Thyroid function, low (hypothyroidism).						
Serum sickness	Serum sickness	—	—	Present	—	Death
NAVIGATION NOTE: Splenic function is graded in the BLOOD/BONE MARROW CATEGORY.						
NAVIGATION NOTE: Urticaria as an isolated symptom is graded as Urticaria (hives, welts, wheals) in the DERMATOLOGY/SKIN CATEGORY.						
Vasculitis	Vasculitis	Mild, intervention not indicated	Symptomatic, non-steroidal medical intervention indicated	Steroids indicated	Ischemic changes; amputation indicated	Death
Allergy/Immunology – Other (Specify, __)	Allergy – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

AUDITORY/EAR

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
NAVIGATION NOTE: Earache (otalgia) is graded as Pain – *Select* in the PAIN CATEGORY.						
Hearing: patients with/without baseline audiogram and enrolled in a monitoring program[1]	Hearing (monitoring program)	Threshold shift or loss of 15 – 25 dB relative to baseline, averaged at 2 or more contiguous test frequencies in at least one ear; or subjective change in the absence of a Grade 1 threshold shift	Threshold shift or loss of >25 – 90 dB, averaged at 2 contiguous test frequencies in at least one ear	Adult only: Threshold shift of >25 – 90 dB, averaged at 3 contiguous test frequencies in at least one ear Pediatric: Hearing loss sufficient to indicate therapeutic intervention, including hearing aids (e.g., ≥20 dB bilateral HL in the speech frequencies; ≥30 dB unilateral HL; and requiring additional speech-language related services)	Adult only: Profound bilateral hearing loss (>90 dB) Pediatric: Audiologic indication for cochlear implant and requiring additional speech-language related services	—
REMARK: Pediatric recommendations are identical to those for adults, unless specified. For children and adolescents (≤18 years of age) without a baseline test, pre-exposure/pre-treatment hearing should be considered to be <5 dB loss.						
Hearing: patients without baseline audiogram and not enrolled in a monitoring program[1]	Hearing (without monitoring program)	—	Hearing loss not requiring hearing aid or intervention (i.e., not interfering with ADL)	Hearing loss requiring hearing aid or intervention (i.e., interfering with ADL)	Profound bilateral hearing loss (>90 dB)	—
REMARK: Pediatric recommendations are identical to those for adults, unless specified. For children and adolescents (≤18 years of age) without a baseline test, pre-exposure/pre-treatment hearing should be considered to be <5 dB loss.						
Otitis, external ear (non-infectious)	Otitis, external	External otitis with erythema or dry desquamation	External otitis with moist desquamation, edema, enhanced cerumen or discharge; tympanic membrane perforation; tympanostomy	External otitis with mastoiditis; stenosis or osteomyelitis	Necrosis of soft tissue or bone	Death
ALSO CONSIDER: Hearing: patients with/without baseline audiogram and enrolled in a monitoring program[1]; Hearing: patients without baseline audiogram and not enrolled in a monitoring program[1].						
Otitis, middle ear (non-infectious)	Otitis, middle	Serous otitis	Serous otitis, medical intervention indicated	Otitis with discharge; mastoiditis	Necrosis of the canal soft tissue or bone	Death

AUDITORY/EAR

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Tinnitus	Tinnitus	—	Tinnitus not interfering with ADL	Tinnitus interfering with ADL	Disabling	—
ALSO CONSIDER: Hearing: patients with/without baseline audiogram and enrolled in a monitoring program[1]; Hearing: patients without baseline audiogram and not enrolled in a monitoring program[1].						
Auditory/Ear – Other (Specify, __)	Auditory/Ear – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

[1] Drug-induced ototoxicity should be distinguished from age-related threshold decrements or unrelated cochlear insult. When considering whether an adverse event has occurred, it is first necessary to classify the patient into one of two groups. (1) The patient is under standard treatment/enrolled in a clinical trial <2.5 years, and has a 15 dB or greater threshold shift averaged across two contiguous frequencies; or (2) The patient is under standard treatment/enrolled in a clinical trial >2.5 years, and the difference between the expected age-related and the observed threshold shifts is 15 dB or greater averaged across two contiguous frequencies. Consult standard references for appropriate age- and gender-specific hearing norms, e.g., Morrell, et al. Age- and gender-specific reference ranges for hearing level and longitudinal changes in hearing level. Journal of the Acoustical Society of America 100:1949-1967, 1996; or Shotland, et al. Recommendations for cancer prevention trials using potentially ototoxic test agents. Journal of Clinical Oncology 19:1658-1663, 2001.

In the absence of a baseline prior to initial treatment, subsequent audiograms should be referenced to an appropriate database of normals. ANSI. (1996)

American National Standard: Determination of occupational noise exposure and estimation of noise-induced hearing impairment, ANSI S 3.44-1996. (Standard S 3.44). New York: American National Standards Institute. The recommended ANSI S3.44 database is Annex B.

BLOOD/BONE MARROW

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Bone marrow cellularity	Bone marrow cellularity	Mildly hypocellular or ≤25% reduction from normal cellularity for age	Moderately hypocellular or >25 – ≤50% reduction from normal cellularity for age	Severely hypocellular or >50 – ≤75% reduction cellularity from normal for age	—	Death
CD4 count	CD4 count	<LLN – 500/mm^3 <LLN – 0.5 x 10^9 /L	<500 – 200/mm^3 <0.5 – 0.2 x 10^9 /L	<200 – 50/mm^3 <0.2 x 0.05 – 10^9 /L	<50/mm^3 <0.05 x 10^9 /L	Death
Haptoglobin	Haptoglobin	<LLN	—	Absent	—	Death
Hemoglobin	Hemoglobin	<LLN – 10.0 g/dL <LLN – 6.2 mmol/L <LLN – 100 g/L	<10.0 – 8.0 g/dL <6.2 – 4.9 mmol/L <100 – 80g/L	<8.0 – 6.5 g/dL <4.9 – 4.0 mmol/L <80 – 65 g/L	<6.5 g/dL <4.0 mmol/L <65 g/L	Death
Hemolysis (e.g., immune hemolytic anemia, drug-related hemolysis)	Hemolysis	Laboratory evidence of hemolysis only (e.g., direct antiglobulin test [DAT, Coombs'] schistocytes)	Evidence of red cell destruction and ≥2 gm decrease in hemoglobin, no transfusion	Transfusion or medical intervention (e.g., steroids) indicated	Catastrophic consequences of hemolysis (e.g., renal failure, hypotension, bronchospasm, emergency splenectomy)	Death
ALSO CONSIDER: Haptoglobin; Hemoglobin.						
Iron overload	Iron overload	—	Asymptomatic iron overload, intervention not indicated	Iron overload, intervention indicated	Organ impairment (e.g., endocrinopathy, cardiopathy)	Death
Leukocytes (total WBC)	Leukocytes	<LLN – 3000/mm^3 <LLN – 3.0 x 10^9 /L	<3000 – 2000/mm^3 <3.0 – 2.0 x 10^9 /L	<2000 – 1000/mm^3 <2.0 – 1.0 x 10^9 /L	<1000/mm^3 <1.0 x 10^9 /L	Death
Lymphopenia	Lymphopenia	<LLN – 800/mm^3 <LLN x 0.8 – 10^9 /L	<800 – 500/mm^3 <0.8 – 0.5 x 10^9 /L	<500 – 200 mm^3 <0.5 – 0.2 x 10^9 /L	<200/mm^3 <0.2 x 10^9 /L	Death
Myelodysplasia	Myelodysplasia	—	—	Abnormal marrow cytogenetics (marrow blasts ≤5%)	RAEB or RAEB-T (marrow blasts >5%)	Death
Neutrophils/granulocytes (ANC/AGC)	Neutrophils	<LLN – 1500/mm^3 <LLN – 1.5 x 10^9 /L	<1500 – 1000/mm^3 <1.5 – 1.0 x 10^9 /L	<1000 – 500/mm^3 <1.0 – 0.5 x 10^9 /L	<500/mm^3 <0.5 x 10^9 /L	Death
Platelets	Platelets	<LLN – 75,000/mm^3 <LLN – 75.0 x 10^9 /L	<75,000 – 50,000/mm^3 <75.0 – 50.0 x 10^9 /L	<50,000 – 25,000/mm^3 <50.0 – 25.0 x 10^9 /L	<25,000/mm^3 <25.0 x 10^9 /L	Death
Splenic function	Splenic function	Incidental findings (e.g., Howell-Jolly bodies)	Prophylactic antibiotics indicated	—	Life-threatening consequences	Death
Blood/Bone Marrow – Other (Specify, __)	Blood – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

CARDIAC ARRHYTHMIA

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Conduction abnormality/ atrioventricular heart block – *Select*: – Asystole – AV Block-First degree – AV Block-Second degree Mobitz Type I (Wenckebach) – AV Block-Second degree Mobitz Type II – AV Block-Third degree (Complete AV block) – Conduction abnormality NOS – Sick Sinus Syndrome – Stokes-Adams Syndrome – Wolff-Parkinson-White Syndrome	Conduction abnormality – *Select*	Asymptomatic, intervention not indicated	Non-urgent medical intervention indicated	Incompletely controlled medically or controlled with device (e.g., pacemaker)	Life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)	Death
Palpitations	Palpitations	Present	Present with associated symptoms (e.g., lightheadedness, shortness of breath)	—	—	—
REMARK: Grade palpitations only in the absence of a documented arrhythmia.						
Prolonged QTc interval	Prolonged QTc	QTc >0.45 – 0.47 second	QTc >0.47 – 0.50 second; ≥0.06 second above baseline	QTc >0.50 second	QTc >0.50 second; life-threatening signs or symptoms (e.g., arrhythmia, CHF, hypotension, shock syncope); Torsade de pointes	Death
Supraventricular and nodal arrhythmia – *Select*: – Atrial fibrillation – Atrial flutter – Atrial tachycardia/Paroxysmal Atrial Tachycardia – Nodal/Junctional – Sinus arrhythmia – Sinus bradycardia – Sinus tachycardia – Supraventricular arrhythmia NOS – Supraventricular extrasystoles (Premature Atrial Contractions; Premature Nodal/Junctional Contractions) – Supraventricular tachycardia	Supraventricular arrhythmia – *Select*	Asymptomatic, intervention not indicated	Non-urgent medical intervention indicated	Symptomatic and incompletely controlled medically, or controlled with device (e.g., pacemaker)	Life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)	Death
NAVIGATION NOTE: Syncope is graded as Syncope (fainting) in the NEUROLOGY CATEGORY.						

CARDIAC ARRHYTHMIA

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Vasovagal episode	Vasovagal episode	—	Present without loss of consciousness	Present with loss of consciousness	Life-threatening consequences	Death
Ventricular arrhythmia – S*elect:* – Bigeminy – Idioventricular rhythm – PVCs – Torsade de pointes – Trigeminy – Ventricular arrhythmia NOS – Ventricular fibrillation – Ventricular flutter – Ventricular tachycardia	Ventricular arrhythmia – S*elect*	Asymptomatic, no intervention indicated	Non-urgent medical intervention indicated	Symptomatic and incompletely controlled medically or controlled with device (e.g., defibrillator)	Life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)	Death
Cardiac Arrhythmia – Other (Specify, __)	Cardiac Arrhythmia – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

CARDIAC GENERAL

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
NAVIGATION NOTE: Angina is graded as Cardiac ischemia/infarction in the CARDIAC GENERAL CATEGORY.						
Cardiac ischemia/infarction	Cardiac ischemia/infarction	Asymptomatic arterial narrowing without ischemia	Asymptomatic and testing suggesting ischemia; stable angina	Symptomatic and testing consistent with ischemia; unstable angina; intervention indicated	Acute myocardial infarction	Death
Cardiac troponin I (cTnI)	cTnI	—	—	Levels consistent with unstable angina as defined by the manufacturer	Levels consistent with myocardial infarction as defined by the manufacturer	Death
Cardiac troponin T (cTnT)	cTnT	0.03 – <0.05 ng/mL	0.05 – <0.1 ng/mL	0.1 – <0.2 ng/mL	0.2 ng/mL	Death
Cardiopulmonary arrest, cause unknown (non-fatal)	Cardiopulmonary arrest	—	—	—	Life-threatening	—
REMARK: Grade 4 (non-fatal) is the only appropriate grade. CTCAE provides three alternatives for reporting Death: 1. A CTCAE term associated with Grade 5. 2. A CTCAE 'Other (Specify, __)' within any CATEGORY. 3. Death not associated with CTCAE term – *Select* in the DEATH CATEGORY.						
NAVIGATION NOTE: Chest pain (non-cardiac and non-pleuritic) is graded as Pain – *Select* in the PAIN CATEGORY.						
NAVIGATION NOTE: CNS ischemia is graded as CNS cerebrovascular ischemia in the NEUROLOGY CATEGORY.						
Hypertension	Hypertension	Asymptomatic, transient (<24 hrs) increase by >20 mmHg (diastolic) or to >150/100 if previously WNL; intervention not indicated Pediatric: Asymptomatic, transient (<24 hrs) BP increase >ULN; intervention not indicated	Recurrent or persistent (≥24 hrs) or symptomatic increase by >20 mmHg (diastolic) or to >150/100 if previously WNL; monotherapy may be indicated Pediatric: Recurrent or persistent (≥24 hrs) BP >ULN; monotherapy may be indicated	Requiring more than one drug or more intensive therapy than previously Pediatric: Same as adult	Life-threatening consequences (e.g., hypertensive crisis) Pediatric: Same as adult	Death
REMARK: Use age and gender-appropriate normal values >95th percentile ULN for pediatric patients.						

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Hypotension	Hypotension	Changes, intervention not indicated	Brief (<24 hrs) fluid replacement or other therapy; no physiologic consequences	Sustained (≥24 hrs) therapy, resolves without persisting physiologic consequences	Shock (e.g., acidemia; impairment of vital organ function)	Death
ALSO CONSIDER: Syncope (fainting).						
Left ventricular diastolic dysfunction	Left ventricular diastolic dysfunction	Asymptomatic diagnostic finding; intervention not indicated	Asymptomatic, intervention indicated	Symptomatic CHF responsive to intervention	Refractory CHF, poorly controlled; intervention such as ventricular assist device or heart transplant indicated	Death
Left ventricular systolic dysfunction	Left ventricular systolic dysfunction	Asymptomatic, resting ejection fraction (EF) <60 – 50%; shortening fraction (SF) <30 – 24%	Asymptomatic, resting EF <50 – 40%; SF <24 – 15%	Symptomatic CHF responsive to intervention; EF <40 – 20% SF <15%	Refractory CHF or poorly controlled; EF <20%; intervention such as ventricular assist device, ventricular reduction surgery, or heart transplant indicated	Death
NAVIGATION NOTE: Myocardial infarction is graded as Cardiac ischemia/infarction in the CARDIAC GENERAL CATEGORY.						
Myocarditis	Myocarditis	—	—	CHF responsive to intervention	Severe or refractory CHF	Death
Pericardial effusion (non-malignant)	Pericardial effusion	Asymptomatic effusion	—	Effusion with physiologic consequences	Life-threatening consequences (e.g., tamponade); emergency intervention indicated	Death
Pericarditis	Pericarditis	Asymptomatic, ECG or physical exam (rub) changes consistent with pericarditis	Symptomatic pericarditis (e.g., chest pain)	Pericarditis with physiologic consequences (e.g., pericardial constriction)	Life-threatening consequences; emergency intervention indicated	Death
NAVIGATION NOTE: Pleuritic pain is graded as Pain – *Select* in the PAIN CATEGORY.						
Pulmonary hypertension	Pulmonary hypertension	Asymptomatic without therapy	Asymptomatic, therapy indicated	Symptomatic hypertension, responsive to therapy	Symptomatic hypertension, poorly controlled	Death
Restrictive cardiomyopathy	Restrictive cardiomyopathy	Asymptomatic, therapy not indicated	Asymptomatic, therapy indicated	Symptomatic CHF responsive to intervention	Refractory CHF, poorly controlled; intervention such as ventricular assist device, or heart transplant indicated	Death

CARDIAC GENERAL

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Right ventricular dysfunction (cor pulmonale)	Right ventricular dysfunction	Asymptomatic without therapy	Asymptomatic, therapy indicated	Symptomatic cor pulmonale, responsive to intervention	Symptomatic cor pulmonale poorly controlled; intervention such as ventricular assist device, or heart transplant indicated	Death
Valvular heart disease	Valvular heart disease	Asymptomatic valvular thickening with or without mild valvular regurgitation or stenosis; treatment other than endocarditis prophylaxis not indicated	Asymptomatic; moderate regurgitation or stenosis by imaging	Symptomatic; severe regurgitation or stenosis; symptoms controlled with medical therapy	Life-threatening; disabling; intervention (e.g., valve replacement, valvuloplasty) indicated	Death
Cardiac General – Other (Specify, __)	Cardiac General – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

COAGULATION

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
DIC (disseminated intravascular coagulation)	DIC	—	Laboratory findings with no bleeding	Laboratory findings and bleeding	Laboratory findings, life-threatening or disabling consequences (e.g., CNS hemorrhage, organ damage, or hemodynamically significant blood loss)	Death
REMARK: DIC (disseminated intravascular coagulation) must have increased fibrin split products or D-dimer. ALSO CONSIDER: Platelets.						
Fibrinogen	Fibrinogen	<1.0 – 0.75 x LLN or <25% decrease from baseline	<0.75 – 0.5 x LLN or 25 – <50% decrease from baseline	<0.5 – 0.25 x LLN or 50 – <75% decrease from baseline	<0.25 x LLN or 75% decrease from baseline or absolute value <50 mg/dL	Death
REMARK: Use % decrease only when baseline is <LLN (local laboratory value).						
INR (International Normalized Ratio of prothrombin time)	INR	>1 – 1.5 x ULN	>1.5 – 2 x ULN	>2 x ULN	—	—
ALSO CONSIDER: Hemorrhage, CNS; Hemorrhage, GI – *Select*; Hemorrhage, GU – *Select*; Hemorrhage, pulmonary/upper respiratory – *Select.*						
PTT (Partial Thromboplastin Time)	PTT	>1 – 1.5 x ULN	>1.5 – 2 x ULN	>2 x ULN	—	—
ALSO CONSIDER: Hemorrhage, CNS; Hemorrhage, GI – *Select*; Hemorrhage, GU – *Select*; Hemorrhage, pulmonary/upper respiratory – *Select.*						
Thrombotic microangiopathy (e.g., thrombotic thrombocytopenic purpura [TTP] or hemolytic uremic syndrome [HUS])	Thrombotic microangiopathy	Evidence of RBC destruction (schistocytosis) without clinical consequences	—	Laboratory findings present with clinical consequences (e.g., renal insufficiency, petechiae)	Laboratory findings and life-threatening or disabling consequences, (e.g., CNS hemorrhage/ bleeding or thrombosis/ embolism or renal failure)	Death
REMARK: Must have microangiopathic changes on blood smear (e.g., schistocytes, helmet cells, red cell fragments). ALSO CONSIDER: Creatinine; Hemoglobin; Platelets.						
Coagulation – Other (Specify, __)	Coagulation – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

CONSTITUTIONAL SYMPTOMS

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Fatigue (asthenia, lethargy, malaise)	Fatigue	Mild fatigue over baseline	Moderate or causing difficulty performing some ADL	Severe fatigue interfering with ADL	Disabling	—
Fever (in the absence of neutropenia, where neutropenia is defined as ANC <1.0 x 10^9/L)	Fever	38.0 – 39.0°C (100.4 – 102.2°F)	>39.0 – 40.0°C (102.3 – 104.0°F)	>40.0°C (>104.0°F) for ≤24 hrs	>40.0°C (>104.0°F) for >24 hrs	Death
REMARK: The temperature measurements listed are oral or tympanic.						
ALSO CONSIDER: Allergic reaction/hypersensitivity (including drug fever).						
NAVIGATION NOTE: Hot flashes are graded as Hot flashes/flushes in the ENDOCRINE CATEGORY.						
Hypothermia	Hypothermia	—	35 – >32°C 95 – >89.6°F	32 – >28°C 89.6 – >82.4° F	≤28 °C 82.4°F or life-threatening consequences (e.g., coma, hypotension, pulmonary edema, acidemia, ventricular fibrillation)	Death
Insomnia	Insomnia	Occasional difficulty sleeping, not interfering with function	Difficulty sleeping, interfering with function but not interfering with ADL	Frequent difficulty sleeping, interfering with ADL	Disabling	—
REMARK: If pain or other symptoms interfere with sleep, do NOT grade as insomnia. Grade primary event(s) causing insomnia.						
Obesity[2]	Obesity	—	BMI 25 – 29.9 kg/m^2	BMI 30 – 39.99 kg/m^2	BMI ≥40 kg/m^2	—
REMARK: BMI = (weight [kg]) / (height [m])^2						
Odor (patient odor)	Patient odor	Mild odor	Pronounced odor	—	—	—
Rigors/chills	Rigors/chills	Mild	Moderate, narcotics indicated	Severe or prolonged, not responsive to narcotics	—	—

[2] NHLBI Obesity Task Force. "Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults," *The Evidence Report,* Obes Res 6:51S-209S, 1998.

CONSTITUTIONAL SYMPTOMS

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Sweating (diaphoresis)	Sweating	Mild and occasional	Frequent or drenching	—	—	—
ALSO CONSIDER: Hot flashes/flushes.						
Weight gain	Weight gain	5 – <10% of baseline	10 – <20% of baseline	≥20% of baseline	—	—
REMARK: Edema, depending on etiology, is graded in the CARDIAC GENERAL or LYMPHATICS CATEGORIES.						
ALSO CONSIDER: Ascites (non-malignant); Pleural effusion (non-malignant).						
Weight loss	Weight loss	5 to <10% from baseline; intervention not indicated	10 – <20% from baseline; nutritional support indicated	≥20% from baseline; tube feeding or TPN indicated	—	—
Constitutional Symptoms – Other (Specify, __)	Constitutional Symptoms – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

DEATH

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Death not associated with CTCAE term – *Select*: – Death NOS – Disease progression NOS – Multi-organ failure – Sudden death	Death not associated with CTCAE term – *Select*	—	—	—	—	Death

REMARK: Grade 5 is the only appropriate grade. 'Death not associated with CTCAE term – *Select'* is to be used where a death:

1. Cannot be attributed to a CTCAE term associated with Grade 5.
2. Cannot be reported within any CATEGORY using a CTCAE 'Other (Specify, __)'.

DERMATOLOGY/SKIN

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Atrophy, skin	Atrophy, skin	Detectable	Marked	—	—	—
Atrophy, subcutaneous fat	Atrophy, subcutaneous fat	Detectable	Marked	—	—	—
ALSO CONSIDER: Induration/fibrosis (skin and subcutaneous tissue).						
Bruising (in absence of Grade 3 or 4 thrombocytopenia)	Bruising	Localized or in a dependent area	Generalized	—	—	—
Burn	Burn	Minimal symptoms; intervention not indicated	Medical intervention; minimal debridement indicated	Moderate to major debridement or reconstruction indicated	Life-threatening consequences	Death
REMARK: Burn refers to all burns including radiation, chemical, etc.						
Cheilitis	Cheilitis	Asymptomatic	Symptomatic, not interfering with ADL	Symptomatic, interfering with ADL	—	—
Dry skin	Dry skin	Asymptomatic	Symptomatic, not interfering with ADL	Interfering with ADL	—	—
Flushing	Flushing	Asymptomatic	Symptomatic	—	—	—
Hair loss/alopecia (scalp or body)	Alopecia	Thinning or patchy	Complete	—	—	—
Hyperpigmentation	Hyperpigmentation	Slight or localized	Marked or generalized	—	—	—
Hypopigmentation	Hypopigmentation	Slight or localized	Marked or generalized	—	—	—
Induration/fibrosis (skin and subcutaneous tissue)	Induration	Increased density on palpation	Moderate impairment of function not interfering with ADL; marked increase in density and firmness on palpation with or without minimal retraction	Dysfunction interfering with ADL; very marked density, retraction or fixation	—	—
ALSO CONSIDER: Fibrosis-cosmesis; Fibrosis-deep connective tissue.						
Injection site reaction/ extravasation changes	Injection site reaction	Pain; itching; erythema	Pain or swelling, with inflammation or phlebitis	Ulceration or necrosis that is severe; operative intervention indicated	—	—
ALSO CONSIDER: Allergic reaction/hypersensitivity (including drug fever); Ulceration.						

DERMATOLOGY/SKIN

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Nail changes	Nail changes	Discoloration; ridging (koilonychias); pitting	Partial or complete loss of nail(s); pain in nailbed(s)	Interfering with ADL	—	—
NAVIGATION NOTE: Petechiae is graded as Petechiae/purpura (hemorrhage/bleeding into skin or mucosa) in the HEMORRHAGE/BLEEDING CATEGORY.						
Photosensitivity	Photosensitivity	Painless erythema	Painful erythema	Erythema with desquamation	Life-threatening; disabling	Death
Pruritus/itching	Pruritus	Mild or localized	Intense or widespread	Intense or widespread and interfering with ADL	—	—
ALSO CONSIDER: Rash/desquamation.						
Rash/desquamation	Rash	Macular or papular eruption or erythema without associated symptoms	Macular or papular eruption or erythema with pruritus or other associated symptoms; localized desquamation or other lesions covering <50% of body surface area (BSA)	Severe, generalized erythroderma or macular, papular or vesicular eruption; desquamation covering ≥50% BSA	Generalized exfoliative, ulcerative, or bullous dermatitis	Death
REMARK: Rash/desquamation may be used for GVHD.						
Rash: acne/acneiform	Acne	Intervention not indicated	Intervention indicated	Associated with pain, disfigurement, ulceration, or desquamation	—	Death
Rash: dermatitis associated with radiation – *Select*: – Chemoradiation – Radiation	Dermatitis – *Select*	Faint erythema or dry desquamation	Moderate to brisk erythema; patchy moist desquamation, mostly confined to skin folds and creases; moderate edema	Moist desquamation other than skin folds and creases; bleeding induced by minor trauma or abrasion	Skin necrosis or ulceration of full thickness dermis; spontaneous bleeding from involved site	Death
Rash: erythema multiforme (e.g., Stevens-Johnson syndrome, toxic epidermal necrolysis)	Erythema multiforme	—	Scattered, but not generalized eruption	Severe (e.g., generalized rash or painful stomatitis); IV fluids, tube feedings, or TPN indicated	Life-threatening; disabling	Death
Rash: hand-foot skin reaction	Hand-foot	Minimal skin changes or dermatitis (e.g., erythema) without pain	Skin changes (e.g., peeling, blisters, bleeding, edema) or pain, not interfering with function	Ulcerative dermatitis or skin changes with pain interfering with function	—	—

DERMATOLOGY/SKIN

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Skin breakdown/ decubitus ulcer	Decubitus	—	Local wound care; medical intervention indicated	Operative debridement or other invasive intervention indicated (e.g., hyperbaric oxygen)	Life-threatening consequences; major invasive intervention indicated (e.g., tissue reconstruction, flap, or grafting)	Death
REMARK: Skin breakdown/decubitus ulcer is to be used for loss of skin integrity or decubitus ulcer from pressure or as the result of operative or medical intervention.						
Striae	Striae	Mild	Cosmetically significant	—	—	—
Telangiectasia	Telangiectasia	Few	Moderate number	Many and confluent	—	—
Ulceration	Ulceration	—	Superficial ulceration <2 cm size; local wound care; medical intervention indicated	Ulceration ≥2 cm size; operative debridement, primary closure or other invasive intervention indicated (e.g., hyperbaric oxygen)	Life-threatening consequences; major invasive intervention indicated (e.g., complete resection, tissue reconstruction, flap, or grafting)	Death
Urticaria (hives, welts, wheals)	Urticaria	Intervention not indicated	Intervention indicated for <24 hrs	Intervention indicated for ≥24 hrs	—	—
ALSO CONSIDER: Allergic reaction/hypersensitivity (including drug fever).						
Wound complication, non-infectious	Wound complication, non-infectious	Incisional separation of ≤25% of wound, no deeper than superficial fascia	Incisional separation >25% of wound with local care; asymptomatic hernia	Symptomatic hernia without evidence of strangulation; fascial disruption/dehiscence without evisceration; primary wound closure or revision by operative intervention indicated; hospitalization or hyperbaric oxygen indicated	Symptomatic hernia with evidence of strangulation; fascial disruption with evisceration; major reconstruction flap, grafting, resection, or amputation indicated	Death
REMARK: Wound complication, non-infectious is to be used for separation of incision, hernia, dehiscence, evisceration, or second surgery for wound revision.						
Dermatology/Skin – Other (Specify, __)	Dermatology – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

ENDOCRINE

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Adrenal insufficiency	Adrenal insufficiency	Asymptomatic, intervention not indicated	Symptomatic, intervention indicated	Hospitalization	Life-threatening; disabling	Death
REMARK: Adrenal insufficiency includes any of the following signs and symptoms: abdominal pain, anorexia, constipation, diarrhea, hypotension, pigmentation of mucous membranes, pigmentation of skin, salt craving, syncope (fainting), vitiligo, vomiting, weakness, weight loss. Adrenal insufficiency must be confirmed by laboratory studies (low cortisol frequently accompanied by low aldosterone). ALSO CONSIDER: Potassium, serum-high (hyperkalemia); Thyroid function, low (hypothyroidism).						
Cushingoid appearance (e.g., moon face, buffalo hump, centripetal obesity, cutaneous striae)	Cushingoid	—	Present	—	—	—
ALSO CONSIDER: Glucose, serum-high (hyperglycemia); Potassium, serum-low (hypokalemia).						
Feminization of male	Feminization of male	—	—	Present	—	—
NAVIGATION NOTE: Gynecomastia is graded in the SEXUAL/REPRODUCTIVE FUNCTION CATEGORY.						
Hot flashes/flushes[3]	Hot flashes	Mild	Moderate	Interfering with ADL	—	—
Masculinization of female	Masculinization of female	—	—	Present	—	—
Neuroendocrine: ACTH deficiency	ACTH	Asymptomatic	Symptomatic, not interfering with ADL; intervention indicated	Symptoms interfering with ADL; hospitalization indicated	Life-threatening consequences (e.g., severe hypotension)	Death
Neuroendocrine: ADH secretion abnormality (e.g., SIADH or low ADH)	ADH	Asymptomatic	Symptomatic, not interfering with ADL; intervention indicated	Symptoms interfering with ADL	Life-threatening consequences	Death
Neuroendocrine: gonadotropin secretion abnormality	Gonadotropin	Asymptomatic	Symptomatic, not interfering with ADL; intervention indicated	Symptoms interfering with ADL; osteopenia; fracture; infertility	—	—
Neuroendocrine: growth hormone secretion abnormality	Growth hormone	Asymptomatic	Symptomatic, not interfering with ADL; intervention indicated	—	—	—
Neuroendocrine: prolactin hormone secretion abnormality	Prolactin	Asymptomatic	Symptomatic, not interfering with ADL; intervention indicated	Symptoms interfering with ADL; amenorrhea; galactorrhea	—	Death

[3] Sloan JA, Loprinzi CL, Novotny PJ, Barton DL, Lavasseur BI, Windschitl HJ, "Methodologic Lessons Learned from Hot Flash Studies," *J Clin Oncol* 2001 Dec 1;19(23):4280-90

ENDOCRINE						Page 2 of 2
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Pancreatic endocrine: glucose intolerance	Diabetes	Asymptomatic, intervention not indicated	Symptomatic; dietary modification or oral agent indicated	Symptoms interfering with ADL; insulin indicated	Life-threatening consequences (e.g., ketoacidosis, hyperosmolar non-ketotic coma)	Death
Parathyroid function, low (hypoparathyroidism)	Hypoparathyroidism	Asymptomatic, intervention not indicated	Symptomatic; intervention indicated	—	—	—
Thyroid function, high (hyperthyroidism, thyrotoxicosis)	Hyperthyroidism	Asymptomatic, intervention not indicated	Symptomatic, not interfering with ADL; thyroid suppression therapy indicated	Symptoms interfering with ADL; hospitalization indicated	Life-threatening consequences (e.g., thyroid storm)	Death
Thyroid function, low (hypothyroidism)	Hypothyroidism	Asymptomatic, intervention not indicated	Symptomatic, not interfering with ADL; thyroid replacement indicated	Symptoms interfering with ADL; hospitalization indicated	Life-threatening myxedema coma	Death
Endocrine – Other (Specify, __)	Endocrine – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

GASTROINTESTINAL

Adverse Event	Short Name	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
NAVIGATION NOTE: Abdominal pain or cramping is graded as Pain – *Select* in the PAIN CATEGORY.						
Anorexia	Anorexia	Loss of appetite without alteration in eating habits	Oral intake altered without significant weight loss or malnutrition; oral nutritional supplements indicated	Associated with significant weight loss or malnutrition (e.g., inadequate oral caloric and/or fluid intake); IV fluids, tube feedings or TPN indicated	Life-threatening consequences	Death
ALSO CONSIDER: Weight loss.						
Ascites (non-malignant)	Ascites	Asymptomatic	Symptomatic, medical intervention indicated	Symptomatic, invasive procedure indicated	Life-threatening consequences	Death
REMARK: Ascites (non-malignant) refers to documented non-malignant ascites or unknown etiology, but unlikely malignant, and includes chylous ascites.						
Colitis	Colitis	Asymptomatic, pathologic or radiographic findings only	Abdominal pain; mucus or blood in stool	Abdominal pain, fever, change in bowel habits with ileus; peritoneal signs	Life-threatening consequences (e.g., perforation, bleeding, ischemia, necrosis, toxic megacolon)	Death
ALSO CONSIDER: Hemorrhage, GI – *Select*.						
Constipation	Constipation	Occasional or intermittent symptoms; occasional use of stool softeners, laxatives, dietary modification, or enema	Persistent symptoms with regular use of laxatives or enemas indicated	Symptoms interfering with ADL; obstipation with manual evacuation indicated	Life-threatening consequences (e.g., obstruction, toxic megacolon)	Death
ALSO CONSIDER: Ileus, GI (functional obstruction of bowel, i.e., neuroconstipation); Obstruction, GI – *Select*.						
Dehydration	Dehydration	Increased oral fluids indicated; dry mucous membranes; diminished skin turgor	IV fluids indicated <24 hrs	IV fluids indicated ≥24 hrs	Life-threatening consequences (e.g., hemodynamic collapse)	Death
ALSO CONSIDER: Diarrhea; Hypotension; Vomiting.						
Dental: dentures or prosthesis	Dentures	Minimal discomfort, no restriction in activities	Discomfort preventing use in some activities (e.g., eating), but not others (e.g., speaking)	Unable to use dentures or prosthesis at any time	—	—

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Dental: periodontal disease	Periodontal	Gingival recession or gingivitis; limited bleeding on probing; mild local bone loss	Moderate gingival recession or gingivitis; multiple sites of bleeding on probing; moderate bone loss	Spontaneous bleeding; severe bone loss with or without tooth loss; osteonecrosis of maxilla or mandible	—	—
REMARK: Severe periodontal disease leading to osteonecrosis is graded as Osteonecrosis (avascular necrosis) in the MUSCULOSKELETAL CATEGORY.						
Dental: teeth	Teeth	Surface stains; dental caries; restorable, without extractions	Less than full mouth extractions; tooth fracture or crown amputation or repair indicated	Full mouth extractions indicated	—	—
Dental: teeth development	Teeth development	Hypoplasia of tooth or enamel not interfering with function	Functional impairment correctable with oral surgery	Maldevelopment with functional impairment not surgically correctable	—	—
Diarrhea	Diarrhea	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4 – 6 stools per day over baseline; IV fluids indicated <24hrs; moderate increase in ostomy output compared to baseline; not interfering with ADL	Increase of ≥7 stools per day over baseline; incontinence; IV fluids ≥24 hrs; hospitalization; severe increase in ostomy output compared to baseline; interfering with ADL	Life-threatening consequences (e.g., hemodynamic collapse)	Death
REMARK: Diarrhea includes diarrhea of small bowel or colonic origin, and/or ostomy diarrhea. ALSO CONSIDER: Dehydration; Hypotension.						
Distension/bloating, abdominal	Distension	Asymptomatic	Symptomatic, but not interfering with GI function	Symptomatic, interfering with GI function	—	—
ALSO CONSIDER: Ascites (non-malignant); Ileus, GI (functional obstruction of bowel, i.e., neuroconstipation); Obstruction, GI – *Select*.						

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Dry mouth/salivary gland (xerostomia)	Dry mouth	Symptomatic (dry or thick saliva) without significant dietary alteration; unstimulated saliva flow >0.2 ml/min	Symptomatic and significant oral intake alteration (e.g., copious water, other lubricants, diet limited to purees and/or soft, moist foods); unstimulated saliva 0.1 to 0.2 ml/min	Symptoms leading to inability to adequately aliment orally; IV fluids, tube feedings, or TPN indicated; unstimulated saliva <0.1 ml/min	—	—
REMARK: Dry mouth/salivary gland (xerostomia) includes descriptions of grade using both subjective and objective assessment parameters. Record this event consistently throughout a patient's participation on study. If salivary flow measurements are used for initial assessment, subsequent assessments must use salivary flow. ALSO CONSIDER: Salivary gland changes/saliva.						
Dysphagia (difficulty swallowing)	Dysphagia	Symptomatic, able to eat regular diet	Symptomatic and altered eating/swallowing (e.g., altered dietary habits, oral supplements); IV fluids indicated <24 hrs	Symptomatic and severely altered eating/swallowing (e.g., inadequate oral caloric or fluid intake); IV fluids, tube feedings, or TPN indicated ≥24 hrs	Life-threatening consequences (e.g., obstruction, perforation)	Death
REMARK: Dysphagia (difficulty swallowing) is to be used for swallowing difficulty from oral, pharyngeal, esophageal, or neurologic origin. Dysphagia requiring dilation is graded as Stricture/stenosis (including anastomotic), GI – *Select*. ALSO CONSIDER: Dehydration; Esophagitis.						
Enteritis (inflammation of the small bowel)	Enteritis	Asymptomatic, pathologic or radiographic findings only	Abdominal pain; mucus or blood in stool	Abdominal pain, fever, change in bowel habits with ileus; peritoneal signs	Life-threatening consequences (e.g., perforation, bleeding, ischemia, necrosis)	Death
ALSO CONSIDER: Hemorrhage, GI – *Select*; Typhlitis (cecal inflammation).						
Esophagitis	Esophagitis	Asymptomatic pathologic, radiographic, or endoscopic findings only	Symptomatic; altered eating/swallowing (e.g., altered dietary habits, oral supplements); IV fluids indicated <24 hrs	Symptomatic and severely altered eating/swallowing (e.g., inadequate oral caloric or fluid intake); IV fluids, tube feedings, or TPN indicated ≥24 hrs	Life-threatening consequences	Death
REMARK: Esophagitis includes reflux esophagitis. ALSO CONSIDER: Dysphagia (difficulty swallowing).						

Adverse Event	Short Name	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Fistula, GI – *Select*: – Abdomen NOS – Anus – Biliary tree – Colon/cecum/appendix – Duodenum – Esophagus – Gallbladder – Ileum – Jejunum – Oral cavity – Pancreas – Pharynx – Rectum – Salivary gland – Small bowel NOS – Stomach	Fistula, GI – *Select*	Asymptomatic, radiographic findings only	Symptomatic; altered GI function (e.g., altered dietary habits, diarrhea, or GI fluid loss); IV fluids indicated <24 hrs	Symptomatic and severely altered GI function (e.g., altered dietary habits, diarrhea, or GI fluid loss); IV fluids, tube feedings, or TPN indicated ≥24 hrs	Life-threatening consequences	Death
REMARK: A fistula is defined as an abnormal communication between two body cavities, potential spaces, and/or the skin. The site indicated for a fistula should be the site from which the abnormal process is believed to have originated. For example, a tracheo-esophageal fistula arising in the context of a resected or irradiated esophageal cancer is graded as Fistula, GI – esophagus.						
Flatulence	Flatulence	Mild	Moderate	—	—	—
Gastritis (including bile reflux gastritis)	Gastritis	Asymptomatic radiographic or endoscopic findings only	Symptomatic; altered gastric function (e.g., inadequate oral caloric or fluid intake); IV fluids indicated <24 hrs	Symptomatic and severely altered gastric function (e.g., inadequate oral caloric or fluid intake); IV fluids, tube feedings, or TPN indicated ≥24 hrs	Life-threatening consequences; operative intervention requiring complete organ resection (e.g., gastrectomy)	Death
ALSO CONSIDER: Hemorrhage, GI – *Select*; Ulcer, GI – *Select*.						
NAVIGATION NOTE: Head and neck soft tissue necrosis is graded as Soft tissue necrosis – *Select* in the MUSCULOSKELETAL/SOFT TISSUE CATEGORY.						
Heartburn/dyspepsia	Heartburn	Mild	Moderate	Severe	—	—
Hemorrhoids	Hemorrhoids	Asymptomatic	Symptomatic; banding or medical intervention indicated	Interfering with ADL; interventional radiology, endoscopic, or operative intervention indicated	Life-threatening consequences	Death

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Ileus, GI (functional obstruction of bowel, i.e., neuroconstipation)	Ileus	Asymptomatic, radiographic findings only	Symptomatic; altered GI function (e.g., altered dietary habits); IV fluids indicated <24 hrs	Symptomatic and severely altered GI function; IV fluids, tube feeding, or TPN indicated ≥24 hrs	Life-threatening consequences	Death
REMARK: Ileus, GI is to be used for altered upper or lower GI function (e.g., delayed gastric or colonic emptying). ALSO CONSIDER: Constipation; Nausea; Obstruction, GI – *Select*; Vomiting.						
Incontinence, anal	Incontinence, anal	Occasional use of pads required	Daily use of pads required	Interfering with ADL; operative intervention indicated	Permanent bowel diversion indicated	Death
REMARK: Incontinence, anal is to be used for loss of sphincter control as sequelae of operative or therapeutic intervention.						
Leak (including anastomotic), GI – *Select*: – Biliary tree – Esophagus – Large bowel – Leak NOS – Pancreas – Pharynx – Rectum – Small bowel – Stoma – Stomach	Leak, GI – *Select*	Asymptomatic radiographic findings only	Symptomatic; medical intervention indicated	Symptomatic and interfering with GI function; invasive or endoscopic intervention indicated	Life-threatening consequences	Death
REMARK: Leak (including anasomotic), GI – *Select* is to be used for clinical signs/symptoms or radiographic confirmation of anastomotic or conduit leak (e.g., biliary, esophageal, intestinal, pancreatic, pharyngeal, rectal), but without development of fistula.						
Malabsorption	Malabsorption	—	Altered diet; oral therapies indicated (e.g., enzymes, medications, dietary supplements)	Inability to aliment adequately via GI tract (i.e., TPN indicated)	Life-threatening consequences	Death

GASTROINTESTINAL

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Mucositis/stomatitis (clinical exam) – *Select*: – Anus – Esophagus – Large bowel – Larynx – Oral cavity – Pharynx – Rectum – Small bowel – Stomach – Trachea	Mucositis (clinical exam) – *Select*	Erythema of the mucosa	Patchy ulcerations or pseudomembranes	Confluent ulcerations or pseudomembranes; bleeding with minor trauma	Tissue necrosis; significant spontaneous bleeding; life-threatening consequences	Death
REMARK: Mucositis/stomatitis (functional/symptomatic) may be used for mucositis of the upper aero-digestive tract caused by radiation, agents, or GVHD.						
Mucositis/stomatitis (functional/symptomatic) – *Select*: – Anus – Esophagus – Large bowel – Larynx – Oral cavity – Pharynx – Rectum – Small bowel – Stomach – Trachea	Mucositis (functional/ symptomatic) – *Select*	Upper aerodigestive tract sites: Minimal symptoms, normal diet; minimal respiratory symptoms but not interfering with function Lower GI sites: Minimal discomfort, intervention not indicated	Upper aerodigestive tract sites: Symptomatic but can eat and swallow modified diet; respiratory symptoms interfering with function but not interfering with ADL Lower GI sites: Symptomatic, medical intervention indicated but not interfering with ADL	Upper aerodigestive tract sites: Symptomatic and unable to adequately aliment or hydrate orally; respiratory symptoms interfering with ADL Lower GI sites: Stool incontinence or other symptoms interfering with ADL	Symptoms associated with life-threatening consequences	Death
Nausea	Nausea	Loss of appetite without alteration in eating habits	Oral intake decreased without significant weight loss, dehydration or malnutrition; IV fluids indicated <24 hrs	Inadequate oral caloric or fluid intake; IV fluids, tube feedings, or TPN indicated ≥24 hrs	Life-threatening consequences	Death
ALSO CONSIDER: Anorexia; Vomiting.						

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Necrosis, GI – *Select*: – Anus – Colon/cecum/appendix – Duodenum – Esophagus – Gallbladder – Hepatic – Ileum – Jejunum – Oral – Pancreas – Peritoneal cavity – Pharynx – Rectum – Small bowel NOS – Stoma – Stomach	Necrosis, GI – *Select*	—	—	Inability to aliment adequately by GI tract (e.g., requiring enteral or parenteral nutrition); interventional radiology, endoscopic, or operative intervention indicated	Life-threatening consequences; operative intervention requiring complete organ resection (e.g., total colectomy)	Death
ALSO CONSIDER: Visceral arterial ischemia (non-myocardial).						
Obstruction, GI – *Select*: – Cecum – Colon – Duodenum – Esophagus – Gallbladder – Ileum – Jejunum – Rectum – Small bowel NOS – Stoma – Stomach	Obstruction, GI – *Select*	Asymptomatic radiographic findings only	Symptomatic; altered GI function (e.g., altered dietary habits, vomiting, diarrhea, or GI fluid loss); IV fluids indicated <24 hrs	Symptomatic and severely altered GI function (e.g., altered dietary habits, vomiting, diarrhea, or GI fluid loss); IV fluids, tube feedings, or TPN indicated ≥24 hrs; operative intervention indicated	Life-threatening consequences; operative intervention requiring complete organ resection (e.g., total colectomy)	Death
NAVIGATION NOTE: Operative injury is graded as Intra-operative injury – *Select Organ or Structure* in the SURGERY/INTRA-OPERATIVE INJURY CATEGORY.						
NAVIGATION NOTE: Pelvic pain is graded as Pain – *Select* in the PAIN CATEGORY.						

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Perforation, GI – *Select*: – Appendix – Biliary tree – Cecum – Colon – Duodenum – Esophagus – Gallbladder – Ileum – Jejunum – Rectum – Small bowel NOS – Stomach	Perforation, GI – *Select*	Asymptomatic radiographic findings only	Medical intervention indicated; IV fluids indicated <24 hrs	IV fluids, tube feedings, or TPN indicated ≥24 hrs; operative intervention indicated	Life-threatening consequences	Death
Proctitis	Proctitis	Rectal discomfort, intervention not indicated	Symptoms not interfering with ADL; medical intervention indicated	Stool incontinence or other symptoms interfering with ADL; operative intervention indicated	Life-threatening consequences (e.g., perforation)	Death
Prolapse of stoma, GI	Prolapse of stoma, GI	Asymptomatic	Extraordinary local care or maintenance; minor revision indicated	Dysfunctional stoma; major revision indicated	Life-threatening consequences	Death
REMARK: Other stoma complications may be graded as Fistula, GI – *Select*; Leak (including anastomotic), GI – *Select*; Obstruction, GI – *Select;* Perforation, GI – *Select*; Stricture/stenosis (including anastomotic), GI – *Select*.						
NAVIGATION NOTE: Rectal or perirectal pain (proctalgia) is graded as Pain – *Select* in the PAIN CATEGORY.						
Salivary gland changes/saliva	Salivary gland changes	Slightly thickened saliva; slightly altered taste (e.g., metallic)	Thick, ropy, sticky saliva; markedly altered taste; alteration in diet indicated; secretion-induced symptoms not interfering with ADL	Acute salivary gland necrosis; severe secretion-induced symptoms interfering with ADL	Disabling	—
ALSO CONSIDER: Dry mouth/salivary gland (xerostomia); Mucositis/stomatitis (clinical exam) – *Select*; Mucositis/stomatitis (functional/symptomatic) – *Select*; Taste alteration (dysgeusia).						
NAVIGATION NOTE: Splenic function is graded in the BLOOD/BONE MARROW CATEGORY.						

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Stricture/stenosis (including anastomotic), GI – *Select*: – Anus – Biliary tree – Cecum – Colon – Duodenum – Esophagus – Ileum – Jejunum – Pancreas/pancreatic duct – Pharynx – Rectum – Small bowel NOS – Stoma – Stomach	Stricture, GI – *Select*	Asymptomatic radiographic findings only	Symptomatic; altered GI function (e.g., altered dietary habits, vomiting, bleeding, diarrhea); IV fluids indicated <24 hrs	Symptomatic and severely altered GI function (e.g., altered dietary habits, diarrhea, or GI fluid loss); IV fluids, tube feedings, or TPN indicated ≥24 hrs; operative intervention indicated	Life-threatening consequences; operative intervention requiring complete organ resection (e.g., total colectomy)	Death
Taste alteration (dysgeusia)	Taste alteration	Altered taste but no change in diet	Altered taste with change in diet (e.g., oral supplements); noxious or unpleasant taste; loss of taste	—	—	—
Typhlitis (cecal inflammation)	Typhlitis	Asymptomatic, pathologic or radiographic findings only	Abdominal pain; mucus or blood in stool	Abdominal pain, fever, change in bowel habits with ileus; peritoneal signs	Life-threatening consequences (e.g., perforation, bleeding, ischemia, necrosis); operative intervention indicated	Death

ALSO CONSIDER: Colitis; Hemorrhage, GI – *Select* ; Ileus, GI (functional obstruction of bowel, i.e., neuroconstipation).

GASTROINTESTINAL

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Ulcer, GI – *Select*: – Anus – Cecum – Colon – Duodenum – Esophagus – Ileum – Jejunum – Rectum – Small bowel NOS – Stoma – Stomach	Ulcer, GI – *Select*	Asymptomatic, radiographic or endoscopic findings only	Symptomatic; altered GI function (e.g., altered dietary habits, oral supplements); IV fluids indicated <24 hrs	Symptomatic and severely altered GI function (e.g., inadequate oral caloric or fluid intake); IV fluids, tube feedings, or TPN indicated ≥24 hrs	Life-threatening consequences	Death
ALSO CONSIDER: Hemorrhage, GI – *Select*.						
Vomiting	Vomiting	1 episode in 24 hrs	2 – 5 episodes in 24 hrs; IV fluids indicated <24 hrs	≥6 episodes in 24 hrs; IV fluids, or TPN indicated ≥24 hrs	Life-threatening consequences	Death
ALSO CONSIDER: Dehydration.						
Gastrointestinal – Other (Specify, __)	GI – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

GROWTH AND DEVELOPMENT

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Bone age (alteration in bone age)	Bone age	—	±2 SD (standard deviation) from normal	—	—	—
Bone growth: femoral head; slipped capital femoral epiphysis	Femoral head growth	Mild valgus/varus deformity	Moderate valgus/varus deformity, symptomatic, interfering with function but not interfering with ADL	Mild slipped capital femoral epiphysis; operative intervention (e.g., fixation) indicated; interfering with ADL	Disabling; severe slipped capital femoral epiphysis >60%; avascular necrosis	—
Bone growth: limb length discrepancy	Limb length	Mild length discrepancy <2 cm	Moderate length discrepancy 2 – 5 cm; shoe lift indicated	Severe length discrepancy >5 cm; operative intervention indicated; interfering with ADL	Disabling; epiphysiodesis	—
Bone growth: spine kyphosis/lordosis	Kyphosis/lordosis	Mild radiographic changes	Moderate accentuation; interfering with function but not interfering with ADL	Severe accentuation; operative intervention indicated; interfering with ADL	Disabling (e.g., cannot lift head)	—
Growth velocity (reduction in growth velocity)	Reduction in growth velocity	10 – 29% reduction in growth from the baseline growth curve	30 – 49% reduction in growth from the baseline growth curve	≥50% reduction in growth from the baseline growth curve	—	—
Puberty (delayed)	Delayed puberty	—	No breast development by age 13 yrs for females; no Tanner Stage 2 development by age 14.5 yrs for males	No sexual development by age 14 yrs for girls, age 16 yrs for boys; hormone replacement indicated	—	—
REMARK: Do not use testicular size for Tanner Stage in male cancer survivors.						
Puberty (precocious)	Precocious puberty	—	Physical signs of puberty <7 years for females, <9 years for males	—	—	—
Short stature	Short stature	Beyond two standard deviations of age and gender mean height	Altered ADL	—	—	—
REMARK: Short stature is secondary to growth hormone deficiency. ALSO CONSIDER: Neuroendocrine: growth hormone secretion abnormality.						
Growth and Development – Other (Specify, __)	Growth and Development – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

HEMORRHAGE/BLEEDING

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Hematoma	Hematoma	Minimal symptoms, invasive intervention not indicated	Minimally invasive evacuation or aspiration indicated	Transfusion, interventional radiology, or operative intervention indicated	Life-threatening consequences; major urgent intervention indicated	Death
REMARK: Hematoma refers to extravasation at wound or operative site or secondary to other intervention. Transfusion implies pRBC. ALSO CONSIDER: Fibrinogen; INR (International Normalized Ratio of prothrombin time); Platelets; PTT (Partial Thromboplastin Time).						
Hemorrhage/bleeding associated with surgery, intra-operative or postoperative	Hemorrhage with surgery	—	—	Requiring transfusion of 2 units non-autologous (10 cc/kg for pediatrics) pRBCs beyond protocol specification; postoperative interventional radiology, endoscopic, or operative intervention indicated	Life-threatening consequences	Death
REMARK: Postoperative period is defined as ≤72 hours after surgery. Verify protocol-specific acceptable guidelines regarding pRBC transfusion. ALSO CONSIDER: Fibrinogen; INR (International Normalized Ratio of prothrombin time); Platelets; PTT (Partial Thromboplastin Time).						
Hemorrhage, CNS	CNS hemorrhage	Asymptomatic, radiographic findings only	Medical intervention indicated	Ventriculostomy, ICP monitoring, intraventricular thrombolysis, or operative intervention indicated	Life-threatening consequences; neurologic deficit or disability	Death
ALSO CONSIDER: Fibrinogen; INR (International Normalized Ratio of prothrombin time); Platelets; PTT (Partial Thromboplastin Time).						

HEMORRHAGE/BLEEDING

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Hemorrhage, GI – *Select*: – Abdomen NOS – Anus – Biliary tree – Cecum/appendix – Colon – Duodenum – Esophagus – Ileum – Jejunum – Liver – Lower GI NOS – Oral cavity – Pancreas – Peritoneal cavity – Rectum – Stoma – Stomach – Upper GI NOS – Varices (esophageal) – Varices (rectal)	Hemorrhage, GI – *Select*	Mild, intervention (other than iron supplements) not indicated	Symptomatic and medical intervention or minor cauterization indicated	Transfusion, interventional radiology, endoscopic, or operative intervention indicated; radiation therapy (i.e., hemostasis of bleeding site)	Life-threatening consequences; major urgent intervention indicated	Death

REMARK: Transfusion implies pRBC.

ALSO CONSIDER: Fibrinogen; INR (International Normalized Ratio of prothrombin time); Platelets; PTT (Partial Thromboplastin Time).

HEMORRHAGE/BLEEDING

Adverse Event	Short Name	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Hemorrhage, GU – *Select*: – Bladder – Fallopian tube – Kidney – Ovary – Prostate – Retroperitoneum – Spermatic cord – Stoma – Testes – Ureter – Urethra – Urinary NOS – Uterus – Vagina – Vas deferens	Hemorrhage, GU – *Select*	Minimal or microscopic bleeding; intervention not indicated	Gross bleeding, medical intervention, or urinary tract irrigation indicated	Transfusion, interventional radiology, endoscopic, or operative intervention indicated; radiation therapy (i.e., hemostasis of bleeding site)	Life-threatening consequences; major urgent intervention indicated	Death
REMARK: Transfusion implies pRBC. ALSO CONSIDER: Fibrinogen; INR (International Normalized Ratio of prothrombin time); Platelets; PTT (Partial Thromboplastin Time).						
Hemorrhage, pulmonary/ upper respiratory – *Select*: – Bronchopulmonary NOS – Bronchus – Larynx – Lung – Mediastinum – Nose – Pharynx – Pleura – Respiratory tract NOS – Stoma – Trachea	Hemorrhage pulmonary – *Select*	Mild, intervention not indicated	Symptomatic and medical intervention indicated	Transfusion, interventional radiology, endoscopic, or operative intervention indicated; radiation therapy (i.e., hemostasis of bleeding site)	Life-threatening consequences; major urgent intervention indicated	Death
REMARK: Transfusion implies pRBC. ALSO CONSIDER: Fibrinogen; INR (International Normalized Ratio of prothrombin time); Platelets; PTT (Partial Thromboplastin Time).						
Petechiae/purpura (hemorrhage/bleeding into skin or mucosa)	Petechiae	Few petechiae	Moderate petechiae; purpura	Generalized petechiae or purpura	—	—
ALSO CONSIDER: Fibrinogen; INR (International Normalized Ratio of prothrombin time); Platelets; PTT (Partial Thromboplastin Time).						

HEMORRHAGE/BLEEDING

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
NAVIGATION NOTE: Vitreous hemorrhage is graded in the OCULAR/VISUAL CATEGORY.						
Hemorrhage/Bleeding – Other (Specify, __)	Hemorrhage – Other (Specify)	Mild without transfusion	—	Transfusion indicated	Catastrophic bleeding, requiring major non-elective intervention	Death

HEPATOBILIARY/PANCREAS

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
NAVIGATION NOTE: Biliary tree damage is graded as Fistula, GI – *Select*; Leak (including anastomotic), GI – *Select*; Necrosis, GI – *Select*; Obstruction, GI – *Select*; Perforation, GI – *Select*; Stricture/stenosis (including anastomotic), GI – *Select* in the GASTROINTESTINAL CATEGORY.						
Cholecystitis	Cholecystitis	Asymptomatic, radiographic findings only	Symptomatic, medical intervention indicated	Interventional radiology, endoscopic, or operative intervention indicated	Life-threatening consequences (e.g., sepsis or perforation)	Death
ALSO CONSIDER: Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils – *Select*; Infection with normal ANC or Grade 1 or 2 neutrophils – *Select*; Infection with unknown ANC – *Select*.						
Liver dysfunction/failure (clinical)	Liver dysfunction	—	Jaundice	Asterixis	Encephalopathy or coma	Death
REMARK: Jaundice is not an AE, but occurs when the liver is not working properly or when a bile duct is blocked. It is graded as a result of liver dysfunction/failure or elevated bilirubin.						
ALSO CONSIDER: Bilirubin (hyperbilirubinemia).						
Pancreas, exocrine enzyme deficiency	Pancreas, exocrine enzyme deficiency	—	Increase in stool frequency, bulk, or odor; steatorrhea	Sequelae of absorption deficiency (e.g., weight loss)	Life-threatening consequences	Death
ALSO CONSIDER: Diarrhea.						
Pancreatitis	Pancreatitis	Asymptomatic, enzyme elevation and/or radiographic findings	Symptomatic, medical intervention indicated	Interventional radiology or operative intervention indicated	Life-threatening consequences (e.g., circulatory failure, hemorrhage, sepsis)	Death
ALSO CONSIDER: Amylase.						
NAVIGATION NOTE: Stricture (biliary tree, hepatic or pancreatic) is graded as Stricture/stenosis (including anastomotic), GI – *Select* in the GASTROINTESTINAL CATEGORY.						
Hepatobiliary/Pancreas – Other (Specify, __)	Hepatobiliary – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

INFECTION

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Colitis, infectious (e.g., Clostridium difficile)	Colitis, infectious	Asymptomatic, pathologic or radiographic findings only	Abdominal pain with mucus and/or blood in stool	IV antibiotics or TPN indicated	Life-threatening consequences (e.g., perforation, bleeding, ischemia, necrosis or toxic megacolon); operative resection or diversion indicated	Death
ALSO CONSIDER: Hemorrhage, GI – *Select*; Typhlitis (cecal inflammation).						
Febrile neutropenia (fever of unknown origin without clinically or microbiologically documented infection) (ANC <1.0 x 10^9/L, fever ≥38.5°C)	Febrile neutropenia	—	—	Present	Life-threatening consequences (e.g., septic shock, hypotension, acidosis, necrosis)	Death
ALSO CONSIDER: Neutrophils/granulocytes (ANC/AGC).						
Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10^9/L) – *Select* *'Select'* AEs appear at the end of the CATEGORY.	Infection (documented clinically) with Grade 3 or 4 ANC – *Select*	—	Localized, local intervention indicated	IV antibiotic, antifungal, or antiviral intervention indicated; interventional radiology or operative intervention indicated	Life-threatening consequences (e.g., septic shock, hypotension, acidosis, necrosis)	Death
REMARK: Fever with Grade 3 or 4 neutrophils in the absence of documented infection is graded as Febrile neutropenia (fever of unknown origin without clinically or microbiologically documented infection). ALSO CONSIDER: Neutrophils/granulocytes (ANC/AGC).						
Infection with normal ANC or Grade 1 or 2 neutrophils – *Select* '*Select*' AEs appear at the end of the CATEGORY.	Infection with normal ANC – *Select*	—	Localized, local intervention indicated	IV antibiotic, antifungal, or antiviral intervention indicated; interventional radiology or operative intervention indicated	Life-threatening consequences (e.g., septic shock, hypotension, acidosis, necrosis)	Death

INFECTION

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Infection with unknown ANC – *Select* *'Select'* AEs appear at the end of the CATEGORY.	Infection with unknown ANC – *Select*	—	Localized, local intervention indicated	IV antibiotic, antifungal, or antiviral intervention indicated; interventional radiology or operative intervention indicated	Life-threatening consequences (e.g., septic shock, hypotension, acidosis, necrosis)	Death
REMARK: Infection with unknown ANC – *Select* is to be used in the rare case when ANC is unknown.						
Opportunistic infection associated with ≥Grade 2 Lymphopenia	Opportunistic infection	—	Localized, local intervention indicated	IV antibiotic, antifungal, or antiviral intervention indicated; interventional radiology or operative intervention indicated	Life-threatening consequences (e.g., septic shock, hypotension, acidosis, necrosis)	Death
ALSO CONSIDER: Lymphopenia.						
Viral hepatitis	Viral hepatitis	Present; transaminases and liver function normal	Transaminases abnormal, liver function normal	Symptomatic liver dysfunction; fibrosis by biopsy; compensated cirrhosis	Decompensated liver function (e.g., ascites, coagulopathy, encephalopathy, coma)	Death
REMARK: Non-viral hepatitis is graded as Infection – *Select*. ALSO CONSIDER: Albumin, serum-low (hypoalbuminemia); ALT, SGPT (serum glutamic pyruvic transaminase); AST, SGOT (serum glutamic oxaloacetic transaminase); Bilirubin (hyperbilirubinemia); Encephalopathy.						
Infection – Other (Specify, __)	Infection – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

INFECTION – *SELECT*

AUDITORY/EAR
- External ear (otitis externa)
- Middle ear (otitis media)

CARDIOVASCULAR
- Artery
- Heart (endocarditis)
- Spleen
- Vein

DERMATOLOGY/SKIN
- Lip/perioral
- Peristomal
- Skin (cellulitis)
- Ungual (nails)

GASTROINTESTINAL
- Abdomen NOS
- Anal/perianal
- Appendix
- Cecum
- Colon
- Dental-tooth
- Duodenum
- Esophagus
- Ileum
- Jejunum
- Oral cavity-gums (gingivitis)
- Peritoneal cavity
- Rectum
- Salivary gland
- Small bowel NOS
- Stomach

GENERAL
- Blood
- Catheter-related
- Foreign body (e.g., graft, implant, prosthesis, stent)
- Wound

HEPATOBILIARY/PANCREAS
- Biliary tree
- Gallbladder (cholecystitis)
- Liver
- Pancreas

LYMPHATIC
- Lymphatic

MUSCULOSKELETAL
- Bone (osteomyelitis)
- Joint
- Muscle (infection myositis)
- Soft tissue NOS

NEUROLOGY
- Brain (encephalitis, infectious)
- Brain + Spinal cord (encephalomyelitis)
- Meninges (meningitis)
- Nerve-cranial
- Nerve-peripheral
- Spinal cord (myelitis)

OCULAR
- Conjunctiva
- Cornea
- Eye NOS
- Lens

PULMONARY/UPPER RESPIRATORY
- Bronchus
- Larynx
- Lung (pneumonia)
- Mediastinum NOS
- Mucosa
- Neck NOS
- Nose
- Paranasal
- Pharynx
- Pleura (empyema)
- Sinus
- Trachea
- Upper aerodigestive NOS
- Upper airway NOS

RENAL/GENITOURINARY
- Bladder (urinary)
- Kidney
- Prostate
- Ureter
- Urethra
- Urinary tract NOS

SEXUAL/REPRODUCTIVE FUNCTION
- Cervix
- Fallopian tube
- Pelvis NOS
- Penis
- Scrotum
- Uterus
- Vagina
- Vulva

LYMPHATICS

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Chyle or lymph leakage	Chyle or lymph leakage	Asymptomatic, clinical or radiographic findings	Symptomatic, medical intervention indicated	Interventional radiology or operative intervention indicated	Life-threatening complications	Death
ALSO CONSIDER: Chylothorax.						
Dermal change lymphedema, phlebolymphedema	Dermal change	Trace thickening or faint discoloration	Marked discoloration; leathery skin texture; papillary formation	—	—	—
REMARK: Dermal change lymphedema, phlebolymphedema refers to changes due to venous stasis.						
ALSO CONSIDER: Ulceration.						
Edema: head and neck	Edema: head and neck	Localized to dependent areas, no disability or functional impairment	Localized facial or neck edema with functional impairment	Generalized facial or neck edema with functional impairment (e.g., difficulty in turning neck or opening mouth compared to baseline)	Severe with ulceration or cerebral edema; tracheotomy or feeding tube indicated	Death
Edema: limb	Edema: limb	5 – 10% inter-limb discrepancy in volume or circumference at point of greatest visible difference; swelling or obscuration of anatomic architecture on close inspection; pitting edema	>10 – 30% inter-limb discrepancy in volume or circumference at point of greatest visible difference; readily apparent obscuration of anatomic architecture; obliteration of skin folds; readily apparent deviation from normal anatomic contour	>30% inter-limb discrepancy in volume; lymphorrhea; gross deviation from normal anatomic contour; interfering with ADL	Progression to malignancy (i.e., lymphangiosarcoma); amputation indicated; disabling	Death
Edema: trunk/genital	Edema: trunk/genital	Swelling or obscuration of anatomic architecture on close inspection; pitting edema	Readily apparent obscuration of anatomic architecture; obliteration of skin folds; readily apparent deviation from normal anatomic contour	Lymphorrhea; interfering with ADL; gross deviation from normal anatomic contour	Progression to malignancy (i.e., lymphangiosarcoma); disabling	Death
Edema: viscera	Edema: viscera	Asymptomatic; clinical or radiographic findings only	Symptomatic; medical intervention indicated	Symptomatic and unable to aliment adequately orally; interventional radiology or operative intervention indicated	Life-threatening consequences	Death

LYMPHATICS

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Lymphedema-related fibrosis	Lymphedema-related fibrosis	Minimal to moderate redundant soft tissue, unresponsive to elevation or compression, with moderately firm texture or spongy feel	Marked increase in density and firmness, with or without tethering	Very marked density and firmness with tethering affecting ≥40% of the edematous area	—	—
Lymphocele	Lymphocele	Asymptomatic, clinical or radiographic findings only	Symptomatic; medical intervention indicated	Symptomatic and interventional radiology or operative intervention indicated	—	—
Phlebolymphatic cording	Phlebolymphatic cording	Asymptomatic, clinical findings only	Symptomatic; medical intervention indicated	Symptomatic and leading to contracture or reduced range of motion	—	—
Lymphatics – Other (Specify, __)	Lymphatics – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

METABOLIC/LABORATORY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Acidosis (metabolic or respiratory)	Acidosis	pH <normal, but ≥7.3	—	pH <7.3	pH <7.3 with life-threatening consequences	Death
Albumin, serum-low (hypoalbuminemia)	Hypoalbuminemia	<LLN – 3 g/dL <LLN – 30 g/L	<3 – 2 g/dL <30 – 20 g/L	<2 g/dL <20 g/L	—	Death
Alkaline phosphatase	Alkaline phosphatase	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	—
Alkalosis (metabolic or respiratory)	Alkalosis	pH >normal, but ≤7.5	—	pH >7.5	pH >7.5 with life-threatening consequences	Death
ALT, SGPT (serum glutamic pyruvic transaminase)	ALT	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	—
Amylase	Amylase	>ULN – 1.5 x ULN	>1.5 – 2.0 x ULN	>2.0 – 5.0 x ULN	>5.0 x ULN	—
AST, SGOT (serum glutamic oxaloacetic transaminase)	AST	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	—
Bicarbonate, serum-low	Bicarbonate, serum-low	<LLN – 16 mmol/L	<16 – 11 mmol/L	<11 – 8 mmol/L	<8 mmol/L	Death
Bilirubin (hyperbilirubinemia)	Bilirubin	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 10.0 x ULN	>10.0 x ULN	—
REMARK: Jaundice is not an AE, but may be a manifestation of liver dysfunction/failure or elevated bilirubin. If jaundice is associated with elevated bilirubin, grade bilirubin.						
Calcium, serum-low (hypocalcemia)	Hypocalcemia	<LLN – 8.0 mg/dL <LLN – 2.0 mmol/L Ionized calcium: <LLN – 1.0 mmol/L	<8.0 – 7.0 mg/dL <2.0 – 1.75 mmol/L Ionized calcium: <1.0 – 0.9 mmol/L	<7.0 – 6.0 mg/dL <1.75 – 1.5 mmol/L Ionized calcium: <0.9 – 0.8 mmol/L	<6.0 mg/dL <1.5 mmol/L Ionized calcium: <0.8 mmol/L	Death
REMARK: Calcium can be falsely low if hypoalbuminemia is present. Serum albumin is <4.0 g/dL, hypocalcemia is reported after the following corrective calculation has been performed: Corrected Calcium (mg/dL) = Total Calcium (mg/dL) – 0.8 [Albumin (g/dL) – 4][4]. Alternatively, direct measurement of ionized calcium is the definitive method to diagnose metabolically relevant alterations in serum calcium.						

[4]Crit Rev Clin Lab Sci 1984;21(1):51-97

METABOLIC/LABORATORY

Adverse Event	Short Name	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Calcium, serum-high (hypercalcemia)	Hypercalcemia	>ULN – 11.5 mg/dL >ULN – 2.9 mmol/L Ionized calcium: >ULN – 1.5 mmol/L	>11.5 – 12.5 mg/dL >2.9 – 3.1 mmol/L Ionized calcium: >1.5 – 1.6 mmol/L	>12.5 – 13.5 mg/dL >3.1 – 3.4 mmol/L Ionized calcium: >1.6 – 1.8 mmol/L	>13.5 mg/dL >3.4 mmol/L Ionized calcium: >1.8 mmol/L	Death
Cholesterol, serum-high (hypercholesteremia)	Cholesterol	>ULN – 300 mg/dL >ULN – 7.75 mmol/L	>300 – 400 mg/dL >7.75 – 10.34 mmol/L	>400 – 500 mg/dL >10.34 – 12.92 mmol/L	>500 mg/dL >12.92 mmol/L	Death
CPK (creatine phosphokinase)	CPK	>ULN – 2.5 x ULN	>2.5 x ULN – 5 x ULN	>5 x ULN – 10 x ULN	>10 x ULN	Death
Creatinine	Creatinine	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 6.0 x ULN	>6.0 x ULN	Death
REMARK: Adjust to age-appropriate levels for pediatric patients. ALSO CONSIDER: Glomerular filtration rate.						
GGT (γ-Glutamyl transpeptidase)	GGT	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	—
Glomerular filtration rate	GFR	<75 – 50% LLN	<50 – 25% LLN	<25% LLN, chronic dialysis not indicated	Chronic dialysis or renal transplant indicated	Death
ALSO CONSIDER: Creatinine.						
Glucose, serum-high (hyperglycemia)	Hyperglycemia	>ULN – 160 mg/dL >ULN – 8.9 mmol/L	>160 – 250 mg/dL >8.9 – 13.9 mmol/L	>250 – 500 mg/dL >13.9 – 27.8 mmol/L	>500 mg/dL >27.8 mmol/L or acidosis	Death
REMARK: Hyperglycemia, in general, is defined as fasting unless otherwise specified in protocol.						
Glucose, serum-low (hypoglycemia)	Hypoglycemia	<LLN – 55 mg/dL <LLN – 3.0 mmol/L	<55 – 40 mg/dL <3.0 – 2.2 mmol/L	<40 – 30 mg/dL <2.2 – 1.7 mmol/L	<30 mg/dL <1.7 mmol/L	Death
Hemoglobinuria	Hemoglobinuria	Present	—	—	—	Death
Lipase	Lipase	>ULN – 1.5 x ULN	>1.5 – 2.0 x ULN	>2.0 – 5.0 x ULN	>5.0 x ULN	—
Magnesium, serum-high (hypermagnesemia)	Hypermagnesemia	>ULN – 3.0 mg/dL >ULN – 1.23 mmol/L	—	>3.0 – 8.0 mg/dL >1.23 – 3.30 mmol/L	>8.0 mg/dL >3.30 mmol/L	Death
Magnesium, serum-low (hypomagnesemia)	Hypomagnesemia	<LLN – 1.2 mg/dL <LLN – 0.5 mmol/L	<1.2 – 0.9 mg/dL <0.5 – 0.4 mmol/L	<0.9 – 0.7 mg/dL <0.4 – 0.3 mmol/L	<0.7 mg/dL <0.3 mmol/L	Death
Phosphate, serum-low (hypophosphatemia)	Hypophosphatemia	<LLN – 2.5 mg/dL <LLN – 0.8 mmol/L	<2.5 – 2.0 mg/dL <0.8 – 0.6 mmol/L	<2.0 – 1.0 mg/dL <0.6 – 0.3 mmol/L	<1.0 mg/dL <0.3 mmol/L	Death
Potassium, serum-high (hyperkalemia)	Hyperkalemia	>ULN – 5.5 mmol/L	>5.5 – 6.0 mmol/L	>6.0 – 7.0 mmol/L	>7.0 mmol/L	Death

METABOLIC/LABORATORY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Potassium, serum-low (hypokalemia)	Hypokalemia	<LLN – 3.0 mmol/L	—	<3.0 – 2.5 mmol/L	<2.5 mmol/L	Death
Proteinuria	Proteinuria	1+ or 0.15 – 1.0 g/24 hrs	2+ to 3+ or >1.0 – 3.5 g/24 hrs	4+ or >3.5 g/24 hrs	Nephrotic syndrome	Death
Sodium, serum-high (hypernatremia)	Hypernatremia	>ULN – 150 mmol/L	>150 – 155 mmol/L	>155 – 160 mmol/L	>160 mmol/L	Death
Sodium, serum-low (hyponatremia)	Hyponatremia	<LLN – 130 mmol/L	—	<130 – 120 mmol/L	<120 mmol/L	Death
Triglyceride, serum-high (hypertriglyceridemia)	Hypertriglyceridemia	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 10 x ULN	>10 x ULN	Death
Uric acid, serum-high (hyperuricemia)	Hyperuricemia	>ULN – 10 mg/dL ≤0.59 mmol/L without physiologic consequences	—	>ULN – 10 mg/dL ≤0.59 mmol/L with physiologic consequences	>10 mg/dL >0.59 mmol/L	Death
ALSO CONSIDER: Creatinine; Potassium, serum-high (hyperkalemia); Renal failure; Tumor lysis syndrome.						
Metabolic/Laboratory – Other (Specify, __)	Metabolic/Lab – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

MUSCULOSKELETAL/SOFT TISSUE

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Arthritis (non-septic)	Arthritis	Mild pain with inflammation, erythema, or joint swelling, but not interfering with function	Moderate pain with inflammation, erythema, or joint swelling interfering with function, but not interfering with ADL	Severe pain with inflammation, erythema, or joint swelling and interfering with ADL	Disabling	Death
REMARK: Report only when the diagnosis of arthritis (e.g., inflammation of a joint or a state characterized by inflammation of joints) is made. Arthralgia (sign or symptom of pain in a joint, especially non-inflammatory in character) is graded as Pain – *Select* in the PAIN CATEGORY.						
Bone: spine-scoliosis	Scoliosis	≤20 degrees; clinically undetectable	>20 – 45 degrees; visible by forward flexion; interfering with function but not interfering with ADL	>45 degrees; scapular prominence in forward flexion; operative intervention indicated; interfering with ADL	Disabling (e.g., interfering with cardiopulmonary function)	Death
Cervical spine-range of motion	Cervical spine ROM	Mild restriction of rotation or flexion between 60 – 70 degrees	Rotation <60 degrees to right or left; <60 degrees of flexion	Ankylosed/fused over multiple segments with no C-spine rotation	—	—
REMARK: 60 – 65 degrees of rotation is required for reversing a car; 60 – 65 degrees of flexion is required to tie shoes.						
Exostosis	Exostosis	Asymptomatic	Involving multiple sites; pain or interfering with function	Excision indicated	Progression to malignancy (i.e., chondrosarcoma)	Death
Extremity-lower (gait/walking)	Gait/walking	Limp evident only to trained observer and able to walk ≥1 kilometer; cane indicated for walking	Noticeable limp, or limitation of limb function, but able to walk ≥0.1 kilometer (1 city block); quad cane indicated for walking	Severe limp with stride modified to maintain balance (widened base of support, marked reduction in step length); ambulation limited to walker; crutches indicated	Unable to walk	—
ALSO CONSIDER: Ataxia (incoordination); Muscle weakness, generalized or specific area (not due to neuropathy) – *Select*.						
Extremity-upper (function)	Extremity-upper (function)	Able to perform most household or work activities with affected limb	Able to perform most household or work activities with compensation from unaffected limb	Interfering with ADL	Disabling; no function of affected limb	—
Fibrosis-cosmesis	Fibrosis-cosmesis	Visible only on close examination	Readily apparent but not disfiguring	Significant disfigurement; operative intervention indicated if patient chooses	—	—

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Fibrosis-deep connective tissue	Fibrosis-deep connective tissue	Increased density, "spongy" feel	Increased density with firmness or tethering	Increased density with fixation of tissue; operative intervention indicated; interfering with ADL	Life-threatening; disabling; loss of limb; interfering with vital organ function	Death
ALSO CONSIDER: Induration/fibrosis (skin and subcutaneous tissue); Muscle weakness, generalized or specific area (not due to neuropathy) – *Select*; Neuropathy: motor; Neuropathy: sensory.						
Fracture	Fracture	Asymptomatic, radiographic findings only (e.g., asymptomatic rib fracture on plain x-ray, pelvic insufficiency fracture on MRI, etc.)	Symptomatic but non-displaced; immobilization indicated	Symptomatic and displaced or open wound with bone exposure; operative intervention indicated	Disabling; amputation indicated	Death
Joint-effusion	Joint-effusion	Asymptomatic, clinical or radiographic findings only	Symptomatic; interfering with function but not interfering with ADL	Symptomatic and interfering with ADL	Disabling	Death
ALSO CONSIDER: Arthritis (non-septic).						
Joint-function[5]	Joint-function	Stiffness interfering with athletic activity; ≤25% loss of range of motion (ROM)	Stiffness interfering with function but not interfering with ADL; >25 – 50% decrease in ROM	Stiffness interfering with ADL; >50 – 75% decrease in ROM	Fixed or non-functional joint (arthrodesis); >75% decrease in ROM	—
ALSO CONSIDER: Arthritis (non-septic).						
Local complication – device/prosthesis-related	Device/prosthesis	Asymptomatic	Symptomatic, but not interfering with ADL; local wound care; medical intervention indicated	Symptomatic, interfering with ADL; operative intervention indicated (e.g., hardware/device replacement or removal, reconstruction)	Life-threatening; disabling; loss of limb or organ	Death
Lumbar spine-range of motion	Lumbar spine ROM	Stiffness and difficulty bending to the floor to pick up a very light object but able to do activity	Some lumbar spine flexion but requires a reaching aid to pick up a very light object from the floor	Ankylosed/fused over multiple segments with no L-spine flexion (i.e., unable to reach to floor to pick up a very light	—	—

[5] Adapted from the *International SFTR Method of Measuring and Recording Joint Motion, International Standard Orthopedic Measurements (ISOM),* Jon J. Gerhardt and Otto A. Russee, Bern, Switzerland, Han Huber 9 Publisher), 1975.

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
				object)		
Muscle weakness, generalized or specific area (not due to neuropathy) – *Select*: – Extraocular – Extremity-lower – Extremity-upper – Facial – Left-sided – Ocular – Pelvic – Right-sided – Trunk – Whole body/generalized	Muscle weakness – *Select*	Asymptomatic, weakness on physical exam	Symptomatic and interfering with function, but not interfering with ADL	Symptomatic and interfering with ADL	Life-threatening; disabling	Death
ALSO CONSIDER: Fatigue (asthenia, lethargy, malaise).						
Muscular/skeletal hypoplasia	Muscular/skeletal hypoplasia	Cosmetically and functionally insignificant hypoplasia	Deformity, hypoplasia, or asymmetry able to be remediated by prosthesis (e.g., shoe insert) or covered by clothing	Functionally significant deformity, hypoplasia, or asymmetry, unable to be remediated by prosthesis or covered by clothing	Disabling	—
Myositis (inflammation/damage of muscle)	Myositis	Mild pain, not interfering with function	Pain interfering with function, but not interfering with ADL	Pain interfering with ADL	Disabling	Death
REMARK: Myositis implies muscle damage (i.e., elevated CPK). ALSO CONSIDER: CPK (creatine phosphokinase); Pain – *Select*.						
Osteonecrosis (avascular necrosis)	Osteonecrosis	Asymptomatic, radiographic findings only	Symptomatic and interfering with function, but not interfering with ADL; minimal bone removal indicated (i.e., minor sequestrectomy)	Symptomatic and interfering with ADL; operative intervention or hyperbaric oxygen indicated	Disabling	Death

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Osteoporosis[6]	Osteoporosis	Radiographic evidence of osteoporosis or Bone Mineral Density (BMD) t-score –1 to –2.5 (osteopenia) and no loss of height or therapy indicated	BMD t-score < –2.5; loss of height <2 cm; anti-osteoporotic therapy indicated	Fractures; loss of height ≥2 cm	Disabling	Death
Seroma	Seroma	Asymptomatic	Symptomatic; medical intervention or simple aspiration indicated	Symptomatic, interventional radiology or operative intervention indicated	—	—
Soft tissue necrosis – *Select*: – Abdomen – Extremity-lower – Extremity-upper – Head – Neck – Pelvic – Thorax	Soft tissue necrosis – *Select*	—	Local wound care; medical intervention indicated	Operative debridement or other invasive intervention indicated (e.g., hyperbaric oxygen)	Life-threatening consequences; major invasive intervention indicated (e.g., tissue reconstruction, flap, or grafting)	Death
Trismus (difficulty, restriction or pain when opening mouth)	Trismus	Decreased range of motion without impaired eating	Decreased range of motion requiring small bites, soft foods or purees	Decreased range of motion with inability to adequately aliment or hydrate orally	—	—
NAVIGATION NOTE: Wound-infectious is graded as Infection – *Select* in the INFECTION CATEGORY.						
NAVIGATION NOTE: Wound non-infectious is graded as Wound complication, non-infectious in the DERMATOLOGY/SKIN CATEGORY.						
Musculoskeletal/Soft Tissue – Other (Specify, __)	Musculoskeletal – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

[6] "Assessment of Fracture Risk and its Application to Screening for Postmenopausal Osteoporosis," Report of a *WHO Study Group Technical Report Series*, No. 843, 1994, v + 129 pages [C*, E, F, R, S], ISBN 92 4 120843 0, Sw.fr. 22.-/US $19.80; in developing countries: Sw.fr. 15.40, Order no. 1100843

NEUROLOGY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
NAVIGATION NOTE: ADD (Attention Deficit Disorder) is graded as Cognitive disturbance.						
NAVIGATION NOTE: Aphasia, receptive and/or expressive, is graded as Speech impairment (e.g., dysphasia or aphasia).						
Apnea	Apnea	—	—	Present	Intubation indicated	Death
Arachnoiditis/ meningismus/radiculitis	Arachnoiditis	Symptomatic, not interfering with function; medical intervention indicated	Symptomatic (e.g., photophobia, nausea) interfering with function but not interfering with ADL	Symptomatic, interfering with ADL	Life-threatening; disabling (e.g., paraplegia)	Death
ALSO CONSIDER: Fever (in the absence of neutropenia, where neutropenia is defined as ANC <1.0 x 10^9/L); Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 109/L) – *Select*; Infection with normal ANC or Grade 1 or 2 neutrophils – *Select*; Infection with unknown ANC – *Select*; Pain – *Select*; Vomiting.						
Ataxia (incoordination)	Ataxia	Asymptomatic	Symptomatic, not interfering with ADL	Symptomatic, interfering with ADL; mechanical assistance indicated	Disabling	Death
REMARK: Ataxia (incoordination) refers to the consequence of medical or operative intervention.						
Brachial plexopathy	Brachial plexopathy	Asymptomatic	Symptomatic, not interfering with ADL	Symptomatic, interfering with ADL	Disabling	Death
CNS cerebrovascular ischemia	CNS ischemia	—	Asymptomatic, radiographic findings only	Transient ischemic event or attack (TIA) ≤24 hrs duration	Cerebral vascular accident (CVA, stroke), neurologic deficit >24 hrs	Death
NAVIGATION NOTE: CNS hemorrhage/bleeding is graded as Hemorrhage, CNS in the HEMORRHAGE/BLEEDING CATEGORY.						
CNS necrosis/cystic progression	CNS necrosis	Asymptomatic, radiographic findings only	Symptomatic, not interfering with ADL; medical intervention indicated	Symptomatic and interfering with ADL; hyperbaric oxygen indicated	Life-threatening; disabling; operative intervention indicated to prevent or treat CNS necrosis/cystic progression	Death
Cognitive disturbance	Cognitive disturbance	Mild cognitive disability; not interfering with work/school/life performance; specialized educational services/devices not indicated	Moderate cognitive disability; interfering with work/school/life performance but capable of independent living; specialized resources on part-time basis indicated	Severe cognitive disability; significant impairment of work/school/life performance	Unable to perform ADL; full-time specialized resources or institutionalization indicated	Death
REMARK: Cognitive disturbance may be used for Attention Deficit Disorder (ADD).						

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Confusion	Confusion	Transient confusion, disorientation, or attention deficit	Confusion, disorientation, or attention deficit interfering with function, but not interfering with ADL	Confusion or delirium interfering with ADL	Harmful to others or self; hospitalization indicated	Death
REMARK: Attention Deficit Disorder (ADD) is graded as Cognitive disturbance.						
NAVIGATION NOTE: Cranial neuropathy is graded as Neuropathy-cranial – *Select*.						
Dizziness	Dizziness	With head movements or nystagmus only; not interfering with function	Interfering with function, but not interfering with ADL	Interfering with ADL	Disabling	—
REMARK: Dizziness includes disequilibrium, lightheadedness, and vertigo. ALSO CONSIDER: Neuropathy: cranial – *Select*; Syncope (fainting).						
NAVIGATION NOTE: Dysphasia, receptive and/or expressive, is graded as Speech impairment (e.g., dysphasia or aphasia).						
Encephalopathy	Encephalopathy	—	Mild signs or symptoms; not interfering with ADL	Signs or symptoms interfering with ADL; hospitalization indicated	Life-threatening; disabling	Death
ALSO CONSIDER: Cognitive disturbance; Confusion; Dizziness; Memory impairment; Mental status; Mood alteration – *Select*; Psychosis (hallucinations/delusions); Somnolence/depressed level of consciousness.						
Extrapyramidal/ involuntary movement/ restlessness	Involuntary movement	Mild involuntary movements not interfering with function	Moderate involuntary movements interfering with function, but not interfering with ADL	Severe involuntary movements or torticollis interfering with ADL	Disabling	Death
NAVIGATION NOTE: Headache/neuropathic pain (e.g., jaw pain, neurologic pain, phantom limb pain, post-infectious neuralgia, or painful neuropathies) is graded as Pain – *Select* in the PAIN CATEGORY.						
Hydrocephalus	Hydrocephalus	Asymptomatic, radiographic findings only	Mild to moderate symptoms not interfering with ADL	Severe symptoms or neurological deficit interfering with ADL	Disabling	Death
Irritability (children <3 years of age)	Irritability	Mild; easily consolable	Moderate; requiring increased attention	Severe; inconsolable	—	—
Laryngeal nerve dysfunction	Laryngeal nerve	Asymptomatic, weakness on clinical examination/testing only	Symptomatic, but not interfering with ADL; intervention not indicated	Symptomatic, interfering with ADL; intervention indicated (e.g., thyroplasty, vocal cord injection)	Life-threatening; tracheostomy indicated	Death

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Leak, cerebrospinal fluid (CSF)	CSF leak	Transient headache; postural care indicated	Symptomatic, not interfering with ADL; blood patch indicated	Symptomatic, interfering with ADL; operative intervention indicated	Life-threatening; disabling	Death
REMARK: Leak, cerebrospinal fluid (CSF) may be used for CSF leak associated with operation and persisting >72 hours.						
Leukoencephalopathy (radiographic findings)	Leukoencephalopathy	Mild increase in subarachnoid space (SAS); mild ventriculomegaly; small (+/- multiple) focal T2 hyperintensities, involving periventricular white matter or <1/3 of susceptible areas of cerebrum	Moderate increase in SAS; moderate ventriculomegaly; focal T2 hyperintensities extending into centrum ovale or involving 1/3 to 2/3 of susceptible areas of cerebrum	Severe increase in SAS; severe ventriculomegaly; near total white matter T2 hyperintensities or diffuse low attenuation (CT)	—	—
REMARK: Leukoencephalopathy is a diffuse white matter process, specifically NOT associated with necrosis. Leukoencephalopathy (radiographic findings) does not include lacunas, which are areas that become void of neural tissue.						
Memory impairment	Memory impairment	Memory impairment not interfering with function	Memory impairment interfering with function, but not interfering with ADL	Memory impairment interfering with ADL	Amnesia	—
Mental status[7]	Mental status	—	1 – 3 point below age and educational norm in Folstein Mini-Mental Status Exam (MMSE)	>3 point below age and educational norm in Folstein MMSE	—	—
Mood alteration – *Select*: – Agitation – Anxiety – Depression – Euphoria	Mood alteration – *Select*	Mild mood alteration not interfering with function	Moderate mood alteration interfering with function, but not interfering with ADL; medication indicated	Severe mood alteration interfering with ADL	Suicidal ideation; danger to self or others	Death
Myelitis	Myelitis	Asymptomatic, mild signs (e.g., Babinski's or Lhermitte's sign)	Weakness or sensory loss not interfering with ADL	Weakness or sensory loss interfering with ADL	Disabling	Death

[7] Folstein MF, Folstein, SE and McHugh PR (1975) "Mini-Mental State: A Practical Method for Grading the State of Patients for the Clinician," *Journal of Psychiatric Research*, 12: 189-198

NEUROLOGY

Adverse Event	Short Name	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
NAVIGATION NOTE: Neuropathic pain is graded as Pain – *Select* in the PAIN CATEGORY.						
Neuropathy: cranial – *Select*: – CN I Smell – CN II Vision – CN III Pupil, upper eyelid, extra ocular movements – CN IV Downward, inward movement of eye – CN V Motor-jaw muscles; Sensory-facial – CN VI Lateral deviation of eye – CN VII Motor-face; Sensory-taste – CN VIII Hearing and balance – CN IX Motor-pharynx; Sensory-ear, pharynx, tongue – CN X Motor-palate; pharynx, larynx – CN XI Motor-sternomastoid and trapezius – CN XII Motor-tongue	Neuropathy: cranial – *Select*	Asymptomatic, detected on exam/testing only	Symptomatic, not interfering with ADL	Symptomatic, interfering with ADL	Life-threatening; disabling	Death
Neuropathy: motor	Neuropathy-motor	Asymptomatic, weakness on exam/testing only	Symptomatic weakness interfering with function, but not interfering with ADL	Weakness interfering with ADL; bracing or assistance to walk (e.g., cane or walker) indicated	Life-threatening; disabling (e.g., paralysis)	Death
REMARK: Cranial nerve motor neuropathy is graded as Neuropathy: cranial – *Select*. ALSO CONSIDER: Laryngeal nerve dysfunction; Phrenic nerve dysfunction.						
Neuropathy: sensory	Neuropathy-sensory	Asymptomatic; loss of deep tendon reflexes or paresthesia (including tingling) but not interfering with function	Sensory alteration or paresthesia (including tingling), interfering with function, but not interfering with ADL	Sensory alteration or paresthesia interfering with ADL	Disabling	Death
REMARK: Cranial nerve sensory neuropathy is graded as Neuropathy: cranial – *Select*.						
Personality/behavioral	Personality	Change, but not adversely affecting patient or family	Change, adversely affecting patient or family	Mental health intervention indicated	Change harmful to others or self; hospitalization indicated	Death
Phrenic nerve dysfunction	Phrenic nerve	Asymptomatic weakness on exam/testing only	Symptomatic but not interfering with ADL; intervention not indicated	Significant dysfunction; intervention indicated (e.g., diaphragmatic plication)	Life-threatening respiratory compromise; mechanical ventilation indicated	Death
Psychosis (hallucinations/ delusions)	Psychosis	—	Transient episode	Interfering with ADL; medication, supervision	Harmful to others or self; life-threatening	Death

NEUROLOGY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
				or restraints indicated	consequences	
Pyramidal tract dysfunction (e.g., ↑ tone, hyperreflexia, positive Babinski, ↓ fine motor coordination)	Pyramidal tract dysfunction	Asymptomatic, abnormality on exam or testing only	Symptomatic; interfering with function but not interfering with ADL	Interfering with ADL	Disabling; paralysis	Death
Seizure	Seizure	—	One brief generalized seizure; seizure(s) well controlled by anticonvulsants or infrequent focal motor seizures not interfering with ADL	Seizures in which consciousness is altered; poorly controlled seizure disorder, with breakthrough generalized seizures despite medical intervention	Seizures of any kind which are prolonged, repetitive, or difficult to control (e.g., status epilepticus, intractable epilepsy)	Death
Somnolence/depressed level of consciousness	Somnolence	—	Somnolence or sedation interfering with function, but not interfering with ADL	Obtundation or stupor; difficult to arouse; interfering with ADL	Coma	Death
Speech impairment (e.g., dysphasia or aphasia)	Speech impairment	—	Awareness of receptive or expressive dysphasia, not impairing ability to communicate	Receptive or expressive dysphasia, impairing ability to communicate	Inability to communicate	—
REMARK: Speech impairment refers to a primary CNS process, not neuropathy or end organ dysfunction. ALSO CONSIDER: Laryngeal nerve dysfunction; Voice changes/dysarthria (e.g., hoarseness, loss, or alteration in voice, laryngitis).						
Syncope (fainting)	Syncope (fainting)	—	—	Present	Life-threatening consequences	Death
ALSO CONSIDER: CNS cerebrovascular ischemia; Conduction abnormality/atrioventricular heart block – *Select*; Dizziness; Supraventricular and nodal arrhythmia – *Select*; Vasovagal episode; Ventricular arrhythmia – *Select*.						
NAVIGATION NOTE: Taste alteration (CN VII, IX) is graded as Taste alteration (dysgeusia) in the GASTROINTESTINAL CATEGORY.						
Tremor	Tremor	Mild and brief or intermittent but not interfering with function	Moderate tremor interfering with function, but not interfering with ADL	Severe tremor interfering with ADL	Disabling	—
Neurology – Other (Specify, __)	Neurology – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

OCULAR/VISUAL

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Cataract	Cataract	Asymptomatic, detected on exam only	Symptomatic, with moderate decrease in visual acuity (20/40 or better); decreased visual function correctable with glasses	Symptomatic with marked decrease in visual acuity (worse than 20/40); operative intervention indicated (e.g., cataract surgery)	—	—
Dry eye syndrome	Dry eye	Mild, intervention not indicated	Symptomatic, interfering with function but not interfering with ADL; medical intervention indicated	Symptomatic or decrease in visual acuity interfering with ADL; operative intervention indicated	—	—
Eyelid dysfunction	Eyelid dysfunction	Asymptomatic	Symptomatic, interfering with function but not ADL; requiring topical agents or epilation	Symptomatic; interfering with ADL; surgical intervention indicated	—	—
REMARK: Eyelid dysfunction includes canalicular stenosis, ectropion, entropion, erythema, madarosis, symblepharon, telangiectasis, thickening, and trichiasis. ALSO CONSIDER: Neuropathy: cranial – *Select*.						
Glaucoma	Glaucoma	Elevated intraocular pressure (EIOP) with single topical agent for intervention; no visual field deficit	EIOP causing early visual field deficit (i.e., nasal step or arcuate deficit); multiple topical or oral agents indicated	EIOP causing marked visual field deficits (i.e., involving both superior and inferior visual fields); operative intervention indicated	EIOP resulting in blindness (20/200 or worse); enucleation indicated	—
Keratitis (corneal inflammation/corneal ulceration)	Keratitis	Abnormal ophthalmologic changes only; intervention not indicated	Symptomatic and interfering with function, but not interfering with ADL	Symptomatic and interfering with ADL; operative intervention indicated	Perforation or blindness (20/200 or worse)	—
NAVIGATION NOTE: Ocular muscle weakness is graded as Muscle weakness, generalized or specific area (not due to neuropathy) – *Select* in the MUSCULOSKELETAL/SOFT TISSUE CATEGORY.						
Night blindness (nyctalopia)	Nyctalopia	Symptomatic, not interfering with function	Symptomatic and interfering with function but not interfering with ADL	Symptomatic and interfering with ADL	Disabling	—

OCULAR/VISUAL

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Nystagmus	Nystagmus	Asymptomatic	Symptomatic and interfering with function but not interfering with ADL	Symptomatic and interfering with ADL	Disabling	—
ALSO CONSIDER: Neuropathy: cranial – *Select*; Ophthalmoplegia/diplopia (double vision).						
Ocular surface disease	Ocular surface disease	Asymptomatic or minimally symptomatic but not interfering with function	Symptomatic, interfering with function but not interfering with ADL; topical antibiotics or other topical intervention indicated	Symptomatic, interfering with ADL; operative intervention indicated	—	—
REMARK: Ocular surface disease includes conjunctivitis, keratoconjunctivitis sicca, chemosis, keratinization, and palpebral conjunctival epithelial metaplasia.						
Ophthalmoplegia/ diplopia (double vision)	Diplopia	Intermittently symptomatic, intervention not indicated	Symptomatic and interfering with function but not interfering with ADL	Symptomatic and interfering with ADL; surgical intervention indicated	Disabling	—
ALSO CONSIDER: Neuropathy: cranial – *Select*.						
Optic disc edema	Optic disc edema	Asymptomatic	Decreased visual acuity (20/40 or better); visual field defect present	Decreased visual acuity (worse than 20/40); marked visual field defect but sparing the central 20 degrees	Blindness (20/200 or worse)	—
ALSO CONSIDER: Neuropathy: cranial – *Select*.						
Proptosis/enophthalmos	Proptosis/enophthalmos	Asymptomatic, intervention not indicated	Symptomatic and interfering with function, but not interfering with ADL	Symptomatic and interfering with ADL	—	—
Retinal detachment	Retinal detachment	Exudative; no central vision loss; intervention not indicated	Exudative and visual acuity 20/40 or better but intervention not indicated	Rhegmatogenous or exudative detachment; operative intervention indicated	Blindness (20/200 or worse)	—
Retinopathy	Retinopathy	Asymptomatic	Symptomatic with moderate decrease in visual acuity (20/40 or better)	Symptomatic with marked decrease in visual acuity (worse than 20/40)	Blindness (20/200 or worse)	—

OCULAR/VISUAL

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Scleral necrosis/melt	Scleral necrosis	Asymptomatic or symptomatic but not interfering with function	Symptomatic, interfering with function but not interfering with ADL; moderate decrease in visual acuity (20/40 or better); medical intervention indicated	Symptomatic, interfering with ADL; marked decrease in visual acuity (worse than 20/40); operative intervention indicated	Blindness (20/200 or worse); painful eye with enucleation indicated	—
Uveitis	Uveitis	Asymptomatic	Anterior uveitis; medical intervention indicated	Posterior or pan-uveitis; operative intervention indicated	Blindness (20/200 or worse)	—
Vision-blurred vision	Blurred vision	Symptomatic not interfering with function	Symptomatic and interfering with function, but not interfering with ADL	Symptomatic and interfering with ADL	Disabling	—
Vision-flashing lights/floaters	Flashing lights	Symptomatic not interfering with function	Symptomatic and interfering with function, but not interfering with ADL	Symptomatic and interfering with ADL	Disabling	—
Vision-photophobia	Photophobia	Symptomatic not interfering with function	Symptomatic and interfering with function, but not interfering with ADL	Symptomatic and interfering with ADL	Disabling	—
Vitreous hemorrhage	Vitreous hemorrhage	Asymptomatic, clinical findings only	Symptomatic, interfering with function, but not interfering with ADL; intervention not indicated	Symptomatic, interfering with ADL; vitrectomy indicated	—	—
Watery eye (epiphora, tearing)	Watery eye	Symptomatic, intervention not indicated	Symptomatic, interfering with function but not interfering with ADL	Symptomatic, interfering with ADL	—	—
Ocular/Visual – Other (Specify, __)	Ocular – Other (Specify)	Symptomatic not interfering with function	Symptomatic and interfering with function, but not interfering with ADL	Symptomatic and interfering with ADL	Blindness (20/200 or worse)	Death

PAIN

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Pain – *Select*: '*Select*' AEs appear at the end of the CATEGORY.	Pain – *Select*	Mild pain not interfering with function	Moderate pain; pain or analgesics interfering with function, but not interfering with ADL	Severe pain; pain or analgesics severely interfering with ADL	Disabling	—
Pain – Other (Specify, __)	Pain – Other (Specify)	Mild pain not interfering with function	Moderate pain; pain or analgesics interfering with function, but not interfering with ADL	Severe pain; pain or analgesics severely interfering with ADL	Disabling	—

PAIN – *SELECT*

AUDITORY/EAR
- – External ear
- – Middle ear

CARDIOVASCULAR
- – Cardiac/heart
- – Pericardium

DERMATOLOGY/SKIN
- – Face
- – Lip
- – Oral-gums
- – Scalp
- – Skin

GASTROINTESTINAL
- – Abdomen NOS
- – Anus
- – Dental/teeth/peridontal
- – Esophagus
- – Oral cavity
- – Peritoneum
- – Rectum
- – Stomach

GENERAL
- – Pain NOS
- – Tumor pain

HEPATOBILIARY/PANCREAS
- – Gallbladder
- – Liver

LYMPHATIC
- – Lymph node

MUSCULOSKELETAL
- – Back
- – Bone
- – Buttock
- – Extremity-limb
- – Intestine
- – Joint
- – Muscle
- – Neck
- – Phantom (pain associated with missing limb)

NEUROLOGY
- – Head/headache
- – Neuralgia/peripheral nerve

OCULAR
- – Eye

PULMONARY/UPPER RESPIRATORY
- – Chest wall
- – Chest/thorax NOS

PULMONARY/UPPER RESPIRATORY (*continued*)
- – Larynx
- – Pleura
- – Sinus
- – Throat/pharynx/larynx

RENAL/GENITOURINARY
- – Bladder
- – Kidney

SEXUAL/REPRODUCTIVE FUNCTION
- – Breast
- – Ovulatory
- – Pelvis
- – Penis
- – Perineum
- – Prostate
- – Scrotum
- – Testicle
- – Urethra
- – Uterus
- – Vagina

PULMONARY/UPPER RESPIRATORY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Adult Respiratory Distress Syndrome (ARDS)	ARDS	—	—	Present, intubation not indicated	Present, intubation indicated	Death
ALSO CONSIDER: Dyspnea (shortness of breath); Hypoxia; Pneumonitis/pulmonary infiltrates.						
Aspiration	Aspiration	Asymptomatic ("silent aspiration"); endoscopy or radiographic (e.g., barium swallow) findings	Symptomatic (e.g., altered eating habits, coughing or choking episodes consistent with aspiration); medical intervention indicated (e.g., antibiotics, suction or oxygen)	Clinical or radiographic signs of pneumonia or pneumonitis; unable to aliment orally	Life-threatening (e.g., aspiration pneumonia or pneumonitis)	Death
ALSO CONSIDER: Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10^9/L) – *Select;* Infection with normal ANC or Grade 1 or 2 neutrophils – *Select;* Infection with unknown ANC – *Select;* Laryngeal nerve dysfunction; Neuropathy: cranial – *Select*; Pneumonitis/pulmonary infiltrates.						
Atelectasis	Atelectasis	Asymptomatic	Symptomatic (e.g., dyspnea, cough), medical intervention indicated (e.g., bronchoscopic suctioning, chest physiotherapy, suctioning)	Operative (e.g., stent, laser) intervention indicated	Life-threatening respiratory compromise	Death
ALSO CONSIDER: Adult Respiratory Distress Syndrome (ARDS); Cough; Dyspnea (shortness of breath); Hypoxia; Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 109/L) – *Select*; Infection with normal ANC or Grade 1 or 2 neutrophils – *Select*; Infection with unknown ANC – *Select*; Obstruction/stenosis of airway – *Select*; Pneumonitis/pulmonary infiltrates; Pulmonary fibrosis (radiographic changes).						
Bronchospasm, wheezing	Bronchospasm	Asymptomatic	Symptomatic not interfering with function	Symptomatic interfering with function	Life-threatening	Death
ALSO CONSIDER: Allergic reaction/hypersensitivity (including drug fever); Dyspnea (shortness of breath).						
Carbon monoxide diffusion capacity (DL_{CO})	DL_{CO}	90 – 75% of predicted value	<75 – 50% of predicted value	<50 – 25% of predicted value	<25% of predicted value	Death
ALSO CONSIDER: Hypoxia; Pneumonitis/pulmonary infiltrates; Pulmonary fibrosis (radiographic changes).						
Chylothorax	Chylothorax	Asymptomatic	Symptomatic; thoracentesis or tube drainage indicated	Operative intervention indicated	Life-threatening (e.g., hemodynamic instability or ventilatory support indicated)	Death
Cough	Cough	Symptomatic, non-narcotic medication only indicated	Symptomatic and narcotic medication indicated	Symptomatic and significantly interfering with sleep or ADL	—	—

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Dyspnea (shortness of breath)	Dyspnea	Dyspnea on exertion, but can walk 1 flight of stairs without stopping	Dyspnea on exertion but unable to walk 1 flight of stairs or 1 city block (0.1km) without stopping	Dyspnea with ADL	Dyspnea at rest; intubation/ventilator indicated	Death
ALSO CONSIDER: Hypoxia; Neuropathy: motor; Pneumonitis/pulmonary infiltrates; Pulmonary fibrosis (radiographic changes).						
Edema, larynx	Edema, larynx	Asymptomatic edema by exam only	Symptomatic edema, no respiratory distress	Stridor; respiratory distress; interfering with ADL	Life-threatening airway compromise; tracheotomy, intubation, or laryngectomy indicated	Death
ALSO CONSIDER: Allergic reaction/hypersensitivity (including drug fever).						
FEV_1	FEV_1	90 – 75% of predicted value	<75 – 50% of predicted value	<50 – 25% of predicted value	<25% of predicted	Death
Fistula, pulmonary/upper respiratory – *Select*: – Bronchus – Larynx – Lung – Oral cavity – Pharynx – Pleura – Trachea	Fistula, pulmonary – *Select*	Asymptomatic, radiographic findings only	Symptomatic, tube thoracostomy or medical management indicated; associated with altered respiratory function but not interfering with ADL	Symptomatic and associated with altered respiratory function interfering with ADL; or endoscopic (e.g., stent) or primary closure by operative intervention indicated	Life-threatening consequences; operative intervention with thoracoplasty, chronic open drainage or multiple thoracotomies indicated	Death
REMARK: A fistula is defined as an abnormal communication between two body cavities, potential spaces, and/or the skin. The site indicated for a fistula should be the site from which the abnormal process is believed to have arisen. For example, a tracheo-esophageal fistula arising in the context of a resected or irradiated esophageal cancer should be graded as Fistula, GI – esophagus in the GASTROINTESTINAL CATEGORY.						
NAVIGATION NOTE: Hemoptysis is graded as Hemorrhage, pulmonary/upper respiratory – *Select* in the HEMORRHAGE/BLEEDING CATEGORY.						
Hiccoughs (hiccups, singultus)	Hiccoughs	Symptomatic, intervention not indicated	Symptomatic, intervention indicated	Symptomatic, significantly interfering with sleep or ADL	—	—
Hypoxia	Hypoxia	—	Decreased O_2 saturation with exercise (e.g., pulse oximeter <88%); intermittent supplemental oxygen	Decreased O_2 saturation at rest; continuous oxygen indicated	Life-threatening; intubation or ventilation indicated	Death

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Nasal cavity/paranasal sinus reactions	Nasal/paranasal reactions	Asymptomatic mucosal crusting, blood-tinged secretions	Symptomatic stenosis or edema/narrowing interfering with airflow	Stenosis with significant nasal obstruction; interfering with ADL	Necrosis of soft tissue or bone	Death
ALSO CONSIDER: Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10^9/L) – *Select;* Infection with normal ANC or Grade 1 or 2 neutrophils – *Select;* Infection with unknown ANC – *Select*.						
Obstruction/stenosis of airway – *Select*: – Bronchus – Larynx – Pharynx – Trachea	Airway obstruction – *Select*	Asymptomatic obstruction or stenosis on exam, endoscopy, or radiograph	Symptomatic (e.g., noisy airway breathing), but causing no respiratory distress; medical management indicated (e.g., steroids)	Interfering with ADL; stridor or endoscopic intervention indicated (e.g., stent, laser)	Life-threatening airway compromise; tracheotomy or intubation indicated	Death
Pleural effusion (non-malignant)	Pleural effusion	Asymptomatic	Symptomatic, intervention such as diuretics or up to 2 therapeutic thoracenteses indicated	Symptomatic and supplemental oxygen, >2 therapeutic thoracenteses, tube drainage, or pleurodesis indicated	Life-threatening (e.g., causing hemodynamic instability or ventilatory support indicated)	Death
ALSO CONSIDER: Atelectasis; Cough; Dyspnea (shortness of breath); Hypoxia; Pneumonitis/pulmonary infiltrates; Pulmonary fibrosis (radiographic changes).						
NAVIGATION NOTE: Pleuritic pain is graded as Pain – *Select* in the PAIN CATEGORY.						
Pneumonitis/pulmonary infiltrates	Pneumonitis	Asymptomatic, radiographic findings only	Symptomatic, not interfering with ADL	Symptomatic, interfering with ADL; O_2 indicated	Life-threatening; ventilatory support indicated	Death
ALSO CONSIDER: Adult Respiratory Distress Syndrome (ARDS); Cough; Dyspnea (shortness of breath); Hypoxia; Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10^9/L) – *Select;* Infection with normal ANC or Grade 1 or 2 neutrophils – *Select;* Infection with unknown ANC – *Select*; Pneumonitis/pulmonary infiltrates; Pulmonary fibrosis (radiographic changes).						
Pneumothorax	Pneumothorax	Asymptomatic, radiographic findings only	Symptomatic; intervention indicated (e.g., hospitalization for observation, tube placement without sclerosis)	Sclerosis and/or operative intervention indicated	Life-threatening, causing hemodynamic instability (e.g., tension pneumothorax); ventilatory support indicated	Death
Prolonged chest tube drainage or air leak after pulmonary resection	Chest tube drainage or leak	—	Sclerosis or additional tube thoracostomy indicated	Operative intervention indicated (e.g., thoracotomy with stapling or sealant application)	Life-threatening; debilitating; organ resection indicated	Death

PULMONARY/UPPER RESPIRATORY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Prolonged intubation after pulmonary resection (>24 hrs after surgery)	Prolonged intubation	—	Extubated within 24 – 72 hrs postoperatively	Extubated >72 hrs postoperatively, but before tracheostomy indicated	Tracheostomy indicated	Death
NAVIGATION NOTE: Pulmonary embolism is graded as Grade 4 either as Thrombosis/embolism (vascular access-related) or Thrombosis/thrombus/embolism in the VASCULAR CATEGORY.						
Pulmonary fibrosis (radiographic changes)	Pulmonary fibrosis	Minimal radiographic findings (or patchy or bi-basilar changes) with estimated radiographic proportion of total lung volume that is fibrotic of <25%	Patchy or bi-basilar changes with estimated radiographic proportion of total lung volume that is fibrotic of 25 – <50%	Dense or widespread infiltrates/consolidation with estimated radiographic proportion of total lung volume that is fibrotic of 50 – <75%	Estimated radiographic proportion of total lung volume that is fibrotic is ≥75%; honeycombing	Death
REMARK: Fibrosis is usually a "late effect" seen >3 months after radiation or combined modality therapy (including surgery). It is thought to represent scar/fibrotic lung tissue. It may be difficult to distinguish from pneumonitis that is generally seen within 3 months of radiation or combined modality therapy. ALSO CONSIDER: Adult Respiratory Distress Syndrome (ARDS); Cough; Dyspnea (shortness of breath); Hypoxia; Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10^9/L) – *Select;* Infection with normal ANC or Grade 1 or 2 neutrophils – *Select;* Infection with unknown ANC – *Select.*						
NAVIGATION NOTE: Recurrent laryngeal nerve dysfunction is graded as Laryngeal nerve dysfunction in the NEUROLOGY CATEGORY.						
Vital capacity	Vital capacity	90 – 75% of predicted value	<75 – 50% of predicted value	<50 – 25% of predicted value	<25% of predicted value	Death
Voice changes/dysarthria (e.g., hoarseness, loss or alteration in voice, laryngitis)	Voice changes	Mild or intermittent hoarseness or voice change, but fully understandable	Moderate or persistent voice changes, may require occasional repetition but understandable on telephone	Severe voice changes including predominantly whispered speech; may require frequent repetition or face-to-face contact for understandability; requires voice aid (e.g., electrolarynx) for ≤50% of communication	Disabling; non-understandable voice or aphonic; requires voice aid (e.g., electrolarynx) for >50% of communication or requires >50% written communication	Death
ALSO CONSIDER: Laryngeal nerve dysfunction; Speech impairment (e.g., dysphasia or aphasia).						
Pulmonary/Upper Respiratory – Other (Specify, __)	Pulmonary – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

RENAL/GENITOURINARY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Bladder spasms	Bladder spasms	Symptomatic, intervention not indicated	Symptomatic, antispasmodics indicated	Narcotics indicated	Major surgical intervention indicated (e.g., cystectomy)	—
Cystitis	Cystitis	Asymptomatic	Frequency with dysuria; macroscopic hematuria	Transfusion; IV pain medications; bladder irrigation indicated	Catastrophic bleeding; major non-elective intervention indicated	Death
ALSO CONSIDER: Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 109/L) – *Select*; Infection with normal ANC or Grade 1 or 2 neutrophils – *Select*; Infection with unknown ANC – *Select*; Pain – *Select*.						
Fistula, GU – *Select*: – Bladder – Genital tract-female – Kidney – Ureter – Urethra – Uterus – Vagina	Fistula, GU – *Select*	Asymptomatic, radiographic findings only	Symptomatic; noninvasive intervention indicated	Symptomatic interfering with ADL; invasive intervention indicated	Life-threatening consequences; operative intervention requiring partial or full organ resection; permanent urinary diversion	Death
REMARK: A fistula is defined as an abnormal communication between two body cavities, potential spaces, and/or the skin. The site indicated for a fistula should be the site from which the abnormal process is believed to have originated.						
Incontinence, urinary	Incontinence, urinary	Occasional (e.g., with coughing, sneezing, etc.), pads not indicated	Spontaneous, pads indicated	Interfering with ADL; intervention indicated (e.g., clamp, collagen injections)	Operative intervention indicated (e.g., cystectomy or permanent urinary diversion)	—
Leak (including anastomotic), GU – *Select*: – Bladder – Fallopian tube – Kidney – Spermatic cord – Stoma – Ureter – Urethra – Uterus – Vagina – Vas deferens	Leak, GU – *Select*	Asymptomatic, radiographic findings only	Symptomatic; medical intervention indicated	Symptomatic, interfering with GU function; invasive or endoscopic intervention indicated	Life-threatening	Death
REMARK: Leak (including anastomotic), GU – *Select* refers to clinical signs and symptoms or radiographic confirmation of anastomotic leak but without development of fistula.						

RENAL/GENITOURINARY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Obstruction, GU – *Select*: – Bladder – Fallopian tube – Prostate – Spermatic cord – Stoma – Testes – Ureter – Urethra – Uterus – Vagina – Vas deferens	Obstruction, GU – *Select*	Asymptomatic, radiographic or endoscopic findings only	Symptomatic but no hydronephrosis, sepsis or renal dysfunction; dilation or endoscopic repair or stent placement indicated	Symptomatic and altered organ function (e.g., sepsis or hydronephrosis, or renal dysfunction); operative intervention indicated	Life-threatening consequences; organ failure or operative intervention requiring complete organ resection indicated	Death
NAVIGATION NOTE: Operative injury is graded as Intra-operative injury – *Select Organ or Structure* in the SURGERY/INTRA-OPERATIVE INJURY CATEGORY.						
Perforation, GU – *Select*: – Bladder – Fallopian tube – Kidney – Ovary – Prostate – Spermatic cord – Stoma – Testes – Ureter – Urethra – Uterus – Vagina – Vas deferens	Perforation, GU – *Select*	Asymptomatic radiographic findings only	Symptomatic, associated with altered renal/GU function	Symptomatic, operative intervention indicated	Life-threatening consequences or organ failure; operative intervention requiring organ resection indicated	Death
Prolapse of stoma, GU	Prolapse stoma, GU	Asymptomatic; special intervention, extraordinary care not indicated	Extraordinary local care or maintenance; minor revision under local anesthesia indicated	Dysfunctional stoma; operative intervention or major stomal revision indicated	Life-threatening consequences	Death
REMARK: Other stoma complications may be graded as Fistula, GU – *Select*; Leak (including anastomotic), GU – *Select*; Obstruction, GU – *Select;* Perforation, GU – *Select*; Stricture/stenosis (including anastomotic), GU – *Select*.						
Renal failure	Renal failure	—	—	Chronic dialysis not indicated	Chronic dialysis or renal transplant indicated	Death
ALSO CONSIDER: Glomerular filtration rate.						

RENAL/GENITOURINARY

Adverse Event	Short Name	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Stricture/stenosis (including anastomotic), GU – *Select*: – Bladder – Fallopian tube – Prostate – Spermatic cord – Stoma – Testes – Ureter – Urethra – Uterus – Vagina – Vas deferens	Stricture, anastomotic, GU – *Select*	Asymptomatic, radiographic or endoscopic findings only	Symptomatic but no hydronephrosis, sepsis or renal dysfunction; dilation or endoscopic repair or stent placement indicated	Symptomatic and altered organ function (e.g., sepsis or hydronephrosis, or renal dysfunction); operative intervention indicated	Life-threatening consequences; organ failure or operative intervention requiring organ resection indicated	Death
ALSO CONSIDER: Obstruction, GU – *Select*.						
Urinary electrolyte wasting (e.g., Fanconi's syndrome, renal tubular acidosis)	Urinary electrolyte wasting	Asymptomatic, intervention not indicated	Mild, reversible and manageable with replacement	Irreversible, requiring continued replacement	—	—
ALSO CONSIDER: Acidosis (metabolic or respiratory); Bicarbonate, serum-low; Calcium, serum-low (hypocalcemia); Phosphate, serum-low (hypophosphatemia).						
Urinary frequency/urgency	Urinary frequency	Increase in frequency or nocturia up to 2 x normal; enuresis	Increase >2 x normal but <hourly	≥1 x/hr; urgency; catheter indicated	—	—
Urinary retention (including neurogenic bladder)	Urinary retention	Hesitancy or dribbling, no significant residual urine; retention occurring during the immediate postoperative period	Hesitancy requiring medication; or operative bladder atony requiring indwelling catheter beyond immediate postoperative period but for <6 weeks	More than daily catheterization indicated; urological intervention indicated (e.g., TURP, suprapubic tube, urethrotomy)	Life-threatening consequences; organ failure (e.g., bladder rupture); operative intervention requiring organ resection indicated	Death
REMARK: The etiology of retention (if known) is graded as Obstruction, GU – *Select*; Stricture/stenosis (including anastomotic), GU – *Select*. ALSO CONSIDER: Obstruction, GU – *Select*; Stricture/stenosis (including anastomotic), GU – *Select*.						
Urine color change	Urine color change	Present	—	—	—	—
REMARK: Urine color refers to change that is not related to other dietary or physiologic cause (e.g., bilirubin, concentrated urine, and hematuria).						
Renal/Genitourinary – Other (Specify, __)	Renal – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

SECONDARY MALIGNANCY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Secondary Malignancy – possibly related to cancer treatment (Specify, __)	Secondary Malignancy (possibly related to cancer treatment)	—	—	Non-life-threatening basal or squamous cell carcinoma of the skin	Solid tumor, leukemia or lymphoma	Death

REMARK: Secondary malignancy excludes metastasis from initial primary. Any malignancy possibly related to cancer treatment (including AML/MDS) should be reported via the routine reporting mechanisms outlined in each protocol. Important: Secondary Malignancy is an exception to NCI Expedited Adverse Event Reporting Guidelines. Secondary Malignancy is "Grade 4, present" but NCI does not require AdEERS Expedited Reporting for any (related or unrelated to treatment) Secondary Malignancy. A diagnosis of AML/MDS following treatment with an NCI-sponsored investigational agent is to be reported using the form available from the CTEP Web site at http://ctep.cancer.gov. Cancers not suspected of being treatment-related are not to be reported here.

SEXUAL/REPRODUCTIVE FUNCTION

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Breast function/lactation	Breast function	Mammary abnormality, not functionally significant	Mammary abnormality, functionally significant	—	—	—
Breast nipple/areolar deformity	Nipple/areolar	Limited areolar asymmetry with no change in nipple/areolar projection	Asymmetry of nipple areolar complex with slight deviation in nipple projection	Marked deviation of nipple projection	—	—
Breast volume/hypoplasia	Breast	Minimal asymmetry; minimal hypoplasia	Asymmetry exists, ≤1/3 of the breast volume; moderate hypoplasia	Asymmetry exists, >1/3 of the breast volume; severe hypoplasia	—	—
REMARK: Breast volume is referenced with both arms straight overhead.						
NAVIGATION NOTE: Dysmenorrhea is graded as Pain – *Select* in the PAIN CATEGORY.						
NAVIGATION NOTE: Dyspareunia is graded as Pain – *Select* in the PAIN CATEGORY.						
NAVIGATION NOTE: Dysuria (painful urination) is graded as Pain – *Select* in the PAIN CATEGORY.						
Erectile dysfunction	Erectile dysfunction	Decrease in erectile function (frequency/rigidity of erections) but erectile aids not indicated	Decrease in erectile function (frequency/rigidity of erections), erectile aids indicated	Decrease in erectile function (frequency/rigidity of erections) but erectile aids not helpful; penile prosthesis indicated	—	—
Ejaculatory dysfunction	Ejaculatory dysfunction	Diminished ejaculation	Anejaculation or retrograde ejaculation	—	—	—
NAVIGATION NOTE: Feminization of male is graded in the ENDOCRINE CATEGORY.						
Gynecomastia	Gynecomastia	—	Asymptomatic breast enlargement	Symptomatic breast enlargement; intervention indicated	—	—
ALSO CONSIDER: Pain – *Select*.						
Infertility/sterility	Infertility/sterility	—	Male: oligospermia/low sperm count Female: diminished fertility/ovulation	Male: sterile/azoospermia Female: infertile/ anovulatory	—	—
Irregular menses (change from baseline)	Irregular menses	1 – 3 months without menses	>3 – 6 months without menses but continuing menstrual cycles	Persistent amenorrhea for >6 months	—	—

SEXUAL/REPRODUCTIVE FUNCTION

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Libido	Libido	Decrease in interest but not affecting relationship; intervention not indicated	Decrease in interest and adversely affecting relationship; intervention indicated	—	—	—
NAVIGATION NOTE: Masculinization of female is graded in the ENDOCRINE CATEGORY.						
Orgasmic dysfunction	Orgasmic function	Transient decrease	Decrease in orgasmic response requiring intervention	Complete inability of orgasmic response; not responding to intervention	—	—
NAVIGATION NOTE: Pelvic pain is graded as Pain – *Select* in the PAIN CATEGORY.						
NAVIGATION NOTE: Ulcers of the labia or perineum are graded as Ulceration in DERMATOLOGY/SKIN CATEGORY.						
Vaginal discharge (non-infectious)	Vaginal discharge	Mild	Moderate to heavy; pad use indicated	—	—	—
Vaginal dryness	Vaginal dryness	Mild	Interfering with sexual function; dyspareunia; intervention indicated	—	—	—
ALSO CONSIDER: Pain – *Select*.						
Vaginal mucositis	Vaginal mucositis	Erythema of the mucosa; minimal symptoms	Patchy ulcerations; moderate symptoms or dyspareunia	Confluent ulcerations; bleeding with trauma; unable to tolerate vaginal exam, sexual intercourse or tampon placement	Tissue necrosis; significant spontaneous bleeding; life-threatening consequences	—
Vaginal stenosis/length	Vaginal stenosis	Vaginal narrowing and/or shortening not interfering with function	Vaginal narrowing and/or shortening interfering with function	Complete obliteration; not surgically correctable	—	—
Vaginitis (not due to infection)	Vaginitis	Mild, intervention not indicated	Moderate, intervention indicated	Severe, not relieved with treatment; ulceration, but operative intervention not indicated	Ulceration and operative intervention indicated	—
Sexual/Reproductive Function – Other (Specify, __)	Sexual – Other (Specify)	Mild	Moderate	Severe	Disabling	Death

SURGERY/INTRA-OPERATIVE INJURY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
NAVIGATION NOTE: Intra-operative hemorrhage is graded as Hemorrhage/bleeding associated with surgery, intra-operative or postoperative in the HEMORRHAGE/BLEEDING CATEGORY.						
Intra-operative injury – *Select Organ or Structure* *'Select'* AEs appear at the end of the CATEGORY.	Intraop injury – *Select*	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated	Life threatening consequences; disabling	—
REMARK: The *'Select'* AEs are defined as significant, unanticipated injuries that are recognized at the time of surgery. These AEs do not refer to additional surgical procedures that must be performed because of a change in the operative plan based on intra-operative findings. Any sequelae resulting from the intra-operative injury that result in an adverse outcome for the patient must also be recorded and graded under the relevant CTCAE Term.						
Intra-operative Injury – Other (Specify, __)	Intraop Injury – Other (Specify)	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated	Life threatening consequences; disabling	—
REMARK: Intra-operative Injury – Other (Specify, __) is to be used only to report an organ/structure not included in the *'Select'* AEs found at the end of the CATEGORY. Any sequelae resulting from the intra-operative injury that result in an adverse outcome for the patient must also be recorded and graded under the relevant CTCAE Term.						

SURGERY/INTRA-OPERATIVE INJURY – *SELECT*

AUDITORY/EAR
- Inner ear
- Middle ear
- Outer ear NOS
- Outer ear-Pinna

CARDIOVASCULAR
- Artery-aorta
- Artery-carotid
- Artery-cerebral
- Artery-extremity (lower)
- Artery-extremity (upper)
- Artery-hepatic
- Artery-major visceral artery
- Artery-pulmonary
- Artery NOS
- Heart
- Spleen
- Vein-extremity (lower)
- Vein-extremity (upper)
- Vein-hepatic
- Vein-inferior vena cava
- Vein-jugular
- Vein-major visceral vein
- Vein-portal vein
- Vein-pulmonary
- Vein-superior vena cava
- Vein NOS

DERMATOLOGY/SKIN
- Breast
- Nails
- Skin

ENDOCRINE
- Adrenal gland
- Parathyroid
- Pituitary

ENDOCRINE (*continued*)
- Thyroid

HEAD AND NECK
- Gingiva
- Larynx
- Lip/perioral area
- Face NOS
- Nasal cavity
- Nasopharynx
- Neck NOS
- Nose
- Oral cavity NOS
- Parotid gland
- Pharynx
- Salivary duct
- Salivary gland
- Sinus
- Teeth
- Tongue
- Upper aerodigestive NOS

GASTROINTESTINAL
- Abdomen NOS
- Anal sphincter
- Anus
- Appendix
- Cecum
- Colon
- Duodenum
- Esophagus
- Ileum
- Jejunum
- Oral
- Peritoneal cavity
- Rectum
- Small bowel NOS

GASTROINTESTINAL (*continued*)
- Stoma (GI)
- Stomach

HEPATOBILIARY/ PANCREAS
- Biliary tree-common bile duct
- Biliary tree-common hepatic duct
- Biliary tree-left hepatic duct
- Biliary tree-right hepatic duct
- Biliary tree NOS
- Gallbladder
- Liver
- Pancreas
- Pancreatic duct

MUSCULOSKELETAL
- Bone
- Cartilage
- Extremity-lower
- Extremity-upper
- Joint
- Ligament
- Muscle
- Soft tissue NOS
- Tendon

NEUROLOGY
- Brain
- Meninges
- Spinal cord

NERVES:
- Brachial plexus
- CN I (olfactory)
- CN II (optic)
- CN III (oculomotor)
- CN IV (trochlear)

NEUROLOGY (*continued*)

NERVES:
- CN V (trigeminal) motor
- CN V (trigeminal) sensory
- CN VI (abducens)
- CN VII (facial) motor-face
- CN VII (facial) sensory-taste
- CN VIII (vestibulocochlear)
- CN IX (glossopharyngeal) motor pharynx
- CN IX (glossopharyngeal) sensory ear-pharynx-tongue
- CN X (vagus)
- CN XI (spinal accessory)
- CN XII (hypoglossal)
- Cranial nerve or branch NOS
- Lingual
- Lung thoracic
- Peripheral motor NOS
- Peripheral sensory NOS
- Recurrent laryngeal
- Sacral plexus
- Sciatic
- Thoracodorsal

OCULAR
- Conjunctiva
- Cornea
- Eye NOS
- Lens
- Retina

PULMONARY/UPPER RESPIRATORY
- Bronchus
- Lung
- Mediastinum
- Pleura
- Thoracic duct
- Trachea
- Upper airway NOS

RENAL/GENITOURINARY
- Bladder
- Cervix
- Fallopian tube
- Kidney
- Ovary
- Pelvis NOS
- Penis
- Prostate
- Scrotum
- Testis
- Ureter
- Urethra
- Urinary conduit
- Urinary tract NOS
- Uterus
- Vagina
- Vulva

SYNDROMES

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
NAVIGATION NOTE: Acute vascular leak syndrome is graded in the VASCULAR CATEGORY.						
NAVIGATION NOTE: Adrenal insufficiency is graded in the ENDOCRINE CATEGORY.						
NAVIGATION NOTE: Adult Respiratory Distress Syndrome (ARDS) is graded in the PULMONARY/UPPER RESPIRATORY CATEGORY.						
Alcohol intolerance syndrome (antabuse-like syndrome)	Alcohol intolerance syndrome	—	—	Present	—	Death
REMARK: An antabuse-like syndrome occurs with some new anti-androgens (e.g., nilutamide) when patient also consumes alcohol.						
NAVIGATION NOTE: Autoimmune reaction is graded as Autoimmune reaction/hypersensitivity (including drug fever) in the ALLERGY/IMMUNOLOGY CATEGORY.						
Cytokine release syndrome/acute infusion reaction	Cytokine release syndrome	Mild reaction; infusion interruption not indicated; intervention not indicated	Requires therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs	Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates)	Life-threatening; pressor or ventilatory support indicated	Death
REMARK: Cytokine release syndromes/acute infusion reactions are different from Allergic/hypersensitive reactions, although some of the manifestations are common to both AEs. An acute infusion reaction may occur with an agent that causes cytokine release (e.g., monoclonal antibodies or other biological agents). Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hrs of completion of infusion. Signs/symptoms may include: Allergic reaction/hypersensitivity (including drug fever); Arthralgia (joint pain); Bronchospasm; Cough; Dizziness; Dyspnea (shortness of breath); Fatigue (asthenia, lethargy, malaise); Headache; Hypertension; Hypotension; Myalgia (muscle pain); Nausea; Pruritis/itching; Rash/desquamation; Rigors/chills; Sweating (diaphoresis); Tachycardia; Tumor pain (onset or exacerbation of tumor pain due to treatment); Urticaria (hives, welts, wheals); Vomiting. ALSO CONSIDER: Allergic reaction/hypersensitivity (including drug fever); Bronchospasm, wheezing; Dyspnea (shortness of breath); Hypertension; Hypotension; Hypoxia; Prolonged QTc interval; Supraventricular and nodal arrhythmia – *Select*; Ventricular arrhythmia – *Select*.						
NAVIGATION NOTE: Disseminated intravascular coagulation (DIC) is graded in the COAGULATION CATEGORY.						
NAVIGATION NOTE: Fanconi's syndrome is graded as Urinary electrolyte wasting (e.g., Fanconi's syndrome, renal tubular acidosis) in the RENAL/GENITOURINARY CATEGORY.						
Flu-like syndrome	Flu-like syndrome	Symptoms present but not interfering with function	Moderate or causing difficulty performing some ADL	Severe symptoms interfering with ADL	Disabling	Death
REMARK: Flu-like syndrome represents a constellation of symptoms which may include cough with catarrhal symptoms, fever, headache, malaise, myalgia, prostration, and is to be used when the symptoms occur in a cluster consistent with one single pathophysiological process.						
NAVIGATION NOTE: Renal tubular acidosis is graded as Urinary electrolyte wasting (e.g., Fanconi's syndrome, renal tubular acidosis) in the RENAL/GENITOURINARY CATEGORY.						

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
"Retinoic acid syndrome"	"Retinoic acid syndrome"	Fluid retention; less than 3 kg of weight gain; intervention with fluid restriction and/or diuretics indicated	Mild to moderate signs/ symptoms; steroids indicated	Severe signs/symptoms; hospitalization indicated	Life-threatening; ventilatory support indicated	Death
REMARK: Patients with acute promyelocytic leukemia may experience a syndrome similar to "retinoic acid syndrome" in association with other agents such as arsenic trioxide. The syndrome is usually manifested by otherwise unexplained fever, weight gain, respiratory distress, pulmonary infiltrates and/or pleural effusion, with or without leukocytosis. ALSO CONSIDER: Acute vascular leak syndrome; Pleural effusion (non-malignant); Pneumonitis/pulmonary infiltrates.						
NAVIGATION NOTE: SIADH is graded as Neuroendocrine: ADH secretion abnormality (e.g., SIADH or low ADH) in the ENDOCRINE CATEGORY.						
NAVIGATION NOTE: Stevens-Johnson syndrome is graded as Rash: erythema multiforme (e.g., Stevens-Johnson syndrome, toxic epidermal necrolysis) in the DERMATOLOGY/SKIN CATEGORY.						
NAVIGATION NOTE: Thrombotic microangiopathy is graded as Thrombotic microangiopathy (e.g., thrombotic thrombocytopenic purpura [TTP] or hemolytic uremic syndrome [HUS]) in the COAGULATION CATEGORY.						
Tumor flare	Tumor flare	Mild pain not interfering with function	Moderate pain; pain or analgesics interfering with function, but not interfering with ADL	Severe pain; pain or analgesics interfering with function and interfering with ADL	Disabling	Death
REMARK: Tumor flare is characterized by a constellation of signs and symptoms in direct relation to initiation of therapy (e.g., anti-estrogens/androgens or additional hormones). The symptoms/signs include tumor pain, inflammation of visible tumor, hypercalcemia, diffuse bone pain, and other electrolyte disturbances. ALSO CONSIDER: Calcium, serum-high (hypercalcemia).						
Tumor lysis syndrome	Tumor lysis syndrome	—	—	Present	—	Death
ALSO CONSIDER: Creatinine; Potassium, serum-high (hyperkalemia).						
Syndromes – Other (Specify, __)	Syndromes – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

VASCULAR

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Acute vascular leak syndrome	Acute vascular leak syndrome	—	Symptomatic, fluid support not indicated	Respiratory compromise or fluids indicated	Life-threatening; pressor support or ventilatory support indicated	Death
Peripheral arterial ischemia	Peripheral arterial ischemia	—	Brief (<24 hrs) episode of ischemia managed non-surgically and without permanent deficit	Recurring or prolonged (≥24 hrs) and/or invasive intervention indicated	Life-threatening, disabling and/or associated with end organ damage (e.g., limb loss)	Death
Phlebitis (including superficial thrombosis)	Phlebitis	—	Present	—	—	—
ALSO CONSIDER: Injection site reaction/extravasation changes.						
Portal vein flow	Portal flow	—	Decreased portal vein flow	Reversal/retrograde portal vein flow	—	—
Thrombosis/embolism (vascular access-related)	Thrombosis/embolism (vascular access)	—	Deep vein thrombosis or cardiac thrombosis; intervention (e.g., anticoagulation, lysis, filter, invasive procedure) not indicated	Deep vein thrombosis or cardiac thrombosis; intervention (e.g., anticoagulation, lysis, filter, invasive procedure) indicated	Embolic event including pulmonary embolism or life-threatening thrombus	Death
Thrombosis/thrombus/ embolism	Thrombosis/thrombus/ embolism	—	Deep vein thrombosis or cardiac thrombosis; intervention (e.g., anticoagulation, lysis, filter, invasive procedure) not indicated	Deep vein thrombosis or cardiac thrombosis; intervention (e.g., anticoagulation, lysis, filter, invasive procedure) indicated	Embolic event including pulmonary embolism or life-threatening thrombus	Death
Vessel injury-artery – *Select*: – Aorta – Carotid – Extremity-lower – Extremity-upper – Other NOS – Visceral	Artery injury – *Select*	Asymptomatic diagnostic finding; intervention not indicated	Symptomatic (e.g., claudication); not interfering with ADL; repair or revision not indicated	Symptomatic interfering with ADL; repair or revision indicated	Life-threatening; disabling; evidence of end organ damage (e.g., stroke, MI, organ or limb loss)	Death
NAVIGATION NOTE: Vessel injury to an artery intra-operatively is graded as Intra-operative injury – *Select Organ or Structure* in the SURGERY/INTRA-OPERATIVE INJURY CATEGORY.						

VASCULAR

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Vessel injury-vein – *Select*: – Extremity-lower – Extremity-upper – IVC – Jugular – Other NOS – SVC – Viscera	Vein injury – *Select*	Asymptomatic diagnostic finding; intervention not indicated	Symptomatic (e.g., claudication); not interfering with ADL; repair or revision not indicated	Symptomatic interfering with ADL; repair or revision indicated	Life-threatening; disabling; evidence of end organ damage	Death
NAVIGATION NOTE: Vessel injury to a vein intra-operatively is graded as Intra-operative injury – *Select Organ or Structure* in the SURGERY/INTRA-OPERATIVE INJURY CATEGORY.						
Visceral arterial ischemia (non-myocardial)	Visceral arterial ischemia	—	Brief (<24 hrs) episode of ischemia managed medically and without permanent deficit	Prolonged (≥24 hrs) or recurring symptoms and/or invasive intervention indicated	Life-threatening; disabling; evidence of end organ damage	Death
ALSO CONSIDER: CNS cerebrovascular ischemia.						
Vascular – Other (Specify, __)	Vascular – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

Appendix 4

GENERIC PHARMACEUTICAL CARE PLAN : CANCER CARE

Surname	Date of birth / age	Sex	Consultant	Ward
Forename	Patient number		General practitioner	
Diagnosis:	Chemotherapy Regimen:		Community Pharmacist	

Initials / Dates of cycles						
Height:	Weight					
Surface Area (m^2)						

RELEVANT MEDICAL HISTORY

Approx date		Problem description	Approx Date		Problem description
1			5		
2			6		
3			7		
4			8		
5					

Known drug sensitivities:

PREVIOUS TREATMENT FOR CANCER

Chemotherapy:	**Date**	**No of cycles**	**Response / toxicities / cumulative doses**
1.			
2			
3			
Radiotherapy:	**Date**	**No Fractions**	**Response / toxicities**

Other treatments (including surgery):

CONCURRENT MEDICATION: update on each cycle of treatment

		DATES				DATES	
		start	stop			start	stop
1				8			
2				9			
3				10			
4				11			
5				12			
6				13			
7				14			

ADR's / OTC medications:

Monitoring Issues:
Cross if no problem, tick if a problem and document in care issues section or annotate N/A if not assessed

Nausea and vomiting ☐ ☐ ☐ ☐ ☐ ☐	Mucositis ☐ ☐ ☐ ☐ ☐ ☐ ☐	Neurology ☐ ☐ ☐ ☐ ☐ ☐ ☐	Bowel habit ☐ ☐ ☐ ☐ ☐ ☐ ☐
Immunosuppression ☐ ☐ ☐ ☐ ☐ ☐	Neutropenic Sepsis ☐ ☐ ☐ ☐ ☐ ☐ ☐	Skin Toxicity ☐ ☐ ☐ ☐ ☐ ☐ ☐	Mouthcare ☐ ☐ ☐ ☐ ☐ ☐ ☐
Pain control ☐ ☐ ☐ ☐ ☐ ☐	Insomnia ☐ ☐ ☐ ☐ ☐ ☐ ☐	Depression ☐ ☐ ☐ ☐ ☐ ☐ ☐	Absorption / distribution ☐ ☐ ☐ ☐ ☐ ☐ ☐
FBC ☐ ☐ ☐ ☐ ☐ ☐	LFT's / bilirubin ☐ ☐ ☐ ☐ ☐ ☐ ☐	Renal function ☐ ☐ ☐ ☐ ☐ ☐ ☐	Other: ☐ ☐ ☐ ☐ ☐ ☐ ☐

Date:	Generic Care Issue	: Action	: Output (initial)
1	Chemotherapy Eligibility (only complete on first cycle)	Refer to local protocol to verify treatment plan from diagnosis, tumour type and performance status ☐ LP ☐ OLP ☐ CT	☐ Verified ☐ Modified
2	Chemotherapy Appropriateness	A: Drugs / doses ☐ ☐ ☐ ☐ ☐ ☐ (Cross if verified B: Administration ☐ ☐ ☐ ☐ ☐ ☐ tick if adjusted) (see monitoring plan for FBC/ CrCl/ LFT's)	
3	Supportive treatment:	Patients needs and appropriateness of treatment verified ☐ ☐ ☐ ☐ ☐ ☐ (cross if verified, tick if adjusted)	
4	Pharmacy Patient Education Requirements	☐ ☐ ☐ ☐ ☐ ☐ (cross if not required, tick if required)	
5	Disharge Issues / ability to self-medicate	☐ ☐ ☐ ☐ ☐ ☐ (cross if no problems , tick if any issues)	

INDIVIDUAL CARE ISSUES			
Date	Care issue	Action	Output (Initial)

Comments:

Appendix 5

CTCAE v3.0 (MedDRA v9.0) Effective July 1, 2006

Adverse Events Category	AE/Supra-ordinate Term	Select AE	MedDRA LLT (v90)/ CTEP Term	MedDRA (v90) Code/ CTEP Provisional Code
ALLERGY/IMMUNOLOGY	Allergic reaction/hypersensitivity (including drug fever)		Hypersensitivity	10020751
ALLERGY/IMMUNOLOGY	Allergic rhinitis (including sneezing, nasal stuffiness, postnasal drip)		Allergic rhinitis	10001723
ALLERGY/IMMUNOLOGY	Allergy/Immunology - Other (Specify, __)		Immune system disorder	10021425
ALLERGY/IMMUNOLOGY	Autoimmune reaction		Autoimmune disorder	10061664
ALLERGY/IMMUNOLOGY	Serum sickness		Serum sickness	10040400
ALLERGY/IMMUNOLOGY	Vasculitis		Vasculitis	10047115
AUDITORY/EAR	Auditory/Ear - Other (Specify, __)		Ear disorder	10014004
AUDITORY/EAR	Hearing: patients with/without baseline audiogram and enrolled in a monitoring program		Hearing test abnormal	10057540
AUDITORY/EAR	Hearing: patients without baseline audiogram and not enrolled in a monitoring program		Hearing loss	10019246
AUDITORY/EAR	Otitis, external ear (non-infectious)		External ear inflammation	10065837
AUDITORY/EAR	Otitis, middle ear (non-infectious)		Middle ear inflammation	10065838
AUDITORY/EAR	Tinnitus		Tinnitus	10043882
BLOOD/BONE MARROW	Blood/Bone Marrow - Other (Specify, __)		Blood disorder	10061590
BLOOD/BONE MARROW	Bone marrow cellularity		Bone marrow hypocellular	10048580
BLOOD/BONE MARROW	CD4 count		CD4 lymphocytes decreased	10007839
BLOOD/BONE MARROW	Haptoglobin		Haptoglobin decreased	10019150
BLOOD/BONE MARROW	Hemoglobin		Hemoglobin decreased	10019483
BLOOD/BONE MARROW	Hemolysis (e.g., immune hemolytic anemia, drug-related hemolysis)		Hemolysis	10019491
BLOOD/BONE MARROW	Iron overload		Iron increased	10022981
BLOOD/BONE MARROW	Leukocytes (total WBC)		Leukopenia	10024384
BLOOD/BONE MARROW	Lymphopenia		Lymphopenia	10025327
BLOOD/BONE MARROW	Myelodysplasia		Myelodysplasia	10028532
BLOOD/BONE MARROW	Neutrophils/granulocytes (ANC/AGC)		Neutrophil count decreased	10029366
BLOOD/BONE MARROW	Platelets		Platelet count decreased	10035528
BLOOD/BONE MARROW	Splenic function		Spleen disorder	10041633
CARDIAC ARRHYTHMIA	Cardiac Arrhythmia - Other (Specify, __)		Arrhythmia	10003119

CARDIAC ARRHYTHMIA	Conduction abnormality/atrioventricular heart block	AV Block-First degree	Atrioventricular block first degree	10003674
CARDIAC ARRHYTHMIA	Conduction abnormality/atrioventricular heart block	AV Block-Second degree Mobitz Type I (Wenckebach)	Mobitz type I	10027787
CARDIAC ARRHYTHMIA	Conduction abnormality/atrioventricular heart block	AV Block-Second degree Mobitz Type II	Mobitz (type) II atrioventricular block	10027786
CARDIAC ARRHYTHMIA	Conduction abnormality/atrioventricular heart block	AV Block-Third degree (Complete AV block)	Atrioventricular block complete	10003673
CARDIAC ARRHYTHMIA	Conduction abnormality/atrioventricular heart block	Asystole	Asystole	10003586
CARDIAC ARRHYTHMIA	Conduction abnormality/atrioventricular heart block	Conduction abnormality NOS	Conduction disorder	10010276
CARDIAC ARRHYTHMIA	Conduction abnormality/atrioventricular heart block	Sick Sinus Syndrome	Sick sinus syndrome	10040639
CARDIAC ARRHYTHMIA	Conduction abnormality/atrioventricular heart block	Stokes-Adams Syndrome	Stokes-Adams syndrome	10042074
CARDIAC ARRHYTHMIA	Conduction abnormality/atrioventricular heart block	Wolff-Parkinson-White Syndrome	Wolff-Parkinson-White syndrome	10048015
CARDIAC ARRHYTHMIA	Palpitations		Palpitations	10033557
CARDIAC ARRHYTHMIA	Prolonged QTc interval		Electrocardiogram QTc interval prolonged	10053698
CARDIAC ARRHYTHMIA	Supraventricular and nodal arrhythmia	Atrial fibrillation	Atrial fibrillation	10003658
CARDIAC ARRHYTHMIA	Supraventricular and nodal arrhythmia	Atrial flutter	Atrial flutter	10003662
CARDIAC ARRHYTHMIA	Supraventricular and nodal arrhythmia	Atrial tachycardia/Paroxysmal Atrial Tachycardia	Atrial tachycardia	10003668
CARDIAC ARRHYTHMIA	Supraventricular and nodal arrhythmia	Nodal/Junctional	Nodal arrhythmia	10029458
CARDIAC ARRHYTHMIA	Supraventricular and nodal arrhythmia	Sinus arrhythmia	Sinus arrhythmia	10040739
CARDIAC ARRHYTHMIA	Supraventricular and nodal arrhythmia	Sinus bradycardia	Sinus bradycardia	10040741
CARDIAC ARRHYTHMIA	Supraventricular and nodal arrhythmia	Sinus tachycardia	Sinus tachycardia	10040752
CARDIAC ARRHYTHMIA	Supraventricular and nodal arrhythmia	Supraventricular arrhythmia NOS	Arrhythmia supraventricular	10003130
CARDIAC ARRHYTHMIA	Supraventricular and nodal arrhythmia	Supraventricular extrasystoles (Premature Atrial Contractions; Premature Nodal/Junctional Contractions)	Supraventricular extrasystoles	10042602
CARDIAC ARRHYTHMIA	Supraventricular and nodal arrhythmia	Supraventricular tachycardia	Supraventricular tachycardia	10042604
CARDIAC ARRHYTHMIA	Vasovagal episode		Syncope vasovagal	10042777
CARDIAC ARRHYTHMIA	Ventricular arrhythmia	Bigeminy	Ventricular bigeminy	10050779
CARDIAC ARRHYTHMIA	Ventricular arrhythmia	Idioventricular rhythm	Rhythm idioventricular	10039111
CARDIAC ARRHYTHMIA	Ventricular arrhythmia	PVCs	Premature ventricular contractions	10036614
CARDIAC ARRHYTHMIA	Ventricular arrhythmia	Torsade de pointes	Torsade de pointes	10044066
CARDIAC ARRHYTHMIA	Ventricular arrhythmia	Trigeminy	Ventricular trigeminy	10050780

CARDIAC ARRHYTHMIA	Ventricular arrhythmia	Ventricular arrhythmia NOS	Ventricular arrhythmia	10047281
CARDIAC ARRHYTHMIA	Ventricular arrhythmia	Ventricular fibrillation	Ventricular fibrillation	10047290
CARDIAC ARRHYTHMIA	Ventricular arrhythmia	Ventricular flutter	Ventricular flutter	10047294
CARDIAC ARRHYTHMIA	Ventricular arrhythmia	Ventricular tachycardia	Ventricular tachycardia	10047302
CARDIAC GENERAL	Cardiac General - Other (Specify, __)		Cardiac disorder	10061024
CARDIAC GENERAL	Cardiac ischemia/infarction		Myocardial ischemia	10028601
CARDIAC GENERAL	Cardiac troponin I (cTnI)		Cardiac troponin I increased	10007612
CARDIAC GENERAL	Cardiac troponin T (cTnT)		Cardiac troponin T increased	10007613
CARDIAC GENERAL	Cardiopulmonary arrest, cause unknown (non-fatal)		Cardiopulmonary arrest	10007644
CARDIAC GENERAL	Hypertension		Hypertension	10020772
CARDIAC GENERAL	Hypotension		Hypotension	10021097
CARDIAC GENERAL	Left ventricular diastolic dysfunction		Diastolic dysfunction	10052337
CARDIAC GENERAL	Left ventricular systolic dysfunction		Left ventricular failure	10024119
CARDIAC GENERAL	Myocarditis		Myocarditis	10028606
CARDIAC GENERAL	Pericardial effusion (non-malignant)		Pericardial effusion	10034474
CARDIAC GENERAL	Pericarditis		Pericarditis	10034484
CARDIAC GENERAL	Pulmonary hypertension		Pulmonary hypertension	10037400
CARDIAC GENERAL	Restrictive cardiomyopathy		Restrictive cardiomyopathy	10038748
CARDIAC GENERAL	Right ventricular dysfunction (cor pulmonale)		Cor pulmonale	10010968
CARDIAC GENERAL	Valvular heart disease		Cardiac valve disease	10061406
COAGULATION	Coagulation - Other (Specify, __)		Coagulopathy	10009802
COAGULATION	DIC (disseminated intravascular coagulation)		Disseminated intravascular coagulation	10013442
COAGULATION	Fibrinogen		Fibrinogen decreased	10016596
COAGULATION	INR (International Normalized Ratio of prothrombin time)		INR increased	10022402
COAGULATION	PTT (Partial Thromboplastin Time)		Activated partial thromboplastin time prolonged	10000636
COAGULATION	Thrombotic microangiopathy (e.g., thrombotic thrombocytopenic purpura [TTP] or hemolytic uremic syndrome [HUS])		Thrombotic microangiopathy	10043645
CONSTITUTIONAL SYMPTOMS	Constitutional Symptoms - Other (Specify, __)		General symptom	10060891
CONSTITUTIONAL SYMPTOMS	Fatigue (asthenia, lethargy, malaise)		Fatigue	10016256
CONSTITUTIONAL SYMPTOMS	Fever (in the absence of neutropenia, where neutropenia is defined as ANC <1.0 x 10e9/L)		Fever	10016558
CONSTITUTIONAL SYMPTOMS	Hypothermia		Hypothermia	10021113

CONSTITUTIONAL SYMPTOMS	Insomnia		Insomnia	10022437
CONSTITUTIONAL SYMPTOMS	Obesity		Obesity	10029883
CONSTITUTIONAL SYMPTOMS	Odor (patient odor)		Body odor	10005901
CONSTITUTIONAL SYMPTOMS	Rigors/chills		Chills	10008531
CONSTITUTIONAL SYMPTOMS	Sweating (diaphoresis)		Sweating	10042661
CONSTITUTIONAL SYMPTOMS	Weight gain		Weight gain	10047896
CONSTITUTIONAL SYMPTOMS	Weight loss		Weight loss	10047900
DEATH	Death not associated with CTCAE term	Death NOS	Death	10011906
DEATH	Death not associated with CTCAE term	Disease progression NOS	Disease progression	10061818
DEATH	Death not associated with CTCAE term	Multi-organ failure	Multi-organ failure	10028154
DEATH	Death not associated with CTCAE term	Sudden death	Sudden death	10042434
DERMATOLOGY/SKIN	Atrophy, skin		Atrophy skin	10003719
DERMATOLOGY/SKIN	Atrophy, subcutaneous fat		Fat atrophy	10016241
DERMATOLOGY/SKIN	Bruising (in absence of Grade 3 or 4 thrombocytopenia)		Bruising	10006504
DERMATOLOGY/SKIN	Burn		Thermal burn	10053615
DERMATOLOGY/SKIN	Cheilitis		Cheilitis	10008417
DERMATOLOGY/SKIN	Dermatology/Skin - Other (Specify, __)		Skin disorder	10040831
DERMATOLOGY/SKIN	Dry skin		Dry skin	10013786
DERMATOLOGY/SKIN	Flushing		Flushing	10016825
DERMATOLOGY/SKIN	Hair loss/alopecia (scalp or body)		Alopecia	10001760
DERMATOLOGY/SKIN	Hyperpigmentation		Skin hyperpigmentation	10040865
DERMATOLOGY/SKIN	Hypopigmentation		Skin hypopigmentation	10040868
DERMATOLOGY/SKIN	Induration/fibrosis (skin and subcutaneous tissue)		Skin induration	10051837
DERMATOLOGY/SKIN	Injection site reaction/extravasation changes		Injection site reaction	10022095
DERMATOLOGY/SKIN	Nail changes		Nail disorder	10028694
DERMATOLOGY/SKIN	Photosensitivity		Photosensitivity	10034966
DERMATOLOGY/SKIN	Pruritus/itching		Pruritus	10037087
DERMATOLOGY/SKIN	Rash/desquamation		Rash desquamating	10037853
DERMATOLOGY/SKIN	Rash: acne/acneiform		Acne	10000496
DERMATOLOGY/SKIN	Rash: dermatitis associated with radiation	Chemoradiation	Radiation recall reaction (dermatologic)	10037767
DERMATOLOGY/SKIN	Rash: dermatitis associated with radiation	Radiation	Dermatitis radiation	10061103
DERMATOLOGY/SKIN	Rash: erythema multiforme (e.g., Stevens-Johnson syndrome, toxic epidermal necrolysis)		Erythema multiforme	10015218
DERMATOLOGY/SKIN	Rash: hand-foot skin reaction		Hand-and-foot syndrome	10019126

DERMATOLOGY/SKIN	Skin breakdown/decubitus ulcer		Decubitus ulcer	10011985
DERMATOLOGY/SKIN	Striae		Skin striae	10040925
DERMATOLOGY/SKIN	Telangiectasia		Telangiectasia	10043189
DERMATOLOGY/SKIN	Ulceration		Skin ulceration	10040947
DERMATOLOGY/SKIN	Urticaria (hives, welts, wheals)		Urticaria	10046735
DERMATOLOGY/SKIN	Wound complication, non-infectious		Wound dehiscence	10048031
ENDOCRINE	Adrenal insufficiency		Adrenal insufficiency	10001367
ENDOCRINE	Cushingoid appearance (e.g., moon face, buffalo hump, centripetal obesity, cutaneous striae)		Cushingoid	10011655
ENDOCRINE	Endocrine - Other (Specify, __)		Endocrine disorder	10014695
ENDOCRINE	Feminization of male		Feminization	10016424
ENDOCRINE	Hot flashes/flushes		Hot flashes	10020407
ENDOCRINE	Masculinization of female		Masculinization	10026859
ENDOCRINE	Neuroendocrine: gonadotropin secretion abnormality		Blood gonadotrophin abnormal	10005561
ENDOCRINE	Neuroendocrine: growth hormone secretion abnormality		Growth hormone abnormal	10018748
ENDOCRINE	Neuroendocrine: prolactin hormone secretion abnormality		Blood prolactin abnormal	10005778
ENDOCRINE	Neuroendocrine:ACTH deficiency		ACTH decreased	10000610
ENDOCRINE	Neuroendocrine:ADH secretion abnormality (e.g., SIADH or low ADH)		ADH abnormal	10001266
ENDOCRINE	Pancreatic endocrine: glucose intolerance		Glucose intolerance	10052426
ENDOCRINE	Parathyroid function, low (hypoparathyroidism)		Hypoparathyroidism	10021041
ENDOCRINE	Thyroid function, high (hyperthyroidism, thyrotoxicosis)		Hyperthyroidism	10020850
ENDOCRINE	Thyroid function, low (hypothyroidism)		Hypothyroidism	10021114
GASTROINTESTINAL	Anorexia		Anorexia	10002646
GASTROINTESTINAL	Ascites (non-malignant)		Ascites	10003445
GASTROINTESTINAL	Colitis		Colitis	10009887
GASTROINTESTINAL	Constipation		Constipation	10010774
GASTROINTESTINAL	Dehydration		Dehydration	10012174
GASTROINTESTINAL	Dental: dentures or prosthesis		Dental prosthesis user	10050857
GASTROINTESTINAL	Dental: periodontal disease		Periodontal disease	10034536
GASTROINTESTINAL	Dental: teeth		Tooth disorder	10044034
GASTROINTESTINAL	Dental:teeth development		Tooth development disorder	10044030
GASTROINTESTINAL	Diarrhea		Diarrhea	10012727

GASTROINTESTINAL	Distension/bloating, abdominal		Abdominal distension	10000060
GASTROINTESTINAL	Dry mouth/salivary gland (xerostomia)		Dry mouth	10013781
GASTROINTESTINAL	Dysphagia (difficulty swallowing)		Dysphagia	10013950
GASTROINTESTINAL	Enteritis (inflammation of the small bowel)		Enteritis	10014866
GASTROINTESTINAL	Esophagitis		Esophagitis	10015461
GASTROINTESTINAL	Fistula, GI	Abdomen NOS	Gastro-intestinal fistula	10017877
GASTROINTESTINAL	Fistula, GI	Anus	Anal fistula	10002156
GASTROINTESTINAL	Fistula, GI	Biliary tree	Biliary fistula	10004665
GASTROINTESTINAL	Fistula, GI	Colon/cecum/appendix	Colonic fistula	10009995
GASTROINTESTINAL	Fistula, GI	Duodenum	Duodenal fistula	10013828
GASTROINTESTINAL	Fistula, GI	Esophagus	Acquired tracheo-oesophageal fistula	10000582
GASTROINTESTINAL	Fistula, GI	Gallbladder	Gallbladder fistula	10017631
GASTROINTESTINAL	Fistula, GI	Ileum	Ileal fistula	10065728
GASTROINTESTINAL	Fistula, GI	Jejunum	Jejunal fistula	10065719
GASTROINTESTINAL	Fistula, GI	Oral cavity	Oral cavity fistula	10065720
GASTROINTESTINAL	Fistula, GI	Pancreas	Pancreatic fistula	10049192
GASTROINTESTINAL	Fistula, GI	Pharynx	Fistula, Pharynx	90030018
GASTROINTESTINAL	Fistula, GI	Rectum	Rectal fistula	10038062
GASTROINTESTINAL	Fistula, GI	Salivary gland	Salivary gland fistula	10039411
GASTROINTESTINAL	Fistula, GI	Small bowel NOS	Fistula of small intestine	10065850
GASTROINTESTINAL	Fistula, GI	Stomach	Gastic fistula	10065713
GASTROINTESTINAL	Flatulence		Flatulence	10016766
GASTROINTESTINAL	Gastritis (including bile reflux gastritis)		Gastritis	10017853
GASTROINTESTINAL	Gastrointestinal - Other (Specify, __)		Gastrointestinal disorder	10017944
GASTROINTESTINAL	Heartburn/dyspepsia		Dyspepsia	10013946
GASTROINTESTINAL	Hemorrhoids		Hemorrhoids	10019611
GASTROINTESTINAL	Ileus, GI (functional obstruction of bowel, i.e., neuroconstipation)		Ileus	10021328
GASTROINTESTINAL	Incontinence, anal		Fecal incontinence	10016296
GASTROINTESTINAL	Leak (including anastomotic), GI	Biliary tree	Biliary anastomotic leak	10050458
GASTROINTESTINAL	Leak (including anastomotic), GI	Esophagus	Esophageal anastomotic leak	10065961
GASTROINTESTINAL	Leak (including anastomotic), GI	Large bowel	Large intestinal anastomotic leak	10065891
GASTROINTESTINAL	Leak (including anastomotic), GI	Leak NOS	Anastomotic leak	10050456
GASTROINTESTINAL	Leak (including anastomotic), GI	Pancreas	Pancreatic anastomotic leak	10050457
GASTROINTESTINAL	Leak (including anastomotic), GI	Pharynx	Pharyngeal anastomotic leak	10065705
GASTROINTESTINAL	Leak (including anastomotic), GI	Rectum	Rectal anastomotic leak	10065894
GASTROINTESTINAL	Leak (including anastomotic), GI	Small bowel	Small intestinal anastomotic leak	10065892

GASTROINTESTINAL	Leak (including anastomotic), GI	Stoma	Intestinal stoma leak	10059095
GASTROINTESTINAL	Leak (including anastomotic), GI	Stomach	Gastric anastomotic leak	10065893
GASTROINTESTINAL	Malabsorption		Malabsorption	10025476
GASTROINTESTINAL	Mucositis/stomatitis (clinical exam)	Anus	Anal exam abnormal	10065734
GASTROINTESTINAL	Mucositis/stomatitis (clinical exam)	Esophagus	Oesophagoscopy abnormal	10030223
GASTROINTESTINAL	Mucositis/stomatitis (clinical exam)	Large bowel	Endoscopy large bowel abnormal	10014810
GASTROINTESTINAL	Mucositis/stomatitis (clinical exam)	Larynx	Laryngoscopy abnormal	10023889
GASTROINTESTINAL	Mucositis/stomatitis (clinical exam)	Oral cavity	Ear, nose and throat examination abnormal	10056848
GASTROINTESTINAL	Mucositis/stomatitis (clinical exam)	Pharynx	Pharyngeal examination abnormal	10065717
GASTROINTESTINAL	Mucositis/stomatitis (clinical exam)	Rectum	Proctoscopy abnormal	10036787
GASTROINTESTINAL	Mucositis/stomatitis (clinical exam)	Small bowel	Endoscopy small intestine abnormal	10014817
GASTROINTESTINAL	Mucositis/stomatitis (clinical exam)	Stomach	Gastroscopy abnormal	10065714
GASTROINTESTINAL	Mucositis/stomatitis (clinical exam)	Trachea	Tracheoscopy abnormal	10065708
GASTROINTESTINAL	Mucositis/stomatitis (functional/symptomatic)	Anus	Anal mucositis	10065721
GASTROINTESTINAL	Mucositis/stomatitis (functional/symptomatic)	Esophagus	Esophageal mucositis	10065726
GASTROINTESTINAL	Mucositis/stomatitis (functional/symptomatic)	Large bowel	Large intestinal mucositis	10065733
GASTROINTESTINAL	Mucositis/stomatitis (functional/symptomatic)	Larynx	Laryngeal mucositis	10065880
GASTROINTESTINAL	Mucositis/stomatitis (functional/symptomatic)	Oral cavity	Mucositis oral	10028130
GASTROINTESTINAL	Mucositis/stomatitis (functional/symptomatic)	Pharynx	Pharyngeal mucositis	10065881
GASTROINTESTINAL	Mucositis/stomatitis (functional/symptomatic)	Rectum	Rectal mucositis	10063190
GASTROINTESTINAL	Mucositis/stomatitis (functional/symptomatic)	Small bowel	Small intestinal mucositis	10065710
GASTROINTESTINAL	Mucositis/stomatitis (functional/symptomatic)	Stomach	Gastric mucositis	10065715
GASTROINTESTINAL	Mucositis/stomatitis (functional/symptomatic)	Trachea	Tracheal mucositis	10065900
GASTROINTESTINAL	Nausea		Nausea	10028813
GASTROINTESTINAL	Necrosis, GI	Anus	Anal necrosis	10065722
GASTROINTESTINAL	Necrosis, GI	Colon/cecum/appendix	Intestinal necrosis	10022686
GASTROINTESTINAL	Necrosis, GI	Duodenum	Duodenal necrosis	10065725
GASTROINTESTINAL	Necrosis, GI	Esophagus	Esophageal necrosis	10065727
GASTROINTESTINAL	Necrosis, GI	Gallbladder	Gallbladder necrosis	10059446

GASTROINTESTINAL	Necrosis, GI	Hepatic	Hepatic necrosis	10019692
GASTROINTESTINAL	Necrosis, GI	Ileum	Ileal necrosis	10065729
GASTROINTESTINAL	Necrosis, GI	Jejunum	Jejunal necrosis	10065731
GASTROINTESTINAL	Necrosis, GI	Oral	Mouth necrosis	10028028
GASTROINTESTINAL	Necrosis, GI	Pancreas	Pancreatic necrosis	10058096
GASTROINTESTINAL	Necrosis, GI	Peritoneal cavity	Peritoneal necrosis	10065704
GASTROINTESTINAL	Necrosis, GI	Pharynx	Pharyngeal necrosis	10065706
GASTROINTESTINAL	Necrosis, GI	Rectum	Rectal necrosis	10065709
GASTROINTESTINAL	Necrosis, GI	Small bowel NOS	Small intestinal necrosis	10065711
GASTROINTESTINAL	Necrosis, GI	Stoma	Gastrointestinal stoma necrosis	10065712
GASTROINTESTINAL	Necrosis, GI	Stomach	Gastric necrosis	10051886
GASTROINTESTINAL	Obstruction, GI	Cecum	Cecal obstruction	10065723
GASTROINTESTINAL	Obstruction, GI	Colon	Colonic obstruction	10010000
GASTROINTESTINAL	Obstruction, GI	Duodenum	Duodenal obstruction	10013830
GASTROINTESTINAL	Obstruction, GI	Esophagus	Esophageal obstruction	10015387
GASTROINTESTINAL	Obstruction, GI	Gallbladder	Gallbladder obstruction	10017636
GASTROINTESTINAL	Obstruction, GI	Ileum	Ileal obstruction	10065730
GASTROINTESTINAL	Obstruction, GI	Jejunum	Jejunal obstruction	10065732
GASTROINTESTINAL	Obstruction, GI	Rectum	Rectal obstruction	10065707
GASTROINTESTINAL	Obstruction, GI	Small bowel NOS	Small intestinal obstruction	10041101
GASTROINTESTINAL	Obstruction, GI	Stoma	Intestinal stoma obstruction	10059094
GASTROINTESTINAL	Obstruction, GI	Stomach	Obstruction gastric	10029957
GASTROINTESTINAL	Perforation, GI	Appendix	Appendicitis perforated	10003012
GASTROINTESTINAL	Perforation, GI	Biliary tree	Perforation bile duct	10034405
GASTROINTESTINAL	Perforation, GI	Cecum	Cecum perforation	10055432
GASTROINTESTINAL	Perforation, GI	Colon	Colonic perforation	10010001
GASTROINTESTINAL	Perforation, GI	Duodenum	Duodenal perforation	10013832
GASTROINTESTINAL	Perforation, GI	Esophagus	Esophageal perforation	10055472
GASTROINTESTINAL	Perforation, GI	Gallbladder	Gallbladder perforation	10017639
GASTROINTESTINAL	Perforation, GI	Ileum	Ileal perforation	10021305
GASTROINTESTINAL	Perforation, GI	Jejunum	Jejunal perforation	10023174
GASTROINTESTINAL	Perforation, GI	Rectum	Rectal perforation	10038073
GASTROINTESTINAL	Perforation, GI	Small bowel NOS	Small intestinal perforation	10041103
GASTROINTESTINAL	Perforation, GI	Stomach	Gastric perforation	10017815
GASTROINTESTINAL	Proctitis		Proctitis	10036774
GASTROINTESTINAL	Prolapse of stoma, GI		Prolapse of intestinal stoma	10065745
GASTROINTESTINAL	Salivary gland changes/saliva		Salivary gland disorder	10061935

GASTROINTESTINAL	Stricture/stenosis (including anastomotic), GI	Anus	Anal stenosis	10002176
GASTROINTESTINAL	Stricture/stenosis (including anastomotic), GI	Biliary tree	Bile duct stenosis	10051341
GASTROINTESTINAL	Stricture/stenosis (including anastomotic), GI	Cecum	Intestinal stenosis	10022699
GASTROINTESTINAL	Stricture/stenosis (including anastomotic), GI	Colon	Colonic stenosis	10010004
GASTROINTESTINAL	Stricture/stenosis (including anastomotic), GI	Duodenum	Duodenal stenosis	10050094
GASTROINTESTINAL	Stricture/stenosis (including anastomotic), GI	Esophagus	Esophageal stenosis	10015448
GASTROINTESTINAL	Stricture/stenosis (including anastomotic), GI	Ileum	Ileal stenosis	10021307
GASTROINTESTINAL	Stricture/stenosis (including anastomotic), GI	Jejunum	Jejunal stenosis	10023176
GASTROINTESTINAL	Stricture/stenosis (including anastomotic), GI	Pancreas/pancreatic duct	Pancreatic duct stenosis	10065703
GASTROINTESTINAL	Stricture/stenosis (including anastomotic), GI	Pharynx	Stricture/stenosis (including anastomotic), Pharynx	90030990
GASTROINTESTINAL	Stricture/stenosis (including anastomotic), GI	Rectum	Rectal stenosis	10038079
GASTROINTESTINAL	Stricture/stenosis (including anastomotic), GI	Small bowel NOS	Small intestinal stenosis	10062263
GASTROINTESTINAL	Stricture/stenosis (including anastomotic), GI	Stoma	Stenosis of gastrointestinal stoma	10065898
GASTROINTESTINAL	Stricture/stenosis (including anastomotic), GI	Stomach	Gastric stenosis	10061970
GASTROINTESTINAL	Taste alteration (dysgeusia)		Taste alteration	10043125
GASTROINTESTINAL	Typhlitis (cecal inflammation)		Typhlitis	10045271
GASTROINTESTINAL	Ulcer, GI	Anus	Anal ulcer	10002180
GASTROINTESTINAL	Ulcer, GI	Cecum	Cecal ulcer	10065724
GASTROINTESTINAL	Ulcer, GI	Colon	Colonic ulcer	10010006
GASTROINTESTINAL	Ulcer, GI	Duodenum	Duodenal ulcer	10013836
GASTROINTESTINAL	Ulcer, GI	Esophagus	Esophageal ulcer	10015451
GASTROINTESTINAL	Ulcer, GI	Ileum	Ileal ulcer	10021309
GASTROINTESTINAL	Ulcer, GI	Jejunum	Jejunal ulcer	10023177
GASTROINTESTINAL	Ulcer, GI	Rectum	Rectal ulcer	10038080
GASTROINTESTINAL	Ulcer, GI	Small bowel NOS	Small intestine ulcer	10041133
GASTROINTESTINAL	Ulcer, GI	Stoma	Stomal ulcer	10042127

GASTROINTESTINAL	Ulcer, GI	Stomach	Gastric ulcer	10017822
GASTROINTESTINAL	Vomiting		Vomiting	10047700
GROWTH AND DEVELOPMENT	Bone age (alteration in bone age)		Bone development abnormal	10005954
GROWTH AND DEVELOPMENT	Bone growth: femoral head; slipped capital femoral epiphysis		Slipped femoral epiphysis	10041028
GROWTH AND DEVELOPMENT	Bone growth:limb length discrepancy		Unequal limb length	10065738
GROWTH AND DEVELOPMENT	Bone growth:spine kyphosis/lordosis		Kyphosis	10023509
GROWTH AND DEVELOPMENT	Growth and Development - Other (Specify, __)		Developmental disturbance	10012563
GROWTH AND DEVELOPMENT	Growth velocity (reduction in growth velocity)		Developmental delay	10012559
GROWTH AND DEVELOPMENT	Puberty (delayed)		Delayed puberty	10012205
GROWTH AND DEVELOPMENT	Puberty (precocious)		Precocious puberty	10058084
GROWTH AND DEVELOPMENT	Short stature		Short stature	10040600
HEMORRHAGE/BLEEDING	Hematoma		Hematoma	10019428
HEMORRHAGE/BLEEDING	Hemorrhage, CNS		Intracranial hemorrhage	10022763
HEMORRHAGE/BLEEDING	Hemorrhage, GI	Abdomen NOS	Intra-abdominal hemorrhage	10055291
HEMORRHAGE/BLEEDING	Hemorrhage, GI	Anus	Anal hemorrhage	10055226
HEMORRHAGE/BLEEDING	Hemorrhage, GI	Biliary tree	Hemorrhage in bile duct	10062778
HEMORRHAGE/BLEEDING	Hemorrhage, GI	Cecum/appendix	Cecal hemorrhage	10065747
HEMORRHAGE/BLEEDING	Hemorrhage, GI	Colon	Colonic hemorrhage	10009998
HEMORRHAGE/BLEEDING	Hemorrhage, GI	Duodenum	Duodenal hemorrhage	10055242
HEMORRHAGE/BLEEDING	Hemorrhage, GI	Esophagus	Esophageal hemorrhage	10015384
HEMORRHAGE/BLEEDING	Hemorrhage, GI	Ileum	Ileal hemorrhage	10055287
HEMORRHAGE/BLEEDING	Hemorrhage, GI	Jejunum	Jejunal hemorrhage	10055300
HEMORRHAGE/BLEEDING	Hemorrhage, GI	Liver	Hepatic hemorrhage	10019678
HEMORRHAGE/BLEEDING	Hemorrhage, GI	Lower GI NOS	Lower gastrointestinal hemorrhage	10051746
HEMORRHAGE/BLEEDING	Hemorrhage, GI	Oral cavity	Oral hemorrhage	10030980
HEMORRHAGE/BLEEDING	Hemorrhage, GI	Pancreas	Pancreatic hemorrhage	10033626
HEMORRHAGE/BLEEDING	Hemorrhage, GI	Peritoneal cavity	Peritoneal hemorrhage	10034667
HEMORRHAGE/BLEEDING	Hemorrhage, GI	Rectum	Rectal hemorrhage	10038064
HEMORRHAGE/BLEEDING	Hemorrhage, GI	Stoma	Intestinal stoma site bleeding	10049468
HEMORRHAGE/BLEEDING	Hemorrhage, GI	Stomach	Gastric hemorrhage	10017789
HEMORRHAGE/BLEEDING	Hemorrhage, GI	Upper GI NOS	Upper gastrointestinal hemorrhage	10055356
HEMORRHAGE/BLEEDING	Hemorrhage, GI	Varices (esophageal)	Esophageal varices hemorrhage	10015453
HEMORRHAGE/BLEEDING	Hemorrhage, GI	Varices (rectal)	Hemorrhoidal hemorrhage	10060640
HEMORRHAGE/BLEEDING	Hemorrhage, GU	Bladder	Bladder hemorrhage	10055231
HEMORRHAGE/BLEEDING	Hemorrhage, GU	Fallopian tube	Hematosalpinx	10060602

HEMORRHAGE/BLEEDING	Hemorrhage, GU	Kidney	Renal hemorrhage	10038463
HEMORRHAGE/BLEEDING	Hemorrhage, GU	Ovary	Ovarian hemorrhage	10065763
HEMORRHAGE/BLEEDING	Hemorrhage, GU	Prostate	Prostatic hemorrhage	10055325
HEMORRHAGE/BLEEDING	Hemorrhage, GU	Retroperitoneum	Retroperitoneal hemorrhage	10038981
HEMORRHAGE/BLEEDING	Hemorrhage, GU	Spermatic cord	Spermatic cord hemorrhage	10065762
HEMORRHAGE/BLEEDING	Hemorrhage, GU	Stoma	Urostomy site bleeding	10065748
HEMORRHAGE/BLEEDING	Hemorrhage, GU	Testes	Testicular hemorrhage	10055347
HEMORRHAGE/BLEEDING	Hemorrhage, GU	Ureter	Ureteric hemorrhage	10065760
HEMORRHAGE/BLEEDING	Hemorrhage, GU	Urethra	Urethral hemorrhage	10055357
HEMORRHAGE/BLEEDING	Hemorrhage, GU	Urinary NOS	Hemorrhage urinary tract	10019591
HEMORRHAGE/BLEEDING	Hemorrhage, GU	Uterus	Uterine hemorrhage	10046789
HEMORRHAGE/BLEEDING	Hemorrhage, GU	Vagina	Vaginal hemorrhage	10046912
HEMORRHAGE/BLEEDING	Hemorrhage, GU	Vas deferens	Vas deferens hemorrhage	10065896
HEMORRHAGE/BLEEDING	Hemorrhage, pulmonary/upper respiratory	Bronchopulmonary NOS	Bronchopulmonary hemorrhage	10065746
HEMORRHAGE/BLEEDING	Hemorrhage, pulmonary/upper respiratory	Bronchus	Bronchial hemorrhage	10065757
HEMORRHAGE/BLEEDING	Hemorrhage, pulmonary/upper respiratory	Larynx	Laryngeal hemorrhage	10065759
HEMORRHAGE/BLEEDING	Hemorrhage, pulmonary/upper respiratory	Lung	Pulmonary hemorrhage	10037397
HEMORRHAGE/BLEEDING	Hemorrhage, pulmonary/upper respiratory	Mediastinum	Mediastinal hemorrhage	10056356
HEMORRHAGE/BLEEDING	Hemorrhage, pulmonary/upper respiratory	Nose	Hemorrhage nasal	10019561
HEMORRHAGE/BLEEDING	Hemorrhage, pulmonary/upper respiratory	Pharynx	Pharyngeal hemorrhage	10055315
HEMORRHAGE/BLEEDING	Hemorrhage, pulmonary/upper respiratory	Pleura	Pleural hemorrhage	10055319
HEMORRHAGE/BLEEDING	Hemorrhage, pulmonary/upper respiratory	Respiratory tract NOS	Respiratory tract hemorrhage	10038730
HEMORRHAGE/BLEEDING	Hemorrhage, pulmonary/upper respiratory	Stoma	Tracheostomy site bleeding	10065749
HEMORRHAGE/BLEEDING	Hemorrhage, pulmonary/upper respiratory	Trachea	Tracheal hemorrhage	10062548
HEMORRHAGE/BLEEDING	Hemorrhage/Bleeding - Other (Specify, __)		Hemorrhage	10019524
HEMORRHAGE/BLEEDING	Hemorrhage/bleeding associated with surgery, intra-operative or postoperative		Postoperative hemorrhage	10055322
HEMORRHAGE/BLEEDING	Petechiae/purpura (hemorrhage/bleeding into skin or mucosa)		Petechiae	10034754
HEPATOBILIARY/PANCREAS	Cholecystitis		Cholecystitis	10008612
HEPATOBILIARY/PANCREAS	Hepatobiliary/Pancreas - Other (Specify, __)		Hepatobiliary disease	10062000
HEPATOBILIARY/PANCREAS	Liver dysfunction/failure (clinical)		Hepatic failure	10019663
HEPATOBILIARY/PANCREAS	Pancreas, exocrine enzyme deficiency		Pancreatic enzymes decreased	10062646
HEPATOBILIARY/PANCREAS	Pancreatitis		Pancreatitis	10033645
INFECTION	Colitis, infectious (e.g., Clostridium difficile)		Colitis, infectious (e.g., Clostridium difficile)	90030994

INFECTION	Febrile neutropenia (fever of unknown origin without clinically or microbiologically documented infection)(ANC <1.0 x 10e9/L, fever >=38.5 degrees C)		Febrile neutropenia	10016288
INFECTION	Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10e9/L)	Abdomen NOS	Abdominal infection	90030154
INFECTION	Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10e9/L)	Anal/perianal	Anal infection	90030156
INFECTION	Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10e9/L)	Appendix	Appendicitis	90030158
INFECTION	Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10e9/L)	Artery	Arteritis infective	90030160
INFECTION	Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10e9/L)	Biliary tree	Biliary tract infection	90030162
INFECTION	Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10e9/L)	Bladder (urinary)	Bladder infection	90030164
INFECTION	Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10e9/L)	Blood	Sepsis	90030984
INFECTION	Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10e9/L)	Bone (osteomyelitis)	Bone infection	90030166
INFECTION	Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10e9/L)	Brain (encephalitis, infectious)	Encephalitis infection	90030168
INFECTION	Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10e9/L)	Brain + Spinal cord (encephalomyelitis)	Encephalomyelitis infection	90030170
INFECTION	Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10e9/L)	Bronchus	Bronchitis	90030172
INFECTION	Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10e9/L)	Catheter-related	Catheter related infection	90030174

INFECTION	Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10e9/L)	Cecum	Cecal infection	90030176
INFECTION	Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10e9/L)	Cervix	Cervicitis	90030178
INFECTION	Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10e9/L)	Colon	Infectious colitis	90030180
INFECTION	Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10e9/L)	Conjunctiva	Conjunctivitis infective	90030182
INFECTION	Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10e9/L)	Cornea	Corneal infection	90030184
INFECTION	Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10e9/L)	Dental-tooth	Tooth infection	90030186
INFECTION	Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10e9/L)	Duodenum	Duodenal infection	90030188
INFECTION	Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10e9/L)	Esophagus	Esophageal infection	90030190
INFECTION	Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10e9/L)	External ear (otitis externa)	Otitis externa	90030192
INFECTION	Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10e9/L)	Eye NOS	Eye infection	90030194
INFECTION	Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10e9/L)	Fallopian tube	Salpingitis infection	90030196
INFECTION	Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10e9/L)	Foreign body (e.g., graft, implant, prosthesis, stent)	Device related infection	90030198
INFECTION	Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10e9/L)	Gallbladder (cholecystitis)	Gallbladder infection	90030200
INFECTION	Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10e9/L)	Heart (endocarditis)	Endocarditis infective	90030202

INFECTION	Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10e9/L)	Ileum	Ileal infection	90030204
INFECTION	Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10e9/L)	Jejunum	Jejunal infection	90030206
INFECTION	Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10e9/L)	Joint	Joint infection	90030208
INFECTION	Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10e9/L)	Kidney	Kidney infection	90030210
INFECTION	Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10e9/L)	Larynx	Laryngitis	90030212
INFECTION	Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10e9/L)	Lens	Eye infection intraocular	90030214
INFECTION	Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10e9/L)	Lip/perioral	Lip infection	90030216
INFECTION	Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10e9/L)	Liver	Hepatic infection	90030218
INFECTION	Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10e9/L)	Lung (pneumonia)	Pneumonia	90030220
INFECTION	Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10e9/L)	Lymphatic	Lymph gland infection	90030222
INFECTION	Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10e9/L)	Mediastinum NOS	Mediastinal infection	90030224
INFECTION	Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10e9/L)	Meninges (meningitis)	Infectious meningitis	90030226
INFECTION	Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10e9/L)	Middle ear (otitis media)	Otitis media	90030228
INFECTION	Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10e9/L)	Mucosa	Mucosal infection	90030230

INFECTION	Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10e9/L)	Muscle (infection myositis)	Infective myositis	90030232
INFECTION	Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10e9/L)	Neck NOS	Infection	90030234
INFECTION	Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10e9/L)	Nerve-cranial	Cranial nerve infection	90030236
INFECTION	Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10e9/L)	Nerve-peripheral	Peripheral nerve infection	90030238
INFECTION	Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10e9/L)	Nose	Rhinitis infective	90030240
INFECTION	Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10e9/L)	Oral cavity-gums (gingivitis)	Gingival infection	90030242
INFECTION	Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10e9/L)	Pancreas	Pancreas infection	90030244
INFECTION	Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10e9/L)	Paranasal	Paranasal sinus infection	90030246
INFECTION	Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10e9/L)	Pelvis NOS	Pelvic infection	90030248
INFECTION	Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10e9/L)	Penis	Penile infection	90030250
INFECTION	Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10e9/L)	Peristomal	Stoma site infection	90030252
INFECTION	Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10e9/L)	Peritoneal cavity	Peritoneal infection	90030254
INFECTION	Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10e9/L)	Pharynx	Pharyngitis	90030256
INFECTION	Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10e9/L)	Pleura (empyema)	Pleural infection	90030258

INFECTION	Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10e9/L)	Prostate	Prostate infection	90030260
INFECTION	Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10e9/L)	Rectum	Anorectal infection	90030262
INFECTION	Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10e9/L)	Salivary gland	Salivary gland infection	90030264
INFECTION	Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10e9/L)	Scrotum	Scrotal infection	90030266
INFECTION	Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10e9/L)	Sinus	Sinusitis	90030268
INFECTION	Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10e9/L)	Skin (cellulitis)	Skin infection	90030270
INFECTION	Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10e9/L)	Small bowel NOS	Small intestine infection	90030272
INFECTION	Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10e9/L)	Soft tissue NOS	Soft tissue infection	90030274
INFECTION	Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10e9/L)	Spinal cord (myelitis)	Spinal cord infection	90030276
INFECTION	Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10e9/L)	Spleen	Splenic infection	90030278
INFECTION	Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10e9/L)	Stomach	Gastric infection	90030280
INFECTION	Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10e9/L)	Trachea	Tracheitis	90030282
INFECTION	Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10e9/L)	Ungual (nails)	Nail infection	90030284
INFECTION	Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10e9/L)	Upper aerodigestive NOS	Upper aerodigestive tract infection	90030286

INFECTION	Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10e9/L)	Upper airway NOS	Upper respiratory infection	90030288
INFECTION	Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10e9/L)	Ureter	Ureteritis	90030290
INFECTION	Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10e9/L)	Urethra	Urethral infection	90030292
INFECTION	Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10e9/L)	Urinary tract NOS	Urinary tract infection	90030294
INFECTION	Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10e9/L)	Uterus	Uterine infection	90030296
INFECTION	Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10e9/L)	Vagina	Vaginal infection	90030298
INFECTION	Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10e9/L)	Vein	Phlebitis infective	90030300
INFECTION	Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10e9/L)	Vulva	Vulval infection	90030302
INFECTION	Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10e9/L)	Wound	Wound infection	90030304
INFECTION	Infection - Other (Specify, __)		Infection	10021789
INFECTION	Infection with normal ANC or Grade 1 or 2 neutrophils	Abdomen NOS	Abdominal infection	90031118
INFECTION	Infection with normal ANC or Grade 1 or 2 neutrophils	Anal/perianal	Anal infection	90030998
INFECTION	Infection with normal ANC or Grade 1 or 2 neutrophils	Appendix	Appendicitis	90030306
INFECTION	Infection with normal ANC or Grade 1 or 2 neutrophils	Artery	Arteritis infective	90030308
INFECTION	Infection with normal ANC or Grade 1 or 2 neutrophils	Biliary tree	Biliary tract infection	90031006
INFECTION	Infection with normal ANC or Grade 1 or 2 neutrophils	Bladder (urinary)	Bladder infection	90031010
INFECTION	Infection with normal ANC or Grade 1 or 2 neutrophils	Blood	Sepsis	90030986

INFECTION	Infection with normal ANC or Grade 1 or 2 neutrophils	Bone (osteomyelitis)	Bone infection	90031014
INFECTION	Infection with normal ANC or Grade 1 or 2 neutrophils	Brain (encephalitis, infectious)	Encephalitis infection	90031034
INFECTION	Infection with normal ANC or Grade 1 or 2 neutrophils	Brain + Spinal cord (encephalomyelitis)	Encephalomyelitis infection	90031038
INFECTION	Infection with normal ANC or Grade 1 or 2 neutrophils	Bronchus	Bronchitis	90031018
INFECTION	Infection with normal ANC or Grade 1 or 2 neutrophils	Catheter-related	Catheter related infection	90030309
INFECTION	Infection with normal ANC or Grade 1 or 2 neutrophils	Cecum	Cecal infection	90030310
INFECTION	Infection with normal ANC or Grade 1 or 2 neutrophils	Cervix	Cervicitis	90031022
INFECTION	Infection with normal ANC or Grade 1 or 2 neutrophils	Colon	Infectious colitis	90030312
INFECTION	Infection with normal ANC or Grade 1 or 2 neutrophils	Conjunctiva	Conjunctivitis infective	90030314
INFECTION	Infection with normal ANC or Grade 1 or 2 neutrophils	Cornea	Corneal infection	90031026
INFECTION	Infection with normal ANC or Grade 1 or 2 neutrophils	Dental-tooth	Tooth infection	90031186
INFECTION	Infection with normal ANC or Grade 1 or 2 neutrophils	Duodenum	Duodenal infection	90030316
INFECTION	Infection with normal ANC or Grade 1 or 2 neutrophils	Esophagus	Esophageal infection	90030318
INFECTION	Infection with normal ANC or Grade 1 or 2 neutrophils	External ear (otitis externa)	Otitis externa	90030319
INFECTION	Infection with normal ANC or Grade 1 or 2 neutrophils	Eye NOS	Eye infection	90031042
INFECTION	Infection with normal ANC or Grade 1 or 2 neutrophils	Fallopian tube	Salpingitis infection	90030320
INFECTION	Infection with normal ANC or Grade 1 or 2 neutrophils	Foreign body (e.g., graft, implant, prosthesis, stent)	Device related infection	90031030
INFECTION	Infection with normal ANC or Grade 1 or 2 neutrophils	Gallbladder (cholecystitis)	Gallbladder infection	90030322
INFECTION	Infection with normal ANC or Grade 1 or 2 neutrophils	Heart (endocarditis)	Endocarditis infective	90031122
INFECTION	Infection with normal ANC or Grade 1 or 2 neutrophils	Ileum	Ileal infection	90030324
INFECTION	Infection with normal ANC or Grade 1 or 2 neutrophils	Jejunum	Jejunal infection	90030326

INFECTION	Infection with normal ANC or Grade 1 or 2 neutrophils	Joint	Joint infection	90031046
INFECTION	Infection with normal ANC or Grade 1 or 2 neutrophils	Kidney	Kidney infection	90031050
INFECTION	Infection with normal ANC or Grade 1 or 2 neutrophils	Larynx	Laryngitis	90030328
INFECTION	Infection with normal ANC or Grade 1 or 2 neutrophils	Lens	Eye infection intraocular	90030330
INFECTION	Infection with normal ANC or Grade 1 or 2 neutrophils	Lip/perioral	Lip infection	90030332
INFECTION	Infection with normal ANC or Grade 1 or 2 neutrophils	Liver	Hepatic infection	90031134
INFECTION	Infection with normal ANC or Grade 1 or 2 neutrophils	Lung (pneumonia)	Pneumonia	90031074
INFECTION	Infection with normal ANC or Grade 1 or 2 neutrophils	Lymphatic	Lymph gland infection	90031146
INFECTION	Infection with normal ANC or Grade 1 or 2 neutrophils	Mediastinum NOS	Mediastinal infection	90031150
INFECTION	Infection with normal ANC or Grade 1 or 2 neutrophils	Meninges (meningitis)	Infectious meningitis	90031138
INFECTION	Infection with normal ANC or Grade 1 or 2 neutrophils	Middle ear (otitis media)	Otitis media	90031062
INFECTION	Infection with normal ANC or Grade 1 or 2 neutrophils	Mucosa	Mucosal infection	90031054
INFECTION	Infection with normal ANC or Grade 1 or 2 neutrophils	Muscle (infection myositis)	Infective myositis	90031142
INFECTION	Infection with normal ANC or Grade 1 or 2 neutrophils	Neck NOS	Infection	90030334
INFECTION	Infection with normal ANC or Grade 1 or 2 neutrophils	Nerve-cranial	Cranial nerve infection	90030336
INFECTION	Infection with normal ANC or Grade 1 or 2 neutrophils	Nerve-peripheral	Peripheral nerve infection	90030338
INFECTION	Infection with normal ANC or Grade 1 or 2 neutrophils	Nose	Rhinitis infective	90031174
INFECTION	Infection with normal ANC or Grade 1 or 2 neutrophils	Oral cavity-gums (gingivitis)	Gingival infection	90031130
INFECTION	Infection with normal ANC or Grade 1 or 2 neutrophils	Pancreas	Pancreas infection	90031154
INFECTION	Infection with normal ANC or Grade 1 or 2 neutrophils	Paranasal	Paranasal sinus infection	90030340
INFECTION	Infection with normal ANC or Grade 1 or 2 neutrophils	Pelvis NOS	Pelvic infection	90030342

INFECTION	Infection with normal ANC or Grade 1 or 2 neutrophils	Penis	Penile infection	90031066
INFECTION	Infection with normal ANC or Grade 1 or 2 neutrophils	Peristomal	Stoma site infection	90030344
INFECTION	Infection with normal ANC or Grade 1 or 2 neutrophils	Peritoneal cavity	Peritoneal infection	90031158
INFECTION	Infection with normal ANC or Grade 1 or 2 neutrophils	Pharynx	Pharyngitis	90031162
INFECTION	Infection with normal ANC or Grade 1 or 2 neutrophils	Pleura (empyema)	Pleural infection	90031070
INFECTION	Infection with normal ANC or Grade 1 or 2 neutrophils	Prostate	Prostate infection	90031170
INFECTION	Infection with normal ANC or Grade 1 or 2 neutrophils	Rectum	Anorectal infection	90031002
INFECTION	Infection with normal ANC or Grade 1 or 2 neutrophils	Salivary gland	Salivary gland infection	90030346
INFECTION	Infection with normal ANC or Grade 1 or 2 neutrophils	Scrotum	Scrotal infection	90031078
INFECTION	Infection with normal ANC or Grade 1 or 2 neutrophils	Sinus	Sinusitis	90031082
INFECTION	Infection with normal ANC or Grade 1 or 2 neutrophils	Skin (cellulitis)	Skin infection	90031178
INFECTION	Infection with normal ANC or Grade 1 or 2 neutrophils	Small bowel NOS	Small intestine infection	90030348
INFECTION	Infection with normal ANC or Grade 1 or 2 neutrophils	Soft tissue NOS	Soft tissue infection	90031086
INFECTION	Infection with normal ANC or Grade 1 or 2 neutrophils	Spinal cord (myelitis)	Spinal cord infection	90031182
INFECTION	Infection with normal ANC or Grade 1 or 2 neutrophils	Spleen	Splenic infection	90031090
INFECTION	Infection with normal ANC or Grade 1 or 2 neutrophils	Stomach	Gastric infection	90031126
INFECTION	Infection with normal ANC or Grade 1 or 2 neutrophils	Trachea	Tracheitis	90031094
INFECTION	Infection with normal ANC or Grade 1 or 2 neutrophils	Ungual (nails)	Nail infection	90031058
INFECTION	Infection with normal ANC or Grade 1 or 2 neutrophils	Upper aerodigestive NOS	Upper aerodigestive tract infection	90030350
INFECTION	Infection with normal ANC or Grade 1 or 2 neutrophils	Upper airway NOS	Upper respiratory infection	90031098
INFECTION	Infection with normal ANC or Grade 1 or 2 neutrophils	Ureter	Ureteritis	90031190

INFECTION	Infection with normal ANC or Grade 1 or 2 neutrophils	Urethra	Urethral infection	90031194
INFECTION	Infection with normal ANC or Grade 1 or 2 neutrophils	Urinary tract NOS	Urinary tract infection	90031102
INFECTION	Infection with normal ANC or Grade 1 or 2 neutrophils	Uterus	Uterine infection	90031106
INFECTION	Infection with normal ANC or Grade 1 or 2 neutrophils	Vagina	Vaginal infection	90031110
INFECTION	Infection with normal ANC or Grade 1 or 2 neutrophils	Vein	Phlebitis infective	90031166
INFECTION	Infection with normal ANC or Grade 1 or 2 neutrophils	Vulva	Vulvitis	90031114
INFECTION	Infection with normal ANC or Grade 1 or 2 neutrophils	Wound	Wound infection	90030351
INFECTION	Infection with unknown ANC	Abdomen NOS	Abdominal infection	10056519
INFECTION	Infection with unknown ANC	Anal/perianal	Anal infection	10061628
INFECTION	Infection with unknown ANC	Appendix	Appendicitis	10003011
INFECTION	Infection with unknown ANC	Artery	Arteritis infective	10065744
INFECTION	Infection with unknown ANC	Biliary tree	Biliary tract infection	10061695
INFECTION	Infection with unknown ANC	Bladder (urinary)	Bladder infection	10005047
INFECTION	Infection with unknown ANC	Blood	Sepsis	10040047
INFECTION	Infection with unknown ANC	Bone (osteomyelitis)	Bone infection	10061017
INFECTION	Infection with unknown ANC	Brain (encephalitis, infectious)	Encephalitis infection	10014594
INFECTION	Infection with unknown ANC	Brain + Spinal cord (encephalomyelitis)	Encephalomyelitis infection	10014621
INFECTION	Infection with unknown ANC	Bronchus	Bronchitis	10006451
INFECTION	Infection with unknown ANC	Catheter-related	Catheter related infection	10007810
INFECTION	Infection with unknown ANC	Cecum	Cecal infection	10065761
INFECTION	Infection with unknown ANC	Cervix	Cervicitis	10008323
INFECTION	Infection with unknown ANC	Colon	Infectious colitis	10021905
INFECTION	Infection with unknown ANC	Conjunctiva	Conjunctivitis infective	10010742
INFECTION	Infection with unknown ANC	Cornea	Corneal infection	10061788
INFECTION	Infection with unknown ANC	Dental-tooth	Tooth infection	10048762
INFECTION	Infection with unknown ANC	Duodenum	Duodenal infection	10065752
INFECTION	Infection with unknown ANC	Esophagus	Esophageal infection	10058804
INFECTION	Infection with unknown ANC	External ear (otitis externa)	Otitis externa	10033072
INFECTION	Infection with unknown ANC	Eye NOS	Eye infection	10015929
INFECTION	Infection with unknown ANC	Fallopian tube	Salpingitis infection	10039461

INFECTION	Infection with unknown ANC	Foreign body (e.g., graft, implant, prosthesis, stent)	Device related infection	10064687
INFECTION	Infection with unknown ANC	Gallbladder (cholecystitis)	Gallbladder infection	10062632
INFECTION	Infection with unknown ANC	Heart (endocarditis)	Endocarditis infective	10014678
INFECTION	Infection with unknown ANC	Ileum	Ileal infection	10065753
INFECTION	Infection with unknown ANC	Jejunum	Jejunal infection	10065754
INFECTION	Infection with unknown ANC	Joint	Joint infection	10023216
INFECTION	Infection with unknown ANC	Kidney	Kidney infection	10023424
INFECTION	Infection with unknown ANC	Larynx	Laryngitis	10023874
INFECTION	Infection with unknown ANC	Lens	Eye infection intraocular	10054762
INFECTION	Infection with unknown ANC	Lip/perioral	Lip infection	10065755
INFECTION	Infection with unknown ANC	Liver	Hepatic infection	10056522
INFECTION	Infection with unknown ANC	Lung (pneumonia)	Pneumonia	10035664
INFECTION	Infection with unknown ANC	Lymphatic	Lymph gland infection	10050823
INFECTION	Infection with unknown ANC	Mediastinum NOS	Mediastinal infection	10057483
INFECTION	Infection with unknown ANC	Meninges (meningitis)	Infectious meningitis	10053638
INFECTION	Infection with unknown ANC	Middle ear (otitis media)	Otitis media	10033078
INFECTION	Infection with unknown ANC	Mucosa	Mucosal infection	10065764
INFECTION	Infection with unknown ANC	Muscle (infection myositis)	Infective myositis	10021918
INFECTION	Infection with unknown ANC	Neck NOS	Infection - Neck	90030432
INFECTION	Infection with unknown ANC	Nerve-cranial	Cranial nerve infection	10065765
INFECTION	Infection with unknown ANC	Nerve-peripheral	Peripheral nerve infection	10065766
INFECTION	Infection with unknown ANC	Nose	Rhinitis infective	10059827
INFECTION	Infection with unknown ANC	Oral cavity-gums (gingivitis)	Gingival infection	10058802
INFECTION	Infection with unknown ANC	Pancreas	Pancreas infection	10051741
INFECTION	Infection with unknown ANC	Paranasal	Paranasal sinus infection	10065770
INFECTION	Infection with unknown ANC	Pelvis NOS	Pelvic infection	10058674
INFECTION	Infection with unknown ANC	Penis	Penile infection	10061912
INFECTION	Infection with unknown ANC	Peristomal	Stoma site infection	10064505
INFECTION	Infection with unknown ANC	Peritoneal cavity	Peritoneal infection	10057262
INFECTION	Infection with unknown ANC	Pharynx	Pharyngitis	10034835
INFECTION	Infection with unknown ANC	Pleura (empyema)	Pleural infection	10061351
INFECTION	Infection with unknown ANC	Prostate	Prostate infection	10050662
INFECTION	Infection with unknown ANC	Rectum	Anorectal infection	10061640
INFECTION	Infection with unknown ANC	Salivary gland	Salivary gland infection	10039413
INFECTION	Infection with unknown ANC	Scrotum	Scrotal infection	10062156
INFECTION	Infection with unknown ANC	Sinus	Sinusitis	10040753

INFECTION	Infection with unknown ANC	Skin (cellulitis)	Skin infection	10040872
INFECTION	Infection with unknown ANC	Small bowel NOS	Small intestine infection	10065771
INFECTION	Infection with unknown ANC	Soft tissue NOS	Soft tissue infection	10062255
INFECTION	Infection with unknown ANC	Spinal cord (myelitis)	Spinal cord infection	10049654
INFECTION	Infection with unknown ANC	Spleen	Splenic infection	10062112
INFECTION	Infection with unknown ANC	Stomach	Gastric infection	10056663
INFECTION	Infection with unknown ANC	Trachea	Tracheitis	10044302
INFECTION	Infection with unknown ANC	Ungual (nails)	Nail infection	10061304
INFECTION	Infection with unknown ANC	Upper aerodigestive NOS	Upper aerodigestive tract infection	10065767
INFECTION	Infection with unknown ANC	Upper airway NOS	Upper respiratory infection	10046300
INFECTION	Infection with unknown ANC	Ureter	Ureteritis	10051250
INFECTION	Infection with unknown ANC	Urethra	Urethral infection	10052298
INFECTION	Infection with unknown ANC	Urinary tract NOS	Urinary tract infection	10046571
INFECTION	Infection with unknown ANC	Uterus	Uterine infection	10062233
INFECTION	Infection with unknown ANC	Vagina	Vaginal infection	10046914
INFECTION	Infection with unknown ANC	Vein	Phlebitis infective	10056627
INFECTION	Infection with unknown ANC	Vulva	Vulvitis	10047780
INFECTION	Infection with unknown ANC	Wound	Wound infection	10048038
INFECTION	Opportunistic infection associated with >=Grade 2 Lymphopenia		Opportunistic infection	10030901
INFECTION	Viral hepatitis		Viral hepatitis	10047446
LYMPHATICS	Chyle or lymph leakage		Lymph leakage	10065773
LYMPHATICS	Dermal change lymphedema, phlebolymphedema		Lymphedema	10025233
LYMPHATICS	Edema:head and neck		Localized edema	10062466
LYMPHATICS	Edema:limb		Edema limbs	10050068
LYMPHATICS	Edema:trunk/genital		Localized edema	10062466
LYMPHATICS	Edema:viscera		Visceral edema	10065939
LYMPHATICS	Lymphatics - Other (Specify, __)		Lymphatic disorder	10052314
LYMPHATICS	Lymphedema-related fibrosis		Fibrosis	10016642
LYMPHATICS	Lymphocele		Lymphocele	10048642
LYMPHATICS	Phlebolymphatic cording		Lymphangitic streak	10065116
METABOLIC/LABORATORY	ALT, SGPT (serum glutamic pyruvic transaminase)		Alanine aminotransferase increased	10001551
METABOLIC/LABORATORY	AST, SGOT(serum glutamic oxaloacetic transaminase)		Aspartate aminotransferase increased	10003481
METABOLIC/LABORATORY	Acidosis (metabolic or respiratory)		Acidosis	10000486
METABOLIC/LABORATORY	Albumin, serum-low (hypoalbuminemia)		Hypoalbuminemia	10020943

METABOLIC/LABORATORY	Alkaline phosphatase		Alkaline phosphatase increased	10001675
METABOLIC/LABORATORY	Alkalosis (metabolic or respiratory)		Alkalosis	10001680
METABOLIC/LABORATORY	Amylase		Amylase increased	10002016
METABOLIC/LABORATORY	Bicarbonate, serum-low		Blood bicarbonate decreased	10005359
METABOLIC/LABORATORY	Bilirubin (hyperbilirubinemia)		Hyperbilirubinemia	10020582
METABOLIC/LABORATORY	CPK (creatine phosphokinase)		Creatine phosphokinase increased	10011349
METABOLIC/LABORATORY	Calcium, serum-high (hypercalcemia)		Hypercalcemia	10020587
METABOLIC/LABORATORY	Calcium, serum-low (hypocalcemia)		Hypocalcemia	10020949
METABOLIC/LABORATORY	Cholesterol, serum-high (hypercholesteremia)		Hypercholesterolemia	10020604
METABOLIC/LABORATORY	Creatinine		Creatinine increased	10011368
METABOLIC/LABORATORY	GGT (gamma-Glutamyl transpeptidase)		Gamma-glutamyltransferase increased	10017693
METABOLIC/LABORATORY	Glomerular filtration rate		Glomerular filtration rate decreased	10018358
METABOLIC/LABORATORY	Glucose, serum-high (hyperglycemia)		Hyperglycemia	10020639
METABOLIC/LABORATORY	Glucose, serum-low (hypoglycemia)		Hypoglycemia	10021005
METABOLIC/LABORATORY	Hemoglobinuria		Hemoglobinuria	10019489
METABOLIC/LABORATORY	Lipase		Lipase increased	10024574
METABOLIC/LABORATORY	Magnesium, serum-high (hypermagnesemia)		Hypermagnesemia	10020670
METABOLIC/LABORATORY	Magnesium, serum-low (hypomagnesemia)		Hypomagnesemia	10021028
METABOLIC/LABORATORY	Metabolic/Laboratory - Other (Specify, __)		Laboratory test abnormal	10023547
METABOLIC/LABORATORY	Phosphate, serum-low (hypophosphatemia)		Hypophosphatemia	10021059
METABOLIC/LABORATORY	Potassium, serum-high (hyperkalemia)		Hyperkalemia	10020647
METABOLIC/LABORATORY	Potassium, serum-low (hypokalemia)		Hypokalemia	10021018
METABOLIC/LABORATORY	Proteinuria		Proteinuria	10037032
METABOLIC/LABORATORY	Sodium, serum-high (hypernatremia)		Hypernatremia	10020680
METABOLIC/LABORATORY	Sodium, serum-low (hyponatremia)		Hyponatremia	10021038
METABOLIC/LABORATORY	Triglyceride, serum-high (hypertriglyceridemia)		Hypertriglyceridemia	10020870
METABOLIC/LABORATORY	Uric acid, serum-high (hyperuricemia)		Hyperuricemia	10020907
MUSCULOSKELETAL/SOFT TISSUE	Arthritis (non-septic)		Arthritis	10003246
MUSCULOSKELETAL/SOFT TISSUE	Bone: spine-scoliosis		Scoliosis	10039722
MUSCULOSKELETAL/SOFT TISSUE	Cervical spine-range of motion		Joint range of motion decreased cervical spine	10065796
MUSCULOSKELETAL/SOFT TISSUE	Exostosis		Exostosis	10015688

MUSCULOSKELETAL/SOFT TISSUE	Extremity-lower (gait/walking)		Gait abnormal	10017573
MUSCULOSKELETAL/SOFT TISSUE	Extremity-upper (function)		Upper extremity dysfunction	10065797
MUSCULOSKELETAL/SOFT TISSUE	Fibrosis-cosmesis		Superficial soft tissue fibrosis	10065798
MUSCULOSKELETAL/SOFT TISSUE	Fibrosis-deep connective tissue		Fibrosis deep connective tissue	10065799
MUSCULOSKELETAL/SOFT TISSUE	Fracture		Fracture	10017076
MUSCULOSKELETAL/SOFT TISSUE	Joint-effusion		Joint effusion	10023215
MUSCULOSKELETAL/SOFT TISSUE	Joint-function		Joint disorder	10023211
MUSCULOSKELETAL/SOFT TISSUE	Local complication -device/prosthesis-related		Device complication	10056488
MUSCULOSKELETAL/SOFT TISSUE	Lumbar spine-range of motion		Joint range of motion decreased lumbar spine	10065800
MUSCULOSKELETAL/SOFT TISSUE	Muscle weakness, generalized or specific area (not due to neuropathy)	Extraocular	Extraocular muscle disorder	10053635
MUSCULOSKELETAL/SOFT TISSUE	Muscle weakness, generalized or specific area (not due to neuropathy)	Extremity-lower	Muscle weakness lower limb	10065776
MUSCULOSKELETAL/SOFT TISSUE	Muscle weakness, generalized or specific area (not due to neuropathy)	Extremity-upper	Muscle weakness upper limb	10065895
MUSCULOSKELETAL/SOFT TISSUE	Muscle weakness, generalized or specific area (not due to neuropathy)	Facial	Facial muscle weakness	10051272
MUSCULOSKELETAL/SOFT TISSUE	Muscle weakness, generalized or specific area (not due to neuropathy)	Left-sided	Muscle weakness left-sided	10065780
MUSCULOSKELETAL/SOFT TISSUE	Muscle weakness, generalized or specific area (not due to neuropathy)	Ocular	Eye muscle weakness	10059456
MUSCULOSKELETAL/SOFT TISSUE	Muscle weakness, generalized or specific area (not due to neuropathy)	Pelvic	Pelvic floor muscle weakness	10064026
MUSCULOSKELETAL/SOFT TISSUE	Muscle weakness, generalized or specific area (not due to neuropathy)	Right-sided	Muscle weakness right-sided	10065794
MUSCULOSKELETAL/SOFT TISSUE	Muscle weakness, generalized or specific area (not due to neuropathy)	Trunk	Muscle weakness trunk	10065795
MUSCULOSKELETAL/SOFT TISSUE	Muscle weakness, generalized or specific area (not due to neuropathy)	Whole body/generalized	Muscle weakness	10028350
MUSCULOSKELETAL/SOFT TISSUE	Muscular/skeletal hypoplasia		Musculoskeletal deformity	10065783
MUSCULOSKELETAL/SOFT TISSUE	Musculoskeletal/Soft Tissue - Other (Specify, __)		Musculoskeletal disorder	10048592

MUSCULOSKELETAL/SOFT TISSUE	Myositis (inflammation/damage of muscle)		Myositis	10028653
MUSCULOSKELETAL/SOFT TISSUE	Osteonecrosis (avascular necrosis)		Osteonecrosis	10031264
MUSCULOSKELETAL/SOFT TISSUE	Osteoporosis		Osteoporosis	10031282
MUSCULOSKELETAL/SOFT TISSUE	Seroma		Seroma	10040102
MUSCULOSKELETAL/SOFT TISSUE	Soft tissue necrosis	Abdomen	Abdominal soft tissue necrosis	10065775
MUSCULOSKELETAL/SOFT TISSUE	Soft tissue necrosis	Extremity-lower	Soft tissue necrosis lower limb	10065777
MUSCULOSKELETAL/SOFT TISSUE	Soft tissue necrosis	Extremity-upper	Soft tissue necrosis upper limb	10065778
MUSCULOSKELETAL/SOFT TISSUE	Soft tissue necrosis	Head	Head soft tissue necrosis	10065779
MUSCULOSKELETAL/SOFT TISSUE	Soft tissue necrosis	Neck	Neck soft tissue necrosis	10065781
MUSCULOSKELETAL/SOFT TISSUE	Soft tissue necrosis	Pelvic	Pelvic soft tissue necrosis	10065793
MUSCULOSKELETAL/SOFT TISSUE	Soft tissue necrosis	Thorax	Chest wall necrosis	10048831
MUSCULOSKELETAL/SOFT TISSUE	Trismus (difficulty, restriction or pain when opening mouth)		Trismus	10044684
NEUROLOGY	Apnea		Apnea	10002972
NEUROLOGY	Arachnoiditis/meningismus/radiculitis		Arachnoiditis	10003074
NEUROLOGY	Ataxia (incoordination)		Ataxia	10003591
NEUROLOGY	Brachial plexopathy		Radiculitis brachial	10037778
NEUROLOGY	CNS cerebrovascular ischemia		Ischemia cerebrovascular	10023030
NEUROLOGY	CNS necrosis/cystic progression		Central nervous system necrosis	10065784
NEUROLOGY	Cognitive disturbance		Cognitive disturbance	10009845
NEUROLOGY	Confusion		Confusion	10010300
NEUROLOGY	Dizziness		Dizziness	10013573
NEUROLOGY	Encephalopathy		Encephalopathy	10014625
NEUROLOGY	Extrapyramidal/involuntary movement/restlessness		Extrapyramidal disorder	10015832
NEUROLOGY	Hydrocephalus		Hydrocephalus	10020508
NEUROLOGY	Irritability (children <3 years of age)		Irritability	10022998
NEUROLOGY	Laryngeal nerve dysfunction		Recurrent laryngeal nerve palsy	10038130
NEUROLOGY	Leak, cerebrospinal fluid (CSF)		Cerebrospinal fluid leakage	10008164

NEUROLOGY	Leukoencephalopathy (radiographic findings)		Leukoencephalopathy	10024382
NEUROLOGY	Memory impairment		Memory impairment	10027175
NEUROLOGY	Mental status		Mental status changes	10048294
NEUROLOGY	Mood alteration	Agitation	Agitation	10001497
NEUROLOGY	Mood alteration	Anxiety	Anxiety	10002855
NEUROLOGY	Mood alteration	Depression	Depression	10012378
NEUROLOGY	Mood alteration	Euphoria	Euphoria	10015533
NEUROLOGY	Myelitis		Myelitis	10028524
NEUROLOGY	Neurology - Other (Specify, __)		Neurological disorder NOS	10029298
NEUROLOGY	Neuropathy: cranial	CN I Smell	Olfactory nerve disorder	10056388
NEUROLOGY	Neuropathy: cranial	CN II Vision	Optic nerve disorder	10061322
NEUROLOGY	Neuropathy: cranial	CN III Pupil, upper eyelid, extra ocular movements	Oculomotor nerve disorder	10053661
NEUROLOGY	Neuropathy: cranial	CN IV Downward, inward movement of eye	IVth nerve disorder	10065836
NEUROLOGY	Neuropathy: cranial	CN IX Motor-pharynx; Sensory-ear, pharynx, tongue	Glossopharyngeal nerve disorder	10061185
NEUROLOGY	Neuropathy: cranial	CN V Motor-jaw muscles; Sensory-facial	Trigeminal nerve disorder	10060890
NEUROLOGY	Neuropathy: cranial	CN VI Lateral deviation of eye	Abducens nerve disorder	10053662
NEUROLOGY	Neuropathy: cranial	CN VII Motor-face; Sensory-taste	Facial nerve disorder	10061457
NEUROLOGY	Neuropathy: cranial	CN VIII Hearing and balance	Acoustic nerve disorder NOS	10000521
NEUROLOGY	Neuropathy: cranial	CN X Motor-palate; pharynx, larynx	Vagus nerve disorder	10061403
NEUROLOGY	Neuropathy: cranial	CN XI Motor-sternomastoid and trapezius	Accessory nerve disorder	10060929
NEUROLOGY	Neuropathy: cranial	CN XII Motor-tongue	Hypoglossal nerve disorder	10061212
NEUROLOGY	Neuropathy: motor		Peripheral motor neuropathy	10034580
NEUROLOGY	Neuropathy: sensory		Peripheral sensory neuropathy	10034620
NEUROLOGY	Personality/behavioral		Personality change	10034719
NEUROLOGY	Phrenic nerve dysfunction		Phrenic nerve paralysis	10064964
NEUROLOGY	Psychosis (hallucinations/delusions)		Psychosis	10037234
NEUROLOGY	Pyramidal tract dysfunction (e.g., increased tone, hyperreflexia, positive Babinski, decreased fine motor coordination)		Pyramidal tract syndrome	10063636
NEUROLOGY	Seizure		Seizure	10039906
NEUROLOGY	Somnolence/depressed level of consciousness		Depressed level of consciousness	10012373

NEUROLOGY	Speech impairment (e.g., dysphasia or aphasia)		Speech disorder	10041466
NEUROLOGY	Syncope (fainting)		Syncope	10042772
NEUROLOGY	Tremor		Tremor	10044565
OCULAR/VISUAL	Cataract		Cataract	10007739
OCULAR/VISUAL	Dry eye syndrome		Dry eye syndrome	10013777
OCULAR/VISUAL	Eyelid dysfunction		Eyelid function disorder	10061145
OCULAR/VISUAL	Glaucoma		Glaucoma	10018304
OCULAR/VISUAL	Keratitis (corneal inflammation/corneal ulceration)		Keratitis	10023332
OCULAR/VISUAL	Night blindness (nyctalopia)		Night blindness	10029404
OCULAR/VISUAL	Nystagmus		Nystagmus	10029864
OCULAR/VISUAL	Ocular surface disease		Conjunctival disorder	10061446
OCULAR/VISUAL	Ocular/Visual - Other (Specify, __)		Eye disorder	10015916
OCULAR/VISUAL	Ophthalmoplegia/diplopia (double vision)		Diplopia	10013036
OCULAR/VISUAL	Optic disc edema		Optic nerve edema	10030934
OCULAR/VISUAL	Proptosis/enophthalmos		Proptosis	10036905
OCULAR/VISUAL	Retinal detachment		Retinal detachment	10038848
OCULAR/VISUAL	Retinopathy		Retinopathy	10038923
OCULAR/VISUAL	Scleral necrosis/melt		Scleral disorder	10061510
OCULAR/VISUAL	Uveitis		Uveitis	10046851
OCULAR/VISUAL	Vision-blurred vision		Vision blurred	10047513
OCULAR/VISUAL	Vision-flashing lights/floaters		Flashing vision	10016758
OCULAR/VISUAL	Vision-photophobia		Photophobia	10034960
OCULAR/VISUAL	Vitreous hemorrhage		Vitreous hemorrhage	10047656
OCULAR/VISUAL	Watery eye (epiphora, tearing)		Watering eyes	10047848
PAIN	Pain	Abdomen NOS	Abdominal pain	10000081
PAIN	Pain	Anus	Anal pain	10002167
PAIN	Pain	Back	Back pain	10003988
PAIN	Pain	Bladder	Bladder pain	10005063
PAIN	Pain	Bone	Bone pain	10006002
PAIN	Pain	Breast	Breast pain	10006298
PAIN	Pain	Buttock	Buttock pain	10048677
PAIN	Pain	Cardiac/heart	Cardiac pain	10054231
PAIN	Pain	Chest wall	Chest wall pain	10008496
PAIN	Pain	Chest/thorax NOS	Chest pain	10008479
PAIN	Pain	Dental/teeth/peridontal	Toothache	10044055

PAIN	Pain	Esophagus	Esophageal pain	10015388
PAIN	Pain	External ear	External ear pain	10065785
PAIN	Pain	Extremity-limb	Pain in extremity	10033425
PAIN	Pain	Eye	Eye pain	10015958
PAIN	Pain	Face	Facial pain	10016059
PAIN	Pain	Gallbladder	Gallbladder pain	10017638
PAIN	Pain	Head/headache	Headache	10019211
PAIN	Pain	Intestine	Gastrointestinal pain	10017999
PAIN	Pain	Joint	Joint pain	10023222
PAIN	Pain	Kidney	Kidney pain	10023432
PAIN	Pain	Larynx	Laryngeal pain	10023848
PAIN	Pain	Lip	Lip pain	10024561
PAIN	Pain	Liver	Hepatic pain	10019705
PAIN	Pain	Lymph node	Lymph node pain	10025182
PAIN	Pain	Middle ear	Ear pain	10014020
PAIN	Pain	Muscle	Myalgia	10028411
PAIN	Pain	Neck	Neck pain	10028836
PAIN	Pain	Neuralgia/peripheral nerve	Neuralgia	10029223
PAIN	Pain	Oral cavity	Oral pain	10031009
PAIN	Pain	Oral-gums	Gingival pain	10018286
PAIN	Pain	Ovulatory	Ovulation pain	10033314
PAIN	Pain	Pain NOS	Pain	10033371
PAIN	Pain	Pelvis	Pelvic pain	10034263
PAIN	Pain	Penis	Penile pain	10034310
PAIN	Pain	Pericardium	Pericardial pain	90030568
PAIN	Pain	Perineum	Perineal pain	10061339
PAIN	Pain	Peritoneum	Peritoneal pain	10065801
PAIN	Pain	Phantom (pain associated with missing limb)	Phantom pain	10056238
PAIN	Pain	Pleura	Pleuritic pain	10035623
PAIN	Pain	Prostate	Prostatic pain	10036968
PAIN	Pain	Rectum	Rectal pain	10038072
PAIN	Pain	Scalp	Scalp pain	10049120
PAIN	Pain	Scrotum	Scrotal pain	10039757
PAIN	Pain	Sinus	Sinus pain	10040747
PAIN	Pain	Skin	Pain of skin	10033474
PAIN	Pain	Stomach	Stomach pain	10042112

PAIN	Pain	Testicle	Testicular pain	10043345
PAIN	Pain	Throat/pharynx/larynx	Pharyngolaryngeal pain	10034844
PAIN	Pain	Tumor pain	Tumor pain	10045158
PAIN	Pain	Urethra	Urethral pain	10046461
PAIN	Pain	Uterus	Uterine pain	10046809
PAIN	Pain	Vagina	Vaginal pain	10046937
PAIN	Pain - Other (Specify, __)		Pain	90004082
PULMONARY/UPPER RESPIRATORY	Adult Respiratory Distress Syndrome (ARDS)		Adult respiratory distress syndrome	10001409
PULMONARY/UPPER RESPIRATORY	Aspiration		Aspiration	10003504
PULMONARY/UPPER RESPIRATORY	Atelectasis		Atelectasis	10003598
PULMONARY/UPPER RESPIRATORY	Bronchospasm, wheezing		Bronchospasm	10006482
PULMONARY/UPPER RESPIRATORY	Carbon monoxide diffusion capacity (DL(co))		Carbon monoxide diffusing capacity decreased	10065906
PULMONARY/UPPER RESPIRATORY	Chylothorax		Chylothorax	10051228
PULMONARY/UPPER RESPIRATORY	Cough		Cough	10011224
PULMONARY/UPPER RESPIRATORY	Dyspnea (shortness of breath)		Dyspnea	10013963
PULMONARY/UPPER RESPIRATORY	Edema, larynx		Laryngeal edema	10023838
PULMONARY/UPPER RESPIRATORY	FEV(1)		Forced expiratory volume decreased	10016987
PULMONARY/UPPER RESPIRATORY	Fistula, pulmonary/upper respiratory	Bronchus	Bronchial fistula	10006437
PULMONARY/UPPER RESPIRATORY	Fistula, pulmonary/upper respiratory	Larynx	Laryngeal fistula	10065786
PULMONARY/UPPER RESPIRATORY	Fistula, pulmonary/upper respiratory	Lung	Pulmonary fistula	10065873
PULMONARY/UPPER RESPIRATORY	Fistula, pulmonary/upper respiratory	Oral cavity	Oral cavity fistula	90030578
PULMONARY/UPPER RESPIRATORY	Fistula, pulmonary/upper respiratory	Pharynx	Pharyngeal fistula	10034825
PULMONARY/UPPER RESPIRATORY	Fistula, pulmonary/upper respiratory	Pleura	Pleural fistula	10065839
PULMONARY/UPPER RESPIRATORY	Fistula, pulmonary/upper respiratory	Trachea	Tracheal fistula	10065787

PULMONARY/UPPER RESPIRATORY	Hiccoughs (hiccups, singultus)		Hiccough	10020037
PULMONARY/UPPER RESPIRATORY	Hypoxia		Hypoxia	10021143
PULMONARY/UPPER RESPIRATORY	Nasal cavity/paranasal sinus reactions		Nasal congestion	10028735
PULMONARY/UPPER RESPIRATORY	Obstruction/stenosis of airway	Bronchus	Bronchial obstruction	10006440
PULMONARY/UPPER RESPIRATORY	Obstruction/stenosis of airway	Larynx	Laryngeal obstruction	10059639
PULMONARY/UPPER RESPIRATORY	Obstruction/stenosis of airway	Pharynx	Pharyngeal stenosis	10050028
PULMONARY/UPPER RESPIRATORY	Obstruction/stenosis of airway	Trachea	Tracheal obstruction	10044291
PULMONARY/UPPER RESPIRATORY	Pleural effusion (non-malignant)		Pleural effusion	10035598
PULMONARY/UPPER RESPIRATORY	Pneumonitis/pulmonary infiltrates		Pneumonitis	10035742
PULMONARY/UPPER RESPIRATORY	Pneumothorax		Pneumothorax	10035759
PULMONARY/UPPER RESPIRATORY	Prolonged chest tube drainage or air leak after pulmonary resection		Postoperative thoracic procedure complication	10056745
PULMONARY/UPPER RESPIRATORY	Prolonged intubation after pulmonary resection (>24 hrs after surgery)		Prolonged intubation after pulmonary resection (>24 hrs after surgery)	90030588
PULMONARY/UPPER RESPIRATORY	Pulmonary fibrosis (radiographic changes)		Pulmonary fibrosis	10037383
PULMONARY/UPPER RESPIRATORY	Pulmonary/Upper Respiratory - Other (Specify, __)		Respiratory disorder	10038683
PULMONARY/UPPER RESPIRATORY	Vital capacity		Vital capacity decreased	10047582
PULMONARY/UPPER RESPIRATORY	Voice changes/dysarthria (e.g., hoarseness, loss or alteration in voice, laryngitis)		Voice alteration	10047681
RENAL/GENITOURINARY	Bladder spasms		Bladder spasm	10048994
RENAL/GENITOURINARY	Cystitis		Cystitis	10011781
RENAL/GENITOURINARY	Fistula, GU	Bladder	Vesical fistula	10047363
RENAL/GENITOURINARY	Fistula, GU	Genital tract-female	Female genital tract fistula	10061149
RENAL/GENITOURINARY	Fistula, GU	Kidney	Renal pelvis fistula	10051985
RENAL/GENITOURINARY	Fistula, GU	Ureter	Ureteric fistula	10046404
RENAL/GENITOURINARY	Fistula, GU	Urethra	Urethral fistula	10046451
RENAL/GENITOURINARY	Fistula, GU	Uterus	Uterine fistula	10065811

RENAL/GENITOURINARY	Fistula, GU	Vagina	Vaginal fistula	10065813
RENAL/GENITOURINARY	Incontinence, urinary		Urinary incontinence	10046543
RENAL/GENITOURINARY	Leak (including anastomotic), GU	Bladder	Bladder anastomotic leak	10065802
RENAL/GENITOURINARY	Leak (including anastomotic), GU	Fallopian tube	Fallopian tube anastomotic leak	10065788
RENAL/GENITOURINARY	Leak (including anastomotic), GU	Kidney	Kidney anastomotic leak	10065803
RENAL/GENITOURINARY	Leak (including anastomotic), GU	Spermatic cord	Spermatic cord anastomotic leak	10065897
RENAL/GENITOURINARY	Leak (including anastomotic), GU	Stoma	Urostomy leak	10065882
RENAL/GENITOURINARY	Leak (including anastomotic), GU	Ureter	Ureteric anastomotic leak	10065814
RENAL/GENITOURINARY	Leak (including anastomotic), GU	Urethra	Urethral anastomotic leak	10065815
RENAL/GENITOURINARY	Leak (including anastomotic), GU	Uterus	Uterine anastomotic leak	10065886
RENAL/GENITOURINARY	Leak (including anastomotic), GU	Vagina	Vaginal anastomotic leak	10065887
RENAL/GENITOURINARY	Leak (including anastomotic), GU	Vas deferens	Vas deferens anastomotic leak	10065888
RENAL/GENITOURINARY	Obstruction, GU	Bladder	Bladder obstruction	10005060
RENAL/GENITOURINARY	Obstruction, GU	Fallopian tube	Fallopian tube obstruction	10065789
RENAL/GENITOURINARY	Obstruction, GU	Prostate	Prostatic obstruction	10055026
RENAL/GENITOURINARY	Obstruction, GU	Spermatic cord	Spermatic cord obstruction	10065805
RENAL/GENITOURINARY	Obstruction, GU	Stoma	Urostomy obstruction	10065883
RENAL/GENITOURINARY	Obstruction, GU	Testes	Testicular obstruction	90030620
RENAL/GENITOURINARY	Obstruction, GU	Ureter	Ureteric obstruction	10046406
RENAL/GENITOURINARY	Obstruction, GU	Urethra	Urethral obstruction	10046459
RENAL/GENITOURINARY	Obstruction, GU	Uterus	Uterine obstruction	10065928
RENAL/GENITOURINARY	Obstruction, GU	Vagina	Vaginal obstruction	10065817
RENAL/GENITOURINARY	Obstruction, GU	Vas deferens	Vas deferens obstruction	10065819
RENAL/GENITOURINARY	Perforation, GU	Bladder	Bladder perforation	10063575
RENAL/GENITOURINARY	Perforation, GU	Fallopian tube	Fallopian tube perforation	10065790
RENAL/GENITOURINARY	Perforation, GU	Kidney	Kidney perforation	10065792
RENAL/GENITOURINARY	Perforation, GU	Ovary	Ovarian rupture	10033279
RENAL/GENITOURINARY	Perforation, GU	Prostate	Prostatic perforation	10065804
RENAL/GENITOURINARY	Perforation, GU	Spermatic cord	Spermatic cord perforation	10065806
RENAL/GENITOURINARY	Perforation, GU	Stoma	Urostomy perforation	10065884
RENAL/GENITOURINARY	Perforation, GU	Testes	Testicular perforation	10065808
RENAL/GENITOURINARY	Perforation, GU	Ureter	Ureteric perforation	10065809
RENAL/GENITOURINARY	Perforation, GU	Urethra	Urethral perforation	10065810
RENAL/GENITOURINARY	Perforation, GU	Uterus	Uterine perforation	10046810
RENAL/GENITOURINARY	Perforation, GU	Vagina	Vaginal perforation	10065818
RENAL/GENITOURINARY	Perforation, GU	Vas deferens	Vas deferens perforation	10065820
RENAL/GENITOURINARY	Prolapse of stoma, GU		Prolapse of urostomy	10065822

RENAL/GENITOURINARY	Renal failure		Renal failure	10038435
RENAL/GENITOURINARY	Renal/Genitourinary - Other (Specify, __)		Urogenital disorder	10046694
RENAL/GENITOURINARY	Stricture/stenosis (including anastomotic), GU	Bladder	Bladder stenosis	10005082
RENAL/GENITOURINARY	Stricture/stenosis (including anastomotic), GU	Fallopian tube	Fallopian tube stenosis	10065791
RENAL/GENITOURINARY	Stricture/stenosis (including anastomotic), GU	Prostate	Prostatic disorder	10036956
RENAL/GENITOURINARY	Stricture/stenosis (including anastomotic), GU	Spermatic cord	Spermatic cord stenosis	10065807
RENAL/GENITOURINARY	Stricture/stenosis (including anastomotic), GU	Stoma	Urostomy stenosis	10065885
RENAL/GENITOURINARY	Stricture/stenosis (including anastomotic), GU	Testes	Testicular stricture/stenosis	90030662
RENAL/GENITOURINARY	Stricture/stenosis (including anastomotic), GU	Ureter	Ureteric stenosis	10046411
RENAL/GENITOURINARY	Stricture/stenosis (including anastomotic), GU	Urethra	Urethral stricture	10046466
RENAL/GENITOURINARY	Stricture/stenosis (including anastomotic), GU	Uterus	Uterine stenosis	10065812
RENAL/GENITOURINARY	Stricture/stenosis (including anastomotic), GU	Vagina	Vaginal stricture	10053496
RENAL/GENITOURINARY	Stricture/stenosis (including anastomotic), GU	Vas deferens	Vas deferens stenosis	10065821
RENAL/GENITOURINARY	Urinary electrolyte wasting (e.g., Fanconi's syndrome, renal tubular acidosis)		Renal tubular disorder	10038537
RENAL/GENITOURINARY	Urinary frequency/urgency		Urinary frequency	10046539
RENAL/GENITOURINARY	Urinary retention (including neurogenic bladder)		Urinary retention	10046555
RENAL/GENITOURINARY	Urine color change		Urine discoloration	10046628
SECONDARY MALIGNANCY	Secondary Malignancy - possibly related to cance treatment (Specify, __)		Treatment related secondary malignancy	10049737
SEXUAL/REPRODUCTIVE FUNCTION	Breast function/lactation		Lactation disorder	10061261
SEXUAL/REPRODUCTIVE FUNCTION	Breast nipple/areolar deformity		Nipple deformity	10065823
SEXUAL/REPRODUCTIVE FUNCTION	Breast volume/hypoplasia		Breast hypoplasia	10049070
SEXUAL/REPRODUCTIVE FUNCTION	Ejaculatory dysfunction		Ejaculation disorder	10014326
SEXUAL/REPRODUCTIVE FUNCTION	Erectile dysfunction		Erectile dysfunction	10061461

SEXUAL/REPRODUCTIVE FUNCTION	Gynecomastia		Gynecomastia	10018801
SEXUAL/REPRODUCTIVE FUNCTION	Infertility/sterility		Infertility	10021926
SEXUAL/REPRODUCTIVE FUNCTION	Irregular menses (change from baseline)		Irregular menstruation	10022992
SEXUAL/REPRODUCTIVE FUNCTION	Libido		Libido decreased	10024419
SEXUAL/REPRODUCTIVE FUNCTION	Orgasmic dysfunction		Orgasm abnormal	10031085
SEXUAL/REPRODUCTIVE FUNCTION	Sexual/Reproductive Function - Other (Specify, __)		Reproductive tract disorder	10061483
SEXUAL/REPRODUCTIVE FUNCTION	Vaginal discharge (non-infectious)		Vaginal discharge	10046901
SEXUAL/REPRODUCTIVE FUNCTION	Vaginal dryness		Vaginal dryness	10046904
SEXUAL/REPRODUCTIVE FUNCTION	Vaginal mucositis		Vaginal mucositis	10064282
SEXUAL/REPRODUCTIVE FUNCTION	Vaginal stenosis/length		Vaginal atresia	10046879
SEXUAL/REPRODUCTIVE FUNCTION	Vaginitis (not due to infection)		Vaginal inflammation	10046916
SURGERY/INTRA-OPERATIVE INJURY	Intra-operative Injury - Other (Specify, __)		Intraoperative complications	10052620
SURGERY/INTRA-OPERATIVE INJURY	Intra-operative injury	Abdomen NOS	Intraoperative gastrointestinal injury	10065825
SURGERY/INTRA-OPERATIVE INJURY	Intra-operative injury	Adrenal gland	Intraoperative endocrine injury	10065834
SURGERY/INTRA-OPERATIVE INJURY	Intra-operative injury	Anal sphincter	Intraoperative gastrointestinal injury - Anal sphincter	90030678
SURGERY/INTRA-OPERATIVE INJURY	Intra-operative injury	Anus	Intraoperative gastrointestinal injury - Anus	90030680
SURGERY/INTRA-OPERATIVE INJURY	Intra-operative injury	Appendix	Intraoperative gastrointestinal injury - Appendix	90030682
SURGERY/INTRA-OPERATIVE INJURY	Intra-operative injury	Artery NOS	Intraoperative arterial injury	10065826
SURGERY/INTRA-OPERATIVE INJURY	Intra-operative injury	Artery-aorta	Intraoperative arterial injury - Artery-aorta	90030686
SURGERY/INTRA-OPERATIVE INJURY	Intra-operative injury	Artery-carotid	Intraoperative arterial injury - Artery-carotid	90030688
SURGERY/INTRA-OPERATIVE INJURY	Intra-operative injury	Artery-cerebral	Intraoperative arterial injury - Artery-cerebral	90030690

SURGERY/INTRA-OPERATIVE INJURY	Intra-operative injury	Artery-extremity (lower)	Intraoperative arterial injury - Artery-extremity (lower)	90030692
SURGERY/INTRA-OPERATIVE INJURY	Intra-operative injury	Artery-extremity (upper)	Intraoperative arterial injury - Artery-extremity (upper)	90030694
SURGERY/INTRA-OPERATIVE INJURY	Intra-operative injury	Artery-hepatic	Intraoperative arterial injury - Artery-hepatic	90030696
SURGERY/INTRA-OPERATIVE INJURY	Intra-operative injury	Artery-major visceral artery	Intraoperative arterial injury - Artery-major visceral artery	90030698
SURGERY/INTRA-OPERATIVE INJURY	Intra-operative injury	Artery-pulmonary	Intraoperative arterial injury - Artery-pulmonary	90030700
SURGERY/INTRA-OPERATIVE INJURY	Intra-operative injury	Biliary tree NOS	Intraoperative hepatobiliary injury	10065827
SURGERY/INTRA-OPERATIVE INJURY	Intra-operative injury	Biliary tree-common bile duct	Intraoperative hepatobiliary injury - Biliary tree-common bile duct	90030704
SURGERY/INTRA-OPERATIVE INJURY	Intra-operative injury	Biliary tree-common hepatic duct	Intraoperative hepatobiliary injury - Biliary tree-common hepatic duct	90030706
SURGERY/INTRA-OPERATIVE INJURY	Intra-operative injury	Biliary tree-left hepatic duct	Intraoperative hepatobiliary injury - Biliary tree-left hepatic duct	90030708
SURGERY/INTRA-OPERATIVE INJURY	Intra-operative injury	Biliary tree-right hepatic duct	Intraoperative hepatobiliary injury - Biliary tree-right hepatic duct	90030710
SURGERY/INTRA-OPERATIVE INJURY	Intra-operative injury	Bladder	Intraoperative urinary injury - Bladder	90030712
SURGERY/INTRA-OPERATIVE INJURY	Intra-operative injury	Bone	Intraoperative musculoskeletal injury	10065829
SURGERY/INTRA-OPERATIVE INJURY	Intra-operative injury	Brain	Intraoperative neurological injury	10065830
SURGERY/INTRA-OPERATIVE INJURY	Intra-operative injury	Breast	Intraoperative breast injury	10065831
SURGERY/INTRA-OPERATIVE INJURY	Intra-operative injury	Bronchus	Intraoperative respiratory injury	10065832
SURGERY/INTRA-OPERATIVE INJURY	Intra-operative injury	Cartilage	Intraoperative musculoskeletal injury - Cartilage	90030722
SURGERY/INTRA-OPERATIVE INJURY	Intra-operative injury	Cecum	Intraoperative gastrointestinal injury - Cecum	90030724
SURGERY/INTRA-OPERATIVE INJURY	Intra-operative injury	Cervix	Intraoperative reproductive tract injury - Cervix	90030726
SURGERY/INTRA-OPERATIVE INJURY	Intra-operative injury	Colon	Intraoperative gastrointestinal injury - Colon	90030728
SURGERY/INTRA-OPERATIVE INJURY	Intra-operative injury	Conjunctiva	Intraoperative ocular injury - Conjunctiva	90030730
SURGERY/INTRA-OPERATIVE INJURY	Intra-operative injury	Cornea	Intraoperative ocular injury - Cornea	90030732

SURGERY/INTRA-OPERATIVE INJURY	Intra-operative injury	Duodenum	Intraoperative gastrointestinal injury - Duodenum	90030734
SURGERY/INTRA-OPERATIVE INJURY	Intra-operative injury	Esophagus	Intraoperative gastrointestinal injury - Esophagus	90030736
SURGERY/INTRA-OPERATIVE INJURY	Intra-operative injury	Extremity-lower	Intraoperative musculoskeletal injury - Extremity-lower	90030738
SURGERY/INTRA-OPERATIVE INJURY	Intra-operative injury	Extremity-upper	Intraoperative musculoskeletal injury - Extremity-upper	90030740
SURGERY/INTRA-OPERATIVE INJURY	Intra-operative injury	Eye NOS	Intraoperative ocular injury	10065841
SURGERY/INTRA-OPERATIVE INJURY	Intra-operative injury	Face NOS	Intraoperative head and neck injury	10065842
SURGERY/INTRA-OPERATIVE INJURY	Intra-operative injury	Fallopian tube	Intraoperative reproductive tract injury - Fallopian tube	90030746
SURGERY/INTRA-OPERATIVE INJURY	Intra-operative injury	Gallbladder	Intraoperative hepatobiliary injury - Gallbladder	90030748
SURGERY/INTRA-OPERATIVE INJURY	Intra-operative injury	Gingiva	Intraoperative gastrointestinal injury - Gingiva	90030750
SURGERY/INTRA-OPERATIVE INJURY	Intra-operative injury	Heart	Intraoperative cardiac injury	10065843
SURGERY/INTRA-OPERATIVE INJURY	Intra-operative injury	Ileum	Intraoperative gastrointestinal injury - Ileum	90030754
SURGERY/INTRA-OPERATIVE INJURY	Intra-operative injury	Inner ear	Intraoperative ear injury	10065844
SURGERY/INTRA-OPERATIVE INJURY	Intra-operative injury	Jejunum	Intraoperative gastrointestinal injury - Jejunum	90030758
SURGERY/INTRA-OPERATIVE INJURY	Intra-operative injury	Joint	Intraoperative musculoskeletal injury - Joint	90030760
SURGERY/INTRA-OPERATIVE INJURY	Intra-operative injury	Kidney	Intraoperative renal injury	10065845
SURGERY/INTRA-OPERATIVE INJURY	Intra-operative injury	Larynx	Intraoperative respiratory injury - Larynx	90030720
SURGERY/INTRA-OPERATIVE INJURY	Intra-operative injury	Lens	Intraoperative ocular injury - Lens	90030766
SURGERY/INTRA-OPERATIVE INJURY	Intra-operative injury	Ligament	Intraoperative musculoskeletal injury	90030768
SURGERY/INTRA-OPERATIVE INJURY	Intra-operative injury	Lip/perioral area	Intraoperative gastrointestinal injury - Lip/perioral area	90030770
SURGERY/INTRA-OPERATIVE INJURY	Intra-operative injury	Liver	Intraoperative hepatobiliary injury - Liver	90030772
SURGERY/INTRA-OPERATIVE INJURY	Intra-operative injury	Lung	Intraoperative respiratory injury - Lung	90030764

SURGERY/INTRA-OPERATIVE INJURY	Intra-operative injury	Mediastinum	Intraoperative respiratory injury - Mediastinum	90030774
SURGERY/INTRA-OPERATIVE INJURY	Intra-operative injury	Meninges	Intraoperative neurological injury - Meninges	90030778
SURGERY/INTRA-OPERATIVE INJURY	Intra-operative injury	Middle ear	Intraoperative ear injury - Middle ear	90030780
SURGERY/INTRA-OPERATIVE INJURY	Intra-operative injury	Muscle	Intraoperative musculoskeletal injury - Muscle	90030782
SURGERY/INTRA-OPERATIVE INJURY	Intra-operative injury	NERVES: Brachial plexus	Intraoperative neurological injury - NERVES: Brachial plexus	90030784
SURGERY/INTRA-OPERATIVE INJURY	Intra-operative injury	NERVES: CN I (olfactory)	Intraoperative neurological injury - NERVES: CN I (olfactory)	90030786
SURGERY/INTRA-OPERATIVE INJURY	Intra-operative injury	NERVES: CN II (optic)	Intraoperative neurological injury - NERVES: CN II (optic)	90030788
SURGERY/INTRA-OPERATIVE INJURY	Intra-operative injury	NERVES: CN III (oculomotor)	Intraoperative neurological injury - NERVES: CN III (oculomotor)	90030790
SURGERY/INTRA-OPERATIVE INJURY	Intra-operative injury	NERVES: CN IV (trochlear)	Intraoperative neurological injury - NERVES: CN IV (trochlear)	90030792
SURGERY/INTRA-OPERATIVE INJURY	Intra-operative injury	NERVES: CN IX (glossopharyngeal) motor pharynx	Intraoperative neurological injury - NERVES: CN IX (glossopharyngeal) motor pharynx	90030794
SURGERY/INTRA-OPERATIVE INJURY	Intra-operative injury	NERVES: CN IX (glossopharyngeal) sensory ear-pharynx-tongue	Intraoperative neurological injury - NERVES: CN IX (glossopharyngeal) sensory ear-pharynx-tongue	90030796
SURGERY/INTRA-OPERATIVE INJURY	Intra-operative injury	NERVES: CN V (trigeminal) motor	Intraoperative neurological injury - NERVES: CN V (trigeminal) motor	90030798
SURGERY/INTRA-OPERATIVE INJURY	Intra-operative injury	NERVES: CN V (trigeminal) sensory	Intraoperative neurological injury - NERVES: CN V (trigeminal) sensory	90030800
SURGERY/INTRA-OPERATIVE INJURY	Intra-operative injury	NERVES: CN VI (abducens)	Intraoperative neurological injury - NERVES: CN VI (abducens)	90030802
SURGERY/INTRA-OPERATIVE INJURY	Intra-operative injury	NERVES: CN VII (facial) motor-face	Intraoperative neurological injury - NERVES: CN VII (facial) motor-face	90030804
SURGERY/INTRA-OPERATIVE INJURY	Intra-operative injury	NERVES: CN VII (facial) sensory-taste	Intraoperative neurological injury - NERVES: CN VII (facial) sensory-taste	90030806
SURGERY/INTRA-OPERATIVE INJURY	Intra-operative injury	NERVES: CN VIII (vestibulocochlear)	Intraoperative neurological injury - NERVES: CN VIII (vestibulocochlear)	90030808
SURGERY/INTRA-OPERATIVE INJURY	Intra-operative injury	NERVES: CN X (vagus)	Intraoperative neurological injury - NERVES: CN X (vagus)	90030810
SURGERY/INTRA-OPERATIVE INJURY	Intra-operative injury	NERVES: CN XI (spinal accessory)	Intraoperative neurological injury - NERVES: CN XI (spinal accessory)	90030812
SURGERY/INTRA-OPERATIVE INJURY	Intra-operative injury	NERVES: CN XII (hypoglossal)	Intraoperative neurological injury - NERVES: CN XII (hypoglossal)	90030814
SURGERY/INTRA-OPERATIVE INJURY	Intra-operative injury	NERVES: Cranial nerve or branch NOS	Intraoperative neurological injury - NERVES: Cranial nerve or branch NOS	90030816

SURGERY/INTRA-OPERATIVE INJURY	Intra-operative injury	NERVES: Lingual	Intraoperative neurological injury - NERVES: Lingual	90030818
SURGERY/INTRA-OPERATIVE INJURY	Intra-operative injury	NERVES: Lung thoracic	Intraoperative neurological injury - NERVES: Lung thoracic	90030820
SURGERY/INTRA-OPERATIVE INJURY	Intra-operative injury	NERVES: Peripheral motor NOS	Intraoperative neurological injury - NERVES: Peripheral motor NOS	90030822
SURGERY/INTRA-OPERATIVE INJURY	Intra-operative injury	NERVES: Peripheral sensory NOS	Intraoperative neurological injury - NERVES: Peripheral sensory NOS	90030824
SURGERY/INTRA-OPERATIVE INJURY	Intra-operative injury	NERVES: Recurrent laryngeal	Intraoperative neurological injury - NERVES: Recurrent laryngeal	90030826
SURGERY/INTRA-OPERATIVE INJURY	Intra-operative injury	NERVES: Sacral plexus	Intraoperative neurological injury - NERVES: Sacral plexus	90030828
SURGERY/INTRA-OPERATIVE INJURY	Intra-operative injury	NERVES: Sciatic	Intraoperative neurological injury - NERVES: Sciatic	90030830
SURGERY/INTRA-OPERATIVE INJURY	Intra-operative injury	NERVES: Thoracodorsal	Intraoperative neurological injury - NERVES: Thoracodorsal	90030832
SURGERY/INTRA-OPERATIVE INJURY	Intra-operative injury	Nails	Intraoperative skin injury - Nails	90030834
SURGERY/INTRA-OPERATIVE INJURY	Intra-operative injury	Nasal cavity	Intraoperative respiratory injury - Nasal cavity	90030776
SURGERY/INTRA-OPERATIVE INJURY	Intra-operative injury	Nasopharynx	Intraoperative respiratory injury - Nasopharynx	90030836
SURGERY/INTRA-OPERATIVE INJURY	Intra-operative injury	Neck NOS	Intraoperative head and neck injury - Neck NOS	90030840
SURGERY/INTRA-OPERATIVE INJURY	Intra-operative injury	Nose	Intraoperative respiratory injury - Nose	90030838
SURGERY/INTRA-OPERATIVE INJURY	Intra-operative injury	Oral	Intraoperative gastrointestinal injury - Oral	90030844
SURGERY/INTRA-OPERATIVE INJURY	Intra-operative injury	Oral cavity NOS	Intraoperative gastrointestinal injury - Oral cavity NOS	90030846
SURGERY/INTRA-OPERATIVE INJURY	Intra-operative injury	Outer ear NOS	Intraoperative ear injury - Outer ear NOS	90030848
SURGERY/INTRA-OPERATIVE INJURY	Intra-operative injury	Outer ear-Pinna	Intraoperative ear injury - Outer ear-Pinna	90030850
SURGERY/INTRA-OPERATIVE INJURY	Intra-operative injury	Ovary	Intraoperative reproductive tract injury - Ovary	90030852
SURGERY/INTRA-OPERATIVE INJURY	Intra-operative injury	Pancreas	Intraoperative gastrointestinal injury -Pancreas	90030854
SURGERY/INTRA-OPERATIVE INJURY	Intra-operative injury	Pancreatic duct	Intraoperative gastrointestinal injury - Pancreatic duct	90030856
SURGERY/INTRA-OPERATIVE INJURY	Intra-operative injury	Parathyroid	Intraoperative endocrine injury - Parathyroid	90030858

SURGERY/INTRA-OPERATIVE INJURY	Intra-operative injury	Parotid gland	Intraoperative gastrointestinal injury - Parotid gland	90030860
SURGERY/INTRA-OPERATIVE INJURY	Intra-operative injury	Pelvis NOS	Intraoperative reproductive tract injury	10065840
SURGERY/INTRA-OPERATIVE INJURY	Intra-operative injury	Penis	Intraoperative reproductive tract injury - Penis	90030864
SURGERY/INTRA-OPERATIVE INJURY	Intra-operative injury	Peritoneal cavity	Intraoperative gastrointestinal injury - Peritoneal cavity	90030866
SURGERY/INTRA-OPERATIVE INJURY	Intra-operative injury	Pharynx	Intraoperative respiratory injury - Pharynx	90030842
SURGERY/INTRA-OPERATIVE INJURY	Intra-operative injury	Pituitary	Intraoperative endocrine injury - Pituitary	90030870
SURGERY/INTRA-OPERATIVE INJURY	Intra-operative injury	Pleura	Intraoperative respiratory injury - Pleura	90030868
SURGERY/INTRA-OPERATIVE INJURY	Intra-operative injury	Prostate	Intraoperative reproductive tract injury - Prostate	90030874
SURGERY/INTRA-OPERATIVE INJURY	Intra-operative injury	Rectum	Intraoperative gastrointestinal injury - Rectum	90030876
SURGERY/INTRA-OPERATIVE INJURY	Intra-operative injury	Retina	Intraoperative ocular injury - Retina	90030878
SURGERY/INTRA-OPERATIVE INJURY	Intra-operative injury	Salivary duct	Intraoperative gastrointestinal injury - Salivary duct	90030880
SURGERY/INTRA-OPERATIVE INJURY	Intra-operative injury	Salivary gland	Intraoperative gastrointestinal injury - Salivary gland	90030882
SURGERY/INTRA-OPERATIVE INJURY	Intra-operative injury	Scrotum	Intraoperative reproductive tract injury - Scrotum	90030884
SURGERY/INTRA-OPERATIVE INJURY	Intra-operative injury	Sinus	Intraoperative respiratory injury - Sinus	90030872
SURGERY/INTRA-OPERATIVE INJURY	Intra-operative injury	Skin	Intraoperative skin injury	10065846
SURGERY/INTRA-OPERATIVE INJURY	Intra-operative injury	Small bowel NOS	Intraoperative gastrointestinal injury - Small bowel NOS	90030890
SURGERY/INTRA-OPERATIVE INJURY	Intra-operative injury	Soft tissue NOS	Intraoperative musculoskeletal injury - Soft tissue NOS	90030892
SURGERY/INTRA-OPERATIVE INJURY	Intra-operative injury	Spinal cord	Intraoperative neurological injury - Spinal cord	90030894
SURGERY/INTRA-OPERATIVE INJURY	Intra-operative injury	Spleen	Intraoperative splenic injury	10065847
SURGERY/INTRA-OPERATIVE INJURY	Intra-operative injury	Stoma (GI)	Intraoperative gastrointestinal injury - Stoma (GI)	90030898
SURGERY/INTRA-OPERATIVE INJURY	Intra-operative injury	Stomach	Intraoperative gastrointestinal injury - Stomach	90030900

SURGERY/INTRA-OPERATIVE INJURY	Intra-operative injury	Teeth	Intraoperative gastrointestinal injury - Teeth	90030902
SURGERY/INTRA-OPERATIVE INJURY	Intra-operative injury	Tendon	Intraoperative musculoskeletal injury - Tendon	90030904
SURGERY/INTRA-OPERATIVE INJURY	Intra-operative injury	Testis	Intraoperative reproductive tract injury - Testis	90030906
SURGERY/INTRA-OPERATIVE INJURY	Intra-operative injury	Thoracic duct	Intraoperative respiratory injury - Thoracic duct	90030886
SURGERY/INTRA-OPERATIVE INJURY	Intra-operative injury	Thyroid	Intraoperative endocrine injury - Thyroid	90030910
SURGERY/INTRA-OPERATIVE INJURY	Intra-operative injury	Tongue	Intraoperative gastrointestinal injury - Tongue	90030912
SURGERY/INTRA-OPERATIVE INJURY	Intra-operative injury	Trachea	Intraoperative respiratory injury - Trachea	90030908
SURGERY/INTRA-OPERATIVE INJURY	Intra-operative injury	Upper aerodigestive NOS	Intraoperative respiratory injury - Upper aerodigestive NOS	90030914
SURGERY/INTRA-OPERATIVE INJURY	Intra-operative injury	Upper airway NOS	Intraoperative respiratory injury	10065832
SURGERY/INTRA-OPERATIVE INJURY	Intra-operative injury	Ureter	Intraoperative urinary injury - Ureter	90030920
SURGERY/INTRA-OPERATIVE INJURY	Intra-operative injury	Urethra	Intraoperative urinary injury - Urethra	90030922
SURGERY/INTRA-OPERATIVE INJURY	Intra-operative injury	Urinary conduit	Intraoperative urinary injury - Urinary conduit	90030924
SURGERY/INTRA-OPERATIVE INJURY	Intra-operative injury	Urinary tract NOS	Intraoperative urinary injury	10065828
SURGERY/INTRA-OPERATIVE INJURY	Intra-operative injury	Uterus	Intraoperative reproductive tract injury - Uterus	90030928
SURGERY/INTRA-OPERATIVE INJURY	Intra-operative injury	Vagina	Intraoperative reproductive tract injury - Vagina	90030930
SURGERY/INTRA-OPERATIVE INJURY	Intra-operative injury	Vein NOS	Intraoperative venous injury	10065848
SURGERY/INTRA-OPERATIVE INJURY	Intra-operative injury	Vein-extremity (lower)	Intraoperative venous injury - Vein-extremity (lower)	90030932
SURGERY/INTRA-OPERATIVE INJURY	Intra-operative injury	Vein-extremity (upper)	Intraoperative venous injury - Vein-extremity (upper)	90030934
SURGERY/INTRA-OPERATIVE INJURY	Intra-operative injury	Vein-hepatic	Intraoperative venous injury - Vein-hepatic	90030936
SURGERY/INTRA-OPERATIVE INJURY	Intra-operative injury	Vein-inferior vena cava	Intraoperative venous injury - Vein-inferior vena cava	90030938
SURGERY/INTRA-OPERATIVE INJURY	Intra-operative injury	Vein-jugular	Intraoperative venous injury - Vein-jugular	90030940

SURGERY/INTRA-OPERATIVE INJURY	Intra-operative injury	Vein-major visceral vein	Intraoperative venous injury - Vein-major visceral vein	90030942
SURGERY/INTRA-OPERATIVE INJURY	Intra-operative injury	Vein-portal vein	Intraoperative venous injury - Vein-portal vein	90030944
SURGERY/INTRA-OPERATIVE INJURY	Intra-operative injury	Vein-pulmonary	Intraoperative venous injury - Vein-pulmonary	90030946
SURGERY/INTRA-OPERATIVE INJURY	Intra-operative injury	Vein-superior vena cava	Intraoperative venous injury - Vein-superior vena cava	90030948
SURGERY/INTRA-OPERATIVE INJURY	Intra-operative injury	Vulva	Intraoperative reproductive tract injury - Vulva	90030950
SYNDROMES	Retinoic acid syndrome		Retinoic acid syndrome	10038921
SYNDROMES	Alcohol intolerance syndrome (antabuse-like syndrome)		Alcohol intolerance	10001598
SYNDROMES	Cytokine release syndrome/acute infusion reaction		Cytokine release syndrome	10052015
SYNDROMES	Flu-like syndrome		Flu-like symptoms	10016797
SYNDROMES	Syndromes - Other (Specify, __)		Ill-defined disorder	10061520
SYNDROMES	Tumor flare		Tumor flare	10045150
SYNDROMES	Tumor lysis syndrome		Tumor lysis syndrome	10045152
VASCULAR	Acute vascular leak syndrome		Capillary leak syndrome	10007196
VASCULAR	Peripheral arterial ischemia		Peripheral ischemia	10034578
VASCULAR	Phlebitis (including superficial thrombosis)		Phlebitis superficial	10034902
VASCULAR	Portal vein flow		Portal hypertension	10036200
VASCULAR	Thrombosis/embolism (vascular access-related)		Vascular access complication	10062169
VASCULAR	Thrombosis/thrombus/embolism		Thrombosis	10043607
VASCULAR	Vascular - Other (Specify, __)		Vascular disorder	10047059
VASCULAR	Vessel injury-artery	Aorta	Aortic injury	10002899
VASCULAR	Vessel injury-artery	Carotid	Injury to carotid artery	10022161
VASCULAR	Vessel injury-artery	Extremity-lower	Arterial injury - Extremity-lower	90030960
VASCULAR	Vessel injury-artery	Extremity-upper	Arterial injury - Extremity-upper	90030962
VASCULAR	Vessel injury-artery	Other NOS	Arterial injury	10003162
VASCULAR	Vessel injury-artery	Visceral	Arterial injury - Visceral	90030966
VASCULAR	Vessel injury-vein	Extremity-lower	Venous injury - Extremity-lower	90030968
VASCULAR	Vessel injury-vein	Extremity-upper	Venous injury - Extremity-upper	90030970
VASCULAR	Vessel injury-vein	IVC	Injury to inferior vena cava	10022213
VASCULAR	Vessel injury-vein	Jugular	Injury to jugular vein	10065849
VASCULAR	Vessel injury-vein	Other NOS	Venous injury	10047228
VASCULAR	Vessel injury-vein	SVC	Injury to superior vena cava	10022356

VASCULAR	Vessel injury-vein	Viscera	Venous injury - Viscera	90030980
VASCULAR	Visceral arterial ischemia (non-myocardial)		Visceral arterial ischemia	10054692

Appendix 6

CTCAE Adverse Events Category	Mapped MHRA MedDRA Term for CTCAE term	ADROIT Class as serious
ALLERGY/IMMUNOLOGY		
	Hypersensitivity	No
	Allergic rhinitis	No
	Immune system disorder	Yes
	Autoimmune disorder	Yes
	Serum sickness	Yes
	Vasculitis	Yes
AUDITORY/EAR		
	Ear disorder	No
	Hearing test abnormal	Yes
	Hearing loss	Yes
	External ear inflammation	No
	Middle ear inflammation	No
	Tinnitus	No
BLOOD/BONE MARROW		
	Blood disorder	Yes
	Bone marrow hypocellular	Yes
	CD4 lymphocytes decreased	Yes
	Haptoglobin decreased	Yes
	Hemoglobin decreased	Yes
	Hemolysis	Yes
	Iron increased	No
	Leukopenia	Yes
	Lymphopenia	Yes
	Myelodysplasia	Yes
	Neutrophil count decreased	Yes

	Platelet count decreased	Yes
	Spleen disorder	No
CARDIAC ARRHYTHMIA		
	Arrhythmia	Yes
	Atrioventricular block first degree	Yes
	Mobitz type I	Yes
	Mobitz (type) II atrioventricular block	Yes
	Atrioventricular block complete	Yes
	Asystole	Yes
	Conduction disorder	Yes
	Sick sinus syndrome	Yes
	Stokes-Adams syndrome	Yes
	Wolff-Parkinson-White syndrome	Yes
	Palpitations	No
	Electrocardiogram QTc interval prolonged	Yes
	Atrial fibrillation	Yes
	Atrial flutter	Yes
	Atrial tachycardia	Yes
	Nodal arrhythmia	Yes
	Sinus arrhythmia	Yes
	Sinus bradycardia	Yes
	Sinus tachycardia	Yes
	Arrhythmia supraventricular	Yes
	Supraventricular extrasystoles	Yes
	Supraventricular tachycardia	Yes
	Syncope vasovagal	Yes
	Ventricular bigeminy	Yes
	Rhythm idioventricular	Yes
	Premature ventricular contractions	Yes
	Torsade de pointes	Yes

	Ventricular trigeminy	Yes
	Ventricular arrhythmia	Yes
	Ventricular fibrillation	Yes
	Ventricular flutter	Yes
	Ventricular tachycardia	Yes
CARDIAC GENERAL		
	Cardiac disorder	Yes
	Myocardial ischemia	Yes
	Cardiac troponin I increased	Yes
	Cardiac troponin T increased	Yes
	Cardiopulmonary arrest	Yes
	Hypertension	Yes
	Hypotension	Yes
	Diastolic dysfunction	Yes
	Left ventricular failure	Yes
	Myocarditis	Yes
	Pericardial effusion	Yes
	Pericarditis	Yes
	Pulmonary hypertension	Yes
	Restrictive cardiomyopathy	Yes
	Cor pulmonale	Yes
	Cardiac valve disease	Yes
COAGULATION		
	Coagulopathy	Yes
	Disseminated intravascular coagulation	Yes
	Fibrinogen decreased	No
	INR increased	Yes
	Activated partial thromboplastin time prolonged	Yes
	Thrombotic microangiopathy	Yes
CONSTITUTIONAL SYMPTOMS		

	General symptom	No
	Fatigue	No
	Fever	No
	Hypothermia	Yes
	Insomnia	No
	Obesity	No
	Body odor	No
	Chills	No
	Sweating	No
	Weight gain	No
	Weight loss	No
DEATH		
	Death	Yes
	Disease progression	Yes
	Multi-organ failure	Yes
	Sudden death	Yes
DERMATOLOGY/SKIN		
	Atrophy skin	No
	Fat atrophy	No
	Bruising	Yes
	Thermal burn	No
	Cheilitis	No
	Skin disorder	No
	Dry skin	No
	Flushing	No
	Alopecia	No
	Skin hyperpigmentation	No
	Skin hypopigmentation	No
	Skin induration	No
	Injection site reaction	No

	Nail disorder	No
	Photosensitivity	Yes
	Pruritus	No
	Rash desquamating	No
	Acne	No
	Radiation recall reaction (dermatologic)	No
	Dermatitis radiation	No
	Erythema multiforme	Yes
	Hand-and-foot syndrome	Yes
	Decubitus ulcer	No
	Skin striae	No
	Telangiectasia	No
	Skin ulceration	No
	Urticaria	No
	Wound dehiscence	No
ENDOCRINE		
	Adrenal insufficiency	Yes
	Cushingoid	Yes
	Endocrine disorder	No
	Feminization	Yes
	Hot flashes	No
	Masculinization	Yes
	Blood gonadotrophin abnormal	No
	Growth hormone abnormal	Yes
	Blood prolactin abnormal	No
	ACTH decreased	No
	ADH abnormal	No
	Glucose intolerance	Yes
	Hypoparathyroidism	Yes
	Hyperthyroidism	Yes

	Hypothyroidism	Yes
GASTROINTESTINAL		
	Anorexia	No
	Ascites	Yes
	Colitis	Yes
	Constipation	No
	Dehydration	No
	Dental prosthesis user	No
	Periodontal disease	No
	Tooth disorder	No
	Tooth development disorder	Yes
	Diarrhea	No
	Abdominal distension	No
	Dry mouth	No
	Dysphagia	Yes
	Enteritis	No
	Esophagitis	No
	Gastro-intestinal fistula	Yes
	Anal fistula	Yes
	Biliary fistula	Yes
	Colonic fistula	Yes
	Duodenal fistula	Yes
	Acquired tracheo-oesophageal fistula	Yes
	Gallbladder fistula	Yes
	Ileal fistula	Yes
	Jejunal fistula	Yes
	Oral cavity fistula	Yes
	Pancreatic fistula	Yes
	Fistula, Pharynx	Yes
	Rectal fistula	Yes

	Salivary gland fistula	Yes
	Fistula of small intestine	Yes
	Gastic fistula	Yes
	Flatulence	No
	Gastritis	No
	Gastrointestinal disorder	No
	Dyspepsia	No
	Hemorrhoids	No
	Ileus	Yes
	Fecal incontinence	Yes
	Biliary anastomotic leak	No
	Esophageal anastomotic leak	No
	Large intestinal anastomotic leak	No
	Anastomotic leak	No
	Pancreatic anastomotic leak	No
	Pharyngeal anastomotic leak	No
	Rectal anastomotic leak	No
	Small intestinal anastomotic leak	No
	Intestinal stoma leak	No
	Gastric anastomotic leak	No
	Malabsorption	Yes
	Anal exam abnormal	No
	Oesophagoscopy abnormal	No
	Endoscopy large bowel abnormal	No
	Laryngoscopy abnormal	No
	Ear, nose and throat examination abnormal	No
	Pharyngeal examination abnormal	No
	Proctoscopy abnormal	No
	Endoscopy small intestine abnormal	No
	Gastroscopy abnormal	No

	Tracheoscopy abnormal	No
	Anal mucositis	No
	Esophageal mucositis	No
	Large intestinal mucositis	No
	Laryngeal mucositis	No
	Mucositis oral	No
	Pharyngeal mucositis	No
	Rectal mucositis	No
	Small intestinal mucositis	No
	Gastric mucositis	No
	Tracheal mucositis	No
	Nausea	No
	Anal necrosis	Yes
	Intestinal necrosis	Yes
	Duodenal necrosis	Yes
	Esophageal necrosis	Yes
	Gallbladder necrosis	Yes
	Hepatic necrosis	Yes
	Ileal necrosis	Yes
	Jejunal necrosis	Yes
	Mouth necrosis	Yes
	Pancreatic necrosis	Yes
	Peritoneal necrosis	Yes
	Pharyngeal necrosis	Yes
	Rectal necrosis	Yes
	Small intestinal necrosis	Yes
	Gastrointestinal stoma necrosis	Yes
	Gastric necrosis	Yes
	Cecal obstruction	Yes
	Colonic obstruction	Yes

	Duodenal obstruction	Yes
	Esophageal obstruction	Yes
	Gallbladder obstruction	Yes
	Ileal obstruction	Yes
	Jejunal obstruction	Yes
	Rectal obstruction	Yes
	Small intestinal obstruction	Yes
	Intestinal stoma obstruction	Yes
	Obstruction gastric	Yes
	Appendicitis perforated	No
	Perforation bile duct	Yes
	Cecum perforation	Yes
	Colonic perforation	Yes
	Duodenal perforation	Yes
	Esophageal perforation	Yes
	Gallbladder perforation	Yes
	Ileal perforation	Yes
	Jejunal perforation	Yes
	Rectal perforation	Yes
	Small intestinal perforation	Yes
	Gastric perforation	Yes
	Proctitis	No
	Prolapse of intestinal stoma	No
	Salivary gland disorder	No
	Anal stenosis	Yes
	Bile duct stenosis	Yes
	Intestinal stenosis	Yes
	Colonic stenosis	Yes
	Duodenal stenosis	Yes
	Esophageal stenosis	Yes

	Ileal stenosis	Yes
	Jejunal stenosis	Yes
	Pancreatic duct stenosis	Yes
	Stricture/stenosis (including anastomotic), Pharynx	Yes
	Rectal stenosis	Yes
	Small intestinal stenosis	Yes
	Stenosis of gastrointestinal stoma	Yes
	Gastric stenosis	Yes
	Taste alteration	No
	Typhlitis	Yes
	Anal ulcer	Yes
	Cecal ulcer	Yes
	Colonic ulcer	Yes
	Duodenal ulcer	Yes
	Esophageal ulcer	Yes
	Ileal ulcer	Yes
	Jejunal ulcer	Yes
	Rectal ulcer	Yes
	Small intestine ulcer	Yes
	Stomal ulcer	Yes
	Gastric ulcer	Yes
	Vomiting	No
GROWTH AND DEVELOPMENT		
	Bone development abnormal	Yes
	Slipped femoral epiphysis	No
	Unequal limb length	Yes
	Kyphosis	No
	Developmental disturbance	Yes
	Developmental delay	Yes
	Delayed puberty	No

	Precocious puberty	Yes
	Short stature	Yes
HEMORRHAGE/BLEEDING		
	Hematoma	Yes
	Intracranial hemorrhage	Yes
	Intra-abdominal hemorrhage	Yes
	Anal hemorrhage	Yes
	Hemorrhage in bile duct	Yes
	Cecal hemorrhage	Yes
	Colonic hemorrhage	Yes
	Duodenal hemorrhage	Yes
	Esophageal hemorrhage	Yes
	Ileal hemorrhage	Yes
	Jejunal hemorrhage	Yes
	Hepatic hemorrhage	Yes
	Lower gastrointestinal hemorrhage	Yes
	Oral hemorrhage	Yes
	Pancreatic hemorrhage	Yes
	Peritoneal hemorrhage	Yes
	Rectal hemorrhage	Yes
	Intestinal stoma site bleeding	No
	Gastric hemorrhage	Yes
	Upper gastrointestinal hemorrhage	Yes
	Esophageal varices hemorrhage	Yes
	Hemorrhoidal hemorrhage	Yes
	Bladder hemorrhage	Yes
	Hematosalpinx	Yes
	Renal hemorrhage	Yes
	Ovarian hemorrhage	Yes
	Prostatic hemorrhage	Yes

	Retroperitoneal hemorrhage	Yes
	Spermatic cord hemorrhage	Yes
	Urostomy site bleeding	No
	Testicular hemorrhage	Yes
	Ureteric hemorrhage	Yes
	Urethral hemorrhage	Yes
	Hemorrhage urinary tract	Yes
	Uterine hemorrhage	Yes
	Vaginal hemorrhage	Yes
	Vas deferens hemorrhage	Yes
	Bronchopulmonary hemorrhage	Yes
	Bronchial hemorrhage	Yes
	Laryngeal hemorrhage	Yes
	Pulmonary hemorrhage	Yes
	Mediastinal hemorrhage	Yes
	Hemorrhage nasal	Yes
	Pharyngeal hemorrhage	Yes
	Pleural hemorrhage	Yes
	Respiratory tract hemorrhage	Yes
	Tracheostomy site bleeding	No
	Tracheal hemorrhage	Yes
	Hemorrhage	Yes
	Postoperative hemorrhage	Yes
	Petechiae	No
HEPATOBILIARY/ PANCREAS		
	Cholecystitis	Yes
	Hepatobiliary disease	Yes
	Hepatic failure	Yes
	Pancreatic enzymes decreased	No
	Pancreatitis	Yes

INFECTION		
	Colitis, infectious (e.g., Clostridium difficile)	Yes
	Febrile neutropenia	Yes
	Abdominal infection	Yes
	Anal infection	Yes
	Appendicitis	No
	Arteritis infective	Yes
	Biliary tract infection	Yes
	Bladder infection	No
	Sepsis	Yes
	Bone infection	No
	Encephalitis infection	Yes
	Encephalomyelitis infection	Yes
	Bronchitis	Yes
	Catheter related infection	No
	Cecal infection	No
	Cervicitis	No
	Infectious colitis	Yes
	Conjunctivitis infective	Yes
	Corneal infection	Yes
	Tooth infection	No
	Duodenal infection	No
	Esophageal infection	No
	Otitis externa	No
	Eye infection	Yes
	Salpingitis infection	No
	Device related infection	No
	Gallbladder infection	No
	Endocarditis infective	Yes
	Ileal infection	No

	Jejunal infection	No
	Joint infection	No
	Kidney infection	Yes
	Laryngitis	No
	Eye infection intraocular	Yes
	Lip infection	No
	Hepatic infection	Yes
	Pneumonia	Yes
	Lymph gland infection	No
	Mediastinal infection	Yes
	Infectious meningitis	Yes
	Otitis media	No
	Mucosal infection	No
	Infective myositis	Yes
	Infection	No
	Cranial nerve infection	Yes
	Peripheral nerve infection	Yes
	Rhinitis infective	No
	Gingival infection	No
	Pancreas infection	Yes
	Paranasal sinus infection	No
	Pelvic infection	No
	Penile infection	No
	Stoma site infection	No
	Peritoneal infection	Yes
	Pharyngitis	No
	Pleural infection	Yes
	Prostate infection	No
	Anorectal infection	No
	Salivary gland infection	No

	Scrotal infection	No
	Sinusitis	No
	Skin infection	No
	Small intestine infection	No
	Soft tissue infection	No
	Spinal cord infection	Yes
	Splenic infection	Yes
	Gastric infection	No
	Tracheitis	No
	Nail infection	No
	Upper aerodigestive tract infection	No
	Upper respiratory infection	No
	Ureteritis	No
	Urethral infection	No
	Urinary tract infection	No
	Uterine infection	No
	Vaginal infection	No
	Phlebitis infective	No
	Vulval infection	No
	Wound infection	No
	Vulvitis	No
	Opportunistic infection	No
	Viral hepatitis	Yes
LYMPHATICS		
	Lymph leakage	No
	Lymphedema	No
	Localized edema	No
	Edema limbs	No
	Localized edema	No
	Visceral edema	Yes

	Lymphatic disorder	No
	Fibrosis	No
	Lymphocele	No
	Lymphangitic streak	No
METABOLIC/LABORATORY		
	Alanine aminotransferase increased	No
	Aspartate aminotransferase increased	No
	Acidosis	Yes
	Hypoalbuminemia	Yes
	Alkaline phosphatase increased	No
	Alkalosis	Yes
	Amylase increased	No
	Blood bicarbonate decreased	No
	Hyperbilirubinemia	No
	Creatine phosphokinase increased	Yes
	Hypercalcemia	Yes
	Hypocalcemia	Yes
	Hypercholesterolemia	No
	Creatinine increased	No
	Gamma-glutamyltransferase increased	No
	Glomerular filtration rate decreased	No
	Hyperglycemia	Yes
	Hypoglycemia	Yes
	Hemoglobinuria	Yes
	Lipase increased	No
	Hypermagnesemia	Yes
	Hypomagnesemia	Yes
	Laboratory test abnormal	No
	Hypophosphatemia	No
	Hyperkalemia	Yes

	Hypokalemia	Yes
	Proteinuria	Yes
	Hypernatremia	Yes
	Hyponatremia	Yes
	Hypertriglyceridemia	No
	Hyperuricemia	No
MUSCULOSKELETAL/ SOFT TISSUE		
	Arthritis	Yes
	Scoliosis	No
	Joint range of motion decreased cervical spine	Yes
	Exostosis	No
	Gait abnormal	Yes
	Upper extremity dysfunction	No
	Superficial soft tissue fibrosis	No
	Fibrosis deep connective tissue	No
	Fracture	No
	Joint effusion	Yes
	Joint disorder	No
	Device complication	No
	Joint range of motion decreased lumbar spine	Yes
	Extraocular muscle disorder	Yes
	Muscle weakness lower limb	Yes
	Muscle weakness upper limb	Yes
	Facial muscle weakness	Yes
	Muscle weakness left-sided	Yes
	Eye muscle weakness	Yes
	Pelvic floor muscle weakness	No
	Muscle weakness right-sided	Yes
	Muscle weakness trunk	Yes
	Muscle weakness	Yes

	Musculoskeletal deformity	No
	Musculoskeletal disorder	No
	Myositis	Yes
	Osteonecrosis	Yes
	Osteoporosis	Yes
	Seroma	Yes
	Abdominal soft tissue necrosis	No
	Soft tissue necrosis lower limb	No
	Soft tissue necrosis upper limb	No
	Head soft tissue necrosis	No
	Neck soft tissue necrosis	No
	Pelvic soft tissue necrosis	No
	Chest wall necrosis	No
	Trismus	Yes
NEUROLOGY		
	Apnea	Yes
	Arachnoiditis	Yes
	Ataxia	Yes
	Radiculitis brachial	Yes
	Ischemia cerebrovascular	Yes
	Central nervous system necrosis	Yes
	Cognitive disturbance	Yes
	Confusion	Yes
	Dizziness	No
	Encephalopathy	Yes
	Extrapyramidal disorder	Yes
	Hydrocephalus	Yes
	Irritability	No
	Recurrent laryngeal nerve palsy	Yes
	Cerebrospinal fluid leakage	Yes

	Leukoencephalopathy	Yes
	Memory impairment	Yes
	Mental status changes	Yes
	Agitation	No
	Anxiety	No
	Depression	Yes
	Euphoria	Yes
	Myelitis	Yes
	Neurological disorder NOS	No
	Olfactory nerve disorder	No
	Optic nerve disorder	Yes
	Oculomotor nerve disorder	Yes
	IVth nerve disorder	No
	Glossopharyngeal nerve disorder	No
	Trigeminal nerve disorder	No
	Abducens nerve disorder	Yes
	Facial nerve disorder	Yes
	Acoustic nerve disorder NOS	Yes
	Vagus nerve disorder	Yes
	Accessory nerve disorder	Yes
	Hypoglossal nerve disorder	Yes
	Peripheral motor neuropathy	Yes
	Peripheral sensory neuropathy	Yes
	Personality change	No
	Phrenic nerve paralysis	Yes
	Psychosis	Yes
	Pyramidal tract syndrome	Yes
	Seizure	Yes
	Depressed level of consciousness	Yes
	Speech disorder	Yes

	Syncope	Yes
	Tremor	No
OCULAR/VISUAL		
	Cataract	Yes
	Dry eye syndrome	Yes
	Eyelid function disorder	No
	Glaucoma	Yes
	Keratitis	Yes
	Night blindness	Yes
	Nystagmus	No
	Conjunctival disorder	No
	Eye disorder	Yes
	Diplopia	No
	Optic nerve edema	Yes
	Proptosis	No
	Retinal detachment	Yes
	Retinopathy	Yes
	Scleral disorder	No
	Uveitis	Yes
	Vision blurred	No
	Flashing vision	No
	Photophobia	No
	Vitreous hemorrhage	Yes
	Watering eyes	No
PAIN		
	Abdominal pain	No
	Anal pain	No
	Back pain	No
	Bladder pain	No
	Bone pain	No

	Breast pain	No
	Buttock pain	No
	Cardiac pain	No
	Chest wall pain	No
	Chest pain	No
	Toothache	No
	Esophageal pain	Yes
	External ear pain	No
	Pain in extremity	No
	Eye pain	No
	Facial pain	No
	Gallbladder pain	No
	Headache	No
	Gastrointestinal pain	Yes
	Joint pain	Yes
	Kidney pain	Yes
	Laryngeal pain	No
	Lip pain	No
	Hepatic pain	No
	Lymph node pain	No
	Ear pain	No
	Myalgia	Yes
	Neck pain	No
	Neuralgia	No
	Oral pain	No
	Gingival pain	No
	Ovulation pain	No
	Pain	No
	Pelvic pain	No
	Penile pain	No

	Pericardial pain	No
	Perineal pain	No
	Peritoneal pain	No
	Phantom pain	No
	Pleuritic pain	No
	Prostatic pain	No
	Rectal pain	No
	Scalp pain	No
	Scrotal pain	No
	Sinus pain	No
	Pain of skin	No
	Stomach pain	No
	Testicular pain	No
	Pharyngolaryngeal pain	No
	Tumor pain	No
	Urethral pain	No
	Uterine pain	No
	Vaginal pain	No
	Pain	No
PULMONARY/ UPPER RESPIRATORY		
	Adult respiratory distress syndrome	Yes
	Aspiration	Yes
	Atelectasis	No
	Bronchospasm	Yes
	Carbon monoxide diffusing capacity decreased	Yes
	Chylothorax	Yes
	Cough	No
	Dyspnea	No
	Laryngeal edema	Yes
	Forced expiratory volume decreased	No

	Bronchial fistula	Yes
	Laryngeal fistula	Yes
	Pulmonary fistula	Yes
	Oral cavity fistula	Yes
	Pharyngeal fistula	Yes
	Pleural fistula	Yes
	Tracheal fistula	Yes
	Hiccough	No
	Hypoxia	Yes
	Nasal congestion	No
	Bronchial obstruction	No
	Laryngeal obstruction	Yes
	Pharyngeal stenosis	Yes
	Tracheal obstruction	Yes
	Pleural effusion	Yes
	Pneumonitis	Yes
	Pneumothorax	Yes
	Postoperative thoracic procedure complication	No
	Prolonged intubation after pulmonary resection (>24 hrs after	No
	Pulmonary fibrosis	Yes
	Respiratory disorder	No
	Vital capacity decreased	No
	Voice alteration	No
RENAL/GENITOURINARY		
	Bladder spasm	Yes
	Cystitis	No
	Vesical fistula	Yes
	Female genital tract fistula	Yes
	Renal pelvis fistula	Yes
	Ureteric fistula	Yes

	Urethral fistula	Yes
	Uterine fistula	Yes
	Vaginal fistula	Yes
	Urinary incontinence	Yes
	Bladder anastomotic leak	No
	Fallopian tube anastomotic leak	No
	Kidney anastomotic leak	No
	Spermatic cord anastomotic leak	No
	Urostomy leak	No
	Ureteric anastomotic leak	No
	Urethral anastomotic leak	No
	Uterine anastomotic leak	No
	Vaginal anastomotic leak	No
	Vas deferens anastomotic leak	No
	Bladder obstruction	Yes
	Fallopian tube obstruction	Yes
	Prostatic obstruction	No
	Spermatic cord obstruction	Yes
	Urostomy obstruction	Yes
	Testicular obstruction	Yes
	Ureteric obstruction	Yes
	Urethral obstruction	No
	Uterine obstruction	Yes
	Vaginal obstruction	Yes
	Vas deferens obstruction	Yes
	Bladder perforation	No
	Fallopian tube perforation	Yes
	Kidney perforation	Yes
	Ovarian rupture	Yes
	Prostatic perforation	Yes

	Spermatic cord perforation	Yes
	Urostomy perforation	Yes
	Testicular perforation	Yes
	Ureteric perforation	Yes
	Urethral perforation	Yes
	Uterine perforation	Yes
	Vaginal perforation	Yes
	Vas deferens perforation	Yes
	Prolapse of urostomy	No
	Renal failure	Yes
	Urogenital disorder	No
	Bladder stenosis	Yes
	Fallopian tube stenosis	Yes
	Prostatic disorder	No
	Spermatic cord stenosis	Yes
	Urostomy stenosis	Yes
	Testicular stricture/stenosis	Yes
	Ureteric stenosis	Yes
	Urethral stricture	No
	Uterine stenosis	Yes
	Vaginal stricture	Yes
	Vas deferens stenosis	Yes
	Renal tubular disorder	Yes
	Urinary frequency	No
	Urinary retention	No
	Urine discoloration	No
SECONDARY MALIGNANCY		
	Treatment related secondary malignancy	Yes
SEXUAL/REPRODUCTIVE FUNCTION		
	Lactation disorder	No

	Nipple deformity	No
	Breast hypoplasia	No
	Ejaculation disorder	No
	Erectile dysfunction	No
	Gynecomastia	No
	Infertility	Yes
	Irregular menstruation	No
	Libido decreased	No
	Orgasm abnormal	No
	Reproductive tract disorder	No
	Vaginal discharge	No
	Vaginal dryness	No
	Vaginal mucositis	No
	Vaginal atresia	Yes
	Vaginal inflammation	No
SYNDROMES		
	Retinoic acid syndrome	Yes
	Alcohol intolerance	Yes
	Cytokine release syndrome	Yes
	Flu-like symptoms	No
	Ill-defined disorder	No
	Tumor flare	Yes
	Tumor lysis syndrome	Yes
VASCULAR		
	Capillary leak syndrome	Yes
	Peripheral ischemia	No
	Phlebitis superficial	Yes
	Portal hypertension	Yes
	Vascular access complication	No
	Thrombosis	Yes

	Vascular disorder	Yes
	Aortic injury	Yes
	Injury to carotid artery	Yes
	Arterial injury - Extremity-lower	Yes
	Arterial injury - Extremity-upper	Yes
	Arterial injury	Yes
	Arterial injury - Visceral	Yes
	Venous injury - Extremity-lower	Yes
	Venous injury - Extremity-upper	Yes
	Injury to inferior vena cava	Yes
	Injury to jugular vein	Yes
	Venous injury	Yes
	Injury to superior vena cava	Yes
	Venous injury - Viscera	Yes
	Visceral arterial ischemia	Yes

Appendix 7

Year…… Audit Enrolment number…….

Oncology Adverse Drug Reactions
Objective 1 Data Collection Form

WGH number				
Patient initials				
Patient age				
Tumour grade	**T M**			
ER Status	Positive Negative			
Chemo regimen	CMF EPI/CMF BONADONNA Paclitaxol Paclitaxel and trastuszumab Docetaxol Trastuzumab Other……..			
Dose				
Number of cycles				
Experienced serious ADR	Yes No			
Admitted to hospital	Yes No			
Admission prolonged	Yes No			
Number of days admitted				
Patient outcome	Recovered – dose reduction Recovered – no dose reduction Patient died Unknown Other:			
Concurrent medicines				
Yellow Card submitted	Yes No If yes, reference number:			
Reporter group submitted by	Hospital pharmacist Hospital doctor Hospital Nurse Other…….			
Comments				

Toxicity Scores

Date	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__
Nausea							
Vomiting							
Diarrhoea							
Stomatitis							
Skin							
Alopecia							
Neuro-hearing							
Neuro-sensory							
Haematological White blood cells Platelets Haemoglobin Granulocyte Lymphocyte							
Other							

Appendix 8

Chemotherapy Prescription Chart: Reference Ranges

NCI Common Toxicity Criteria

Toxicity	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Nausea	none	able to eat reasonable intake	intake significantly decreased but can eat	no significant intake	_____
Vomiting	none	once in 24 hours	2-5 times in 24 hours	6-10 times in 24 hours	>10 times in 24 hours requiring IV support
Diarrhoea	none	increase of 2-3 stools/day over pre-Rx	increase of 4-6 stools/day or nocturnal stools or moderate cramping	increase of 7-9 stools/day or incontinence or severe cramping	increase of >10 stools/day or grossly bloody diarrhoea or need for parenteral support
Stomatitis	none	painless ulcers, erythema or mild soreness	painful erythema, oedema or ulcers, but can eat	painful erythema, oedema or ulcers, but cannot eat	requires parenteral or enteral support
Skin	none or no change	scattered macular or papular eruption or erythema that is asymptomatic	scattered macular or papular eruption or erythema with pruritis or other associate symptoms	Generalised symptomatic macular, papular or vesicular eruption	exfoliative dermatitis or ulcerating dermatatis
Alopecia	no loss	mild hair loss	Pronounced or total hair loss	_____	_____
Neuro-hearing	none or no change	asymptomatic hearing loss on audiometry only	tinnitus	Hearing loss interfering with function	deafness not correctable
Neuro-sensory	none or no change	mild paresthesia, loss of deep tendon reflexes	Mild or moderate objective sensory loss, moderate paresthesia	Severe objective sensory loss or paresthesia that interfere with function	_____
Haematological					
White blood cells	>4.0	3.0-3.9	2.0-2.9	1.0-1.9	<1
Platelets	normal limits	75-normal	50-74	25-49	<25
Haemoglobin	normal limits	10.0-normal	8.0-10.0	6.5-7.9	<6.5
Granulocyte	>2.0	1.5-1.9	1.0-1.4	0.5-0.9	<0.5
Lymphocyte	>2.0	1.5-1.9	1.0-1.4	0.5-0.9	<0.5
Other	none	mild	moderate	severe	Life-threatening

Non CTC Graded Criteria Grade 1 = mild grade 2 = moderate grade 3 = severe Grade 4 = life threatening

WHO PERFORMANCE STATUS

0	Able to carry out all normal activity without restriction
1	Restricted in physically strenuous activity but ambulatory and able to do light work
2	Ambulatory and capable of all self-care but unable to carry out any work Up and about more than 50% of waking hours
2	Capable of limited self-care, confined to bed or chair more than 50% of waking hours
3	Completely disabled. Cannot carry on self-care. Totally confined to bed or chair.

KEY TO ABBREVIATIONS

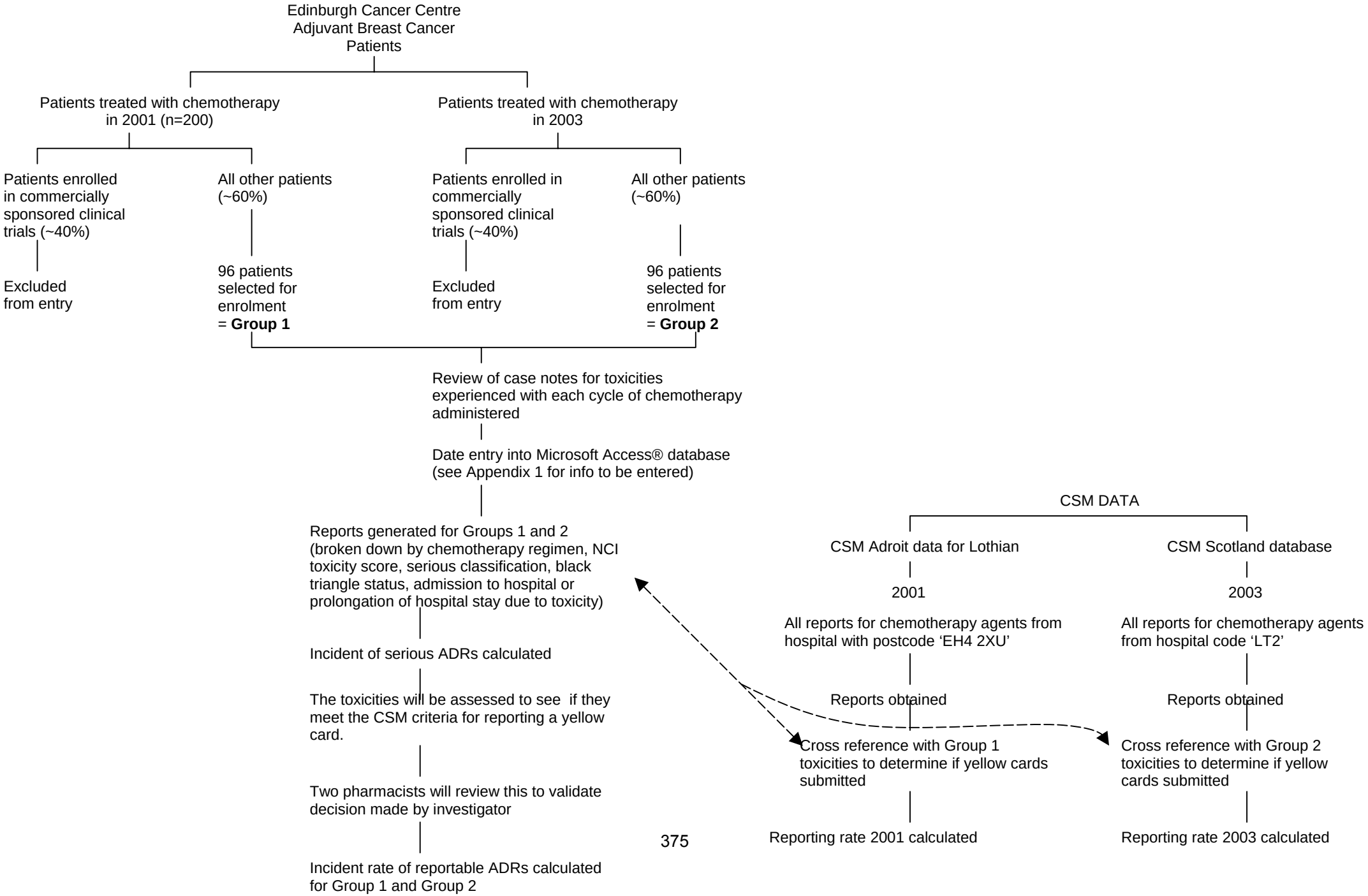
LFTs	liver Function tests	Bili	bilirubin
m^2	square meters	creat	creatinine
NTE	not to exceed	GFR	renal clearance
SA	surface area in m^2	Hb	haemoglobin
WNL	within normal limits	neut	neutrophils
Wt	weight	plat	platelets
		wbc	white blood count

Toxicity Scores

Date	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__
Nausea							
Vomiting							
Diarrhoea							
Stomatitis							
Skin							
Alopecia							
Neuro-hearing							
Neuro-sensory							
Haematological White blood cells Platelets Haemoglobin Granulocyte Lymphocyte							
Other							

Appendix 9

Objective 1: To Quantify the potential for improvement in spontaneous ADR reporting before and after a pharmacist led ADR reporting initiative **Appendix 9**



Appendix 10

Cuthbert, Melinda

From: Dale Keir [Dale.Keir@lhb.scot.nhs.uk]
Sent: 09 November 2004 15:46
To: Cuthbert, Melinda
Subject: Re: FW: Is submission to ethics committee necessary for this?

Dear Miss Cuthbert,

I can confirm that I have consulted with the Chairman of the Lothian Research Ethics Committee 02 with regards to your query and he has confirmed that you **do not** require ethical approval for your proposal.

Yours sincerely,

Miss Dale Keir

>>> "Cuthbert, Melinda" <melinda.cuthbert@luht.scot.nhs.uk> 01/11/04 11:24:27 am >>>
Dear Sir or Madam

Could you please advise if a decison has been made on the following that I previously e-mailed about on the 14 October. I look forward to your response.

Many thanks
Melinda Cuthbert
Senior Pharmacist
Medicines Information/ CSM Scotland
Royal Infirmary of Edinburgh
0131 242 2919
0131 242 2925 (fax)
-----Original Message-----
From: Cuthbert, Melinda
Sent: 14 October 2004 13:36
To: 'lrec@lhb.scot.nhs.uk'
Subject: Is submission to ethics committee necessary for this?

Dear Sir or Madam

I am currently enrolled in a MPhil in oncology Adverse Reactions titled "Improving pharmacovigilance standards in oncology". I am finalising my protocol at present and there will be 4 seperate sections to the reasearch. For objective one I will be assessing the base-line incidence of serious adverse drug reactions experienced by adjuvant breast cancer patients. We had previously audited in 2002 the number of yellow card reports that were being submitted by pharmacists at the Edinburgh Cancer Centre but at the time we did not establish the actual incident rate of reportable ADRs so we were not able to determine the actual capture rate.

Therefore, to set a base line for my research my first objective was to determine the incident rate of serious adverse drug reactions in 2001 (before we introduced the training for pharmacists to report ADRs via yellow cards) and 2003 (the year after our audit), then compare this to the yellow cards that were submitted to the CSM. One of the supervisors for my project is Dr N Bateman and he thought that this part would come under audit and that ethics approval would not be required. For all 3 other objectives I know that ethics approval will be required and I will submit in due course. However, I am due to go on maternity leave in January and would like to complete the audit for objective 1 prior to that and having to seek ethics approval would certainly cut into this time left.

I am attaching a summary chart of the proposed audit for your review. If you could advise If I will require ethics approval before commencing I would be grateful.

Many thanks

Melinda Cuthbert

Senior Pharmacist
Medicines Information/ CSM Scotland
Royal Infirmary of Edinburgh
0131 242 2919
0131 242 2925 (fax)

****
The information contained in this message may be confidential or legally privileged and is intended for the addressee only, If you have received this message in error or there are any problems please notify the originator immediately. The unauthorised use, disclosure, copying or alteration of this message is strictly forbidden.
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Appendix 11

Questions for semi-structured interview

Date _____ Time _____
Professional affiliation: _____Pharmacist _____ Nurse _____Clinician
Number of years working in oncology:_____Years

Question	Yes	No	Other Notes (Comments,expand)
1. Are you familiar with the Yellow Card Scheme for spontaneous reporting of ADRs? How does it work? Points covered: ___ Submit paper copy or electronically ___Who can report ___Black triangle ___Serious ADRs ___ Areas of special interest			
2. What purpose do you think this scheme serves? Points covered: ___ Protect patients ___ identify ADRs not previously recognised ___monitor safety of a medicine throughout its lifetime			
3. Do you think it is beneficial to public safety?			
4. Have you ever reported a suspected ADR via the Yellow Card Scheme?			
Prompts: If yes, was it easy to do so? Any suggestions on how to improve? If no, any particular reason why?			
5. Have you ever reported oncology related ADR via the Yellow Card Scheme?			
Prompt: If yes, what types? If no, any reason why?			
6. What types of oncology ADRs would you report?			
Prompts: a. If reply positive ask which of the examples below they would report (if not given) b. If reply negative ask why they would not report oncology ADRs via the YC scheme. Give following examples to illicit their view on whether they would report any of the following?			
<u>Examples:</u> Patient admitted to hospital with neutropenic sepsis. Patient develops grade 4 stomatisis Patient develops grade 2 thrombocytopenia Patient presents with DVT & PE Anaphylasis post-chemo infusion			

7. Are oncology ADRs under reported in your opinion? Prompts: If reply is yes, why do you think so? If reply is no, why do you say that?			
8. Would more specific guidance from the MHRA on the types and grades of oncology adverse events (toxicities) to be reported be more beneficial to help you in recognising what types of oncology ADRs to report? Prompts: If reply positive, do you think you would report more oncology ADRs via the Yellow Card Scheme? If no, why do you think that?			
9. There is a separate reporting scheme for reporting HIV ADRs (i.e. Blue Card) to the MHRA. Do you think there would be any advantage of having a separate one for oncology ADRs? Prompts: If yes, what would be the advantages? What kind of information would be most useful for the scheme to collate? If no, why do you think that it would be of no added benefit?			
10. Have you reported NCI common toxicity grades to industry in sponsored trials or via EUDRACT? Prompts: What do you think is the purpose of this? What do you think are the benefits of doing so? Would a continuation of this out with a clinical trial be beneficial to clinicians and/or patient safety?			
11. Do you think electronic prescribing and capture of NCI toxicity grades in clinical practice would be beneficial? Prompts: a. Would a nationwide annonymised aggregate of this data be of benefit? b. Would you be happy to contribute your patients' data to such a database? c. Do you think it would be feasible to develop such a database in Scotland?			
12. Do you think patient ADR reporting in oncology would be of any value?			

Appendix 12

Yellow Card Centre Scotland
Centre for Adverse Reactions to Drugs (Scotland)

Royal Infirmary of Edinburgh
51 Little France Crescent
EDINBURGH
EH16 4SA

Telephone 0131 242 2919
Fax 0131 242 2925
E-mail:
melinda.cuthbert@luht.scot.nhs.uk
Your Ref:
Our Ref: h:/mphil/obj2/invite letter

NHS SCOTLAND

YellowCard
Helping to make medicines safer

Dear Colleague

Improving Standards of Pharmacovigilance Practice in Oncology

I am undertaking the above research as a component of my MPhil. The primary aim of this part of my research is to obtain an in-site into the attitudes and reasons for under-reporting of adverse drug reactions in oncology, and need for improvement. I hope to carry out the interviews with members of the oncology multidisciplinary team to help establish key concepts on knowledge, attitudes and current practice of adverse drug reaction reporting in oncology. The information from these interviews will be used to develop a questionnaire for circulation to healthcare professionals working within oncology across NHS Scotland.

I am, therefore, seeking your consent to participate as an interviewee. The interview will take no more than 30 minutes, and I would be happy to arrange a date, time and venue most suitable to you. If you agree to participate I would like to confirm that the information that you would provide would be treated in confidence, and would be anonymous (other than to your professional affiliation). If you participate I would appreciate if you would also agree to me taping the interview, as this would enable me to have an accurate record of your views and also help me when I analyse the results. The tape will be destroyed following analysis.

Please contact me by 23 March 2007 if you are not happy to participate. I can be contacted via e-mail (Melinda.Cuthbert@luht.scot.nhs.uk) or via telephone on 0131 242 2919. If I do not hear from you by then I will contact you to arrange a date, time and venue. I appreciate that you have many demands on your time and thank you in advance for your participation. I look forward to your reply.

Yours sincerely

Melinda Cuthbert
Senior Pharmacist

Appendix 13

Interview – Objective 2
Information to be given to Interviewee

Thank you for agreeing to participate in this interview.

Reason for undertaking the interviews: I am currently doing an MPhil (Topic: Improving standards of pharmacovigilance in Oncology). The purpose of these interviews is to obtain information on attitudes of healthcare professionals on reporting of ADRs in oncology. The information will be used to develop a questionnaire on oncology ADR reporting to be distributed Scotland wide to the multi-professional oncology group.

As explained in my letter I would like to tape record the interview as this will allow me to have an accurate record of your views and also help me when I go to analyse the results. Are you willing to permit me to do this? (If not I will record your answers directly onto the answer sheet).

Show respondent the form

The format of the interview will be:

I will read you 12 questions about various aspects of ADR reporting and specific questions applicable to oncology.

I would like you to consider each question and answer Yes, No or as appropriate. If you wish me to repeat the question please ask me to do so.

After you have answered each question I will give you an opportunity to explain or expand upon your answers and I may ask you questions to help me clearly understand the response you have made. Your additional comments are an extremely helpful part of the interview.

I would like to confirm that the information which you provide will be treated in confidence, and will be anonymous. (If agreed to taping let them know that the tapes will be destroyed after transcription).

There are no right or wrong answers to these questions and your opinion will be most helpful to me in my research.

The interview will last for no more than 30 minutes.

Appendix 14

Post Interview Comment Sheet
Objective 2
Improving Standards of Pharmacovigilance

	Stongly Agree	Agree	Undecided	Disagree	Strongly Disagree
The interview went well?	5	4	3	2	1
The interview finished within 30 minutes?	5	4	3	2	1
I felt at ease with the interviewer?	5	4	3	2	1
I felt I could express my opinions freely on questions posed?	5	4	3	2	1
The interviewer gave me adequate time to answer questions?	5	4	3	2	1
There were questions asked that I did not understand?	5	4	3	2	1
The interview took place in a room free from interruptions or distractions?	5	4	3	2	1
I enjoyed the interview?	5	4	3	2	1
I feel the interview was worthwhile?	5	4	3	2	1

Further Comments:

_____
_____
_____
_____
_____
_____

Appendix 15

Objective 2
One-to-one Interview
Interview 1

MC: Are you familiar with the Yellow Card Scheme for spontaneous reporting of ADRs? How does it work?

Nurse 1: I am aware that there is a scheme for reporting adverse drug reactions. Nurses who are treating patients should complete the details (of an ADR) and pass it to pharmacy, who send it away and then you get a reply back, I think. Does that sound right? I am getting mixed up with the yellow cards and green cards aren't I? Green cards are where you draw pictures of the extravasations

MC: Yes, Green cards are for extravasation.

Nurse 1: and the yellow cards you get in the back of the BNFs

***MC: Yellow cards are for adverse* drug reaction reporting yes. You are aware that nurses can report to the Yellow Card Scheme are you aware of anyone else that can report as well?**

Nurse 1: Nurses, doctors and pharmacists I presume. I presume there is some kind of mechanism for patients to report ADRs but I am not sure.

MC: Yes that is right. Recently they have been added but use a separate card to report. Do you know what types of reactions should be reported?

Nurse 1: Any type of ADR cause you are interested in whatever drugs are doing to the majority of patients, I would think. It is not really feasible to say only to report more serious ones because who gets to decide what is serious or not a serious one? Does that make sense?

MC: Yes.

Nurse1: So any type of reaction, I think, can be reported.

MC: Are you aware of any areas of special interest that we are also looking for reports on?

Nurse 1: Do you mean any specific drug or groups of drugs?

MC: Patients groups and drugs yes.

Nurse 1: I would imagine you would be interested in all the stuff you get from early phase trial drugs – so that's always reported. I would imagine there would be others but I can't actually tell you what they would be.

MC: That would actually go (reported) through a different mechanism…

Nurse 1: It goes through their Data collection system or something…

MC: …through the company or whoever sponsors the trials

Nurse 1: I can't remember anything else.

MC: That is fine

MC: What purpose do you think the Yellow Card Scheme serves?

Nurse 1: I think that it draws together lots of information from different places on drugs that are being used probably world wide. And you do see different reactions in different groups of patients. So different ethnic groups can have

different reactions to different groups of drugs; depending upon their background and so forth. So it is to get information on safety of using the drugs and … take that forward.

MC: Do you think it is beneficial to public safety?

Nurse 1: I think if it is used properly then inevitably it will be beneficial.

MC: When you say 'properly' what do you mean?

Nurse 1: It gets the attention that it deserves. If people take it seriously enough to report any kind of ADR, or anything that might be an ADR, but if people are a bit complacent about it then you will not get the details that you need from the report. So people need to be aware of the system and they need to know what they are looking for and take it back appropriately. If they don't do that then, at the end of the day, you don't get what you are looking for do you?

MC: Basically what we say is "If in doubt report". If you have any degree of suspicion then that would be enough to report.

MC: Have you ever reported a suspected ADR via the Yellow Card Scheme?

Nurse 1: Not in this hospital. Along time ago, probably.

MC: When you did (report) did you find it easy to do so?

Nurse 1: I don't remember really. I know I had to get a yellow card from the back of the BNF and fill in the details, but I don't know anything about it being difficult or having huge problems with it.

MC: Have you ever any reported oncology related ADR via the Yellow Card Scheme?

Nurse 1: No. I think the medics do more of the ADRs.

MC: Is that the main reason why you wouldn't report or…

Nurse 1: The other thing, if I am being totally honest, is I wonder if we get a bit complacent about ADRs in oncology. But you know, how many times a day do we see a taxol reaction?

MC: What type of reaction is that?

Nurse 1: A hypersensitivity reaction to taxol and I do not think that a yellow card gets done for everyone. In fact I can quite clearly say that we do not do a yellow card for every one of those. Whereas, I suppose, if you want the right data, then every reaction should be reported in the same way. We should follow the same (guidelines for reporting).

MC: Why do you think that all are not reported?

Nurse 1: I think it is because you see so many you think of it more as a recognised side effect rather than as an ADR. It probably is an ADR as much as it is a side effect though isn't it?

MC: Do you think that this is a common held belief?

Nurse 1: I think that it is a bit like "what is an ADR of Herception, whereas what is a documented recognised side effect". We always have that argument as well. Sometimes the doctor will pre-treat them/ pre-medicate them with an antihistamine with Herceptin and so on. Whereas I tend to think maybe they had a bit of shivers and not really and ADR… that was a side effect with Herceptin.

MC: So when you think if that you expect it, then you consider …

Nurse 1: The taxanes I suppose is different. That is an ADR, no two ways about it but if someone is a bit shivery or fluey at night with Herceptin then is that an ADR? Since know it is going to happen… or chances are since it is a known side effect. So it is a bit … you know

MC: I think that it makes a difference how it (ADR) occurs. If the patient gets anything happening after they receive the medication and you think it is possibly due to the medication then it is considered an ADR. The most commonly known side effects/ or ADRs are the ones that are listed in the SPC for the products. But you are correct if people think that if it is known then you do not need to report it. I think that is the common conception that is held.

MC: What types of oncology ADRs would you report? *Do you have any you can think of or I can give you some example.*

Nurse 1: I can think of some that should absolutely be reported every time that they happen but I am not 100% convinced that it happens.

MC: Which ones?

Nurse 1: Your hypersensitivities to taxols and herceptin; your oxalaplatins with laryngeal spasms. That should be yellow carded and reported each time.

MC: Is the laryngeal spasms secondary to a Grade 4 stomatitis or it is something with the nerves?

Nurse 1: I guess it is a combination of everything really… no, they all have a grade 4 mouth thing going on it is a separate issue but I cannot remember what the exact mechanism is. I do know that the only thing that fixes it is hot water.

MC: Are there any other ones you can think of it that you would report?

Nurse1: Specifically in oncology…I suppose if hand and foot is an ADR to capecitabine. They all are aren't they? They are all ADRs. I suppose we take it for granted it is a side effect when it happens so all of these should be happening (reporting) with capecitabine; and I suppose things like diarrhea with capecitabine and so on are ADR. And we use a lot of antibiotics to reduce things that makes you a bit nauseated and puts you off your appetite, gives you a bit of diarrhea. Is that an ADR or do you just think that antibiotics just do that?

MC: If I give you some examples will you respond to these as to whether or not you think they should be reported?

Nurse 1: Yeh.

MC: Patient admitted to hospital with neutropenic sepsis.

Nurse 1: Yes

MC: Patient develops grade 4 stomatisis

Nurse 1: Yes that should be reported.

MC: Do you think if it were lower grades you would report it?

Nurse 1: Whether it happens or not is questionable but I think what you said earlier about 'if in doubt report' and I do not think the severity is particularly relevant, if that makes sense. You know a reaction is a reaction isn't it and it doesn't matter whether it is severe or not. Because if you only wanted to know about the serious reactions that is what you would ask for.

MC: Patient develops grade 2 thrombocytopenia

Nurse 1: No get a bit complacent with that in oncology don't you because we know it happens with chemotherapy. But don't ask me to tell you why that is different from the other ones. I think it is because we expect it; it is what you intend to happen with the drug really to an extent.

MC: Patient presents with DVT & PE

Nurse 1: I suppose again if you are in doubt you should report but is it an ADR or is a symptom of the condition. But I suppose if you are in doubt you should (report) and let the people who know make the decision to how relevant it is. I can see us all day filling in yellow cards!

MC: Yes so there has to be some happy medium and sensible guidance at the end of the day

MC: Anaphylaxis post-chemo infusion

Nurse 1: Yes

MC: We have already touched on that.

MC: Are oncology ADRs under reported in your opinion?

Nurse 1: Yes

MC: Why do you think that is so?

Nurse1: Probably just what I have said, mainly we are a bit complacent about what is and what isn't an ADR. You know we see a lot of the same things; we see dozens of ADRs with taxanes in a month so I suppose we become a bit use to it and don't really see it as an ADR.

MC: Would more specific guidance from the MHRA on the types and grades of oncology adverse events (toxicities) to be reported be more beneficial to help you in recognising what types of oncology ADRs to report?

Nurse 1: Yes probably if you are given more specific guidelines it raises your awareness and you're more likely to do that, I suppose. At the moment we are thinking of a competency based orientation document where we want to cover lots of aspects of what happens in ward one and how to deal with it, and I suppose we should think about covering something like… Because I cannot remember the yellow card stuff is ever covered in anything other than the very basic pharmacology stuff that we did our training. I do not remember it being repeated anywhere else; in induction or…

MC: It might not be actually. Nurses were actually recently added in 2002 so nurses themselves are relatively new to reporting. So it is understandable that it probably may not have come up in training. I guess an opportunity is there for…

Nurse 1: …to do that and something like an induction programme would be a good idea.

MC: There is a separate reporting scheme for reporting HIV ADRs (i.e. Blue Card) to the MHRA. Do you think there would be any advantage of having a separate one for oncology ADRs?

Nurse 1: I am not really sure. I think that … yeh, I suppose if you had a separate card scheme to report oncology things, and you do a training session and introduction to it then it raises the awareness of it and you might get more compliance with it. So I suppose there is always that aspect of it isn't it… if you look at it that way.

***MC: Do you think th*at it would have any adv*antag*es or the regular yellow card scheme though?**

Nurse 1: No I think what probably needs to be done is a general awareness session isn't you know. It shouldn't really matter that is an oncology drug or not. It should be treated the same way; the reporting should be done in the same way.

MC: What type of information would be most useful for the scheme to collate on oncology ADRs?

Nurse 1: Do you mean what types of reactions it most useful…

MC: Or what types of information in general…Is there anything with regard to ADRs in oncology that would be useful to yourself or the patient?

Nurse 1: I think that it probably would be useful to know how common a specific ADR is, but whether that would then lead you to thinking well then it happens all the time and you become a bit complacent about it I don't know. I suppose it is useful to have information you can pass on to new staff and so on about how common things are for specific drugs. It is nice to have that information in you head and makes you feel a bit more secure about administering them. I thinking about for instance recently we repatriated herceptin to the Borders, and when it first started we were inundated with phone calls 'What about this? What about that? This is happened, what will we do?" Whereas if they had more accessible information about the frequency about whatever the side effect happened to be, they would have been more secure. That makes sense you know… So instead of panicking… you know they were really phoning us and we were saying that is ok, and what we would do. Just a bit of reassurance really was what they needed. And we were quite happy to do that, to provide that reassurance.

MC: With yourselves it came from experience

Nurse 1: Absolutely so maybe if you had, and we actually spoke about this just last week at a capacity planning meeting, where peripheral units could benefit quite possibly – and role we might think about taking on – a chat from one of the nurses at ECC of this is what we see in practice, this is what we do; how frequently we see it; whether it resolves quickly or these are things we have had particular problems with. So we have talked about whether it is appropriate for someone from here to go and have a chat if they are taking on a new drug regime for instance because as you know most of the new stuff comes through here first and then eventually finds its way out. It is working and getting there quite significantly recently so we have thought about that… and reassurance does make it a lot easier.

MC: Have you reported NCI common toxicity grades to industry in sponsored trials or via EUDRACT?

Nurse 1: I have been involved in collecting toxicity assessments for commercial trials and non-commercial trials; and to a certain lesser extent involved in the actual recoding of that data in Case Report Forms (CRFs) and electronic CRFs and things.

MC: In the recording of those I assume you recorded all toxicities regardless of grade?

Nurse 1: Yes. We use the common toxicity criteria routinely here anyway. However the data collected for trials seem to be a bit more thorough, quite a lot more thorough and, in particular, the big commercial trials (small numbers but the amount of work that is involved in the data collection is massive) the CRFs are massive big ring binders and they want to know absolutely everything – how many times a day you had diarrhea, what grade. Also the time the cannula went in the time the bloods were taken, all previous toxicities, time of administration of drugs, when it started and when it finished, Data managers have cut down on the amount of work for the nurses now though. A lot of the newer trials are going to be electronic data collection and that would be through EUDRACT.

MC: Do you think that will expediate things.

Nurse 1: To be honest with you, I wasn't involved long enough to see a result from it but the information from the companies suggested it would be a better method of collection because you have these big folders for collecting all the data – you fill them in or a data manager, then someone from the company monitor comes to check the folder to ensure all that information is accurate and transcribed properly. There is an audit trail for everything – electronic

reporting would still have an audit trail (since just as easy to make mistakes) but the data queries seem to be more easily dealt with. Also being dealt with at the time rather than 3 months later.

MC: So is the patient case record electronic now as well?

Nurse 1: Some of them the case record is electronic but some of them still have a CRF file. The ones with no CRF file the data managers are transcribing direct. We do design our own forms for collection of toxicities though since impossible to do the treating and computing at the same time since in two different areas.

MC: Is that due to a lack of availability of computers or …

Nurse 1: No a lot of the commercial trials I did provided you with a laptop and some provide you with a dedicated phone line , internet line but you needed to have the paper copy for the audit trail anyway so it can be checked.

MC: Do you think the continuation of this out with a clinical trial be beneficial to clinicians and/or patient safety?

Nurse 1: No, I do not think it is feasible and I also think that where do you decide to stop. You know yes you want to collect information on ADRs but a drug that is in use several times a day, everyday use – using it frequently- has been through all these trails and will hopefully have ironed out the problems so we won't be seeing … or its safety has been proven hasn't it to a certain extent. So the level of data collection that trials need is maybe a bit too much (not too much for what they need for at that time) but to carry on might be.

MC: Do you think electronic prescribing and capture of NCI toxicity grades in clinical practice would be beneficial?

Nurse 1: I know that electronic prescribing is being actively looked at the moment but not too involved with that. I think the publicity and the bumf sounds good, you know it is going to be an all singing all dancing thing and you will be able to have everything captured electronically. You won't have, for instance one of major problems at the moment is the case notes going missing and having to give chemo, to give chemo with missing case notes. Somethings do change but this frequency has increased (i.e. in peripheral units, with the regs, or wherever and you cannot find them). So a benefit will be that the case notes will always be there but a possible disadvantage is that it might crash and you will need a seriously efficient back-up.

MC: With the new system they are looking at are they looking at recording the patient's toxicities directly into the system without paper copies.

Nurse 1: Just know at the moment it will be all singing all dancing and do everything - prescribing, signing off, etc so assume that the documentation of the toxicities will be done electronically as well. Not aware that there is a plan for a paper back-up but worried about that.

MC: Do you think that you will then run into the same issues has you did with the clinical trial patients and having to record into the computer instead of having a paper copy?

Nurse 1: I think will have to do the paper recording and then electronic recording although it will be double the work. The implications on resources are huge but how many circumstances have we been in a situation where the computer systems have went down – makes life so difficult. So what will it be like and everything goes down!

MC: Do you think a nationwide anonymised aggregate of toxicities would be of benefit to clinicians?

Nurse 1: Yes I suppose that. Yes almost any additional information would be of help to the clinicians. It would help them with the decision of what drugs to use. For some if there were horrendous toxicities, and they could see that across the board nationwide then they may chose to use something less toxic for there particular patients.

MC: Do you think most people would be happy to contribute their patient's data to such a database?

Nurse 1: I can't see why they wouldn't be happy to put anonymised data on it but it always other implications for how much work is actually required to do it but if it is part and parcel of the normal data collection then it should not be an issue.

MC: Do you think it would be feasible to develop such a database in Scotland?

Nurse 1: I would imagine anything is possible with computer literate people but I don't know.

MC: Do you think patient ADR reporting in oncology would be of any value?

Nurse 1: Yes possibly. I think you might get wild and varied results. I think that there will always some groups of patients who will be more willing to report then others. For instance, take the red chemo diary by Lilly (It gives hints and tips on how to complete and serves as a basic tool for assessing degree of toxicities experienced during cycle. You know what it is like, you have not seen them for three weeks so in the first week their life may have been hell but by the time they come back they may have forgotten it). I can tell you who uses them and who does not. That may sound a bit cynical but it is not, it is a fact. The breast patient's fill them in religiously while the prostate patients do not bother. There will always be groups who are willing to give you information.

MC: Well that is all the questions I have for you but do you have any questions you would like to ask?

Nurse 1: No I don't think so. But I would like to add that there is no point in having a system that is not user friendly or people do not know about.

Objective 2
One-to-one Interview
Interview 2

MC: Are you familiar with the Yellow Card Scheme for spontaneous reporting of ADRs? How does it work?

Pharmacist 1: I am familiar with it and I know that when you fill it in (the yellow card). In practice here if the patient comes into the ward they fill it in and send it down to us (ward 1 outpatient area for chemo) and what we do when the patient comes back for the next cycle is fill in what the outcome was and then send it to yourselves.

MC: With regard to submission do you use paper copies or do you use electronic copies?

Pharmacist 1: We use paper basically… and we got lots of them.

MC: Do you know who can report to the Yellow Card Scheme?

Pharmacist 1: Yes. I believe doctors, community and hospital pharmacists; and nurses can too as well now. Also I think patients can report as well.

MC: Yes it is a separate card though which has come out for patients.

Pharmacist 1: It is not the yellow card then?

MC: No it is not the one used by health care professionals.

MC: Do you know what types of ADRs in general should be reported?

Pharmacist 1: Anything that is supposedly a rare side effect of the drug or if it a black triangle drug in the BNF. I would say that what I generally would report, apart from in oncology, when I have worked as a clinical pharmacist I tended to report anything that was very rare or a side effect that is not often seen or is not listed as a common side effect (for the medicine).

MC: Just rare side effects or rare and serious?

Pharmacist 1: Rare in particular but it if was serious I would still … but I think … mind you it was a rare and serious one. So I suppose rare and serious.

MC: Are you aware of any areas of special interest that the MHRA is looking to obtain reports on in particular?

Pharmacist 1: Do you mean which clinical area?

MC: Patient populations or clinical areas.

Pharmacist 1: No not specifically. Is that bad?

MC: No, no just asking. I am just trying to see what the knowledge on these things are out there about things.

MC: What purpose do you think the Yellow Card Scheme serves?

Pharmacist 1: Well I think in terms of reporting, I suppose it gives a good database of what is common with certain drugs and then at least you can have more data, like post-launch data /post-marketing surveillance. So at least you can get some information on the drug when it is actually being used in the population since previously to that it will have been used in a small, select population in trials etcetera. So from that point of view, and I suppose as well anecdotally if it is a very rare side effect that is serious you may only have a few patients coming in with that so you

can at least someone else will have heard of it and you can find out how they treated it etcetera. So I think it is to support the network throughout the UK. So you have information coming in from everywhere.

MC: Do you think it is beneficial to public safety?

Pharmacist 1: Em? I think it is, however, I think that there are certain things … like for example if we are filling in one (yellow card) for every neutropenic patient who comes in to oncology, we already know that is an established side effect and I think that we should rather be filling in yellow cards for patients maybe have deceased from neutropenic sepsis or something like that as opposed to every single patient who have had neutropenia with chemotherapy. So that is just my personal opinion in my own area but yeh I think it would be beneficial to public safety yeh.

MC: Have you ever reported a suspected ADR via the Yellow Card Scheme?

Pharmacist 1: Yes

MC: Was it quite easy to do so?

Pharmacist 1: Yes it was.

MC: Do you have any suggestions upon how it could be improved?

Pharmacist 1: Em… no I found it was alright to fill in. I think the card is quite congested. I think that was one thing if you had to write a little spill about what had happened and what medications was stopped and when they came... You know how there were 3 or 4 list of events after the actual event itself … like creatinine went off and this improved and that improved, and you had to list them all, I think there is not much space. But then I am a big writer. The system itself is all right.

MC: Have you ever any reported oncology related ADR via the Yellow Card Scheme?

Pharmacist 1: Yes

MC: What types?

Pharmacist 1: Neutropenic sepsis

MC: Was that going by the SOP?

Pharmacist 1: No it wasn't. I must admit I have not actually seen that SOP. It was more going by the induction given to the oncology department here when I was covering the wards. I don't think I have done any others other than neutropenic sepsis. Oh no… there was one. It was non-neutropenic sepsis, it was osteonecrosis of the jaw (ONJ) for Zometa.

MC: If you were going to report oncology ADRs which ones would you report?

Pharmacist 1: I would be more inclined to report something like ONJ or neutropenic sepsis if the patient ended up in ITU or something like that, not necessarily if they have just been neutropenic and admitted for some IV antibiotics because I don't think that is severe. But that is just my opinion. Again maybe like some of the new drugs that have come out on the market… I haven't actually reported anything for drugs like Terceva even though we have had a lot of patients with extremely bad rash on Terceva because it is documented well in the SPC that is a very common side effect. So we haven't tended to go down that road.

MC: If I give you some examples will you respond to these as to whether or not you think they should be reported?

Pharmacist 1: Yes

MC: Patient admitted to hospital with neutropenic sepsis. I think we may already have the answer to that one. Unless you wish to expand upon it further again.

Pharmacist 1: No

MC: Patient develops grade 4 stomatisis

Pharmacist 1: Yes

MC: Patient develops grade 2 thrombocytopenia

Pharmacist 1: No

MC: Patient presents with DVT & PE

Pharmacist 1: As side effect of the drug or the cancer? I probably would if thought attributed to the drug but you do have some patients who are risk of a DVT from the cancer , so would be probably harder to say if actually a side effect of that drug. But , yeh, I would (report) if I thought it was the drug.

MC: So if you had a degree of suspicion but you didn't know for 100% would you still report?

Pharmacist 1: Probably not actually

MC: Anaphylaxis post-chemo infusion?

Pharmacist 1: I would have to say no since we do not report this for the Herceptin patients. Although if it were a chemo infusion that did not have anaphylaxis documented as a known side effect in the SPC then I possibly would. Like if an anaphylaxis occurred with epirubicin, whereas if it were docetaxel in which we already pre-treat for that then I probably wouldn't.

MC: Are oncology ADRs under reported in your opinion?

Pharmacist 1: Probably yeh, in light of what you have said above actually because we don't report things like with every anaphylaxis with Herceptin.

MC: Why do you think that is so?

Pharmacist 1: Possible because anaphylaxis is quite common with Herceptin. Like more common than you possibly think since we do see quite a lot so it becomes second nature to staff; and there is a protocol in place to follow and we follow the master prescription (i.e. on the master prescription it says what to do if you have this anaphylaxis reaction. It is kind of almost expecting it and pre-empting it so therefore I wouldn't say we would report it. Therefore since we have quite robust master prescriptions, that tells us how to deal with any side effects, it wouldn't even cross our minds to put a yellow card in.

MC: What percentage of your Herceptin patients do you think would develop anaphylaxis (not just flushing or rash)?

Pharmacist 1: We have had quite a few believe it or not because there are a couple of patients … maybe less than I think since we have had a few because we refer them to chemotherapy at home and they have to have 2 cycles in the hospital with no reaction before the can get it at home and I have seen a couple who needed Piriton and infusion stopped. Then had to bring them back the next day and we found that there was only one patient not fine on re-challenge.

MC: Do healthcare at home monitor toxicities as well?

Pharmacist 1: Yeh

MC: Would more specific guidance from the MHRA on the types and grades of oncology adverse events (toxicities) to be reported be more beneficial to help you in recognising what types of oncology ADRs to report?

Pharmacist 1: I think absolutely since at least if we had that … I mean every so often we have a meeting and we say can you all please remember to put a yellow card in and I think if we actually had criteria , especially for some of the B-grade pharmacists that are rotating through here since they would probably put everything in because to them it is all side effect. I think if you actually said no it is only say grade 3 and above or … I think that would absolutely be beneficial. I think it would be good across Scotland to actually ensure that everyone was doing the same thing.

MC: And do you think it would help you personally to report more oncology ADRs?

Pharmacist 1: Yeh, definitely.

MC: There is a separate reporting scheme for reporting HIV ADRs (i.e. Blue Card) to the MHRA. Do you think there would be any advantage of having a separate one for oncology ADRs?

Pharmacist 1: I mean we already have the green extravasation card, which I know is not going to you, but we fill it in with the extravasations. So there already is …

MC: You get the extravasation but nothing else though don't you?

Pharmacist 1: Yeh that is just the extravasation and they (green cards) are kept inside of the kits. So I suppose if you were going to have a separate yellow card, and that probably would be quite good, but you would have to have advice from the MHRA on this is when to use a yellow card, this is when to use a say red card and … you know what I mean.

MC: Do you think that it would have any advantages or the regular yellow card scheme though?

Pharmacist 1: Well I suppose in a way if you have a lot of people admitted with the same … say neutropenic sepsis… and you are filling in a card for them then I suppose it would highlight the fact of the difference in patients getting admitted with neutropenic sepsis with different types of drugs (i.e. urology versus chemotherapy).

MC: What type of information would be most useful for the scheme to collate on oncology ADRs?

Pharmacist 1: I suppose you would want to know side effects on new drugs on the market. I mean we have got a lot of new things coming through, as you know. I think the difficulty in oncology, as well, is that a lot of those drugs are still being used on a trial basis so there (the side effects) reported through the trials so they probably do not reach the MHRA. Even with phase 3 trials you would want to report these via the yellow card scheme.

MC: Have you reported NCI common toxicity grades to industry in sponsored trials or via EUDRACT?

Pharmacist 1: I have been involved in clinical trails but not the actual reporting

MC: What do you think is the purpose of monitoring in pre-marketing phase of trials with medicines are?

Pharmacist 1: I suppose when the drug becomes commercially available you have an idea of percentage of side effects to expect, and that also helps with… like when Herceptin came out 7% patients get diarrhea, and so many with get cardiac failure and need their ejection fractions monitored. It also helps you with cost implications since we not only have to pay for the herceptin but also for the testing (i.e. ejection fractions three monthly in this case) which

is a cost we have to find as well. So I think it gives you idea of what to expect and what is important meds are going to be needed and what monitoring is required.

MC: What do you think are the benefits of doing so? You may have already answered this one…

Pharmacist 1: Yeh, I think I have

MC: Is there anything else you would like to add to it?

Pharmacist 1: Not really I think I have covered it.

MC: Do you think the continuation of this out with a clinical trial be beneficial to clinicians and/or patient safety?

Pharmacist 1: I think it would be too difficult to do it intensively because once the drug is commercially available (e.g. 90 people being treated by healthcare at home so to monitor them all intensively would be very, very difficult. I think once the trial has ran for a year and a half … so you already have that experience of use with the drug so you don't need to be so intense (with monitoring) but I think you do need something or some facility of being able to report a strange reaction, which we obviously kind of have.

MC: Do you think electronic prescribing and capture of NCI toxicity grades in clinical practice would be beneficial?

Pharmacist 1: Yes

MC: Why do you think this?

Pharmacist 1: I think electronic prescribing from the point of view of the paper notes that are going around now…Ideally we would have an electronic prescribing system that would link in with pharmacy so would generate worksheets and labels at the same time ; and the whole record would be there. The main difficulty would be with passwords and things. So to go paperless with no notes would be heaven but at the same time when the computer system goes down … But I think it would definitely benefit the fact that the information would be there (i.e. less likely to miss an annotation of a toxicity in the notes since it would be on the screen (i.e. prompt)

MC: If you went to a new electronic system do you anticipate the Scottish Pharmacist Cancer Care Plan would get incorporated into it?

Pharmacist 1: If not quite sure. But pharmacy would probably still want to keep a separate copy for documenting toxicities, etc…

MC: Do you think a nationwide anonymised aggregate of toxicities would be of benefit to clinicians?

Pharmacist 1: Well I suppose it would potentially be since it could potentially highlight a change in practice. For instance if our centre was having lots of anaphylactic reactions to a certain drug then you would maybe think why are we having it compared to London (for instance). So then maybe you could think maybe we are not pre-treating enough and it would maybe possibly help you.

MC: Do you think most people would be happy to contribute their patient's data to such a database?

Pharmacist 1: Yeh. But I would also like it to be a non-time consuming thing that you would have to fill at the same time because I think that that is part of the reason why things (yellow cards) potentially are not filled in.

MC: Do you think it would be feasible to develop such a database in Scotland?

Pharmacist 1: I am not IT minded at all but certainly I think that if electronic prescribing is rolled out Scotland wide then maybe it could be a programme that would interface with that. I think we already have a programme for filling

in near misses and incidents. So you are filling in that and your filling in the patient's notes and you have to do a yellow card, it is a lot of paper work plus your care plan.

MC: Do you think patient ADR reporting in oncology would be of any value?
Pharmacist 1:Yeh I think they would tend to under report … that would be my only concern (i.e. oncology patients are more likely to down play something in order that they will get there chemo). I think patients tend to down play things e.g. Oh yeh I had a temperature for 2 days and went to bed, and we say you didn't call the hospital or the GP. So I would could actually under report.

MC: Do you think there would be any added value from the reports they would submit? Or would they be any different from what a healthcare professional would report?

Pharmacist 1: Yeh, I think living with a side effect everyday … and especially... no yeh, I think that it would be of benefit actually. Definitely.

MC: Well that is all the questions I have for you but do you have any questions you would like to ask?

Pharmacist 1: No but hopefully I have answered all your questions. However I would like to add that I would like to see companies more involved in side effect monitoring post marketing (i.e. more interested) since whenever you call up about a possible side effect they just quote you what is in the SPC for the product and do not offer anything else. You almost feel like once they have the drug on the market, then well… its there.

MC: Do they no put you through to their pharmacovigilance surveillance team?

Pharmacist 1: No I have never had that. It seems they are not interested once the drug is licensed and on the market. So I would like them to be more proactive and doing follow up with the cancer centre once the medicine is licensed and we are using it. For example with Terceva we know it causes rashes and we have been collecting information via the nurses on what creams work for the patients but it costs £4500 per month but since it has been on the market we have not heard anything from the company saying how are your patients doing.

MC: So with that drug in particular you are monitoring it and the nurses are doing work on the creams but do you think that they would ever consider changing the dosage on it or is there any suggestion that the doses being received is the problem?

Pharmacist 1: They have sometimes decreased the doses but I think that once the patient has the drug in the system that is the side effect. A lot of patients are willing to put up with it because they feel this is their last chance since they have failed chemotherapy. So they shower with emollients and use creams. Which is fine and the company have made a big leaflet about it but if you are not filling in a yellow card for every patient perhaps they don't know really know how many patients out there are really experiencing it.

Objective 2
One-to-one Interview
Interview 3

MC: ***Are you familiar with the Yellow Card Scheme for spontaneous reporting of ADRs? If so, how does it work?***

Pharmacist 2: Yes I am familiar with it and we will usually fill out once a week for sepsis grade 4 toxicities so we collect patient details, what happened with the patient at the time when they experienced the adverse event, document past medical history, allergy, current drug therapy; and if chemotherapy related then we would then attach that to the care plan and follow up at the next cycle and document any dose reduction before we complete our name, clinicians name and send it off to CSM Scotland

MC: ***So you are doing that paper copies?***

Pharmacist 2 They just tend to take paper copies here

MC: ***I guess you know that you are able to report electronically – I assume that it might be a bit more difficult getting access to it?***

Pharmacist 2: Yeah – we just carry a pile of yellow cards round with us round the wards for ease and just do them there and then with the Kardex open and the notes there and….. I am aware of it but I have never done it I have to admit.

MC: ***Do you know who can report to yellow card scheme – which members are the most likely/allowed to report***

Pharmacist 2: Pharmacists can report, medical staff and I think nursing staff can now as well report. Um that's all I know

MC: ***Do you know what type of reports we like to receive via the yellow card scheme – what criteria for reporting – in general not just oncology***

Pharmacist 2: Any serious adverse effect which I think that caused the patient to be hospitalized or appear with an adverse drug reaction; and also any newly marketed drugs with the black triangle sign in the BNF.

MC: ***Are you aware of any areas of special interest that the MHRA like to receive reports for with regard to patient groups?***

Pharmacist 2: Emm – No I am not aware

MC: ***What purpose do you think the Yellow Card Scheme serves?***

Pharmacist 2: Um – well with drugs that are newly licensed with the black triangle, obviously, it gives the companies and the clinicians more information about the adverse effects that may not have been documented in clinical trials, build up a better safety the profile of the drug. Em and for drugs that have been around for quite a while it just gets the companies more information. I suppose its rarely documented side effects and all the common ones have probably been experienced during trials at the time but you do get rare instances adverse effects that you would get after marketing it.

MC: ***Do you think it is beneficial to public safety?***

Pharmacist 2: Yes definitely. I think as drugs are licensed and especially when they are new no-one is going to have that much of an idea about the or going to have the common side effects but I think if

the likes of the public know about other serious effects they may encounter with their medication that they maybe not expect and it just gives the patient a fuller picture and the clinicians. They are not going to list every side effect but they can say there are reports of this and that. It also helps patients thin to know what to look out for I guess

MC: ***Have you ever reported a suspected ADR via the yellow card scheme?***

Pharmacist 2: Yes

MC: ***Was it easy to do so?***

Pharmacist 2: Yes

MC: ***Was there anything that you could suggest as to how it could be improved?***

Pharmacist 2: I think one of the things you notice is that the space to record the drug at the top, especially if chemotherapy regimen, there is often not enough lines, OK if they are on very simple things but if there are on 4 drugs it's a bit of a squash; and also the drug history – the concurrent drug therapy section is a fairly small, especially with chemotherapy patients but I guess that they do that to put it on one side of a card so there would be reason for it but

MC: ***Do you find that you have insert other paper with it?***

Pharmacist 2: Or sometimes you put the supportive medicines on (a separate piece of paper) and just put the usual drugs (on the yellow card itself) which again probably isn't the correct thing to do or isn't the correct thing to do but I guess the time constraints as well, but generally we list all the chemotherapy drugs, we wouldn't miss them out, but if on senna and lactulose then tend to (miss them out).

MC: ***You said that in the mid-section there is a little bit of space – do you find that with chemotherapy regimens that it could be designed any better to record it or anything like that? Or is it just space in general?***

Pharmacist 2: I think it is just space in general. It is also quite hard to put in the start from date on the medicine section if they have been on a PPI for years, it is quite hard to give an exact date and things I suppose it is just a general idea. I think it would be fine for chemotherapy if there was a bit more space but I can understand why it is on one side so.

MC: ***Have you ever reported oncology related ADR via the Yellow Card Scheme?***

Pharmacist 2: Yes

MC: ***What type have you reported – do you know offhand?***

Pharmacist 2: Mainly neutropenic sepsis, grade 4, and a couple of instances of drugs for example alendronate where someone developed massive mouth ulcer. I put that on a yellow card although it is not a brand new drug obviously but we considered it a serious adverse effect, it was affecting the patient swallowing; and reported skin eruptions, skin problems with rituximab as well black triangle drug but mainly neutropenic sepsis.

MC: ***And for neutropenic sepsis was it grade 4 or grade 4 and hospitalized or just 4 general?***

Pharmacist 2: Grade 4 and hospitalized – I would only see those hospitalized I guess. I wouldn't see the people that aren't hospitalized. I don't work in out-patients.

MC: ***The next question follows on from that – If I give you some examples of what types of***

adverse drug reactions you should report can you tell me whether or not you think they should be reported?

MC: ***Patient is in hospital with neutropenic sepsis and grade 4 stomatitis***

Pharmacist 2: Yes – It is serious and probably affecting eating and things as well and infection

MC: ***Patient develops grade 2 thrombocytopenia***

Pharmacist 2: No

MC: ***Any particular reason?***

Pharmacist 2: I think grade 2 I can't remember what the cut off is I think it is over 50 but less than 75 platelets for people who are treated especially in haematology with platelets way less than that so I personally probably wouldn't report it

MC: ***Do you think that it is not seen to be clinically significant?***

Pharmacist 2: Yeah – the patient well would probably get a delay of a day or 2 but probably wouldn't be delayed that long to have any significant, you know wouldn't be hospitalized, wouldn't have usually any other serious consequences of it

MC: ***Patient presents with a DVT or PE?***

Pharmacist 2: Depends what medication they are on. I probably wouldn't report that as an ADR because especially in oncology it is more likely to be related to the malignancy rather than an actual drug, but I guess I would need to know what medication they were on

MC: ***So you would kind of try and figure out if there was any association with ….***

Pharmacist 2: With the drugs or whether it is just part of their disease

MC: ***If you had any suspicion at all that it was due to the medication would you report or would you want a positive conclusive?***

Pharmacist 2: I think I would want it a more positive. DVTs can be caused by other causes as well just drugs, I think I would want to have a more definite cause of it?

MC: ***Anaphylaxis post chemo infusion?***

Pharmacist 2: It would be depend on the severity of the anaphylaxis. I know sometimes carboplatin people can get a mild anaphylaxis and problems breathing for like a couple of minutes and then it all seems to resolve fairly quickly so again it would depend on the severity of it I think. So yes bigger anaphylaxis definitely but if it was just require hydrocortisone and piriton cover next time and they were fine then I probably wouldn't report it.

MC: ***Are oncology ADRs under-reported in your opinion?***

Pharmacist 2: No I think they are not under-reported I think

MC: ***What would you say about those?***

Pharmacist 2: I know for neutropenic sepsis we all ,well we are all told to fill out yellow cards and as far as I know people in the in-patients do and fill out yellow cards for it. I think with the newer drugs because most of us have had to do Formulary submissions I think we are more aware of side

effects expected and they are all black triangle so we know to report anything serious about it so I don't think in oncology they are genuinely under-reported

MC: ***So with the black triangle then if it is a serious one then they are getting reported?***

Pharmacist 2: Well I know that I would do it but do not know what others do.

MC: ***Would more specific guidance from the MHRA on the types and grades of oncology toxicities or adverse events to be reported be beneficial to help you in recognising what types of oncology ADRs to report – do you think that would improve your practice or make any difference to your practice or?***

Pharmacist 2: I think it would be good to get some guidance from them. You mentioned a grade 2 thrombocytopenia, I am now thinking maybe I should be reporting things like that – I don't know – so yes.

MC: ***Do you think you would report more oncology ADRs if there were more guidance or is your practice quite good at the moment anyway, or do you …. ?***

Pharmacist 2: Yeah – I think it is quite good, a very confident answer, but I think it is quite good just now but I think that if we had more guidance I we would probably pick up more things we are not reporting that should be reported from an education point of view.

MC: ***There is a separate reporting scheme for reporting HIV medicines, it is called a blue card, to the MHRA, a lot of people are not aware or sure what the feel of Infectious Diseases, you may not have come across it. Do you think there would be any advantage for having a separate adverse reaction card for oncology? Or do you think that the yellow card scheme is quite sufficient to cover your needs?***

Pharmacist 2: I think it is quite sufficient to cover our needs. Maybe with some more guidance as I said in the last question if it is a grade 2 report, but I think the yellow card itself gives all the information that you need I think

MC: ***So there wouldn't be any benefit from having anything separate?***

Pharmacist 2: No I don't personally think so.

MC: ***Have you ever reported NCI common toxicity grades to industry in sponsored trials or via EUDRACT? You may not have been involved in that you might be more along the lines of making them up?***

Pharmacist 2: No we tend to let the trial nurses document any serious adverse effects in clinical trials. I have never

MC: ***What purpose do you think the recording of the toxicities, which is more intensive in clinical trials serves?***

Pharmacist 2: I think it just gives the pharmacist and medical staff more of an idea of the toxicity because they are going to be documented much more. Easier documentation because they are prompted, there are lots more trial nurses around who have got time to fill out these forms than doctors and pharmacists probably do. So I think it helps fill out a bigger picture if you are using different combinations of drugs or different doses of drugs, especially in Phase 1 trials as well … or phase 2 and you can see more side effects and build up the bigger picture. So when it comes to get a licence you already have a fairly in-depth amount of side effect knowledge

MC: ***So what do you think the benefits are from the increased reporting for building up the bigger***

picture?

Pharmacist 2: Well it benefits the patients when the clinicians are able to explain more side effects probably and maybe side effects that they weren't expected that have been reported. So patient safety and another benefit would be if the doctors can't decide which chemotherapy regimen to put somebody on and there is an adverse effect associated with one particular trial then that may worsen the patients other conditions etc.

MC: ***Do you think a continuation of the intensive monitoring that is done with drugs over the clinical trial period would be beneficial to clinicians or patient safety out-with once they become licensed in the post-marketing period?***

Pharmacist 2: I think it would be beneficial because you could then follow-up these for a longer time period so may pick up on another one that had not been experienced so far but I suppose logistically it is time possibly, not possibly but definitely time issues about it and who would follow it up, whose responsibility would it be?

MC: ***Do you think electronic prescribing and capturing all of the toxicity grades in clinical practice would be beneficial? As opposed to the paper – do you think that electronic prescribing and capture all toxicities in clinical practice would be beneficial whilst the patient is being seen the toxicities are being recorded then and there as opposed to from paper documents***

Pharmacist 2: It would probably be easier electronically to help to collate all the information so you could then maybe pull out one particular drug. Depends on the program I guess but if you could pull out one particular drug and then look at all the adverse effects either by grade wise or say nausea; and if one drug was associated with one particular toxicity. So it would be easier to go back and look at all the information rather than get lots of paper copies

MC: ***Would a nationwide anonymised aggregate of this data be of benefit do you think? So if you were able to do this, or if anyone could take the data and anonymise it to use it, do you think there would be any benefit in that?***

Pharmacist 2: I think probably for the newer drugs it would be, but I guess for the older drugs that have been about for years for chemotherapy side effect wise probably quite well known, but for newer drugs it would be quite good to, across the UK say, be able to see what has been experienced elsewhere and build up a more complete picture.

MC: ***Would you be happy for patients that you see to have their data on such a database if it were anonymised?***

Pharmacist 2: Yes

MC: ***Or do you think that it would be feasible to develop such a database or pursue such a development in Scotland?***

Pharmacist 2: With the right IT support and programmes etc, I suppose funding might be a big issue as well and then who would complete it, who would keep it up to date and who would run off reports etc but yeah I think it would be doable but it would be a lot of work, but I suppose somebody would have to take responsibility for it.

MC: ***Do you think patient ADR reporting in oncology would be of any value?***

Pharmacist 2: I don't think, no I think it is better the way it is at the moment where the pharmacists, clinicians and nursing staff can report. I think if patients were to report they would also need to be educated and not to report you know nausea for example, it's not a severe adverse effect. I

think it would be harder to control and need an awful lot of patient education. I think at the moment I know that I probably don't know many medical staff that actually report actually but I think it is the role of the pharmacist or trial nurse, I don't think there would probably be a big push on for patients to report adverse effect I think they get given enough information etc and then to ask them to report adverse effects would just require more time with education spent with them and I think it is probably good the way that it is at the moment.

MC: ***You wouldn't think that there would be any added value from anything that the patient would report or do you think that it would be of lesser value or…?***

Pharmacist 2: I don't think of lesser value, it would be different, I suppose different terminology used etc and you would get it from the patient's point of view rather than us reporting it as they have come into hospital and we report about the skin reaction to whatever drug, but I think it would not be any less better information but at the same time I don't know what it would maybe add other than sort of a personal opinion which at the end of the day we are looking for I think we are looking for to see what has been reported and what is serious etc.

MC: ***OK then that's all the questions I have for you do you have any questions form me?***

Pharmacist 2: No I don't think so.

MC: ***Ok then Thank you***

Objective 2
One-to-one Interview
Interview 4

MC: ***Are you familiar with the Yellow Card Scheme for spontaneous reporting of ADRs? If so, how does it work?***

Nurse 2: Yes. You fill in the form, well I am probably more aware of the green card, which is for extravasation, but I have heard of the yellow card and as far as I am aware you fill it in and then you send it back to the address it says to send back to. I would also probably fill in an incident form as well. The hospital incident form to let you know so that it goes through the Directorate as well so that if there was a drug reaction you would send off the yellow card but you would also send an incident form.

MC: ***Do you do your adverse drug reactions through your incident forms?***

Nurse 2 Yeah

MC: ***Or is it only if it was a result of incorrect administration or just period all adverse drug reactions?***

Nurse 2 No I would probably still do an incident form if somebody had a drug reaction I would do a an incident form as well as the yellow card and the same with the green card.

MC: ***So you would normally use paper copies? Were you aware it is also available electronically now as well?***

Nurse 2 I wasn't no.

MC: ***Do you know who the reporter groups are who can report to yellow card scheme?***

Nurse 2: Yeah. Well I would have thought doctors, nurses and pharmacists

MC: ***Do you know what the criteria are for reporting – what types of reports do they like to receive via the yellow card scheme?***

Nurse 2: No

MC: ***There are some areas of special interest that the MHRA also have that they encourage reporting for different patient groups. Were you aware of that?***

Nurse 2: No

MC: ***There are certain groups like children, the elderly …***

Nurse 2: No I didn't known that no.

MC: ***What purpose do you think the Yellow Card Scheme serves?***

Nurse 2: Well I presume it would be to I suppose to prevent the kind of reactions also you know the drug companies and various bodies looking into them know how these drug affect people and also to get a bit of information about the drugs so they know kind of what of reactions can happen. I suppose to try and prevent these reactions or you know if there were a reaction happening all over the country it would happening to everybody that you know that maybe the drug wasn't safe , whether it should be withdrawn etc

MC: ***Do you think that the scheme is beneficial to public safety?***

Nurse 2: Oh yes

MC: ***Why do you say that?***

Nurse 2: I think cause we are keeping a close eye on the drugs. I think for example with Vioxx wasn't there, which is a prime example of you know I presume that these things were picked up by people filling in yellow cards whatever, you know so I think it a good thing to have to pick up these problems with drugs.

MC: ***Have you ever reported a suspected ADR via the yellow card scheme?***

Nurse 2: I don't think I have, I think I have just done the green card

MC: ***Any particular reason why? Is it that you haven't the opportunity or just….***

Nurse 2: Yeah probably I suppose maybe I am trying to think whether anybody has had a reaction. I suppose it may be that I haven't classed, you know maybe somebody is vomiting or had various antibiotics I maybe haven't classed that as a reaction but I suppose it is, but I would not have gone to fill in a card if that makes sense? We give a lot of antibiotics and things so I suppose if somebody had vomiting and diarrhea with them, we know that these are reactions that can happen but I don't if we should be filling in a yellow card for that? I don't know.

MC: ***Are you thinking that because the patient, the chemo can cause it, you don't know if it is the meds or is it just period for patients?***

Nurse 2: Just for any patient, even if we kind of give antibiotics to somebody who has a chest infection or something that comes to clinic then they say "oh those antibiotics didn't agree with me" you know and we know some of the side effects from that can be vomiting or diarrhoea, should be put that as a yellow card – see what I mean ?

MC: ***I think it comes back to the criteria of what they would like to in normal circumstances receive reports for is what they call black triangle medicine***

Nurse 2: Right

MC: ***Which are all new medicines on the market - for which they like to receive all reports. So in the case where if that were a new medicine on the market and you were giving***

Nurse 2: Yeah Yea uh-hu

MC: ***Then you would report it, diarrhea you know in the normal sense, not like a grade 4 diarrhoea***

Nurse 2: Yes, Yes

MC: ***Then with the medicines that have been on the market for a long for a while it isn't considered serious as such unless they have been admitted to the hospital because of it.***

Nurse 2: Yeah

MC: ***In which case it becomes medically significant***

Nurse 2: Uh-huh

MC: ***So I think it is more that with what type of medicine which causes it***

Nurse 2: Yeah Yeah

MC: ***With your oncology patient, I mean obviously they are getting chemotherapy, and if they were getting diarrhoea and vomiting from that, I mean would you consider reporting or is in those circumstances or …***

Nurse 2: Probably not because you would probably put it down to the treatment or you know so no, and I suppose if they had a reaction to the chemotherapy drug I would again probably do it ….. no I would do it with a yellow card cause it's not an extravasation. I am trying to think if I have done it with a yellow card – I don't think I have.

MC: ***It might be that pharmacist has reported it or something***

Nurse 2: Yeah

MC: ***Have you ever reported oncology related ADR via the Yellow Card Scheme?***

Nurse 2: Not that I can remember

MC: ***Any particular reason or just that?***

Nurse 2: No I just don't think it has been necessary

MC: ***Necessary in that you haven't had the opportunity***

Nurse 2: I haven't had the opportunity. I think that probably the pharmacists would probably do that and fill it in

MC: ***What types or oncology ADRs would you report?***

Nurse 2: I suppose it depends on the drugs. I suppose if we had a new chemotherapy drug or any chemotherapy drug that had an adverse reaction to them. I suppose some antibiotics if you got them coming in for IV antibiotics with neutropenic sepsis and thing if they had any adverse reactions then. I suppose things like morphine you know we use that. I suppose steroids as we use a lot of steroids as well but you know if anybody has maybe kind of got a wee bit of psychosis or a wee bit hyperactive on steroid I might not necessarily, you know if that's just a side effect more than an adverse reaction if that makes sense

MC: ***I think that there is a lot of misinterpretation of what is a side effect and one is an adverse reaction. It is basically the same, it's just the different way of referring to it. I think that when you think of side effect what do you think of?***

Nurse 2: Side effects I think of a side effect of dexmatheasone is you know Cushingoid, increasing the appetite can cause psychosis, people can get agitated with it, it can cause fluid retention things like that I see as a side effect.

MC: ***So are they then the ones that would be listed in the Summary of Product Characteristics for the drug or known, so you would consider as a side effect***

Nurse 2: Uh-huh

MC: ***So what do you consider an adverse drug reaction then when you think of an ADR?***

Nurse 2: I would not normally think of something like that as you know almost as an anaphylaxis to the drug so like an adverse reaction to it – so somebody …. Does that make sense?

MC: ***Yeah – I just think that it is pure interpretation of it – so this is the kind of information that is useful to me. I think that there is some misconception out there as to what the difference is between the two or if there is any difference between the two***

Nurse 2: Yeah – I now that with some chemotherapy drugs especially docetaxel you know that then one of the known side effects of that is actually anaphylaxis but I would not class that as an adverse drug reaction if you see what I mean – even though it is a known and documented side effect of docetaxel that people can get an anaphylaxis so that happens.

MC: ***And is there any particular reason why anaphylaxis sticks in your mind is it because you consider it to be serious?***

Nurse 2: Yes

MC: ***If I give you some examples of things would you tell me whether or not you would report these to the ADR scheme as an ADR***

Nurse 2: Yes, certainly

MC: ***Patient is in hospital with neutropenic sepsis?***

Nurse 2: Emm…… to be honest I wouldn't say that .., gosh …. They have become neutropenic sepsis because of drugs or infection - No I wouldn't fill in a yellow card for that. But now you have got me thinking.

MC: ***Patient develops grade 4 stomatitis?***

Nurse 2: Yes I would because that is a grade 4 because it is severe

MC: ***so it is the severity***

Nurse 2: Yeah is it is actually the severity of it yeah uh-huh

MC: ***Patient develops grade 2 thrombocytopenia?***

Nurse 2: I would class a severe thrompbocytopenua less than 10 so no for a grade 2 but I would for a grade 4.

MC: ***Patient presents with a DVT or PE who is on chemotherapy?***

Nurse 2: I probably wouldn't but we should because that can happen, again you see it is difficult as this whole conversation of side effects or because we know that what effects can chemotherapy can cause clots so probably not no.

MC ***Anaphylaxis post chemo infusion***

Nurse 2: If you ask me yes - definitely

MC: ***Are oncology ADRs under-reported in your opinion?***

Nurse 2: Probably yes

MC: ***Is there any reason that you would think that?***

Nurse 2: I think probably in a way because you know with things like chemotherapy I suppose because

they are given, don't want to use the word blasé, but I think because they are given in such high turnover that probably people don't think that neutropenic sepsis should be yellow carded – does that make sense? So it is probably just because they are maybe not recognized maybe not informed, maybe I don't know if there should be certain guidelines there that should be telling about chemotherapy adverse reactions which ones we should be highlighting on the yellow card thing – does that make sense?

MC: ***So would more specific guidance from the MHRA on the types and grades of oncology toxicities or be beneficial to help you in recognising what types of oncology ADRs to report?***

Nurse 2: Yes definitely.

MC: ***Do you think that if they were given to you, you would report more oncology ADRs via the yellow card scheme?***

Nurse 2: I would if I knew,

MC: ***So do you think that that is your biggest problem with reporting – lack of reporting – is it because you are not certain as to which ones?***

Nurse 2: Yeah – I think that's its not really highlighted or it is not a major issue really the yellow card. For myself anyway we don't kind of get a lot of information about it or you know people coming in and saying that you need to fill in a yellow cards, I mean I don't know if there has been any audit trail done about it or this is me being totally ignorant but it, nobody had really come round and said have you filled in a yellow card for that or are you doing this you know it really hasn't been talked about as such. I say probably the green card – the green card people know about

MC: ***The green card yeah that seems to have been kinda driven home through the years …***

Nurse 2: But maybe the yellow card hasn't been with nurses

MC: ***Nurses have only been added to the group for reporting back in 2002 so it is fairly new so it might be that in the programme when you enter initially it wasn't there and it might be that the induction programme may not necessarily cover it to any degree …***

Nurse 2: I think that is probably right yeah. It would be interesting to ask new staff nurses on the ward if they are told any information about the yellow card. You know it would be interesting to know what information they get, if they get information at college or uni or whatever cause it was certainly a long time ago now, but I can't remember getting anything any formal training about it, but ….

MC ***Is there anything else that you wanted to add to that section?***

Nurse 2: No I think probably now I would probably go out there and ask who knows about the yellow card and do you get any formal training on it? You know just doing this interview has highlighted to me that probably we should be reporting more.

MC: ***There is a separate reporting scheme for reporting HIV ADRs, it is called a blue card, a lot of people are not aware or sure what the unless you actually work in Infectious Diseases, you may not have come across it. Do you think there would be any advantage for having a separate reporting scheme for oncology ADRs? Rather than just reporting via the yellow card?***

Nurse 2: I suppose it depends on then what you are going to do with that information and what people it would be going to. I suppose that is something, I mean I would probably be interested, I would

have to ask an oncologist if they got that information what they would do with it and I suppose in a way you know it might help clinical trial, it might help, I don't know managing toxicities in oncology and chemotherapy and things so it might be worthwhile but I suppose it depends on what you actually do with that

MC: ***Do you anticipate that there would be any advantages in having a separate scheme other than just what you have brought up the management, dissemination of information to?***

Nurse 2: I suppose just really you would know chemotherapy toxicities better.

MC: ***What kind of information do you think would be most useful for the scheme to collate – is there anything in particular that you can think of?***

Nurse 2: You mean in relation to the drugs we give?

MC: ***With regard to oncology regimens – what kind of information regarding adverse reactions would be most useful to you?***

Nurse 2: Just what I found out yesterday that I didn't know was that cisplatin, I don't know if this has just come out officially at the Western, but cisplatin they feel is not good for anyone who has had a stroke already because people can have strokes with it. I only found out yesterday that I wasn't aware of, but on don't know if that is just something that the WGH has picked up on or if that, certainly when I given cisplatin for a good many of years now and I have never heard that

MC: ***So the stroke patients do get them at the moment – they are not contra-indicated in getting them?***

Nurse 2: Well when given at WGH, I think in hindsight we have never given any stroke patients here cisplatin, but it was given yesterday and I didn't actually know that and I wonder if it is something that has just been picked up in the Cancer centre because I am not convinced it is in the datasheets or anything.

MC: ***It would be interesting to look into the data sheet to see if there is any information listed there otherwise it would***

Nurse 2: Because I thought that would be quite good and then that information should be disseminated to oncology

MC: ***It might just be that local knowledge isn't being reported or fed back to anyone in the team that could actually pick up***

Nurse 2: That might actually help and I didn't know that about (cisplatin). Well seemingly I think that it is cisplatin is obviously for somebody who has had a stroke it makes a lot of sense but they also mention people who have come in for radical treatment and had a stroke and they have put it down to cisplatin, which I obviously didn't know about.

MC: ***Have you ever reported NCI common toxicity grades to industry in sponsored trials or via EUDRACT the new system for reporting clinical trials or haven't you been involved in clinical trials?***

Nurse 2: No I haven't, no.

MC: ***What purpose do you think the collection of the toxicities more intensively in the clinical trials serves?***

Nurse 2: Usually just to look at the safety of the drug and you know for future use and dosing of the drugs. I suppose in a lung cancer especially, I know they do trials in looking at what kind of quality of life and you know actual outcomes, so actually seeing which chemotherapies are better tolerated than others.

MC: ***What do you think are the benefits of doing so?***

Nurse 2: Well again it I suppose it is you are not giving patients treatment that are going to make them a lot worse and also safety again, public safety you mentioned earlier, and just making sure that we are giving drugs that are safe.

MC: ***Do you think that continuation of the more intensive monitoring of the adverse events or toxicities that you see in clinical trials would be of benefit once the drug is actually marketed?***

Nurse 2: I am not sure, I mean I do not know how many times compared to how many times we do it to what the trials do it. I suppose you have got to think of the patient, I know with trials they have to go to hospital a lot more, and again you would have to think about what people would do with the information if they had it. I suppose if you have done clinical trials and have the information there then you would hope that the criteria that is put on mass prescriptions is what they feel is appropriate and how often the toxicity should be checked if that is what is safe and appropriate. I don't know if it would benefit.

MC: ***Clinical trials basically I think everything is scrutinized in all the toxicities and they are all recorded and all reported to industry and I think that it is very inclusive and very time consuming.***

Nurse 2: Yeah I think probably that in the climate at work we wouldn't have the time with all the chemotherapy, with all the drugs that are given and things I think time would be an issue here to monitor it that closely.

MC: ***Do you think electronic prescribing and capture of the toxicity grades in clinical practice would be beneficial? So rather than doing your paper documentation you are actually doing it electronically instead.***

Nurse 2: Yeah, that probably would be quite good. I suppose the only thing is you don't have a signature as such have you know if its like a marked description for chemotherapy I don't know how that would work electronically

MC: ***There are come prescription programmes that would allow you to do that***

Nurse 2: Uh-hu yeah well I think that would be a good idea. Certainly it would be helpful with notes getting misplaced you can't find notes paper documentation and things so yeah.

MC: ***Would a nationwide anonymised aggregate of the toxicity data do you think would be benefit? So if you the computers were electronically catching all your toxicities from patients and you could download that but it would be anonymous do you think that would then be beneficial?***

Nurse 2: Well I suppose if you had a computer to catch it you could then monitor toxicities and I suppose you could maybe then find trends by doing that.

MC: ***Would you be happy to contribute your patient's data to such a database if it were anonomised?***

Nurse 2: Yep

MC: ***Do you think that it would be feasible to develop such a database in Scotland?***

Nurse 2: I would hope so but I don't know how much problems you would have getting IT to …. But I don't see why not

MC: ***Do you think patient ADR reporting in oncology would be of any value?***

Nurse 2: I think so yeah.

MC: ***Why do you think that?***

Nurse 2: I suppose just the drugs we deal with but I suppose maybe you could warn the patient more about different adverse reactions and I suppose just to educate them, the more we know about it then the more equipped we are to deal with these things and also to educate patients, inform them as much as we can about the treatment they are going to be receiving

MC: ***Do you think there would be any difference in the quality of the information you would get from a patient report rather as opposed to from a clinicians, pharmacist or nurse?***

Nurse 2: I think from as you mean the patient is filling it in themselves.. yeah I think it would be much better from the patient

MC: ***Do you think so?***

Nurse 2: We have the kind of the red chemotherapy book and you know the majority of patients will fill in everything and they will tick what you know I think they are helping you. No I think patients would yeah – I think that anything they can do it is almost taking control as well it is something they can control and contribute to so yeah

MC: ***Do you have any questions form me?***

Nurse 2: No

Objective 2
One-to-one Interview
Interview 5

MC: ***Are you familiar with the Yellow Card Scheme for spontaneous reporting of ADRs? If so, how does it work?***

Clinician 1: I am familiar with it. You fill in a yellow card and send it off if you suspect something is an ADR. I suspect we anticipate a large number of ADRs and just don't bother to report

MC: ***Do you know who the reporter groups are who can report to yellow card scheme?***

Clinician 1: No, I presume we are(clinicians) and registrars but I assume pharmacists can as well.

MC: ***Do you know what the criteria the MHRA have for reporting?***

Clinician 1: No

MC: ***There are some areas of special interest that the MHRA also have that they encourage reporting for different patient groups. Were you aware of that?***

Clinician 1: No I am aware of the letters they send out from time to time about individual events with particular drugs but I am not sure they particularly call for specific reporting.

MC: ***What purpose do you think the Yellow Card Scheme serves?***

Clinician 1: I guess it is post marketing surveillance of unexpected or rare side effects mainly. There is a great danger of being swamped with expected toxicities particularly for oncology drugs where if we reported every expected event we see.

MC: ***Do you think that the scheme is beneficial to public safety?***

Clinician 1: Yes I am sure it is. I know on several occasions drugs that have had new or unexpected side effects have been detected through that system.

MC: ***Have you ever reported a suspected ADR via the yellow card scheme?***

Clinician 1: Yes I have. Maybe twice in my life.

MC: ***Did you find it easy to do so?***

Clinician 1: Yes

MC: ***Do you have any suggestions on how reporting might be improved?***

Clinician 1: I mean the major issue to me is I think technically speaking we would be entitled to report for example every febrile neutropenic event, and to me that would be a fruitless use of the system. In my view it should be restricted to those events that are unexpected, in that they have not been described in the SPC for example and therefore might focus the system on identifying those rare events that only become evident in the post-marketing phase when large number are exposed. To me perhaps that is the most valuable aspect of the scheme. That is why I wouldn't use it in every instance where it might be used.

MC: ***Have you ever reported oncology related ADR via the Yellow Card Scheme?***

Clinician 1: Well the patients in whom I have reported in are oncology patients. Usually oncology drugs… severe respiratory reactions , ARDS type reaction unexpected with … cannot remember the name of the drug.

MC: ***That is ok.***

MC: ***If I give you some examples of things would you tell me whether or not you think these should be reported via the Yellow Card Scheme?***

Clinician 1: Certainly

MC: ***Patient is in hospital with neutropenic sepsis?***

Clinician 1: Can I ask should it be reported under the current criteria or in my opinion?

MC: ***In your opinion.***

Clinician 1: If expected then the answer would be no.

MC: ***Patient develops grade 4 stomatitis?***

Clinician 1: No

MC: ***Patient develops grade 2 thrombocytopenia?***

Clinician 1: No

MC: ***Patient presents with a DVT or PE who is on chemotherapy?***

Clinician 1: No

MC: ***Anaphylaxis post chemotherapy infusion?***

Clinician 1: Yes

MC: ***Are there any other ones you can think of that should be reported other than ones you said were unexpected?***

Clinician 1: Arrythmias in relation to newly introduced drugs, for example herceptin. In general those that you had good clinical ground to suspect they were drug related but not expected in the sense that they were not described already in the SPC. To me that is the criteria we should be using but I am sure it is not the criteria for the Yellow Card System.

MC: ***Are oncology ADRs under-reported in your opinion?***

Clinician 1: Yes definitely if you mean by criteria of the Yellow Card Scheme.

MC: ***But in your opinion the ones that should be reported are the unexpected side effects, do you think they are under reported?***

Clinician 1: I suspect they probably are too. I suspect generally speaking they are under-reported.

MC: ***Would more specific guidance from the MHRA on the types and grades of oncology toxicities or be beneficial to help you in recognising what types of oncology ADRs to report?***

Clinician 1: Yes definitely.

MC: ***Do you think that if they were given to you, you would report more oncology ADRs via the yellow card scheme?***

Clinician 1: Yes particularly if there was more focused and targeted. In other words we weren't expected to report every event we have already described to our patients as an expected event. I mean you

otherwise be simply flooded with unmanageable and unnecessary work

MC: ***There is a separate reporting scheme for reporting HIV ADRs, it is called a blue card, a lot of people are not aware or sure what the unless you actually work in Infectious Diseases, you may not have come across it. Do you think there would be any advantage for having a separate reporting scheme for oncology ADRs?***

Clinician 1: Yes possible would be. Certainly it is an area more rapid development and more drugs explored at an earlier stage in their development in a large number of patients I suspect.

MC: ***What kind of information do you think would be most useful for the scheme to collate if there were a separate scheme?***

Clinician 1: I guess such a scheme is always going to be a post-marketing scheme. So it wouldn't serve a purpose in the early phase development of drugs so whether it would be useful in specific are of oncology I am less certain. But it seems to me the major issue is that many of the oncology drugs are being exposed to say 4000 or 5000 patients before it comes to the market but it needs to be exposed to 10's of thousands of patients before the rarer (i.e. those occurring in less than 1/10,000 are most important to identify) events are detected.

MC: ***Have you ever reported NCI common toxicity grades to industry in sponsored trials or via EUDRACT the new system for reporting clinical trials or haven't you been involved in clinical trials?***

Clinician 1: Yes

MC: ***What purpose do you think the collection of the toxicities more intensively in the clinical trials serves?***

Clinician 1: In the trials development I think that it is the only way to get a reasonable good handle on the frequency of common adverse events and it is absolutely essential that these are well understood.

MC: ***What do you think are the benefits of doing so? Probably already just touched on this but do you have anything else to add?***

Clinician 1: No basically you need to know what your drug is going to do in terms of common toxicities. But can I make another point though…

MC: ***Yes***

Possible events that would be important but generally difficult to capture in any other way, that is latent effects. I am not sure if this scheme is a way of capturing latent events, but secondary malignancies, organ specific toxicities are specific examples; exposure of infants in utero to oncology drugs which there is not an awful lot of information about but I suspect that we need to accumulate a lot more information on exposures during pregnancy since you will not get it from a clinical trial. So the only way to capture events for exposures to these types of drugs by this type of scheme.

MC: ***Do you think that continuation of the more intensive monitoring of the adverse events or toxicities that you see in clinical trials would be of benefit to clinicians and/or patient safety do you think?***

Clinician 1: That type of question is a risk/benefit that only an economic analysis could answer because it is akin to the question of follow-up. In general in oncology patients what is the benefit from intensive monitoring over and above standard monitoring in terms of safety, and what is the cost for the effort involved or what other thing could you do in the time available? So the

question has to be familial with experience with the toxicities that are expected, and that is usually enough to allow for safe monitoring. Obviously with every cycle of chemotherapy patients are monitored by nursing staff by a grading system. So in that sense it is very close to being intensively monitored already and I am not sure what else is to be gained by doing otherwise.

MC: ***Do you think electronic prescribing and capture of the toxicity grades in clinical practice would be beneficial? So rather than doing your paper documentation you are actually giving it electronically instead.***

Clinician 1: Yes definitely.

MC: ***Would a nationwide anonymised aggregate of the toxicity data do you think would be benefit? So if you the computers were electronically catching all your toxicities from patients and you could download that but it would be anonymous do you think that would then be beneficial?***

Clinician 1: Yes. I must say there is one thing that I think we are bad at in oncology … for example we do not have ready access to linking deaths to chemo events so unlike surgeons we do not have good morbidity/mortality audit of our chemotherapy events. And I know that from an Audit done in 2002 , there were a significant number of deaths within 30 days of chemo but we do not know the cause of death because they died in some hospice or at home. That would be an advantage of electronic prescribing when it can be linked directly to the capture of data nation wide or deaths for example or major morbid events because I think we do not know that type of data. We know the toxicities of cycles quite well but the major events like deaths we are quite poor at. So that we be a big advantage from electronic linkage I think.

MC: ***Would you be happy to contribute your patient's data to such a database if it were anonomised?***

Clinician 1: Yes definitely.

MC: ***Do you think that it would be feasible to develop such a database in Scotland?***

Clinician 1: Yes by database do you mean a link?

MC: ***Electronic linkage of annonymised datasets like electronic prescribing systems with ISD cancer registry, death registry for example…***

Clinician 1: Absolutely I would really, really like to see that. That is absolutely essential to the future in my view and if you got an initiative that could lead to that, that would be fantastic. At present, in general, we have poor follow up data on our patients at this centre and it is probably the same elsewhere for all that I know. Currently it is captured manually by coding staff from the notes and it is often many months behind; and you know and it is about the case that an electronic system could massively change what we actually achieve.

MC: ***Do you think patient ADR reporting in oncology would be of any value?***

Clinician 1: I think that if they did it electronically and you captured the data that way it might work. However the problem might be grading. A patient's perception and they are not trained people either, and accuracy is even difficult with trained staff. The quality of the data would then be an issue but I guess averages or a big enough aggregate data might give you trends, regional differences. There would be lots of confounding variables though … education, social aspects, all sorts of things.

MC: ***That is all my questions for you, do you have any questions form me?***

Clinician 1: Teach me about the Yellow Card Scheme!

Objective 2
One-to-one Interview
Interview 6

MC: ***Are you familiar with the Yellow Card Scheme for spontaneous reporting of ADRs? If so, how does it work?***

Clinician 2: Yes. Individuals taking medicines get unexpected reactions, whether it is clear that they are related to the drug or not, clinicians are encouraged to fill in a form reporting the suspect drug and other concomitant drugs and what the reaction is; and possibly the outcome of the reaction. There are drugs where you are meant to report all ADR and there are certain ones where you just report unexpected ADRs .

MC: ***Do you know who the reporter groups are who can report to yellow card scheme?***

Clinician 2: I don't know. Reports seem to come predominantly from clinicians and pharmacists but I would be surprised if the nursing staff were not allowed to report as well. I had a patient who was interested in reporting himself but we reported because he needed some information that he didn't have.

MC: ***Are you aware of the areas of special interest that the MHRA also like to receive reports on specifically?***

Clinician 2: My impression is that just want drugs that are newer on the market but then presumably those that are serious or cause long-term consequences.

MC: ***What purpose do you think the Yellow Card Scheme serves?***

Clinician 2: I think there are certain drugs where ADRs tend to be serious but not common enough to be picked up in clinical trials. So if there is any effect occurring in less than 1% (of patients) it probably will not be picked up in clinical research and could potentially serious and significant. And separate to that there are drug interactions which might not well been seen in clinical trials. Often patients in clinical trials are pre-selected for limited co-morbidity and therefore limited concomitant medications. My impression is that would be the two most frequent areas of interest for the yellow card scheme.

MC: ***Do you think that the scheme is beneficial to public safety?***

Clinician 2: It depends how well it is administered. I think it is an important thing to do because it would be hard to pick up adverse effects otherwise. Some drugs when they come on the market are pretty widely prescribed quite quickly that interestingly it is the things that are not considered to be adverse effects that maybe is more serious; like increased risk of cardiovascular disease which I suspect is much less clearly picked up by an ADR reporting scheme. Because the difficulty with the scheme is that it relies on someone has considered something an adverse effect, and that's the problem with that I guess. I assume there are certain facts that people are likely to miss and they might be quite significant ones but clinicians are not going to report everything that happens to every patient. I guess that is why people are encouraged to report everything so it can pick up somethings… So it can be helpful but the benefits are probably limited by the implication that people have to draw an association between the facts which might not be obvious. You take the clear time relationship.

MC: ***Have you ever reported a suspected ADR via the Yellow Card Scheme?***

Clinician 2: Yes quite a number actually.

MC: ***Have you ever reported oncology related ADR via the Yellow Card Scheme?***

Clinician 2: Yes

MC: ***Can you remember what types or oncology ADRs you reported?***

Clinician 2: Things like hepatic problems with drugs; one went into renal failure with a drug; patient developed a significant GI symptom with a drug that I though initially was not associated with the drug but his family wanted us to report it given temporal relationship and given the severity of his symptoms we thought they may have been right. I have reported a couple a year ever since I have been practicing but those were the most recent ones and serious.

With the one lady that went into renal failure and we ended up not being able to treat the cancer and she died quite quickly. So it had serious consequences in that we could not treat her cancer.

I have come across the pharmacist reporting things that I might not bother like neutropenic sepsis with chemotherapy drugs. I am not saying they are wrong to do that but if someone is admitted with toxicity it is very expected.

MC: ***That takes us quite nicely to the next question, if I give you some examples of things would you tell me whether or not you would report these to the ADR scheme as an ADR?***

MC: ***Patient is in hospital with neutropenic sepsis?***

Clinician 2: Depends upon what the drug is. .. so if it is a chemotherapy drug that has been on the market for a while and it is in the datasheet as a side effect that is well reported then no. But if I had someone on imatinib admitted to hospital with neutropenic sepsis then I would because my impression is that neutropenic sepsis is not an anticipated side effect and that depends upon me knowing that. So not usually but I would sometimes.

MC: ***Patient develops grade 4 stomatitis?***

Clinician 2: Not usually maybe sometimes.

MC: ***Patient develops grade 2 thrombocytopenia?***

Clinician 2: Again it depends upon the drug but not routinely if they are on chemotherapy no because it is a perfectly relevant thing to see

MC: ***Patient presents with a DVT or PE who is on chemotherapy?***

Clinician 2: With my pancreatic patients a large number have DVTs and PEs and I have significant concerns which drugs exacerbate that and which don't. But no not with my patients I wouldn't because it is such a common symptom of the cancer … but it concerns me that we do not know the relationship between the drugs and thromboembolic disease.

MC ***Anaphylaxis post chemo infusion***

Clinician 2: Not with the taxanes or platins because it is a common expected side effect.

MC: ***Are oncology ADRs under-reported in your opinion?***

Clinician 2: When I report an ADR I get back a list of other reported ADRs and I am quite surprised how small the numbers are that have been reported so I suspect the answer to that is yes. So if I report something and see they have only had 300 other reports (in total) then it can be quite surprising .

MC: ***With oncology medicines Is there any reason that you think that they report less?***

Clinician 2: I am not sure that they do report less. I am not sure that is the case is it? Are you?

MC: ***Well you had said when you got it back there were only 300 reports and that surprised you and you suspected that maybe…***

Clinician 2: I suspect that not all adverse effects are reported but I am sure that is true in all spheres not just unique to oncology.

MC: ***Would more specific guidance from the MHRA on the types and grades of oncology toxicities or be beneficial to help you in recognising what types of oncology ADRs to report?***

Clinician 2: Maybe if we knew what they wanted.

MC: ***Do you think that if they were given to you, you would report more oncology ADRs via the yellow card scheme?***

Clinician 2: I suspect that with pharmacists more reports would come through but it would not have so much effect on the clinicians, but that does not matter does it as long as it comes through. I tend to think the pharmacists are more robust in that sense and maybe the chemotherapy nurses but that doesn't really matter where it comes from along as the information comes. When it comes to following guidelines you tend to find physicians are the worst at it. But once it is flagged by the team it doesn't matter.

MC: ***There is a separate reporting scheme for reporting HIV ADRs, it is called a blue card. Do you think there would be any advantage for having a separate reporting scheme for oncology ADRs? Rather than just reporting via the yellow card?***

Clinician 2: No

MC: ***Why do you think that there would be no benefit from it?***

Clinician 2: I think the implication is that it is different. The problem in oncology is that we often work within a narrow therapeutic window so we do cause quite a lot of toxicity, which we are use to managing and it is fairly easy to recognize as well. I don't think the lot so be separated out. I think that all drugs should go through the same regulatory reporting mechanism. I am not sure there would be any advantage from separating things (drugs) out. There then becomes a definition problem of whether it is an oncology drug or not as well. I don't know how helpful that is.

MC: ***Have you ever reported NCI common toxicity grades to industry in sponsored trials or via EUDRACT the new system for reporting clinical trials or haven't you been involved in clinical trials?***

Clinician 2: Yes

MC: ***What purpose do you think the collection of the toxicities more intensively in the clinical trials serves?***

Clinician 2: It is used partly to get a sort of more objective sense of use of common criteria. The aim is to get a more objective rather than subjective of the severity of symptoms so that you can actually pin point down what the patient cost is of what you are trying to do, which for the majority of patients that we see is a very important part of their decision of what chemotherapy to accept. The more robust we can be about that the more informed their decision can be. For instance if we can tell them there is a 10% chance they may be admitted to hospital or a grade 3 or 4 toxicity then that can really help them to make a decision.

MC: ***What do you think are the benefits of doing so? I think maybe you just described that but do you have anything further to add to that?***

Clinician 2: I think it is also a way of comparing treatments. So that if you are comparing treatments of relatively similar efficacy or lack of proprietary then the toxicity profile might be important. I treat a number of diseases which are relatively rare and in the absence of comparative efficacy data we have used toxicity data to decide which therapy to have since it seems to be the appropriate choice. So that becomes quite important.

MC: ***Do you think that continuation of intensive monitoring of adverse events or toxicities that you see in clinical trials would be of benefit once the drug is actually marketed?***

Clinician 2: I think it is helpful to have relatively robust figures of serious consequences. Minor things people would like to know what is the absolute risk for this to occur of having an hemipalegic stroke with chemotherapy or developing renal failure – a really life threatening toxicity and often clinical trials are not robust enough to give us that information but you can't monitor all drugs like that forever. I always presume that is why there were drugs you were to report more on but I have never seen a list of them. There must be a document somewhere which tells you though.

MC ***There is a easier way. I will discuss it with you after the interview.***

Clinician 2: Is there?

MC: ***Do you think electronic prescribing and capture of the toxicity grades in clinical practice would be beneficial?***

Clinician 2: I guess if you want to report toxicity grades the fewer times you have to transcribe the data the better but because of that a lot of places are moving towards that. But I kind of hope that with grade 3 or 4 toxicities then capture of those would be rather robust anyway. The advantages of electronic scheme might be that it could flag up what the various criteria mean. Since there seem to be some people reporting toxicities criteria who appear not to be very robust as to what the gradings of the various symptoms would be. An electronic system would have the possibility of a pop-up flag to remind you of what each grade means. So I think it is probably a good idea.

It would also allow the patient to put in themselves.

MC: ***Would a nationwide anonymised aggregate of the toxicity data do you think would be benefit? So if you were able to have linkage of computer systems throughout Scotland for instances and capture toxicities and link them anonymously, do you think that would then be beneficial?***

Clinician 2: I guess it is a form of audit as such it captures more information. That is not a bad thing so long as the quality of the information is adequate and that depends upon a little bit… but the more robust the information you have the more informative that is for people making decisions about treatments particularly in the palliative setting.

MC: ***When you say quality is that coming back to the people who assess the toxicities?***

Clinician 2: I suspect the data is put in relatively robustly when people attend for chemotherapy but for some who have one cycle of treatment and subsequently withdraw from treatment and never have any more then those are the ones whose data is never collected. Those are the ones we probably want it most so I think the problem with that is who puts the data in if people are not attending, like who puts in the toxicities of the final cycle of treatment; and I think those kind of things don't get reflected because what we do is when people attend for chemo we report the

toxicities from the previous cycle of treatment but people with the worst toxicities do not attend for any more chemo… so could be gaps in the dataset. And don't always come back to oncology either so the gaps will be with the patients with the most problems, and in clinical trials that is the data that is always hardest to get. So we spend a lot of time chasing that up. We really don't have a mechanism to get around that and the hospital admission data is a lot worst then that. So not really sure how you would deal with that.

MC: ***Would you be happy to contribute your patient's data to such a database if it were anonymised?***

Clinician 2: Oh yes.

MC: ***Do you think that it would be feasible to develop such a database in Scotland?***

Clinician 2: I think we are looking to on-line prescribing here and collection of toxicities, and they are already doing it in the West so I suspect we are already half-way there. It is just a long line of data that we collect, I suspect in that sense we are but as I say my concern is that you miss out the data from the worst end of the spectrum.

MC: ***Do you think patient ADR reporting in oncology would be of any value?***

Clinician 2: There is a certain amount of evidence that it is. I think peoples concerns are often how to deal with the data rather than the benefit of it. The patient hand held booklet often tell you quite a lot so I suspect that ¾ patients could quite easily input data directly themselves, and we would get it much more frequently. But the concern at the other end is what to do with the patients with toxicities who have not contacted you.

MC: ***That is all the questions I have for you but do you have any questions form me?***

Clinician 2: No

Appendix 16

Summary of coded analysis of semi-structured interviews

Number of years working in oncology

Profession	*Number of years working in oncology*
Pharmacist 1	5
Pharmacist 2	5
Nurse 1	6
Nurse 2	12
Clinician 1	10
Clinician 2	13

A. Yellow Card Scheme General Knowledge	Interviewee	Supporting Statement	Comments
Know there is a scheme for reporting ADRs	Nurse 1	I am aware that there is a scheme for reporting adverse drug reactions.	All aware that scheme exists
	Nurse 2	Yes.	
	Pharmacist 1	I am familiar with it	
	Pharmacist 2	Yes I am familiar with it	
	Clinician 1	I am familiar with it.	
	Clinician 2	Yes	
How it works?	Nurse 1	Nurses who are treating patients should complete the details (of an ADR) and pass it to pharmacy, who send it away and then you get a reply back	Yes but some confusion with Green Card for nurses
	Nurse 2	You fill in the form, well I am probably more aware of the green card, which is for extravasation, but I have heard of the yellow card and as far as I am aware you fill it in and then you send it back to the address it says to send back to.	
	Pharmacist 1	In practice here if the patient comes into the ward they fill it in and send it down to us (ward 1 outpatient area for chemo) and what we do when the patient comes back for the next cycle is fill in what the outcome was and then send it to yourselves.	Gives details specific to their own practice at ECC

	Pharmacist 2	we will usually fill out once a week for sepsis grade 4 toxicities so we collect patient details, what happened with the patient at the time when they experienced the adverse event, document past medical history, allergy, current drug therapy; and if chemotherapy related then we would then attach that to the care plan and follow up at the next cycle and document any dose reduction before we complete our name, clinicians name and send it off to CSM Scotland	
	Clinician 1	You fill in a yellow card and send it off if you suspect something is an ADR.	
	Clinician 2	Individuals taking medicines get unexpected reactions, whether it is clear that they are related to the drug or not, clinicians are encouraged to fill in a form reporting the suspect drug and other concomitant drugs and what the reaction is; and possibly the outcome of the reaction. There are drugs where you are meant to report all ADR and there are certain ones where you just report unexpected ADRs .	
Aware paper copy and/or electronic	Nurse 1	yellow cards you get in the back of the BNFs... I know I had to get a yellow card from the back of the BNF and fill in the details...	Paper used by all – Question: Is paper the preferred way of reporting? If yes, why?
	Nurse 2	***So you would normally use paper copies? Were you aware it is also available electronically now as well?*** I wasn't no.	
	Pharmacist 1	We use paper basically	
	Pharmacist 2	They just tend to take paper copies here ...we just carry a pile of yellow cards round with us round the wards for ease and just do them there and then with the Kardex open and the notes there and..... I am aware of it (electronic reporting) but I have never done it I have to admit.	
	Clinician 1	Paper	
	Clinician 2	Not discussed	
Who can report?	Nurse 1	Nurses, doctors and pharmacists I presume. I presume there is some kind of mechanism for patients to report ADRs	All except one say doctors, nurses and pharmacists. However only one says so with certainty. Therefore not confident who the reporter groups are. Two also say maybe patients can as well.
	Nurse 2	Well I would have thought doctors, nurses and pharmacists	
	Pharmacist 1	I believe doctors, community and hospital pharmacists; and nurses can too as well now. Also I think patients can report as well.	
	Pharmacist 2	Pharmacists can report, medical staff and I think nursing staff can now as well	
	Clinician 1	No, I presume we are(clinicians) and registrars but I assume pharmacists can as well.	

	Clinician 2	I don't know. Reports seem to come predominantly from clinicians and pharmacists but I would be surprised if the nursing staff were not allowed to report as well.	
Criteria for reporting	Nurse 1	Any type of ADR cause you are interested in whatever drugs are doing to the majority of patients, I would think. It is not really feasible to say only to report more serious ones because who gets to decide what is serious or not a serious one? So any type of reaction, I think, can be reported.	Nurses do not know criteria
	Nurse 2	No	
	Pharmacist 1	Anything that is supposedly a rare side effect of the drug or if it a black triangle drug in the BNF. I would say that what I generally would report, ***apart from in oncology***, when I have worked as a clinical pharmacist I tended to report anything that was very rare or a side effect that is not often seen or is not listed as a common side effect (for the medicine).	"apart from in oncology" = Implies oncology ADR reporting criteria is different here Pharmacist aware of criteria
	Pharmacist 2	Any serious adverse effect which I think that caused the patient to be hospitalized or appear with an adverse drug reaction; and also any newly marketed drugs with the black triangle sign in the BNF.	
	Clinician 1	No	One clinician does not know, the other clinician is aware
	Clinician 2	My impression is that just want drugs that are newer on the market but then presumably those that are serious or cause long-term consequences.	
Mentions Black triangle medicine	Nurse 1	Not mentioned	3 mention black triangle under criteria
	Nurse 2	Not mentioned	
	Pharmacist 1	Yes	
	Pharmacist 2	Yes	
	Clinician 1	No	
	Clinician 2	I always presume that is why there were drugs you were to report more on but I have never seen a list of them. There must be a document somewhere which tells you though.	
Mentions serious ADRs	Nurse 1	It is not really feasible to say only to report more serious ones because who gets to decide what is serious or not a serious one? I do not think the severity is particularly relevant, if that makes sense. You know a reaction is a reaction isn't it and it doesn't matter whether it is severe or not. Because if you only wanted to know about the serious reactions that is what you would ask for.	Three mention as a criteria in reporting

	Nurse 2	Not mentioned	
	Pharmacist 1	Rare in particular but it if was serious I would still … but I think … mind you it was a rare and serious one. So I suppose rare and serious.	
	Pharmacist 2	Any serious adverse effect which I think that caused the patient to be hospitalized or appear with an adverse drug reaction	
	Clinician 1	No	
	Clinician 2	Yes	
Areas of special interest	Nurse 1	No	None are aware of any areas of special interest
	Nurse 2	No	
	Pharmacist 1	No not specifically.	
	Pharmacist 2	No I am not aware	
	Clinician 1	No I am aware of the letters they send out from time to time about individual events with particular drugs but I am not sure they particularly call for specific reporting.	
	Clinician 2	No	
Confusion over what is an ADR and what is a side effect?	Nurse 1	I think it is because you see so many you think of it more as a recognised side effect rather than as an ADR. It probably is an ADR as much as it is a side effect though isn't it? I think that it is a bit like "what is an ADR of Herception, whereas what is a documented recognised side effect". We always have that argument as well. Sometimes the doctor will pre-treat them/ pre-medicate them with an antihistamine with Herceptin and so on. Whereas I tend to think maybe they had a bit of shivers and not really and ADR… that was a side effect with Herceptin. …we use a lot of antibiotics to reduce things that makes you a bit nauseated and puts you off your appetite, gives you a bit of diarrhea. Is that an ADR or do you just think that antibiotics just do that?	Nurses are confused over what is a side effect and what is an ADR?

	Nurse 2	***when you think of side effect what do you think of?*** Side effects I think of a side effect of dexmatheasone is you know Cushingoid, increasing the appetite can cause psychosis, people can get agitated with it, it can cause fluid retention things like that I see as a side effect. ***So what do you consider an adverse drug reaction then when you think of an ADR?*** I would not normally think of something like that as you know almost as an anaphylaxis to the drug so like an adverse reaction to it – so somebody …. Does that make sense? Yeah – I now that with some chemotherapy drugs especially docetaxel you know that then one of the known side effects of that is actually anaphylaxis but I would not class that as an adverse drug reaction if you see what I mean – even though it is a known and documented side effect of docetaxel that people can get an anaphylaxis so that happens.	
	Pharmacist 1	Not mentioned	
	Pharmacist 2	Not mentioned	
	Clinician 1	Not mentioned	
	Clinician 2	Not mentioned	

B. Purpose the Yellow Card Scheme Serves?			
Safety of medicines	Nurse 1	So it is to get information on safety of using the drugs and … take that forward.	
	Nurse 2	I suppose to try and prevent these reactions or you know if there were a reaction happening all over the country it would happening to everybody that you know that maybe the drug wasn't safe , whether it should be withdrawn	
	Pharmacist 1	Not mentioned	
	Pharmacist 2	… build up a better safety the profile of the drug; and for drugs that have been around for quite a while it just gets the companies more information.	
	Clinician 1	Not mentioned	
	Clinician 2	Not mentioned	
Identify ADRs	Nurse 1	Not mentioned	
	Nurse 2	…how these drug affect people and also to get a bit of information about the drugs so they know kind of what of reactions can happen.	

	Pharmacist 1	So from that point of view, and I suppose as well anecdotally if it is a very rare side effect that is serious you may only have a few patients coming in with that so you can at least someone else will have heard of it and you can find out how they treated it etcetera.	
	Pharmacist 2	...information about the adverse effects...	
	Clinician 1	... surveillance of unexpected or rare side effects mainly.	
	Clinician 2	... potentially serious and significant (side effects).	
Detect differences in patient groups	Nurse 1	And you do see different reactions in different groups of patients. So different ethnic groups can have different reactions to different groups of drugs; depending upon their background and so forth.	
	Nurse 2	Not mentioned	
	Pharmacist 1	Not mentioned	
	Pharmacist 2	Not mentioned	
	Clinician 1	Not mentioned	
	Clinician 2	Not mentioned	
Beneficial to public safety?	Nurse 1	I think if it is used properly then inevitably it will be beneficial. ***When you say 'properly' what do you mean?*** It gets the attention that it deserves. If people take it seriously enough to report any kind of ADR, or anything that might be an ADR, but if people are a bit complacent about it then you will not get the details that you need from the report. So people need to be aware of the system and they need to know what they are looking for and take it back appropriately. If they don't do that then, at the end of the day, you don't get what you are looking for do you?	If used or administered properly
	Nurse 2	Oh yes...cause we are keeping a close eye on the drugs. I think for example with Vioxx wasn't there, which is a prime example of you know I presume that these things were picked up by people filling in yellow cards ...	
	Pharmacist 1	I think it is, however, I think that there are certain things ... like for example if we are filling in one (yellow card) for every neutropenic patient who comes in to oncology, we already know that is an established side effect and I think that we should rather be filling in yellow cards for patients maybe have deceased from neutropenic sepsis or something like that as opposed to every single patient who have had neutropenia with chemotherapy. So that is just my personal opinion in my own area but yeh I think it would be beneficial to public safety yeh.	Do not think benefit of collecting ADRs that are already known and expected in oncology

	Pharmacist 2	Yes definitely. I think as drugs are licensed and especially when they are new no-one is going to have that much of an idea about the or going to have the common side effects but I think if the likes of the public know about other serious effects they may encounter with their medication that they maybe not expect and it just gives the patient a fuller picture and the clinicians. They are not going to list every side effect but they can say there are reports of this and that. It also helps patients then to know what to look out for I guess	
	Clinician 1	Yes I am sure it is. I know on several occasions drugs that have had new or unexpected side effects have been detected through that system.	
	Clinician 2	It depends how well it is administered. I think it is an important thing to do because it would be hard to pick up adverse effects otherwise. Some drugs when they come on the market are pretty widely prescribed quite quickly that interestingly it is the things that are not considered to be adverse effects that maybe is more serious; like increased risk of cardiovascular disease which I suspect is much less clearly picked up by an ADR reporting scheme. Because the difficulty with the scheme is that it relies on someone has considered something an adverse effect, and that's the problem with that I guess. I assume there are certain facts that people are likely to miss and they might be quite significant ones but clinicians are not going to report everything that happens to every patient. I guess that is why people are encouraged to report everything so it can pick up somethings… So it can be helpful but the benefits are probably limited by the implication that people have to draw an association between the facts which might not be obvious. You take the clear time relationship.	can be helpful but limited by the implication that people have to draw an association between the facts which might not be obvious
Protect Patients?	Nurse 1	Not mentioned	No one stated explicitly that the scheme helped in protecting patients
	Nurse 2	Not mentioned	
	Pharmacist 1	Not mentioned	
	Pharmacist 2	Not mentioned	
	Clinician 1	Not mentioned	
	Clinician 2	Not mentioned	
Collection network for ADRs in the UK	Nurse 1	I think that it draws together lots of information from different places on drugs that are being used probably world wide…	
	Nurse 2	Not mentioned	

	Pharmacist 1	So I think it is to support the network throughout the UK. So you have information coming in from everywhere.	
	Pharmacist 2	Not mentioned	
	Clinician 1	Not mentioned	
	Clinician 2	Not mentioned	
Post-marketing monitoring of medicines to detect rare side effects	Nurse 1	Not mentioned	All but nurses said played a role post-marketing
	Nurse 2	Not mentioned	
	Pharmacist 1	I suppose it gives a good database of what is common with certain drugs and then at least you can have more data, like post-launch data /post-marketing surveillance. So at least you can get some information on the drug when it is actually being used in the population since previously to that it will have been used in a small, select population in trials etcetera.	
	Pharmacist 2	…with drugs that are newly licensed with the black triangle, obviously, it gives the companies and the clinicians more information about the adverse effects that may not have been documented in clinical trials,… I suppose its rarely documented side effects and all the common ones have probably been experienced during trials at the time but you do get rare instances adverse effects that you would get after marketing it.	
	Clinician 1	I guess it is post marketing surveillance of unexpected or rare side effects mainly. There is a great danger of being swamped with expected toxicities particularly for oncology drugs where if we reported every expected event we see.	
	Clinician 2	I think there are certain drugs where ADRs tend to be serious but not common enough to be picked up in clinical trials. So if there is any effect occurring in less than 1% (of patients) it probably will not be picked up in clinical research and could potentially serious and significant.	
Drug interactions	Nurse 1	Not Mentioned	Only one mentioned aiding in detection of drug interactions.
	Nurse 2	Not Mentioned	
	Pharmacist 1	Not Mentioned	
	Pharmacist 2	Not Mentioned	
	Clinician 1	Not Mentioned	

	Clinician 2	And separate to that there are drug interactions which might not well been seen in clinical trials. Often patients in clinical trials are pre-selected for limited co-morbidity and therefore limited concomitant medications.	

C. Reporting via Yellow Card Scheme			
Have you ever reported a suspected ADR via the Yellow Card Scheme?	Nurse 1	Not in this hospital. Along time ago, probably	Nurses only group not to report previously
	Nurse 2	I don't think I have	
	Pharmacist 1	Yes	
	Pharmacist 2	Yes	
	Clinician 1	Yes I have. Maybe twice in my life.	
	Clinician 2	Yes quite a number actually.	
Easy to do so?	Nurse 1	I don't remember really… I don't know anything about it being difficult or having huge problems with it.	
	Nurse 2	Yes it was.	
	Pharmacist 1	Yes	
	Pharmacist 2	Yes	
	Clinician 1	Yes	
	Clinician 2	No comment	
How it could be improved?	Nurse 1	No comment made	Congested paper card Clinician states that only those events that are unexpected, in that they have not been described in the SPC for example should be the focus the system/
	Nurse 2	No comment made	
	Pharmacist 1	I think the card is quite congested. I think that was one thing if you had to write a little spill about what had happened and what medications was stopped and when they came… You know how there were 3 or 4 list of events after the actual event itself … like creatinine went off and this improved and that improved, and you had to list them all, I think there is not much space. The system itself is all right.	
	Pharmacist 2	I think one of the things you notice is that the space to record the drug at the top, especially if chemotherapy regimen, there is often not enough lines; and also the drug history – the concurrent drug therapy section is a fairly small, especially with chemotherapy patients but I guess that they do that to put it on one side of a card so there would be reason for it but… I think it is just space in general.	

	Clinician 1	I mean the major issue to me is I think technically speaking we would be entitled to report for example every febrile neutropenic event, and to me that would be a fruitless use of the system. In my view it should be restricted to those events that are unexpected, in that they have not been described in the SPC for example and therefore might focus the system on identifying those rare events that only become evident in the post-marketing phase when large number are exposed. To me perhaps that is the most valuable aspect of the scheme. That is why I wouldn't use it in every instance where it might be used.	
	Clinician 2	Not discussed	

D. Oncology ADR reporting via Yellow Card			
Have you ever reported oncology related ADR via the Yellow Card Scheme?	Nurse 1	No. I think the medics do more of the ADRs.	All but nurses have reported oncology ADRs
	Nurse 2	Not that I can remember... I just don't think it has been necessary	
	Pharmacist 1	Yes	
	Pharmacist 2	Yes	
	Clinician 1	Well the patients in whom I have reported in are oncology patients. Usually oncology drugs... severe respiratory reactions , ARDS type reaction unexpected with ... cannot remember the name of the drug.	
	Clinician 2	I have reported a couple a year ever since I have been practicing but those were the most recent ones and serious.	
What types would you report?	Nurse 1	Your hypersensitivities to taxols and herceptin; your oxalaplatins with laryngeal spasms. hand and foot is an ADR to capecitabine... I suppose things like diarrhea with capecitabine Neutropenic sepsis Grade 4 stomatitis, as well as al other grades of stomatitis DVT or PE - is it an ADR or is a symptom of the condition. But I suppose if you are in doubt you should (report) and let the people who know make the decision to how relevant it is. Anaphylaxis post chemo infusion	

	Nurse 2	I suppose it depends on the drugs. I suppose if we had a new chemotherapy drug or any chemotherapy drug that had an adverse reaction to them. I suppose some antibiotics if you got them coming in for IV antibiotics with neutropenic sepsis and thing if they had any adverse reactions then. I suppose things like morphine you know we use that. Grade 4 stomatitis - Yes I would because that is a grade 4 because it is severe Anaphylaxis post chemo infusion - definitely
	Pharmacist 1	I would be more inclined to report something like Osteonecrosis of the jaw or neutropenic sepsis if the patient ended up in ITU or something like that, not necessarily if they have just been neutropenic and admitted for some IV antibiotics because I don't think that is severe. Grade 4 stomatitis
	Pharmacist 2	Mainly neutropenic sepsis, grade 4, a couple of instances of drugs for example alendronate where someone developed massive mouth ulcer. I put that on a yellow card although it is not a brand new drug obviously but we considered it a serious adverse effect, it was affecting the patient swallowing skin eruptions, skin problems with rituximab as well black triangle drug Grade 4 stomatitis - It is serious and probably affecting eating and things as well and infection Anaphylaxis post chemo infusion - It would be depend on the severity of the anaphylaxis. I know sometimes carboplatin people can get a mild anaphylaxis and problems breathing for like a couple of minutes and then it all seems to resolve fairly quickly so again it would depend on the severity of it I think. So yes bigger anaphylaxis definitely but if it was just require hydrocortisone and piriton cover next time and they were fine then I probably wouldn't report it.

	Clinician 1	severe respiratory reactions , ARDS type reaction unexpected with … cannot remember the name of the drug. Anaphylaxis post chemo infusion Arrythmias in relation to newly introduced drugs, for example herceptin. In general those that you had good clinical ground to suspect they were drug related but not expected in the sense that they were not described already in the SPC. To me that is the criteria we should be using but I am sure it is not the criteria for the Yellow Card System.	
	Clinician 2	hepatic problems with drugs; one went into renal failure with a drug; patient developed a significant GI symptom with a drug With the one lady that went into renal failure and we ended up not being able to treat the cancer and she died quite quickly. So it had serious consequences in that we could not treat her cancer.	
What types would you not report?	Nurse 1	Grade 2 thrombocytopenia	
	Nurse 2	I suppose steroids as we use a lot of steroids as well but you know if anybody has maybe kind of got a wee bit of psychosis or a wee bit hyperactive on steroid I might not necessarily, you know if that's just a side effect more than an adverse reaction if that makes sense… They have become neutropenic sepsis because of drugs or infection - No I wouldn't fill in a yellow card for that. But now you have got me thinking. Grade 2 thrombocytopenia - I would class a severe thrompbocytopenua less than 10 so no for a grade 2 but I would for a grade 4. DVT or PE - I probably wouldn't but we should because that can happen, again you see it is difficult as this whole conversation of side effects or because we know that what effects can chemotherapy can cause clots so probably not no.	

	Pharmacist 1	if we are filling in one (yellow card) for every neutropenic patient who comes in to oncology, we already know that is an established side effect and I think that we should rather be filling in yellow cards for patients maybe have deceased from neutropenic sepsis or something like that as opposed to every single patient who have had neutropenia with chemotherapy. Again maybe like some of the new drugs that have come out on the market… I haven't actually reported anything for drugs like Terceva even though we have had a lot of patients with extremely bad rash on Terceva because it is documented well in the SPC that is a very common side effect. Grade 2 thrombocytopenia Anaphylaxis post-chemo infusion - I would have to say no since we do not report this for the Herceptin patients. Although if it were a chemo infusion that did not have anaphylaxis documented as a known side effect in the SPC then I possibly would. Like if an anaphylaxis occurred with epirubicin, whereas if it were docetaxel in which we already pre-treat for that then I probably wouldn't. As side effect of the drug or the cancer? I probably would if thought attributed to the drug but you do have some patients who are risk of a DVT from the cancer , so would be probably harder to say if actually a side effect of that drug. But , yeh, I would (report) if I thought it was the drug. ***So if you had a degree of suspicion but you didn't know for 100% would you still report?*** Probably not actually	Depends upon whether it is a known side effect with medicine and the seriousness of the reaction Where pharmacists and nurses think a grade 4 stomatitis should be reported clinicians did not. All agreed that grade 2 thrombocytopenia should not be reported. One pharmacist and 2 clinicians do not think neutropenic sepsis should be reported as the norm.
	Pharmacist 2	Grade 2 thrombocytopenia DVT or PE - Depends what medication they are on. I probably wouldn't report that as an ADR because especially in oncology it is more likely to be related to the malignancy rather than an actual drug, but I guess I would need to know what medication they were on	
	Clinician 1	Neutropenic sepsis Grade 2 thrombocytopenia Grade 4 stomatitis DVT or PE post chemotherapy	

	Clinician 2	I have come across the pharmacist reporting things that I might not bother like neutropenic sepsis with chemotherapy drugs. I am not saying they are wrong to do that but if someone is admitted with toxicity it is very expected. Neutropenic sepsis - Depends upon what the drug is. .. so if it is a chemotherapy drug that has been on the market for a while and it is in the datasheet as a side effect that is well reported then no. But if I had someone on imatinib admitted to hospital with neutropenic sepsis then I would because my impression is that neutropenic sepsis is not an anticipated side effect and that depends upon me knowing that. So not usually but I would sometimes. Grade 4 stomatitis – not usually but maybe sometimes Grade 2 thrombocytopenia - Again it depends upon the drug but not routinely if they are on chemotherapy no because it is a perfectly relevant thing to see. With my pancreatic patients a large number have DVTs and PEs and I have significant concerns which drugs exacerbate that and which don't. But no not with my patients I wouldn't because it is such a common symptom of the cancer … but it concerns me that we do not know the relationship between the drugs and thromboembolic disease. Anaphylaxis post chemo infusion - Not with the taxanes or platins because it is a common expected side effect.	
Are oncology ADRs under reported in your opinion?	Nurse 1	Yes	Perception is not under-reporting for one pharmacist, however all others thought there was. One clinician did not think under-reporting was any worst in oncology than in any other clinical area. One clinician also did not agree with the current MHRA criteria
	Nurse 2	Probably yes I think probably in a way because you know with things like chemotherapy I suppose because they are given, don't want to use the word blasé, but I think because they are given in such high turnover that probably people don't think that neutropenic sepsis should be yellow carded – does that make sense? So it is probably just because they are maybe not recognized maybe not informed, maybe I don't know if there should be certain guidelines there that should be telling about chemotherapy adverse reactions which ones we should be highlighting on the yellow card thing – does that make sense?	
	Pharmacist 1	Probably yeh…	

	Pharmacist 2	No I think they are not under-reported… I know for neutropenic sepsis we all ,well we are all told to fill out yellow cards and as far as I know people in the in-patients do and fill out yellow cards for it. I think with the newer drugs because most of us have had to do Formulary submissions I think we are more aware of side effects expected and they are all black triangle so we know to report anything serious about it so I don't think in oncology they are genuinely under-reported	
	Clinician 1	Yes definitely if you mean by criteria of the Yellow Card Scheme. ***But in your opinion the ones that should be reported are the unexpected side effects, do you think they are under reported*** I suspect they probably are too. I suspect generally speaking they are under-reported.	
	Clinician 2	I am not sure that they do report less. I am not sure that is the case is it? Are you? When I report an ADR I get back a list of other reported ADRs and I am quite surprised how small the numbers are that have been reported so I suspect the answer to that is yes. So if I report something and see they have only had 300 other reports (in total) then it can be quite surprising . I suspect that not all adverse effects are reported but I am sure that is true in all spheres not just unique to oncology.	

E. Reasons for not reporting			
Already a known side effect	Nurse 1	But you know, how many times a day do we see a taxol reaction? I can quite clearly say that we do not do a yellow card for every one of those. I think that it is a bit like "what is an ADR of Herception, whereas what is a documented recognised side effect". We always have that argument as well. The taxanes I suppose is different. That is an ADR, no two ways about it but if someone is a bit shivery or fluey at night with Herceptin then is that an ADR? Since know it is going to happen… or chances are since it is a known side effect. … I think it is because we expect it; it is what you intend to happen with the drug really to an extent.	

	Nurse 2	We give a lot of antibiotics and things so I suppose if somebody had vomiting and diarrhea with them, we know that these are reactions that can happen but I don't if we should be filling in a yellow card for that? … even if we kind of give antibiotics to somebody who has a chest infection or something that comes to clinic then they say "oh those antibiotics didn't agree with me" you know and we know some of the side effects from that can be vomiting or diarrhoea, should be put that as a yellow card – see what I mean ? I now that with some chemotherapy drugs especially docetaxel you know that then one of the known side effects of that is actually anaphylaxis but I would not class that as an adverse drug reaction if you see what I mean – even though it is a known and documented side effect of docetaxel that people can get an anaphylaxis so that happens.	
	Pharmacist 1	I haven't actually reported anything for drugs like Terceva even though we have had a lot of patients with extremely bad rash on Terceva because it is documented well in the SPC that is a very common side effect. …if it were a chemo infusion that did not have anaphylaxis documented as a known side effect in the SPC then I possibly would (report). Like if an anaphylaxis occurred with epirubicin, whereas if it were docetaxel in which we already pre-treat for that then I probably wouldn't.	
	Pharmacist 2	Does not think under reporting occurs so no discussion on this point.	
	Clinician 1	In other words we weren't expected to report every event we have already described to our patients as an expected event. I mean you otherwise be simply flooded with unmanageable and unnecessary work	
	Clinician 2	Not mentioned	

Complacency	Nurse 1	I wonder if we get a bit complacent about ADRs in oncology… No get a bit complacent with that in oncology don't you because we know it happens with chemotherapy …mainly we are a bit complacent about what is and what isn't an ADR. You know we see a lot of the same things; we see dozens of ADRs with taxanes in a month so I suppose we become a bit use to it and don't really see it as an ADR.	
	Nurse 2	…because you know with things like chemotherapy I suppose because they are given, don't want to use the word blasé,…	
	Pharmacist 1	Not mentioned	
	Pharmacist 2	Does not think under reporting occurs so no discussion on this point.	
	Clinician 1	Not mentioned	
	Clinician 2	Not mentioned	
Shear volume of ADRs in oncology	Nurse 1	I can see us all day filling in yellow cards!	
	Nurse 2	…but I think because they are given in such high turnover that probably people don't think that neutropenic sepsis should be yellow carded – does that make sense?	
	Pharmacist 1	Not mentioned	
	Pharmacist 2	Does not think under reporting occurs so no discussion on this point.	
	Clinician 1	I suspect we anticipate a large number of ADRs and just don't bother to report… There is a great danger of being swamped with expected toxicities particularly for oncology drugs where if we reported every expected event we see. … I mean you otherwise be simply flooded with unmanageable and unnecessary work…	
	Clinician 2	Not mentioned	

Lack of training	Nurse 1	I cannot remember the yellow card stuff is ever covered in anything other than the very basic pharmacology stuff that we did our training. I do not remember it being repeated anywhere else; in induction... ...a training session and introduction to it then it raises the awareness of it and you might get more compliance with it. I think what probably needs to be done is a general awareness session isn't you know ... no point in having a system that is not user friendly or people do not know about.	
	Nurse 2	So it is probably just because they are maybe not recognized maybe not informed, maybe I don't know if there should be certain guidelines there that should be telling about chemotherapy adverse reactions which ones we should be highlighting on the yellow card thing I think that's its not really highlighted or it is not a major issue really the yellow card. For myself anyway we don't kind of get a lot of information about it or you know people coming in and saying that you need to fill in a yellow cards, I mean I don't know if there has been any audit trail done about it or this is me being totally ignorant but it, nobody had really come round and said have you filled in a yellow card for that or are you doing this you know it really hasn't been talked about as such. I think that is probably right yeah. It would be interesting to ask new staff nurses on the ward if they are told any information about the yellow card. You know it would be interesting to know what information they get, if they get information at college or uni or whatever cause it was certainly a long time ago now, but I can't remember getting anything any formal training about it, but	
	Pharmacist 1	Not mentioned	
	Pharmacist 2	Does not think under reporting occurs so no discussion on this point.	
	Clinician 1	Not mentioned	
	Clinician 2	Not mentioned	

Have experience dealing with (not viewed as an ADR)	Nurse 1	...Sometimes the doctor will pre-treat them/ pre-medicate them with an antihistamine with Herceptin and so on. Whereas I tend to think maybe they had a bit of shivers and not really and ADR... that was a side effect with Herceptin. ...nurses at ECC of this is what we see in practice, this is what we do; how frequently we see it; whether it resolves quickly or these are things we have had particular problems with.	
	Nurse 2	I am trying to think whether anybody has had a reaction. I suppose it may be that I haven't classed, you know maybe somebody is vomiting or had various antibiotics I maybe haven't classed that as a reaction but I suppose it is, but I would not have gone to fill in a card if that makes sense?	
	Pharmacist 1	Possible because anaphylaxis is quite common with Herceptin. Like more common than you possibly think since we do see quite a lot so it becomes second nature to staff; and there is a protocol in place to follow and we follow the master prescription (i.e. on the master prescription it says what to do if you have this anaphylaxis reaction. It is kind of almost expecting it and pre-empting it so therefore I wouldn't say we would report it. Therefore since we have quite robust master prescriptions, that tells us how to deal with any side effects, it wouldn't even cross our minds to put a yellow card in. For example with Terceva we know it causes rashes and we have been collecting information via the nurses on what creams work for the patients	
	Pharmacist 2	Not mentioned	
	Clinician 1	Not mentioned	
	Clinician 2	Not mentioned	
Another member of the team would report	Nurse 1	I think the medics do more of the ADRs.	
	Nurse 2	I haven't had the opportunity. I think that probably the pharmacists would probably do that and fill it in	
	Pharmacist 1	Not mentioned	
	Pharmacist 2	Not mentioned	
	Clinician 1	Not mentioned	
	Clinician 2	Not mentioned	
Not clinically significant	Nurse 1	Not mentioned	
	Nurse 2	Not mentioned	
	Pharmacist 1	Not mentioned	

	Pharmacist 2	I think grade 2 (thrombocytopenia), I can't remember what the cut off is I think it is over 50 but less than 75 platelets for people who are treated especially in haematology with platelets way less than that so I personally probably wouldn't report it…the patient well would probably get a delay of a day or 2 but probably wouldn't be delayed that long to have any significant, you know wouldn't be hospitalized, wouldn't have usually any other serious consequences of it	
	Clinician 1	Not mentioned	
	Clinician 2	Not mentioned	

F. Possible ways of improving oncology ADR reporting			
Would more specific guidance from the MHRA on the types and grades of oncology adverse events (toxicities) be beneficial in helping you to report?	Nurse 1	Yes probably if you are given more specific guidelines it raises your awareness and you're more likely to do that	General agreement that this would be beneficial. One clinician particularly thought that if focused target criteria would be beneficial.
	Nurse 2	Yes definitely. …maybe I don't know if there should be certain guidelines there that should be telling about chemotherapy adverse reactions which ones we should be highlighting on the yellow card thing	
	Pharmacist 1	I think that would absolutely be beneficial. I think it would be good across Scotland to actually ensure that everyone was doing the same thing.	
	Pharmacist 2	I think it would be good to get some guidance from them. You mentioned a grade 2 thrombocytopenia, I am now thinking maybe I should be reporting things like that – I don't know – so yes. I think that if we had more guidance I we would probably pick up more things we are not reporting that should be reported from an education point of view.	
	Clinician 1	Yes definitely…particularly if there was more focused and targeted. In other words we weren't expected to report every event we have already described to our patients as an expected event. I mean you otherwise be simply flooded with unmanageable and unnecessary work	

	Clinician 2	Maybe if we knew what they wanted. I suspect that with pharmacists more reports would come through but it would not have so much effect on the clinicians, but that does not matter does it as long as it comes through. I tend to think the pharmacists are more robust in that sense and maybe the chemotherapy nurses but that doesn't really matter where it comes from along as the information comes. When it comes to following guidelines you tend to find physicians are the worst at it. But once it is flagged by the team it doesn't matter	
Inclusion in orientation packages	Nurse 1	At the moment we are thinking of a competency based orientation document where we want to cover lots of aspects of what happens in ward one and how to deal with it, and I suppose we should think about covering something like… Because I cannot remember the yellow card stuff is ever covered in anything other than the very basic pharmacology stuff that we did our training. I do not remember it being repeated anywhere else; in induction	
	Nurse 2	Not mentioned	
	Pharmacist 1	Not mentioned	
	Pharmacist 2	Not mentioned	
	Clinician 1	Not mentioned	
	Clinician 2	Not mentioned	
Separate reporting scheme (like HIV Blue Card)	Nurse 1	I am not really sure. I think that … yeh, I suppose if you had a separate card scheme to report oncology things, and you do a training session and introduction to it then it raises the awareness of it and you might get more compliance with it. ***Do you think th*****at it would have any adv*****antag*****es or the regular yellow card scheme though?** No ... It shouldn't really matter that is an oncology drug or not. It should be treated the same way; the reporting should be done in the same way.	1 = maybe 3 = no 2 = yes
	Nurse 2	I suppose it depends on then what you are going to do with that information and what people it would be going to… I would have to ask an oncologist if they got that information what they would do with it … I don't know managing toxicities in oncology and chemotherapy and things so it might be worthwhile but I suppose it depends on what you actually do with that I suppose just really you would know chemotherapy toxicities better.	

	Pharmacist 1	that probably would be quite good, but you would have to have advice from the MHRA on this is when to use a yellow card, this is when to use a say red card and … you know what I mean. if you have a lot of people admitted with the same … say neutropenic sepsis… and you are filling in a card for them then I suppose it would highlight the fact of the difference in patients getting admitted with neutropenic sepsis with different types of drugs (i.e. urology versus chemotherapy).	
	Pharmacist 2	No I don't personally think so. I think it is quite sufficient to cover our needs. Maybe with some more guidance as I said in the last question if it is a grade 2 report, but I think the yellow card itself gives all the information that you need I think	
	Clinician 1	Yes possible would be. Certainly it is an area more rapid development and more drugs explored at an earlier stage in their development in a large number of patients I suspect. I guess such a scheme is always going to be a post-marketing scheme. So it wouldn't serve a purpose in the early phase development of drugs so whether it would be useful in specific are of oncology I am less certain. But it seems to me the major issue is that many of the oncology drugs are being exposed to say 4000 or 5000 patients before it comes to the market but it needs to be exposed to 10's of thousands of patients before the rarer (i.e. those occurring in less than 1/10,000 are most important to identify) events are detected.	
	Clinician 2	No I think the implication is that it is different. The problem in oncology is that we often work within a narrow therapeutic window so we do cause quite a lot of toxicity, which we are use to managing and it is fairly easy to recognize as well. I don't think the lot so be separated out. I think that all drugs should go through the same regulatory reporting mechanism. I am not sure there would be any advantage from separating things (drugs) out. There then becomes a definition problem of whether it is an oncology drug or not as well. I don't know how helpful that is.	

G. Types of information on oncology ADRs			

that would be helpful			
Frequency	Nurse 1	...would be useful to know how common a specific ADR ...if they had more accessible information about the frequency about whatever the side effect happened to be, they would have been more secure	
	Nurse 2	Not mentioned	
	Pharmacist 1	Not mentioned	
	Pharmacist 2	Not mentioned	
	Clinician 1	Not mentioned	
	Clinician 2	Not mentioned	
Dissemination of local knowledge	Nurse 1	Not mentioned	
	Nurse 2	I found out yesterday something that I didn't know was that cisplatin, I don't know if this has just come out officially at the Western, but cisplatin they feel is not good for anyone who has had a stroke already because people can have strokes with it. I only found out yesterday that I wasn't aware of, but on don't know if that is just something that the WGH has picked up on or if that, certainly when I given cisplatin for a good many of years now and I have never heard that... I didn't actually know that and I wonder if it is something that has just been picked up in the Cancer centre because I am not convinced it is in the datasheets or anything. ... Because I thought that would be quite good and then that information should be disseminated to oncology	
	Pharmacist 1	Not mentioned	
	Pharmacist 2	Not mentioned	
	Clinician 1	Not mentioned	
	Clinician 2	Not mentioned	
Side effect profile of new medicine	Nurse 1	Not mentioned	
	Nurse 2	Not mentioned	
	Pharmacist 1	I suppose you would want to know side effects on new drugs on the market. I mean we have got a lot of new things coming through, as you know. I think the difficulty in oncology, as well, is that a lot of those drugs are still being used on a trial basis so there (the side effects) reported through the trials so they probably do not reach the MHRA.	
	Pharmacist 2	Not mentioned	

	Clinician 1	Not mentioned	
	Clinician 2	Not mentioned	
Detection of unknown rare side effects (not detected in clinical trials), including latent events	Nurse 1	Not mentioned	
	Nurse 2	Not mentioned	
	Pharmacist 1	Not mentioned	
	Pharmacist 2	Not mentioned	
	Clinician 1	But it seems to me the major issue is that many of the oncology drugs are being exposed to say 4000 or 5000 patients before it comes to the market but it needs to be exposed to 10's of thousands of patients before the rarer (i.e. those occurring in less than 1/10,000 are most important to identify) events are detected. Possible events that would be important but generally difficult to capture in any other way, that is latent effects. I am not sure if this scheme is a way of capturing latent events, but secondary malignancies, organ specific toxicities are specific examples; exposure of infants in utero to oncology drugs which there is not an awful lot of information about but I suspect that we need to accumulate a lot more information on exposures during pregnancy since you will not get it from a clinical trial. So the only way to capture events for exposures to these types of drugs by this type of scheme.	
	Clinician 2	Not mentioned	

H. NCI Common Adverse Event Criteria			
Have you reported toxicity grades during clinical trails to industry or EUDRACT?	Nurse 1	Yes the data collected for trials seem to be a bit more thorough, quite a lot more thorough and, in particular, the big commercial trials… and they want to know absolutely everything…	3 = yes 3 = no
	Nurse 2	No I haven't	
	Pharmacist 1	have been involved in clinical trails but not the actual reporting	
	Pharmacist 2	No we tend to let the trial nurses document any serious adverse effects in clinical trials. I have never…	
	Clinician 1	Yes	
	Clinician 2	Yes	
What is the purpose of this?	Nurse 1	No comment	

	Nurse 2	Usually just to look at the safety of the drug and you know for future use and dosing of the drugs. I suppose in a lung cancer especially, I know they do trials in looking at what kind of quality of life and you know actual outcomes, so actually seeing which chemotherapies are better tolerated than others.	Common adverse events See which therapies better tolerated, helps in decision making process of what chemo regimen to use Quality of life and outcomes Establishes monitoring parameters required Establish dosing regimens and drug combinations
	Pharmacist 1	I suppose when the drug becomes commercially available you have an idea of percentage of side effects to expect, and that also helps with… like when Herceptin came out 7% patients get diarrhea, and so many with get cardiac failure and need their ejection fractions monitored.	
	Pharmacist 2	I think it just gives the pharmacist and medical staff more of an idea of the toxicity because they are going to be documented much more... So I think it helps fill out a bigger picture if you are using different combinations of drugs or different doses of drugs, especially in Phase 1 trials as well … or phase 2 and you can see more side effects and build up the bigger picture. So when it comes to get a licence you already have a fairly in-depth amount of side effect knowledge…	
	Clinician 1	… basically you need to know what your drug is going to do in terms of common toxicities.	
	Clinician 2	It is used partly to get a sort of more objective sense of use of common criteria. The aim is to get a more objective rather than subjective of the severity of symptoms so that you can actually pin point down what the patient cost is of what you are trying to do, which for the majority of patients that we see is a very important part of their decision of what chemotherapy to accept. The more robust we can be about that the more informed their decision can be. For instance if we can tell them there is a 10% chance they may be admitted to hospital or a grade 3 or 4 toxicity then that can really help them to make a decision.	
What is the benefit of this?	Nurse 1	No comment	Ensure medicines being used are safe Aids in establishing full cost of therapy Aids in determining which chemotherapy regimen to offer based on adverse event profile comparisons
	Nurse 2	I suppose it is you are not giving patients treatment that are going to make them a lot worse and also safety again, public safety you mentioned earlier, and just making sure that we are giving drugs that are safe.	
	Pharmacist 1	It also helps you with cost implications since we not only have to pay for the herceptin but also for the testing (i.e. ejection fractions three monthly in this case) which is a cost we have to find as well. So I think it gives you idea of what to expect and what is important meds are going to be needed and what monitoring is required.	

	Pharmacist 2	Well it benefits the patients when the clinicians are able to explain more side effects probably and maybe side effects that they weren't expected that have been reported. So patient safety and another benefit would be if the doctors can't decide which chemotherapy regimen to put somebody on and there is an adverse effect associated with one particular trial then that may worsen the patients other conditions etc.	Only way to get a good adverse event profile for common side effects of medicines
	Clinician 1	I think that it is the only way to get a reasonable good handle on the frequency of common adverse events and it is absolutely essential that these are well understood.	
	Clinician 2	I think it is also a way of comparing treatments. So that if you are comparing treatments of relatively similar efficacy or lack of proprietary then the toxicity profile might be important. I treat a number of diseases which are relatively rare and in the absence of comparative efficacy data we have used toxicity data to decide which therapy to have since it seems to be the appropriate choice. So that becomes quite important.	
Would a continuation of this out with clinical trials be of benefit?	Nurse 1	I do not think it is feasible and I also think that where do you decide to stop. You know yes you want to collect information on ADRs but a drug that is in use several times a day, everyday use – using it frequently- has been through all these trails and will hopefully have ironed out the problems so we won't be seeing … or its safety has been proven hasn't it to a certain extent. So the level of data collection that trials need is maybe a bit too much (not too much for what they need for at that time) but to carry on might be.	3 = No 1 = Yes 2 = questionable Main constraint = time
	Nurse 2	I am not sure, … I suppose if you have done clinical trials and have the information there then you would hope that the criteria that is put on mass prescriptions is what they feel is appropriate and how often the toxicity should be checked if that is what is safe and appropriate. I don't know if it would benefit. I think probably that in the climate at work we wouldn't have the time with all the chemotherapy, with all the drugs that are given and things I think time would be an issue here to monitor it that closely.	
	Pharmacist 1	I think it would be too difficult to do it intensively because once the drug is commercially available … you already have that experience of use with the drug so you don't need to be so intense (with monitoring) but I think you do need something or some facility of being able to report a strange reaction, which we obviously kind of have.	

	Pharmacist 2	I think it would be beneficial because you could then follow-up these for a longer time period so may pick up on another one that had not been experienced so far but I suppose logistically it is time possibly, not possibly but definitely time issues about it and who would follow it up, whose responsibility would it be?	
	Clinician 1	That type of question is a risk/benefit that only an economic analysis could answer because it is akin to the question of follow-up. In general in oncology patients what is the benefit from intensive monitoring over and above standard monitoring in terms of safety, and what is the cost for the effort involved or what other thing could you do in the time available? So the question has to be familial with experience with the toxicities that are expected, and that is usually enough to allow for safe monitoring. Obviously with every cycle of chemotherapy patients are monitored by nursing staff by a grading system. So in that sense it is very close to being intensively monitored already and I am not sure what else is to be gained by doing otherwise.	
	Clinician 2	I think it is helpful to have relatively robust figures of serious consequences. Minor things people would like to know what is the absolute risk for this to occur of having an hemipalegic stroke with chemotherapy or developing renal failure – a really life threatening toxicity and often clinical trials are not robust enough to give us that information but you can't monitor all drugs like that forever.	

I. Electronic prescribing and capture of adverse events			
Would the electronic capture of NCI common adverse event scores in clinical practice be beneficial?	Nurse 1	I know that electronic prescribing is being actively looked at ... I think the publicity and the bumf sounds good, you know it is going to be an all singing all dancing thing and you will be able to have everything captured electronically.	5 = Yes 1 = unsure
	Nurse 2	Yeah, that probably would be quite good.	
	Pharmacist 1	Yes	
	Pharmacist 2	Yes	
	Clinician 1	Yes definitely.	
	Clinician 2	Yes	

Advantages	Nurse 1	You won't have, for instance one of major problems at the moment is the case notes going missing and having to give chemo, to give chemo with missing case notes. Somethings do change but this frequency has increased (i.e. in peripheral units, with the regs, or wherever and you cannot find them). So a benefit will be that the case notes will always be there	Paperless – case notes always available Less likely to miss important annotations of adverse events Easier to collate information So could possibly compare toxicity profiles on chemotherapy regimens Fewer transcription of data Make grading criteria clearer to those doing assessments
	Nurse 2	Certainly it would be helpful with notes getting misplaced you can't find notes paper documentation	
	Pharmacist 1	... would generate worksheets and labels at the same time ; and the whole record would be there. So to go paperless with no notes would be heaven but at the same time when the computer system goes down ... But I think it would definitely benefit the fact that the information would be there (i.e. less likely to miss an annotation of a toxicity in the notes since it would be on the screen (i.e. prompt)	
	Pharmacist 2	It would probably be easier electronically to help to collate all the information so you could then maybe pull out one particular drug. Depends on the program I guess but if you could pull out one particular drug and then look at all the adverse effects either by grade wise or say nausea; and if one drug was associated with one particular toxicity. So it would be easier to go back and look at all the information rather than get lots of paper copies	
	Clinician 1	Not mentioned	
	Clinician 2	...it could flag up what the various criteria mean. Since there seem to be some people reporting toxicities criteria who appear not to be very robust as to what the gradings of the various symptoms would be. An electronic system would have the possibility of a pop-up flag to remind you of what each grade means. So I think it is probably a good idea. I guess if you want to report toxicity grades the fewer times you have to transcribe the data the better but because of that a lot of places are moving towards that.	
Disadvantages	Nurse 1	...but a possible disadvantage is that it might crash and you will need a seriously efficient back-up.	Computer crash Time Passwords
	Nurse 2	I think probably that in the climate at work we wouldn't have the time with all the chemotherapy, with all the drugs that are given and things I think time would be an issue here to monitor it that closely.	

	Pharmacist 1	The main difficulty would be with passwords and things. …pharmacy would probably still want to keep a separate copy for documenting toxicities, etc…	Pharmacy would still need to keep a separate documentation Gaps in datasets
	Pharmacist 2	Not mentioned	
	Clinician 1	Not mentioned	
	Clinician 2	Gaps in datasets - some who have one cycle of treatment and subsequently withdraw from treatment and never have any more then those are the ones whose data is never collected. Those are the ones we probably want it most so I think the problem with that is who puts the data in if people are not attending, like who puts in the toxicities of the final cycle of treatment; and I think those kind of things don't get reflected because what we do is when people attend for chemo we report the toxicities from the previous cycle of treatment but people with the worst toxicities do not attend for any more chemo… so could be gaps in the dataset. And don't always come back to oncology either so the gaps will be with the patients with the most problems, and in clinical trials that is the data that is always hardest to get. So we spend a lot of time chasing that up. We really don't have a mechanism to get around that and the hospital admission data is a lot worst then that. So not really sure how you would deal with that.	
Anonymised aggregate of data and linkage Scotland wide be beneficial?	Nurse 1	Yes almost any additional information would be of help to the clinicians. It would help them with the decision of what drugs to use. For some if there were horrendous toxicities, and they could see that across the board nationwide then they may chose to use something less toxic for there particular patients.	Response positive for all. Benefits: See trends on toxicities so could elect to use another regimen so could either use another regimen or pre-treat better Highlight change in practice Linkage of datasets nationwide to capture deaths or major morbid events
	Nurse 2	Well I suppose if you had a computer to catch it you could then monitor toxicities and I suppose you could maybe then find trends by doing that.	
	Pharmacist 1	Well I suppose it would potentially be since it could potentially highlight a change in practice. For instance if our centre was having lots of anaphylactic reactions to a certain drug then you would maybe think why are we having it compared to London (for instance). So then maybe you could think maybe we are not pre-treating enough and it would maybe possibly help you.	
	Pharmacist 2	I think probably for the newer drugs it would be, but I guess for the older drugs that have been about for years for chemotherapy side effect wise probably quite well known, but for newer drugs it would be quite good to, across the UK say, be able to see what has been experienced elsewhere and build up a more complete picture.	

	Clinician 1	Yes. I must say there is one thing that I think we are bad at in oncology … for example we do not have ready access to linking deaths to chemo events so unlike surgeons we do not have good morbidity/mortality audit of our chemotherapy events. And I know that from an Audit done in 2002 , there were a significant number of deaths within 30 days of chemo but we do not know the cause of death because they died in some hospice or at home. That would be an advantage of electronic prescribing when it can be linked directly to the capture of data nation wide or deaths for example or major morbid events because I think we do not know that type of data. We know the toxicities of cycles quite well but the major events like deaths we are quite poor at. So that we be a big advantage from electronic linkage I think.	
	Clinician 2	I guess it is a form of audit as such it captures more information. That is not a bad thing so long as the quality of the information is adequate and that depends upon a little bit… but the more robust the information you have the more informative that is for people making decisions about treatments particularly in the palliative setting.	
Feasibility of developing Scotland wide?	Nurse 1	I would imagine anything is possible with computer literate people but I don't know.	All think possibility, especially with electronic prescribing in oncology coming Scotland wide, but rate determining factor = IT funding and capabilities
	Nurse 2	I would hope so but I don't know how much problems you would have getting IT to …. But I don't see why not…	
	Pharmacist 1	I am not IT minded at all but certainly I think that if electronic prescribing is rolled out Scotland wide then maybe it could be a programme that would interface with that. I think we already have a programme for filling in near misses and incidents. So you are filling in that and your filling in the patient's notes and you have to do a yellow card, it is a lot of paper work plus your care plan.	
	Pharmacist 2	With the right IT support and programmes etc, I suppose funding might be a big issue as well and then who would complete it, who would keep it up to date and who would run off reports etc but yeah I think it would be doable but it would be a lot of work, but I suppose somebody would have to take responsibility for it.	

	Clinician 1	Absolutely I would really, really like to see that. That is absolutely essential to the future in my view and if you got an initiative that could lead to that, that would be fantastic. At present, in general, we have poor follow up data on our patients at this centre and it is probably the same elsewhere for all that I know. Currently it is captured manually by coding staff from the notes and it is often many months behind; and you know and it is about the case that an electronic system could massively change what we actually achieve.	
	Clinician 2	I think we are looking to on-line prescribing here and collection of toxicities, and they are already doing it in the West so I suspect we are already half-way there. It is just a long line of data that we collect, I suspect in that sense we are but as I say my concern is that you miss out the data from the worst end of the spectrum.	
Would you be happy to contribute your data to such a database?	Nurse 1	I can't see why they wouldn't be happy to put anonymised data on it but it always other implications for how much work is actually required to do it but if it is part and parcel of the normal data collection then it should not be an issue.	Yes for all
	Nurse 2	Yes	
	Pharmacist 1	Yeh. But I would also like it to be a non-time consuming thing that you would have to fill at the same time because I think that that is part of the reason why things (yellow cards) potentially are not filled in.	
	Pharmacist 2	Yes	
	Clinician 1	Yes definitely.	
	Clinician 2	Oh yes.	

J. Patient reporting of ADRs in oncology			
Would patient reporting in oncology have any value?	Nurse 1	Yes possibly. I think you might get wild and varied results. I think that there will always some groups of patients who will be more willing to report then others. For instance, take the red chemo diary by Lilly (It gives hints and tips on how to complete and serves as a basic tool for assessing degree of toxicities experienced during cycle. You know what it is like, you have not seen them for three weeks so in the first week their life may have been hell but by the time they come back they may have forgotten it).	3 = Yes 1 = No 2 = possible Concerns: Wide and varied reports Would tend to under report

	Nurse 2	I think so yeah… yeah I think it would be much better from the patient … We have the kind of the red chemotherapy book and you know the majority of patients will fill in everything and they will tick what you know I think they are helping you. No I think patients would yeah – I think that anything they can do it is almost taking control as well it is something they can control and contribute to so yeah	Patient education Do not know if would add anything to the quality of the data received Patient grading of adverse events might be an issue that would affect quality of the data Red book gives a good indicator of how well patients will record their adverse events after each cycle of chemo
	Pharmacist 1	Yeh I think they would tend to under report … that would be my only concern (i.e. oncology patients are more likely to down play something in order that they will get there chemo). I think patients tend to down play things e.g. Oh yeh I had a temperature for 2 days and went to bed, and we say you didn't call the hospital or the GP. So I would could actually under report. Yeh, I think living with a side effect everyday … and especially... no yeh, I think that it would be of benefit actually. Definitely.	
	Pharmacist 2	no I think it is better the way it is at the moment where the pharmacists, clinicians and nursing staff can report. I think if patients were to report they would also need to be educated and not to report you know nausea for example, it's not a severe adverse effect. I think it would be harder to control and need an awful lot of patient education. I think at the moment I know that I probably don't know many medical staff that actually report actually but I think it is the role of the pharmacist or trial nurse, I don't think there would probably be a big push on for patients to report adverse effect I think they get given enough information etc and then to ask them to report adverse effects would just require more time with education spent with them and I think it is probably good the way that it is at the moment … I don't think of lesser value, it would be different, I suppose different terminology used etc and you would get it from the patient's point of view rather than us reporting it as they have come into hospital and we report about the skin reaction to whatever drug, but I think it would not be any less better information but at the same time I don't know what it would maybe add other than sort of a personal opinion which at the end of the day we are looking for I think we are looking for to see what has been reported and what is serious etc.	

	Clinician 1	I think that if they did it electronically and you captured the data that way it might work. However the problem might be grading. A patient's perception and they are not trained people either, and accuracy is even difficult with trained staff. The quality of the data would then be an issue but I guess averages or a big enough aggregate data might give you trends, regional differences. There would be lots of confounding variables though … education, social aspects, all sorts of things.	
	Clinician 2	There is a certain amount of evidence that it is. I think peoples concerns are often how to deal with the data rather than the benefit of it. The patient hand held booklet often tell you quite a lot so I suspect that ¾ patients could quite easily input data directly themselves, and we would get it much more frequently. But the concern at the other end is what to do with the patients with toxicities who have not contacted you.	

Appendix 17

Oncology Healthcare Professionals' Attitudes and Opinions on

Demographics

1. What is your profession?

- ◯ Doctor
- ◯ Nurse
- ◯ Pharmacist
- ◯ Other (please specify)

2. Number of years qualified?

3. Number of years working in oncology?

4. How much of your job is devoted to direct patient care in oncology?

- ◯ None
- ◯ < 25%
- ◯ 25 - 50%
- ◯ 51 - 75%
- ◯ > 75%

5. Gender?

- ◯ Male
- ◯ Female

6. Age?

- ◯ 20-30
- ◯ 31-40
- ◯ 41-50
- ◯ 51-60
- ◯ >60

7. How many times, if ever, have you completed a Yellow Card report for an adverse drug reaction during your career?

- ◯ Never
- ◯ 1 – 5 times
- ◯ 6 – 10 times
- ◯ 11 – 20 times
- ◯ > 20

8. Of the Yellow Card reports you have completed for adverse drug reactions during your career how many were for oncology patients?

- ◯ None
- ◯ 1 – 5
- ◯ 6 – 10
- ◯ 11 – 20
- ◯ > 20

9. Yellow Card reporting can be done on paper (sent via post) or electronically at www.yellowcard.gov.uk . Please tick the box of your preference for reporting

- ◯ I prefer to complete paper Yellow Cards
- ◯ I prefer to complete electronic Yellow Cards
- ◯ I have no preferred choice

If you have a preference, please explain why

10. When you do complete a Yellow Card where do you normally complete the report?

- ◯ Ward
- ◯ Outpatient
- ◯ Pharmacy
- ◯ Office
- ◯ Other (please specify)

11. Do any of the following statements about Yellow Card Reporting apply to you? Please tick all that apply.

- [ ] I have wanted to report an ADR but was unable to find a yellow card
- [ ] I have wanted to report an ADR but was unable to obtain access to the electronic Yellow Card
- [ ] I have seen ADRs in clinical oncology practice but I am not sure which ones the MHRA want me to report
- [ ] I have completed a Yellow Card for an ADR but did not send it
- [ ] I often recognise ADRs in patients receiving chemotherapy but choose not to report believing that they are inevitable consequence of therapy and little relevance for reporting
- [ ] None of the above

12. What proportion of your patients receiving chemotherapy do you estimate suffers any kind of adverse event (toxicity); and what proportion suffers a serious adverse event (toxicity)? Please tick one box only in each row from the following options:

	<1%	<5%	<10%	<25%	<50%	<75%	>75%
Any kind of adverse event (toxicity)	◯	◯	◯	◯	◯	◯	◯
Serious adverse event (toxicity)only	◯	◯	◯	◯	◯	◯	◯

13. Which of the following oncology adverse events (toxicities) do you think you would report on a Yellow Card?

	Yes	Not Sure	No
Patient develops Grade 2 diarrhoea after second cycle of Xeloda (capecitabine)	◯	◯	◯
Patient develops Grade 3 bloating after receiving cisplatin	◯	◯	◯
Patient develops fatigue after receiving docetaxel (third cycle)and first dose of Herceptin (trastuzumab)	◯	◯	◯
Patient receiving Herceptin(trastuzumab)develops acute renal failure (Grade 3; no dialysis required)	◯	◯	◯
Patient develops Grade 3 Nausea after receiving first cycle of CMF (cyclophosphamide, Methotrexate and 5FU)	◯	◯	◯
Patient with normal liver function and no known liver metastasis develops severe liver dysfunction after 4 cycles of epirubicin	◯	◯	◯
Patient receiving docetaxel develops a Grade 2 hypersensitivity reaction (rash, flushing urticaria, dyspnoea and temperature of 39o C	◯	◯	◯
Patient receiving Herceptin (trastuzumab) develops a Grade 2 hypersensitivity reaction (rash, flushing urticaria, dyspnoea and temperature of 39o C)	◯	◯	◯
Patient is hospitalised with neutropenic sepsis after second dose of Myocet (liposomal doxorubicin)	◯	◯	◯
Patient develops Grade 3 constipation after first dose of Alimta (pemetrexed)	◯	◯	◯
Patient develops superficial ulceration (Grade 2) around the injection site after a dose of Alimta (pemetrexed)	◯	◯	◯
Patient develops Grade 3 cough after first cycle of Alimta (pemetrexed)	◯	◯	◯
Patient develops Grade 3 Palmar-Plantar Syndrome after 2 cycles of Caelyx (liposomal doxorubicin)	◯	◯	◯
Patient develops laryngitis (Grade 2) after receiving docetaxel	◯	◯	◯
Patient presents with a DVT after 2 doses of Erbitux (cetuximab)	◯	◯	◯

14. Please indicate whether you think the following are roles of the Yellow Card Scheme?

	Yes	Not Sure	No
To ensure public safety	◯	◯	◯
To identify potentially serious ADRs that were too rare to be picked up during clinical trials	◯	◯	◯
To identify factors that might predispose to toxicity/ADRs (e.g. dose, age, renal function, liver function)	◯	◯	◯
To enable ADRs of medicines in similar therapeutic classes to be compared	◯	◯	◯
To identify any previously unknown reactions to a medicine (i.e. not listed in the Summary of Product Characteristics for the medicine)	◯	◯	◯
To monitor the safety of a medicine throughout its life	◯	◯	◯

15. A number of factors influence a health professional's decision when to send a Yellow Card Report. Which of the following would apply to you?

	Yes	Not Sure	No
Seriousness of a reaction	◯	◯	◯
Unusual ADRs not normally seen in oncology	◯	◯	◯
ADR not listed as a known side effect in the SPC	◯	◯	◯
A newly licensed medicine	◯	◯	◯
A new combination chemotherapy regimen (not necessarily containing a new medicine)	◯	◯	◯
Patient hospitalised or hospitalisation prolonged because of an ADR	◯	◯	◯
Significant drug interactions	◯	◯	◯
Latent drug induced cancers	◯	◯	◯
Adverse events resulting in dose delays	◯	◯	◯
A suspension of chemotherapy due to an adverse event (toxicity)	◯	◯	◯
Grade of adverse event (toxicity)	◯	◯	◯

If grade of toxicity is a factor, which grades?

16. There are a number of possible reasons why healthcare professionals do not make Yellow Card reports. Please consider the following opinions and indicate your level of agreement with each.

	Strongly Agree	Agree	Disagree	Strongly Disagree
Really serious ADRs are well documented by the time the medicine is marketed so do not see any point in reporting	◯	◯	◯	◯
Not certain of the causality of an ADR with a specific medicine	◯	◯	◯	◯
Inadequate information sources on ADRs to aid in determining which drug could be causing an ADR	◯	◯	◯	◯
Not a high priority in everyday clinical practice	◯	◯	◯	◯
Do not know what types of ADRs that should be reported via the Yellow Card scheme	◯	◯	◯	◯
Sheer volume of ADRs seen in oncology make it impossible to report them all	◯	◯	◯	◯
A single report is not enough to add to medical knowledge	◯	◯	◯	◯
Reporting is too time-consuming	◯	◯	◯	◯
Lack of professional obligation to report	◯	◯	◯	◯
Feeling of being personal liabile for ADR	◯	◯	◯	◯
Do not see benefit in reporting well recognised ADRs which are seen routinely in everyday clinical practice	◯	◯	◯	◯
Do not view oncology adverse events(toxicities) as an ADR(i.e. expect to see them and know how to prevent them or reduce their severity with pre-medication)	◯	◯	◯	◯
Lack of specific guidance on the types and grades of oncology ADRs to report via the Yellow Card Scheme	◯	◯	◯	◯
The Yellow Card form is too congested	◯	◯	◯	◯
People prefer to report directly to the pharmaceutical company instead of via the Yellow Card Scheme	◯	◯	◯	◯
Do not know how the information reported in Yellow Cards is utilised	◯	◯	◯	◯
Lack of feedback on reports received via the Yellow Card Scheme	◯	◯	◯	◯
Lack of adequate access to advice on ADR reporting or the Yellow Card Scheme	◯	◯	◯	◯
Fear that if I report an ADR via the Yellow Card I will be badgered to provide more information	◯	◯	◯	◯
Fear of looking stupid to other members of the patient care team (if they were to see a copy of the report)	◯	◯	◯	◯

17. In general ADRs are known to be under-reported. Please indicate your views on the following statements with respect to oncology by selecting one corresponding answer for each statement.

	Strongly Agree	Agree	Disagree	Strongly Disagree
Oncology ADRs are under-reported	◯	◯	◯	◯
The reporting rate of oncology ADRs is not any less than in other clinical areas	◯	◯	◯	◯
A reporting form that took less time to complete might help increase reporting in oncology (i.e. more tick boxes; less free format text; pre-populated fields on an electronic report such as patient details, medicines, past medical history, etc)	◯	◯	◯	◯

Any additional comments

18. Patient reporting via the Yellow Card Scheme was piloted by the MHRA in 2005 and officially launched in February 2008. Please indicate your opinion on the following statements regarding patient reporting of oncology ADRs

	Strongly Agree	Agree	Disagree	Strongly Disagree
Patient reporting of ADRs in oncology would be beneficial	◯	◯	◯	◯
Patients are not adequately trained to detect ADRs so accuracy of grading might be a problem	◯	◯	◯	◯
Patients would not be able to distinguish what ADR was serious enough to report without education	◯	◯	◯	◯
Patients might under-report ADRs (i.e. downplay toxicities to avoid having treatment delays)	◯	◯	◯	◯

Any additional comments

19. At present electronic prescribing systems are receiving some investment across Scotland. Within these systems electronic capture of NCI CTCAE (National Cancer Institute Common Terminology Criteria for Adverse Events)grades will most likely occur. Please give your opinion on the following statements in relation to this

	Strongly Agree	Agree	Disagree	Strongly Disagree
Electronic capture of NCI CTCAE grades in clinical practice will be beneficial	◯	◯	◯	◯
Anonymised, aggregate data resulting from electronic capture of NCI CTCAE grades would be beneficial in monitoring oncology adverse events Scotland wide	◯	◯	◯	◯
If the anonymised, aggregate data of NCI CTCAE grades could identify adverse event trends, this would be helpful to clinicians (possibly in making decisions on which medicines or regimens to use)	◯	◯	◯	◯
I would be interested in any results from aggregate data on oncology adverse event trends if it became available	◯	◯	◯	◯
I would be happy to contribute my patients' anonymised NCI CTCAE data for electronic linkage	◯	◯	◯	◯

Any additional comments

This is the end of the questionnaire. Thank you for your participation. A summary of the information obtained from this questionnaire will be available to all individuals who participated upon request.

Appendix 18

NHS Lothian –
University Hospitals Division

Department of Pharmacy
Royal Infirmary of Edinburgh
51 Little France Crescent
Old Dalkeith Road
EDINBURGH
EH16 4SA

Telephone 0131 242 2919
Fax 0131 242 2925
E-mail: Melinda.cuthbert@luht.scot.nhs.uk

Your Ref:
Our Ref: crossfire/mphil/questionnaire/letterver1

Certificate No: FS 31228

Dear Colleague

Questionnaire for Clinicians, pharmacists and nurses working in oncology in Scotland

I am a pharmacist working at the Royal Infirmary of Edinburgh within Medicines Information/ Yellow Card Centre Scotland. I am currently enrolled in a MPhil at the University of Strathclyde. The title for my research project is "Improving standards of pharmacovigilance practice in oncology". One of my research objectives is to identify the range of knowledge and attitudes of oncology healthcare professionals on the need for reporting of ADRs in oncology. This questionnaire would help me to ascertain this information.

All healthcare professionals working in oncology will encounter ADRs on a daily basis in their clinical practice. Not all of the ADRs, which meet the criteria for reporting, get reported via the Yellow Card Scheme however. The reasons why oncology healthcare professionals do not report these ADRs via the Yellow Card Scheme are of interest to me in my research. Specifically all ADRs observed in oncology (neo-adjuvant, adjuvant or palliative) out with clinical trials. To complete this questionnaire please go to the web page:

http://www.surveymonkey.com/s.aspx?sm=X7nAk_2b7LujSmnLMD3dQ57A_3d_3d

It should take about 10 minutes to complete and I would appreciate if you could complete the questionnaire by 19 November 2008. All information provided will be treated confidentially. I will send a reminder letter in 3 weeks, if you have already responded please disregard this letter.

Please contact me via telephone or e-mail (see above for details) if you have any questions or require any further information. Thank you very much for taking the time to complete this questionnaire.

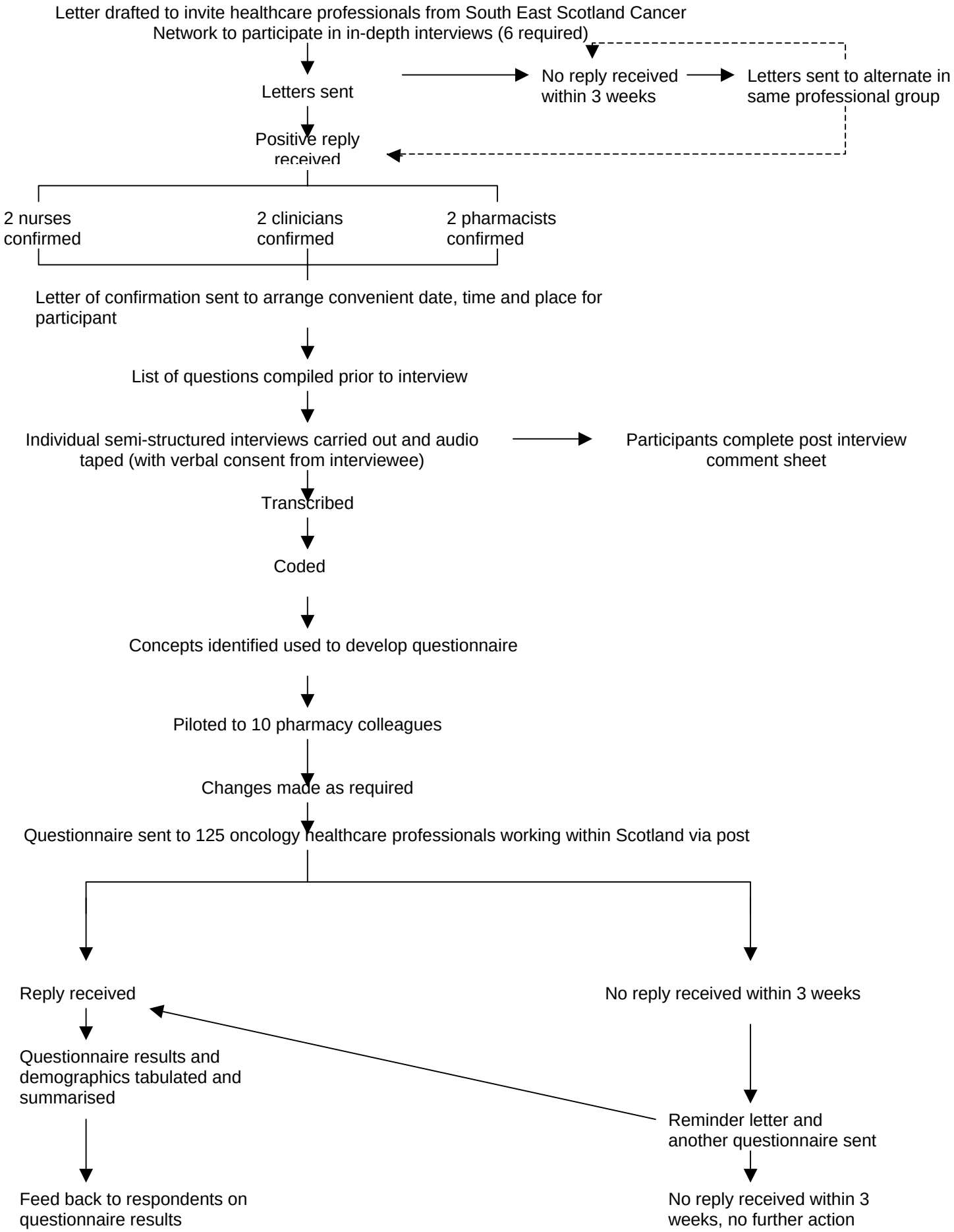
Yours Sincerely

Melinda Cuthbert
Senior Pharmacist

The Yellow Card Scheme is the voluntary adverse drug reporting scheme ran by the Medicines and Healthcare products Regulatory Agency and the Commission on Human Medicines in the UK. Healthcare professionals and patients can report suspected ADRs via the Yellow Card Scheme. More information on the Yellow Card Scheme can be viewed at:
http://www.mhra.gov.uk/Safetyinformation/Howwemonitorthesafetyofproducts/Medicines/TheYellowCardScheme/index.htm

Appendix 19

Objective 2: To identify the range of attitudes of oncology healthcare professionals on the need for improving reporting of ADRs in oncology



Appendix 20

From: Bailey, Alex
Sent: 04 June 2008 09:12
To: Cuthbert, Melinda
Subject: ethics

Dear Melinda,

Walter Hunter forwarded your email regarding ethical approval of your MPhil project as I am the scientific adviser for Scotland A REC. Following on from the chair of Scotland A RECs comments that part I does not require ethical review. Looking at the questionnaire for part II, I can advise you that this does not require review by an NHS REC as it is a service evaluation. If you could forward me a complete protocol for the project, I can produce a letter to this effect for you (if your require it).

Regards,

Alex

Alex Bailey
Deaconess House
148 Pleasance
Edinburgh
EH9 9RS
Tel: 0131 536 9050

-----Original Message-----
From: Hunter, Walter
Sent: 06 March 2007 11:55
To: Cuthbert, Melinda
Subject: Re: FW: FW: Is submission to ethics committee necessary for this?

Hi Melinda

The Chairman has considered the outline of your project. He commented:

No need for REC review of part I. Part II may also escape but difficult to tell without knowing something of the content of the nascent questionnaire."

Hope this is helpful.

Walter Hunter
Committee Co-ordinator
MRTEC for Scotland A
Tel: 0131 536 9026

From: Cuthbert, Melinda
Sent: 13 February 2007 12:28
To: 'lrec@lhb.scot.nhs.uk'
Subject: FW: FW: Is submission to ethics committee necessary for this?

Dear Sir or Madam

I am currently enrolled in a MPhil in oncology Adverse Reactions titled "Improving pharmacovigilance standards in oncology". I am about to start on objective 2 of my research protocol which involves doing exploratory interviews individually with 6 members of clinical staff within the Oncology centre at Edinburgh Cancer Centre who are previous collegues of mine when I worked there. These interviews will help to form the basis of a questionnaire that will be developed to obtain views on oncology ADR reporting, and it will be circulated Scotland wide to members of the oncology multidisciplinary team.

I am attaching a summary chart of the proposed objective 2 for your review. If you could advise If I will require ethics approval before performing the interviews with colleagues I would be grateful. Also I am almost certain that I will need to seek ethic approval from MREC for the questionnaire once designed but if you could confirm it would be appreciated.

Many thanks
Melinda Cuthbert
Senior Pharmacist

Appendix 21

Question 1	*Are you familiar with the Yellow Card Scheme for spontaneous reporting of ADRs? How does it work?*

Summary of responses

All interviewees reported that they were aware of the Yellow Card Scheme.
Most appeared to know how the scheme is designed to operate although there was some confusion with the Green Card for nurses. Some gave details of how the scheme operated in their own workplace, rather than describing the general underlying principles.
Some of those interviewed were aware that an electronic system of reporting is available, but no-one used it.

When asked who can use the scheme to report an ADR there was uncertainty among participants. All but one suggested that doctors, nurses and pharmacists can do this, and two added that perhaps patients can also do so.

In relation to the criteria for reporting an ADR, interviewees' knowledge was uneven. Nurses were unaware of the criteria; pharmacists showed awareness although one indicated that the criteria for reporting are different in oncology. One clinician demonstrated knowledge of the criteria while the other did not. Both pharmacists and one clinician mentioned newly licensed drugs listed with a black triangle in the BNF as one of the criteria, and three of the six interviewees suggested that 'serious' ADRs should be reported.
No interviewee was aware of any areas of specific interest, and the nurses suggested that they are confused about the difference between a side-effect and an ADR.

Illustrative quotations

- 'I am aware that there is a scheme for reporting adverse drug reactions'
- 'You fill in a yellow card and send it off if you suspect something is an ADR'
- 'In practice here if the patient comes into the ward they fill it in and send it down to us….'
- 'Nurses, doctors and pharmacists I presume [can use the scheme]. I presume there is some kind of mechanism for patients to report ADRs but I'm not sure.'
- 'Anything that is supposedly a rare side effect of the drug [can be reported], or if it is a black triangle drug in the BNF'
- 'Any type of ADR [can be reported] because you're interested in whatever drugs are doing to the majority of patients.'
- '…apart from in oncology, when I have worked as a clinical pharmacist I tended to report anything that was very rare or a side effect that is not often seen…..'
- '..I know that with some chemotherapy drugs…one of the known side effects of that is actually anaphylaxis but I wouldn't class that as an adverse drug reaction if you see what I mean…'
- '..you see so many you think of it more as a recognised side effect rather than as an ADR. It probably is an ADR as much as it is a side effect though, isn't it?'

Question 2	*What purpose do you think this scheme serves?*

All participants indicated that the scheme gathers information and four suggested that it serves to identify potentially serious ADRs that may be too rare to show up in clinical trials. Two interviewees mentioned that the scheme serves to increase safety of medicines, and one suggested that it can help to show up differences between patient groups in their reaction to drugs.

Illustrative quotations

- 'So at least you can get some information on the drug when it is actually being used in the population since previously to that it will have been used in a small select population in trials..'
- 'I think there are certain drugs where ADRs tend to be serious but not common enough to be picked up in clinical trials…and separate to that there are drug interactions which might not be seen in clinical trials'
- '…build up a better safety profile of the drug.'
- 'It is to get information on safety of using the drugs…'

Question 3	*Do you think it is beneficial to public safety?*

All interviewees felt that the scheme is beneficial or potentially beneficial to public safety. Supporting comments included that the scheme monitors drug problems, gives a fuller picture, and can detect unexpected ADRs. Three people qualified their answer: one pointed out that the system depends on an adverse effect being recognised; one suggested that it is important to distinguish between established side effects and ADRs; and the third emphasised that the healthcare professionals need to take the scheme seriously and to report anything that might be an ADR.

Illustrative quotations

- 'Oh yes…because we're keeping a close eye on the drugs.'
- 'It can be helpful…the difficulty with the scheme is that it relies on someone considering something an adverse effect.'
- 'Yes, I'm sure it is. I know on several occasions drugs that have had new or unexpected side effects have been detected through the system.
- 'If people are a bit complacent about it then you won't get the details that you need from the report.'

Question 4	*Have you ever reported a suspected ADR via the Yellow Card Scheme? Was it easy to do? Any suggestions of improvements?*

The pharmacists and clinicians reported that they had used the Yellow Card Scheme, and it was seen to be easy to use. In relation to suggested improvements, one interviewee felt that the scheme should be restricted to unexpected events that have not been described in the SPC, while two others felt that there was inadequate space to write on the paper card.

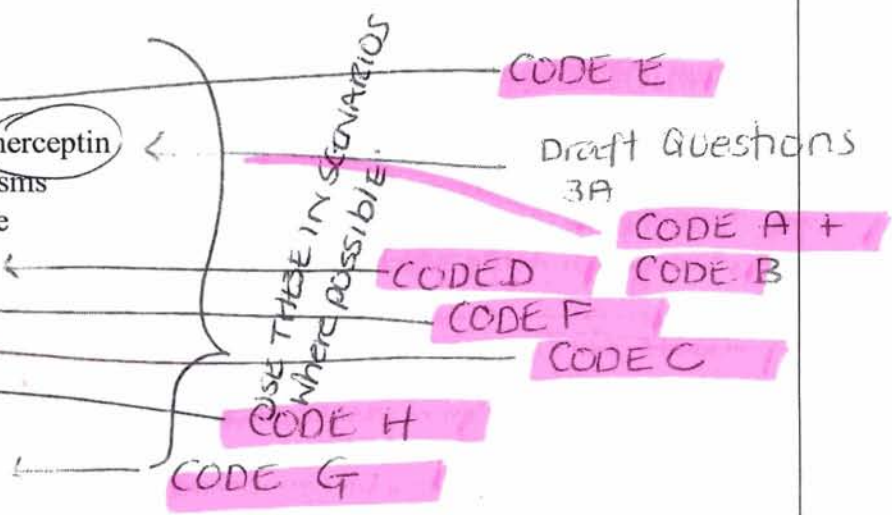
Illustrative quotations

- 'In my view it should be restricted to those events that are unexpected …[this] might focus the system on identifying those rare events that only become evident in the post-marketing phase when large numbers are exposed.'
- '…the space to record the drug at the top, especially if chemotherapy regimen, there are often not enough lines….and also the drug history, the concurrent drug therapy section is fairly small…'
- 'I think the card is quite congested'

Questions 5 & 6	*Have you ever reported an oncology-related ADR via the Yellow Card Scheme? What types would you report?*

The pharmacists and clinicians said that they had reported oncology-related ADRs.
The types of ADR that interviewees mentioned that they would report were:

- problems with IV antibiotics
- problems with Morphine
- problems with Steroids
- Skin eruptions
- Hypersensitivities to taxol and herceptin
- Oxalaplatins with laryngeal spasms
- Hand and foot with capecitabine
- Diarrhoea with capecitabine
- Hepatic problems
- Renal failure
- Significant GI symptom
- Severe respiratory reactions
- Neutropenic sepsis, grade 4



Interviewees were given a list of ADRs and asked whether they think they should be reported:

Neutropenic sepsis Two said that they would report, two said no, and two replied that they would not if this were an expected side effect of the particular drug.

Grade 4 stomatisis Four replied that they would report, one said sometimes, and one said no.

Grade 2 thrombocytopenia None of the interviewees said that they would report this.

DVT or PE Three people said that they would report if they though this was caused by the drug rather than the condition. Three thought that they would not.

Anaphylaxis post chemo infusion Three interviewees said yes, two said only if it was an unexpected side effect, and one replied that it would depend on the severity.

Illustrative quotations

- '…we do see quite a lot so it becomes second nature to staff, and there is a protocol in place to follow….It is kind of almost expecting it and pre-empting it.'
- 'I probably wouldn't report that as an ADR because especially in oncology it's more likely to be related to the malignancy than rather than an actual drug.'
- 'Depends upon what the drug is. So if it's a chemotherapy drug that has been on the market for a while and it's in the datasheet as a side effect that's well reported, then no.'

Question 7	*Are oncology ADRs underreported in your opinion?*

Five of those interviewed felt that oncology ADRs are probably underreported, while one person did not.

Illustrative quotations

- 'I know for neutropenic sepsis we are all told to fill out yellow cards….with the newer drugs..I think we are more aware of side effects expected and they are all black triangle so we know to report anything serious..'
- 'You know we see a lot of the same things; we see dozens of ADRs with taxanes in a month so I suppose we become a bit used to it and don't see it as an ADR.'
- 'I don't know if there should be certain guidelines there that should be telling about chemotherapy ADRs, which ones we should be highlighting on the yellow card..'

Question 8	*Would more specific guidance from the MHRA on the types and grades of oncology and adverse events (toxicities) to be reported help you in recognising what types of oncology ADRs to report?*

Everyone interviewed agreed that more guidance from the MHRA would encourage people to use the Yellow Card Scheme.

Illustrative quotations

- 'I think that would absolutely be beneficial. I think it would be good across Scotland to actually ensure that everyone was doing the same thing.'
- 'Maybe if we knew what they wanted'
- 'Yes, particularly if it was more focused and more targeted. In other words we weren't expected to report every event we have already described to our patients as an expected event.'
- 'Yes, probably if you are given more specific guidelines it raises your awareness and you're more likely to do that.'
- 'I think it is quite good just now but I think that if we had more guidance we would probably pick up things we are not reporting that should be reported from an education point of view.'

Question 9	*There is a separate reporting scheme for HIV ADRs. Do you think there would be any advantage of having a separate one for oncology ADRs?*

Three interviewees answered that there would be no advantage, while three thought that there might be.

Illustrative quotations

- 'I think that all drugs should go through the same regulatory reporting mechanism.
- 'It seems to me the major issue is that many of the oncology drugs are being exposed to say four or five thousand patients before they come to the market but they need to be exposed to tens of thousands of patients before the rarer…events are detected.'
- 'I think it probably would be useful to know how common a specific ADR is..'
- 'I suppose you would want to know side effects of new drugs on the market…a lot of these [oncology] drugs are still being used on a trial basis so [side effects] are reported through the trials so they probably don't reach the MHRA.'

Question 10a	*Have you reported NCI common toxicity grades to industry via sponsored trials or via EUDRACT? What is the purpose/benefit of this?*
Four people said that they had had some level of involvement in trials. Sponsored trials and EUDRACT were seen to provide valuable information on the frequency of common events and latent effects and to build a bigger picture on cost implications and patient safety to aid prescribing decisions. They were also thought to provide a means of comparing treatments.	
Illustrative quotations 'I think it gives you an idea of what to expect…and what monitoring is required.' 'You can see more side effects and build up the bigger picture..' '..if you're comparing treatments of relatively similar efficacy.. then the toxicity profile might be important.'	

Question 10b	*Would a continuation of such intensive monitoring be beneficial?*
In general, participants acknowledged the value of intensive monitoring but recognised that there are logistical problems about continuing at such a level. The time of staff and patients is a factor, and some felt that most side effects would have been identified during the trials.	
Illustrative quotations • 'A drug that is … in everyday use.. has been through all these trials and will hopefully have ironed out the problems.' • 'I think probably in the climate at work we wouldn't have the time…' • '..time issues about it, and who would follow it up, whose responsibility would it be?' • 'I think that once the trial has run for a year and a half ...you already have that experience of use with the drug…' • 'Often clinical trials are not robust enough to give us the information but you can't monitor all drugs like that forever.'	

CODE Q

Question 11a	*Do you think electronic prescribing and capture of NCI toxicity grades in clinical practice would be beneficial?*
All of those interviewed replied that electronic prescribing and recording of NCI toxicity grades would be beneficial; five people appeared to be wholly positive about this idea, suggesting that it could reduce variability in interpreting the criteria, lessen the chance of missing a toxicity, collate data and allow easier access to it, and avoid the problem of missing casenotes. One interviewee qualified their comments with concerns that such a system would cause an increased workload, and also that there would be a serious problem if the electronic system crashed.	
Illustrative quotations 'An electronic system would have the possibility of a pop-up flag to remind you of what each grade means.' 'Ideally we would have an electronic prescribing system that would link in with pharmacy…and the whole record would be there.' 'I think we'll have to do the paper recording and the electronic recording, it will be double the work. [And] what will it be like when [the computer system] goes down!'	

CODE S

CODE R

CODE T

Question 11b	Would a nationwide anonymised aggregate of these data be of benefit?

Potential benefits of aggregated data were suggested as monitoring toxicities, gathering national data and identifying trends, and helping clinicians decide what drug to use.

All 6 interviewees said that they would be willing to contribute data to such a database, although two were concerned that this might increase the workload.

Most people thought that it would be feasible to develop such a database in Scotland, but it was pointed out that this would need to be resourced adequately.

Illustrative quotations

'For newer drugs it would be quite good to, across the UK say, be able to see what has been experienced elsewhere and build up a more complete picture'

'I think we already have a programme for filling in near misses and incidents. So you are filling in that and you're filling in the patient's notes and you have to do a yellow card, it is a lot of paperwork plus your care plan.'

'[It] would be an advantage of electronic prescribing when it can be linked directly to the capture of data nationwide, on deaths for example or major morbid events, because I think we do not know that kind of data.'

[To develop such a database in Scotland] is absolutely essential to the future in my view…at present in general we have poor follow-up data on our patients…'

'..I suspect we are already halfway there.'

'..People with the worst toxicities do not attend for any more chemo.. so there could be gaps in the dataset. And they don't always come back to oncology either so the gaps will be with the patients with the most problems…'

Question 12	Do you think that patient reporting of ADRs in oncology would be of any value?

Five of the interviewees were generally fairly positive about the idea of patient reporting of ADRs. One disagreed, seeing it as a problem that patients are not trained to identify ADRs; other reservations expressed were whether the quality of the data might vary and whether patients would under-report.

Illustrative quotations

' I suspect that three-quarters of patients could quite easily input data directly themselves, and we would get it much more frequently. But the concern… is what to do with the patients with toxicities who have not contacted you.'

'.. there will always be some groups of patients who will be more willing to report than others.'

'..the problem might be grading. …they are not trained people …and accuracy is even difficult with trained staff.'

'..they would also need to be educated and not to report, you know, nausea for example, it's not a severe adverse effect.'

'I think patients tend to downplay things.'

Appendix 22

Draft questions for questionnaire

Demographics Type Questions

[YUN1]

1 What is your profession?

□ Doctor
□ Nurse
□ Pharmacist
□ Other, Please specify_____

2 Number of years qualified? _____Years

3 Number of years working in oncology? _____Years

4 Your main focus of your job?[YUN2]

□ Managerial
□ Strategic
□ Clinical
□ Research
□ Other, please specify_____

5 Number of patients seen each day in clinical practice

□ <10
□ 11-20[YUN3]
□ 20-30
□ >30

6 Sex

□ Male
□ Female

7 Age

□ 20-30
□ 31-40
□ 41-50
□ 51-60
□ >60

Behaviour type questions

8 Have you completed a Yellow Card report for an adverse drug reaction during your career?

Never	□
1 – 5 times	□
6 – 10 times	□
11 – 20 times	□
20 or more	□

If you have never completed a Yellow Card report please go now to question 11.

9 Of the Yellow Card reports you have completed for adverse drug reactions during your career how many were for oncology patients?

None □
1 – 5 □
6 – 10 □
11 – 20 □
Over 20 □

10 Yellow Card reporting can be done on paper (sent via post) or electronically at www.yellowcard.gov.uk .

Please tick the box for your preference for reporting below

I prefer to use paper Yellow Cards	
I prefer to complete electronic Yellow Cards	
Why?	

Could you please tick the box(es) that apply to you below:

Where do you normally complete the Yellow Card?	*Ward* _____ *Office* _____ *Pharmacy* _____ *Other, Please specify* _____

11 Do any of the following statements about Yellow Card Reporting apply to you?

I have wanted to report an ADR via the Yellow Card Scheme but was unable to find a yellow card	Yes	*No*
I have wanted to report an ADR via the Yellow Card Scheme but was unable to obtain access to the electronic Yellow Card	Yes	*No*
I have had a suspicion of an ADR or knew that an ADR has occurred but did not have time to complete	Yes	*No*
I have seen ADRs in clinical practice but I am not sure which ones the MHRA want me to report	Yes	*No*
I have thought about reporting an ADR but did not do it at the time it occurred and then forgot to do it later	Yes	*No*
I have completed a Yellow Card for an ADR but did not send it	*Yes*	*No*

12 Which of the following oncology adverse events (toxicities) would you report[YUN4]?

Matrix for questions that need to be covered in this section

Is the Side Effect listed in the SPC	Is side effect serious?	Status of medicine			
		Black Triangle		Older Medicine	
		Grade 1-2	Grade 3-4	Grade 1-2	Grade 3-4
Known side effect	Serious	a	e	i	m
	Not Serious	b	f	j	n
Not a known side effect	Serious	c	g	k	o
	Not Serious	d	h	l	p

A	Patient receiving Herceptin develops a Grade 2 hypersensitivity reaction (rash, flushing urticaria, dyspnoea and temperature of 39° C) (Code A)	Yes	Not Sure	No
B	Patient develops superficial ulceration (Grade 2) around the injection site after a dose of Myocet (liposomal doxorubicin) (Code E)	Yes	Not Sure	No

C	Patient receiving Avastin (bevacizumab) develops acute renal failure (Grade 3; no dialysis required) (Code C)	Yes	Not Sure	No
D	Patient develops Grade 2 watery eyes after receiving second cycle of Myocet (liposomal doxorubicin)	Yes	Not Sure	No
E	Patient is hospitalised with neutropenic sepsis after second dose of Myocet (liposomal doxorubicin) (Code G)	Yes	Not Sure	No
F	Patient develops Grade 2 constipation after first dose of Alimta (pemtrexed)	Yes	Not Sure	No
G	Patient presents with a DVT after 2 doses of Erbitux (cetuximab)	Yes	Not Sure	No
H	Patient develops Grade 3 cough after first cycle of Alimta (pemtrexed)	Yes	Not Sure	No
I	Patient receiving docetaxel develops a Grade 2 hypersensitivity reaction (rash, flushing urticaria, dyspnoea and temperature of 39^{o} C (Code B)	Yes	Not Sure	No
J	Patient develops Grade 2 diarrhoea after second cycle of Xeloda (capecitabine) (Code D)	Yes	Not Sure	No
K	Patient develops laryngitis (Grade 2) after receiving docetaxel	Yes	Not Sure	No
L	Patient develops grade 2 obesity after completing 6 cycles of irinotecan	Yes	Not Sure	No
M	Patient develops Grade 3 Palmar-Plantar Syndrome after 2 cycles of Caelyx (lioposomal doxorubicin)	Yes	Not Sure	No
N	Patient develops Grade 3 Nausea after receiving first cycle of CMF (cyclophosphamide, Methotrexate and 5FU)	Yes	Not Sure	No
O	Patient with normal liver function and no known liver metastasis develops severe liver dysfunction after 4 cycles of epirubicin (Code F)	Yes	Not Sure	No
P	Patient develops Grade 3 bloating after receiving cisplatin (Code H)	Yes	Not Sure	No

Knowledge type questions

13 There are numerous terms used in pharmacovigilance. Please indicate your understanding of the following by …

An adverse Drug Reaction (ADR) is defined as any response to a medicine that is noxious and unintended and occurs at doses normally used for prophylaxis, diagnosis or therapy or disease, or for modification of physiological function	Yes	Not Sure	No
An adverse event is any untoward medical occurrence that may present during treatment with a pharmaceutical product but which does not necessarily have a causal relationship with this treatment	Yes	Not Sure	No
Adverse events are collected during clinical trials	Yes	Not Sure	No
In oncology adverse events are referred to as toxicities	Yes	Not Sure	No
All ADRs are adverse events but not all adverse events are ADRs	Yes	Not Sure	No
An unexpected adverse drug reaction is an adverse reaction, the nature or severity of which is not consistent with domestic labelling or market authorization, or expected from characteristics of the drug	Yes	Not Sure	No
The term side effect is used synonymously with adverse drug reaction (Code BB)	Yes	Not Sure	No
Patient's toxicity scores (accessed after each cycle of	Yes	Not Sure	No

chemotherapy) are all adverse events			
Patient's toxicity scores (accessed after each cycle of chemotherapy) are all adverse drug reactions	Yes	Not Sure	No
Pre-marketing clinical trials and post-marketing surveillance address different issues	Yes	Not Sure	No
Post-marketing surveillance data provide new information that was unavailable in pre-marketing studies	Yes	Not Sure	No
The side effects listed in the Summary of Product Characteristics for a medicine are ADRs (Code CC)	Yes	Not Sure	No

[YUN5]

14 Can you indicate from the following which factors you think are important in oncology when trying to make a decision whether to send a Yellow Card Report?

	Yes	Not Sure	No
Seriousness of a reaction	Yes	Not Sure	No
Unusual ADRs not normally seen in oncology	Yes	Not Sure	No
ADR not listed as a known side effect in the SPC	Yes	Not Sure	No
A newly licensed medicine	Yes	Not Sure	No
A new combination chemotherapy regimen (not necessarily containing a new medicine)	Yes	Not Sure	No
Patient hospitalised or hospitalisation prolonged because of an ADR	Yes	Not Sure	No
Significant drug interactions	Yes	Not Sure	No
Latent drug induced cancers	Yes	Not Sure	No
Grade of toxicity	Yes	Not Sure	No
Any additional comments:			

15 Can you indicate from the following what you think is the purpose of the Yellow Card Scheme?

	Yes	Not Sure	No
To ensure public safety (Code K)	Yes	Not Sure	No
To identify potentially serious ADRs that were too rare to be picked up during clinical trials (Code I)	Yes	Not Sure	No
To increase the safety profile of medicines (Code J)	Yes	Not Sure	No
To identify factors that might predispose to toxicity/ADRs (e.g. dose, age, renal function, liver function)	Yes	Not Sure	No
To enable ADRs of medicines in similar therapeutic classes to be compared	Yes	Not Sure	No
To identify any previously unknown reactions to a medicine (i.e. not listed in the Summary of Product Characteristics for the medicine)	Yes	Not Sure	No
To monitor the safety of a medicine throughout its life	Yes	Not Sure	No

[YUN6]

16 What proportion of your patients receiving chemotherapy do you estimate suffers any kind of adverse drug reaction; and what proportion suffers a serious ADR? Please tick one box only in each row from the following options:

	<1%	1 – 10%	11 – 20%	21 – 30%	31 - 40%	41 – 60 %	61 - 80%	>80%

								[YUN7]
Any kind of ADR								
Serious ADR only								

Attitude/Opinion Type Questions

17 There are a number of possible reasons why healthcare professionals do not make Yellow Card reports. Please indicate your views on the following statements from the perspective of oncology by …

	Strongly Agree	Agree	Disagree	Strongly Disagree
Really serious ADRs are well documented by the time the medicine is marketed				
I would only report an ADR if I were sure about the causality with a specific medicine				
I do not have adequate information sources on ADRs to allow me to determine which drug could be causing an ADR				
I do not have time while in clinical practice to consider the involvement of a medicine or other causes when an adverse event occurs in an oncology patient				
ADR reporting is not a high priority in everyday clinical practice				
I do not know the types of ADRs I should report via the Yellow Card scheme				
I know the criteria for which the MHRA would like to receive a Yellow Card report for but the shear volume of ADRs seen in oncology make it impossible to report them all (Code N)				
The one report of an individual healthcare professional of an ADR could not contribute to medical knowledge[YUN8]				
I would be more likely to report if there were an easier method (e.g. contact via telephone; electronic Yellow Card that can be pre-populated with patient details, medicines, past medical history, etc)				
I think the best way to report an ADR is in the medical literature not via the Yellow Card Scheme[YUN9]				
I do not have a professional obligation to report ADRs				
I would report ADRs more often if there was a financial incentive[YUN10]				
Reporting ADRs increases personal liability				
Complacency (i.e. see so many in every day practice you come to expect the ADRs) contributes to not reporting oncology ADRs (Code M)				
I do not think it is necessary to report well recognised ADRs				

There is no point in reporting ADRs that are commonly seen or a known side effect in oncology (i.e. expect to see them and know how to prevent them or reduce their severity with pre-medication) (Code DD)				
All serious ADRs should be reported				
Only unexpected ADRs should be reported (Code EE)				
Specific guidance (i.e. focused and targeted) from the MHRA on the types and grades of oncology ADRs to report via the Yellow Card Scheme in oncology might assist me to report more ADRs (Code O)				
A separate reporting scheme for oncology (e.g. specifically abbreviated form with more tick boxes and less free text) would encourage me to report more (Code P)				
The Yellow Card form is too congested (Code FF)				
I report ADRs to pharmaceutical company directly instead of via the Yellow Card Scheme				
I do not know how the information reported in Yellow Cards is utilised				
I would be more inclined to report ADRs via the Yellow Card Scheme if there was greater feedback on the types of ADRs				
I do not have adequate access to advice on ADR reporting or the Yellow Card Scheme				
If I report an ADR via the Yellow Card I will be badgered to provide more information				
I do not report possible ADRs for fear of looking stupid to other members of the multi-professional team (if they were to be sent a copy of the report)				

18 In general ADRs are known to be under-reported. Please indicate your views on the following statements in respect to oncology by …

	Strongly Agree	Agree	Disagree	Strongly Disagree
Oncology ADRs are under-reported (Code K)				
The reporting rate of oncology ADRs is not any worst then in other clinical area (Code L)				
Any additional comments				

19 A Black Triangle status is applied to a medicine first when it is licensed. The criterion for reporting via the Yellow Card Scheme for Black Triangle medicines is that all suspected reactions should be reported. This means that all suspected adverse effects (regardless of seriousness) of a medicine should be reported even if it is listed as a known expected side effect in the Summary of Product Characteristics for the product. Please indicate your views on the following statements by …

	Strongly	Agree	Disagree	Strongly

	Agree			Disagree
Reporting of all suspected ADRs in oncology is not practical for new oncology medicines once licensed				
Reporting of all suspected ADRs for new oncology medicines once licensed is not beneficial to increasing the safety of the medicine				
I would report all suspected ADRs for a new medicine in oncology once licensed				
I would report suspected ADRs for a new oncology medicine only if it were not listed as a known suspected side effect in the Summary of Product Characteristics				
I would report only serious suspected ADRs for a new oncology medicine once licensed				
I would not report more common oncology ADRs (i.e. ones that you see most often) for a new oncology medicine even if it were not listed as a known suspected side effect in the Summary of Product Characteristics				

20 The general definition for a serious ADR is defined as *any ADR that results in as any untoward medical occurrence that at any dose results in death, requires hospital admission or prolongation of existing hospital stay, results in persistent disability/incapacity, or is life threatening.* Please give your opinion on the following statements with application to oncology by…

	Strongly Agree	Agree	Disagree	Strongly Disagree
Haematological ADRs (e.g. thrombocytopenia, leucopenia, anaemia, neutropenia) are serious ADRs				
The grade of a toxicity will determine if it is serious or not				
Grade 4 toxicities are serious				
Grade 3 toxicities are serious				
Grade 2 toxicities are serious				
Grade 1 toxicities are serious				
Dose delays due to toxicities are serious				
Hypersensitivity reactions to medicines are serious				
Suspending treatment with a chemotherapy agent/regimen due to toxicities would be serious				
Other comments on serious ADRs in oncology:				

21 At present electronic prescribing systems are being invested in across Scotland. Within these systems electronic capture of NCI CAEC grades will most likely occur. Please give your opinion on the following statements in relation to this

	Strongly Agree	Agree	Disagree	Strongly Disagree
Electronic capture of NCI CAEC grades in clinical				

practice will be beneficial (Code Q)				
Annonymised, aggregate data resulting from electronic capture of NCI CAEC grades would be beneficial in monitoring oncology adverse events Scotland wide (Code U)				
If the annonymised, aggregate data of NCI CAEC grades could identify adverse event trends, this would be helpful to clinicians (possibly in making decisions on which medicines or regimens to use) (Code V)				
I would be interested in any results from aggregate data on oncology adverse event trends if it became available				
I would be happy to contribute my patients' anonymised NCI CAEC data for electronic linkage (Code W)				
Any additional comments:				

22 Patient reporting via the Yellow Card Scheme was launched by the MHRA in 2005. Please indicate your opinion on the following statements regarding patient reporting of oncology ADRs

	Strongly Agree	Agree	Disagree	Strongly Disagree
Patient reporting of ADRs in oncology would be beneficial (Code X)				
Patients are not adequately trained to detect ADRs so accuracy of grading might be a problem (Code Y)				
Patients would not be able to distinguish what ADR was serious enough to report without education (Code Z)				
Patients might under-report ADRs (i.e. downplay toxicities to avoid having treatment delays) (Code AA)				
Any additional comments:				

Appendix 23

Oncology Healthcare Professionals' Attitudes and Opinions on ADR

Demographics

1. What is your profession?

- ◯ Doctor
- ◯ Nurse
- ◯ Pharmacist
- ◯ Other (please specify)

2. Number of years qualified?

3. Number of years working in oncology?

4. How much of your job is devoted to patient care in oncology?

- ◯ None
- ◯ < 25%
- ◯ 25 - 50%
- ◯ 51 - 75%
- ◯ > 75%

5. Gender?

- ◯ Male
- ◯ Female

6. Age?

- ◯ 20-30
- ◯ 31-40
- ◯ 41-50
- ◯ 51-60
- ◯ >60

Pilot of Questionnaire

Comments to Melinda Cuthbert by 13 June 2008 please (if at all possible)

Oncology Healthcare Professionals' Attitudes and Opinions on ADR

7. How many times, if ever, have you completed a Yellow Card report for an adverse drug reaction during your career?

- ◯ Never
- ◯ 1 - 5 times
- ◯ 6 - 10 times
- ◯ 11 - 20 times
- ◯ > 20

IF NEVER PLEASE GO TO Question 11.

8. Of the Yellow Card reports you have completed for adverse drug reactions during your career how many were for oncology patients?

- ◯ None
- ◯ 1 - 5
- ◯ 6 - 10
- ◯ 11 - 20
- ◯ > 20

9. Yellow Card reporting can be done on paper (sent via post) or electronically at www.yellowcard.gov.uk . Please tick the box of your preference for reporting

- ◯ I prefer to complete paper Yellow Cards
- ◯ I prefer to complete electronic Yellow Cards
- ◯ I have no preferred choice

If you have a preference, please explain why

10. When you do complete a Yellow Card where do you normally complete the report?

- ◯ Ward
- ◯ Outpatient
- ◯ Pharmacy
- ◯ Office
- ◯ Other (please specify)

11. Do any of the following statements about Yellow Card Reporting apply to you? Please tick all that apply.

- ☐ I have wanted to report an ADR but was unable to find a yellow card
- ☐ I have wanted to report an ADR but was unable to obtain access to the electronic Yellow Card
- ☐ I have seen ADRs in clinical oncology practice but I am not sure which ones the MHRA want me to report
- ☐ I have completed a Yellow Card for an ADR but did not send it
- ☐ I often recognise ADRs in patients receiving chemotherapy but choose not to report believing that they are inevitable consequence of therapy and little relevance for reporting
- ☐ None of the above

12. What proportion of your patients receiving chemotherapy do you estimate suffers any kind of adverse event (toxicity); and what proportion suffers a serious adverse event (toxicity)? Please tick one box only in each row from the following options:

	<1%	<5%	<10%	<25%	<50%	<75%	>75%
Any kind of adverse event (toxicity)	○	○	○	○	○	○	○
Serious adverse event (toxicity)only	○	○	○	○	○	○	○

13. Which of the following oncology adverse events (toxicities) do you think you would report on a Yellow Card?

	Yes	Not Sure	No
Patient develops Grade 3 Palmar-Plantar Syndrome after 2 cycles of Caelyx (liposomal doxorubicin)	○	○	○
Patient develops Grade 3 bloating after receiving cisplatin	○	○	○
Patient receiving Herceptin(trastuzumab)develops acute renal failure (Grade 3; no dialysis required)	○	○	○
Patient develops fatigue after receiving docetaxel(third cycle)and first dose of Herceptin (trastuzumab)	○	○	○
Patient is hospitalised with neutropenic sepsis after second dose of Myocet (liposomal doxorubicin)	○	○	○
Patient receiving Herceptin (trastuzumab) develops a Grade 2 hypersensitivity reaction (rash, flushing urticaria, dyspnoea and temperature of 39o C)	○	○	○
Patient develops Grade 2 diarrhoea after second cycle of Xeloda (capecitabine)	○	○	○
Patient develops Grade 3 cough after first cycle of Alimta (pemtrexed)	○	○	○
Patient develops Grade 3 Nausea after receiving first cycle of CMF (cyclophosphamide, Methotrexate and 5FU)	○	○	○
Patient develops superficial ulceration (Grade 2) around the injection site after a dose of Alimta (pemetrexed)	○	○	○
Patient develops Grade 2 constipation after first dose of Alimta (pemtrexed)	○	○	○
Patient develops laryngitis (Grade 2) after receiving docetaxel	○	○	○
Patient presents with a DVT after 2 doses of Erbitux (cetuximab)	○	○	○
Patient receiving docetaxel develops a Grade 2 hypersensitivity reaction (rash, flushing urticaria, dyspnoea and temperature of 39o C	○	○	○
Patient with normal liver function and no known liver metastasis develops severe liver dysfunction after 4 cycles of epirubicin	○	○	○

14. Please indicate from the following what you think is the purpose of the Yellow Card Scheme?

	Yes	Not Sure	No
To ensure public safety	○	○	○
To identify potentially serious ADRs that were too rare to be picked up during clinical trials	○	○	○
To identify factors that might predispose to toxicity/ADRs (e.g. dose, age, renal function, liver function)	○	○	○
To enable ADRs of medicines in similar therapeutic classes to be compared	○	○	○
To identify any previously unknown reactions to a medicine (i.e. not listed in the Summary of Product Characteristics for the medicine)	○	○	○
To monitor the safety of a medicine throughout its life	○	○	○

15. A number of factors influence a health professional's decision when to send a Yellow Card Report. Which of the following would apply to you?

	Yes	Not Sure	No
Seriousness of a reaction	○	○	○
Unusual ADRs not normally seen in oncology	○	○	○
ADR not listed as a known side effect in the SPC	○	○	○
A newly licensed medicine	○	○	○
A new combination chemotherapy regimen (not necessarily containing a new medicine)	○	○	○
Patient hospitalised or hospitalisation prolonged because of an ADR	○	○	○
Significant drug interactions	○	○	○
Latent drug induced cancers	○	○	○
Adverse events resulting in dose delays	○	○	○
A suspension of chemotherapy due to an adverse event (toxicity)	○	○	○
Grade of adverse event (toxicity)	○	○	○

If grade of toxicity is a factor, which grades?

Oncology Healthcare Professionals' Attitudes and Opinions on ADR

16. There are a number of possible reasons why healthcare professionals do not make Yellow Card reports. Please consider the following opinions and indicate your level of agreement with each.

	Strongly Agree	Agree	Disagree	Strongly Disagree
Really serious ADRs are well documented by the time the medicine is marketed so do not see any point in reporting	○	○	○	○
Not certain of the causality of an ADR with a specific medicine	○	○	○	○
Inadequate information sources on ADRs to aid in determining which drug could be causing an ADR	○	○	○	○
Not a high priority in everyday clinical practice	○	○	○	○
Do not know what types of ADRs that should be reported via the Yellow Card scheme	○	○	○	○
Sheer volume of ADRs seen in oncology make it impossible to report them all	○	○	○	○
A single report is not enough to add to medical knowledge	○	○	○	○
Reporting is too time-consuming	○	○	○	○
Lack of professional obligation to report	○	○	○	○
Personal liability	○	○	○	○
Do not see benefit in reporting well recognised ADRs which are seen routinely in everyday clinical practice	○	○	○	○
Do not view oncology adverse events(toxicities) as an ADR(i.e. expect to see them and know how to prevent them or reduce their severity with pre-medication)	○	○	○	○
Lack of specific guidance on the types and grades of oncology ADRs to report via the Yellow Card Scheme	○	○	○	○
The Yellow Card form is too congested	○	○	○	○
Reports go directly to the pharmaceutical company instead of via the Yellow Card Scheme	○	○	○	○
Do not know how the information reported in Yellow Cards is utilised	○	○	○	○
Lack of feedback on reports received via the Yellow Card Scheme	○	○	○	○
Lack of adequate access to advice on ADR reporting or the Yellow Card Scheme	○	○	○	○
Fear that if I report an ADR via the Yellow Card I will be badgered to provide more information	○	○	○	○
Fear of looking stupid to other members of the multi-professional team (if they were to be sent a copy of the report)prevents me from reporting	○	○	○	○

Oncology Healthcare Professionals' Attitudes and Opinions on ADR

17. In general ADRs are known to be under-reported. Please indicate your views on the following statements with respect to oncology by selecting one corresponding answer for each statement.

	Strongly Agree	Agree	Disagree	Strongly Disagree
Oncology ADRs are under-reported	○	○	○	○
The reporting rate of oncology ADRs is not any less than in other clinical areas	○	○	○	○
A reporting form that took less time to complete might help increase reporting in oncology (i.e. more tick boxes; less free format text; pre-populated fields on an electronic report such as patient details, medicines, past medical history, etc)	○	○	○	○

Any additional comments

18. Patient reporting via the Yellow Card Scheme was piloted by the MHRA in 2005 and officially launched in February 2008. Please indicate your opinion on the following statements regarding patient reporting of oncology ADRs

	Strongly Agree	Agree	Disagree	Strongly Disagree
Patient reporting of ADRs in oncology would be beneficial	○	○	○	○
Patients are not adequately trained to detect ADRs so accuracy of grading might be a problem	○	○	○	○
Patients would not be able to distinguish what ADR was serious enough to report without education	○	○	○	○
Patients might under-report ADRs (i.e. downplay toxicities to avoid having treatment delays)	○	○	○	○

Any additional comments

Oncology Healthcare Professionals' Attitudes and Opinions on ADR

19. At present electronic prescribing systems are receiving some investment across Scotland. Within these systems electronic capture of NCI CAEC grades will most likely occur. Please give your opinion on the following statements in relation to this

	Strongly Agree	Agree	Disagree	Strongly Disagree
Electronic capture of NCI CAEC grades in clinical practice will be beneficial	○	○	○	○
Anonymised, aggregate data resulting from electronic capture of NCI CAEC grades would be beneficial in monitoring oncology adverse events Scotland wide	○	○	○	○
If the anonymised, aggregate data of NCI CAEC grades could identify adverse event trends, this would be helpful to clinicians (possibly in making decisions on which medicines or regimens to use)	○	○	○	○
I would be interested in any results from aggregate data on oncology adverse event trends if it became available	○	○	○	○
I would be happy to contribute my patients' anonymised NCI CAEC data for electronic linkage	○	○	○	○

Any additional comments

This is the end of the questionnaire. Thank you for your participation. A summary of the information obtained from this questionnaire will be available to all individuals who participated upon request.

Appendix 24

Matrix for questions to be covered in knowledge question

Is the Side Effect listed in the SPC	Is side effect serious?	Status of medicine			
		Black Triangle		Older Medicine	
		Grade 1-2	Grade 3-4	Grade 1-2	Grade 3-4
Known side effect	Serious	a	e	i	m
	Not Serious	b	f	j	n
Not a known side effect	Serious	c	g	k	o
	Not Serious	d	h	l	p

Matrix Letter	Question	Reporting required by Yellow Card reporting criteria
A	Patient receiving Herceptin develops a Grade 2 hypersensitivity reaction (rash, flushing urticaria, dyspnoea and temperature of 39^{o} C)	Yes
B	Patient develops superficial ulceration (Grade 2) around the injection site after a dose of Alimta (pemtrexed)	Yes
C	Patient presents with a DVT after 2 doses of Erbitux (cetuximab)	Yes
D	Patient develops Grade 2 watery eyes after receiving second cycle of Myocet (liposomal doxorubicin)	Yes
E	Patient is hospitalised with neutropenic sepsis after second dose of Myocet (liposomal doxorubicin)	Yes
F	Patient develops Grade 3 constipation after first dose of Alimta (pemtrexed)	Yes
G	Patient receiving Herceptin (trastuzumab) develops acute renal failure (Grade 3; no dialysis required)	Yes
H	Patient develops Grade 3 cough after first cycle of Alimta (pemtrexed)	Yes
I	Patient receiving docetaxel develops a Grade 2 hypersensitivity reaction (rash, flushing urticaria, dyspnoea and temperature of 39^{o} C	Yes
J	Patient develops Grade 2 diarrhoea after second cycle of Xeloda (capecitabine)	No
K	Patient develops laryngitis (Grade 2) after receiving docetaxel	Yes
L	Patient develops Grade 2 obesity after completing 6 cycles of irinotecan	No
M	Patient develops Grade 3 Palmar-Plantar Syndrome after 2 cycles of Caelyx (lioposomal doxorubicin)	Yes
N	Patient develops Grade 3 Nausea after receiving first cycle of CMF (cyclophosphamide, Methotrexate and 5FU)	No
O	Patient with normal liver function and no known liver metastasis develops severe liver dysfunction after 4 cycles of epirubicin	Yes
P	Patient develops Grade 3 bloating after receiving cisplatin	No
Q	Patient develops fatigue after receiving docetaxel (third cycle) and first dose Herceptin (trastuzumab)	Yes

The decision to omit matrix example D and L was made due to being non-serious, Low grade side effects that would add nothing to the questionnaire analysis or outcome. However one additional question Q was added to give an example of a black triangle medicine and a non-black triangle medicine combination with a non-serious, known side effect.

Appendix 25

NHS Lothian –
University Hospitals Division

Department of Pharmacy
Royal Infirmary of Edinburgh
51 Little France Crescent
Old Dalkeith Road
EDINBURGH
EH16 4SA

Telephone 0131 242 2919
Fax 0131 242 2925
E-mail: melinda.cuthbert@luht.scot.nhs.uk

Your Ref:
Our Ref: crossfire/mphil/nominal group/letter

Certificate No: FS 31228

Dear Colleague

Nominal group process to develop criteria for Yellow Card reporting in oncology patients receiving chemotherapy

As you may be aware, I am a pharmacist working at the Royal Infirmary of Edinburgh within Medicines Information/ Yellow Card Centre Scotland who is currently enrolled part-time in a MPhil at the University of Strathclyde (Research title: "Improving standards of pharmacovigilance practice in oncology"). The majority of you have either participated or collaborated in some other aspects of this project over the last few years; and I would like to take this opportunity to thank you for your involvement. One of my final research objectives is to develop standards to operationalise the classification of serious oncology ADRs and proposed criteria for Yellow Card reporting in oncology patients receiving chemotherapy.

All healthcare professionals working in oncology encounter numerous ADRs on a daily basis in their clinical practice in oncology. However not all of the ADRs, which meet the MHRA criteria for reporting, get reported via the Yellow Card Scheme. From the recent questionnaire, 95% of oncology healthcare professionals surveyed within Scotland agreed that oncology ADRs are under reported. There are numerous contributing factors to this under-reporting but one of the major reasons given is that there are too many adverse reactions seen in oncology to report them all; and it is not seen by oncology healthcare professionals best use of their time to be reporting ADRs that are known or expected. As a result it is important that criteria specific to oncology are developed to ensure that appropriate serious and/or unknown ADRs are reported in oncology.

As part of my research, I will be facilitating a nominal group process to help draft standards to operationalise the classification of serious oncology ADRs and proposed criteria for Yellow Card reporting in oncology patients receiving chemotherapy. I propose to hold a meeting in mid August. The meeting will take no more than 2 hours and will take place in Edinburgh at a mutually agreed location and time to suit participants. Prior to the meeting background information, including mapped NCI Common Terminology for Cancer Adverse Events (CTCAE) and resultant criteria for oncology ADRs reporting from a recent questionnaire will be distributed. Participants will be asked to score these standards for agreement and select terms from the mapped NCI CTCAE that they feel are serious and should be considered for reporting in oncology. These items will be returned to me two weeks before the meeting for collation. A summary of the responses will be available for discussion at the meeting in August, where the participants will be asked to agree final proposed standards and criteria for reporting ADRs via the Yellow Card Scheme in oncology.

I would be most grateful if you would consent to being involved in this nominal group process. Please contact me via telephone on 0131 242 2917 or e-mail (melinda.cuthbert@luht.scot.nhs.uk) if you have any questions or require any further information. Please **reply by 10 July 2009** to confirm or decline this invitation. I will then seek potential dates and times you will be available; and send the initial documents for preparation for the meeting in August. I thank you in anticipation for your participation.

Yours Sincerely

Melinda Cuthbert
Principal Pharmacist

The Yellow Card Scheme is the voluntary adverse drug reporting scheme ran by the Medicines and Healthcare products Regulatory Agency and the Commission on Human Medicines in the UK. Healthcare professionals and patients can report suspected ADRs via the Yellow Card Scheme. More information on the Yellow Card Scheme can be viewed at:
http://www.mhra.gov.uk/Safetyinformation/Howwemonitorthesafetyofproducts/Medicines/TheYellowCardScheme/index.htm

Appendix 26

Nominal Group Process to develop standards/criteria for Yellow

Directions for completion

Please complete the following as indicated. The demographics information is confidential and will be destroyed at end of the nominal group process. In the other two questions please indicate your level of agreement with the statements given for criteria and scenarios when to complete a Yellow Card report in oncology.

Demographics

1. What is your name?

2. Number of years working in oncology?

3. Age?

- ◯ 20-30
- ◯ 31-40
- ◯ 41-50
- ◯ 51-60
- ◯ >60

Criteria to consider when making a Yellow Card report in Oncology

Nominal Group Process to develop standards/criteria for Yellow

* 4. Please indicate your level of agreement on a scale of 1 to 9 which of the following factors should prompt an oncology healthcare professional to consider sending a Yellow Card Report.

	Strongly Disagree		Disagree		Neutral		Agree		Strongly Agree
An ADR not listed as a known side effect in the SPC	◯	◯	◯	◯	◯	◯	◯	◯	◯
Unusual ADRs not normally seen in oncology	◯	◯	◯	◯	◯	◯	◯	◯	◯
An ADR considered serious	◯	◯	◯	◯	◯	◯	◯	◯	◯
A newly licensed medicine	◯	◯	◯	◯	◯	◯	◯	◯	◯
A new combination chemotherapy regimen (not necessarily containing a new medicine)	◯	◯	◯	◯	◯	◯	◯	◯	◯
Patient hospitalised or hospitalisation prolonged because of an ADR	◯	◯	◯	◯	◯	◯	◯	◯	◯
Significant drug interactions	◯	◯	◯	◯	◯	◯	◯	◯	◯
Latent drug induced cancers	◯	◯	◯	◯	◯	◯	◯	◯	◯
Adverse events resulting in dose delays	◯	◯	◯	◯	◯	◯	◯	◯	◯
A suspension of chemotherapy due to an adverse event (toxicity)	◯	◯	◯	◯	◯	◯	◯	◯	◯

Any other criteria not listed that should be considered (please specify)

Scenarios for submitting a Yellow Card report

Nominal Group Process to develop standards/criteria for Yellow

* 5. Please indicate your level of agreement on a scale of 1 to 9 on the following situations that a Yellow Card report should be considered previously agreed by oncology healthcare professionals in a prior questionnaire.

	Strongly Disagree		Disagree		Neutral		Agree		Strongly Agree
Black triangle Status medicine (i.e. new medicine), serious reaction, not a known side effect of a medicine, and Grade 3-4 toxicity.	◯	◯	◯	◯	◯	◯	◯	◯	◯
Non-Black triangle status medicine (i.e. older medicine), serious reaction, not a known side effect of a medicine, and Grade 3-4 toxicity.	◯	◯	◯	◯	◯	◯	◯	◯	◯

Other scenarios you would suggest be considered (please specify)

Thank you for completing.

This is the end of the pre-nominal group meeting questions. thank you for completing. Please return to Melinda Cuthbert in enclosed Freepost Envelop.

Appendix 27

CTCAE Adverse Events Category	Mapped MedDRA Term for CTCAE term	Class as serious adverse reaction in oncology? If Yes please complete columns H and I. If No please go to next term.	If serious in oncology should it be considered for reporting via the Yellow Card Scheme (if suspect due to medicines)?		Other comments
ALLERGY/IMMUNOLOGY					
	Hypersensitivity		**Yes**	**No**	
	Allergic rhinitis		**Yes**	**No**	
	Immune system disorder		**Yes**	**No**	
	Autoimmune disorder		**Yes**	**No**	
	Serum sickness		**Yes**	**No**	
	Vasculitis		**Yes**	**No**	
AUDITORY/EAR					
	Ear disorder		**Yes**	**No**	
	Hearing test abnormal		**Yes**	**No**	
	Hearing loss		**Yes**	**No**	
	External ear inflammation		**Yes**	**No**	
	Middle ear inflammation		**Yes**	**No**	
	Tinnitus		**Yes**	**No**	
BLOOD/BONE MARROW					
	Blood disorder		**Yes**	**No**	
	Bone marrow hypocellular		**Yes**	**No**	

	CD4 lymphocytes decreased	**Yes**	**No**
	Haptoglobin decreased	**Yes**	**No**
	Hemoglobin decreased	**Yes**	**No**
	Hemolysis	**Yes**	**No**
	Iron increased	**Yes**	**No**
	Leukopenia	**Yes**	**No**
	Lymphopenia	**Yes**	**No**
	Myelodysplasia	**Yes**	**No**
	Neutrophil count decreased	**Yes**	**No**
	Platelet count decreased	**Yes**	**No**
	Spleen disorder	**Yes**	**No**
CARDIAC ARRHYTHMIA			
	Arrhythmia	**Yes**	**No**
	Atrioventricular block first degree	**Yes**	**No**
	Mobitz type I	**Yes**	**No**
	Mobitz (type) II atrioventricular block	**Yes**	**No**
	Atrioventricular block complete	**Yes**	**No**
	Asystole	**Yes**	**No**
	Conduction disorder	**Yes**	**No**
	Sick sinus syndrome	**Yes**	**No**

	Stokes-Adams syndrome	**Yes**	**No**
	Wolff-Parkinson-White syndrome	**Yes**	**No**
	Palpitations	**Yes**	**No**
	Electrocardiogram QTc interval prolonged	**Yes**	**No**
	Atrial fibrillation	**Yes**	**No**
	Atrial flutter	**Yes**	**No**
	Atrial tachycardia	**Yes**	**No**
	Nodal arrhythmia	**Yes**	**No**
	Sinus arrhythmia	**Yes**	**No**
	Sinus bradycardia	**Yes**	**No**
	Sinus tachycardia	**Yes**	**No**
	Arrhythmia supraventricular	**Yes**	**No**
	Supraventricular extrasystoles	**Yes**	**No**
	Supraventricular tachycardia	**Yes**	**No**
	Syncope vasovagal	**Yes**	**No**
	Ventricular bigeminy	**Yes**	**No**
	Rhythm idioventricular	**Yes**	**No**
	Premature ventricular contractions	**Yes**	**No**
	Torsade de pointes	**Yes**	**No**
	Ventricular trigeminy	**Yes**	**No**

	Ventricular arrhythmia	**Yes**	**No**
	Ventricular fibrillation	**Yes**	**No**
	Ventricular flutter	**Yes**	**No**
	Ventricular tachycardia	**Yes**	**No**
CARDIAC GENERAL			
	Cardiac disorder	**Yes**	**No**
	Myocardial ischemia	**Yes**	**No**
	Cardiac troponin I increased	**Yes**	**No**
	Cardiac troponin T increased	**Yes**	**No**
	Cardiopulmonary arrest	**Yes**	**No**
	Hypertension	**Yes**	**No**
	Hypotension	**Yes**	**No**
	Diastolic dysfunction	**Yes**	**No**
	Left ventricular failure	**Yes**	**No**
	Myocarditis	**Yes**	**No**
	Pericardial effusion	**Yes**	**No**
	Pericarditis	**Yes**	**No**
	Pulmonary hypertension	**Yes**	**No**
	Restrictive cardiomyopathy	**Yes**	**No**
	Cor pulmonale	**Yes**	**No**
	Cardiac valve disease	**Yes**	**No**
COAGULATION			

	Coagulopathy	**Yes**	**No**
	Disseminated intravascular coagulation	**Yes**	**No**
	Fibrinogen decreased	**Yes**	**No**
	INR increased	**Yes**	**No**
	Activated partial thromboplastin time prolonged	**Yes**	**No**
	Thrombotic microangiopathy	**Yes**	**No**
CONSTITUTIONAL SYMPTOMS			
	General symptom	**Yes**	**No**
	Fatigue	**Yes**	**No**
	Fever	**Yes**	**No**
	Hypothermia	**Yes**	**No**
	Insomnia	**Yes**	**No**
	Obesity	**Yes**	**No**
	Body odor	**Yes**	**No**
	Chills	**Yes**	**No**
	Sweating	**Yes**	**No**
	Weight gain	**Yes**	**No**
	Weight loss	**Yes**	**No**
DEATH			

	Death	**Yes**	**No**
	Disease progression	**Yes**	**No**
	Multi-organ failure	**Yes**	**No**
	Sudden death	**Yes**	**No**
DERMATOLOGY/SKIN			
	Atrophy skin	**Yes**	**No**
	Fat atrophy	**Yes**	**No**
	Bruising	**Yes**	**No**
	Thermal burn	**Yes**	**No**
	Cheilitis	**Yes**	**No**
	Skin disorder	**Yes**	**No**
	Dry skin	**Yes**	**No**
	Flushing	**Yes**	**No**
	Alopecia	**Yes**	**No**
	Skin hyperpigmentation	**Yes**	**No**
	Skin hypopigmentation	**Yes**	**No**
	Skin induration	**Yes**	**No**
	Injection site reaction	**Yes**	**No**
	Nail disorder	**Yes**	**No**
	Photosensitivity	**Yes**	**No**
	Pruritus	**Yes**	**No**
	Rash desquamating	**Yes**	**No**

	Acne	**Yes**	**No**
	Radiation recall reaction (dermatologic)	**Yes**	**No**
	Dermatitis radiation	**Yes**	**No**
	Erythema multiforme	**Yes**	**No**
	Hand-and-foot syndrome	**Yes**	**No**
	Decubitus ulcer	**Yes**	**No**
	Skin striae	**Yes**	**No**
	Telangiectasia	**Yes**	**No**
	Skin ulceration	**Yes**	**No**
	Urticaria	**Yes**	**No**
	Wound dehiscence	**Yes**	**No**
ENDOCRINE			
	Adrenal insufficiency	**Yes**	**No**
	Cushingoid	**Yes**	**No**
	Endocrine disorder	**Yes**	**No**
	Feminization	**Yes**	**No**
	Hot flashes	**Yes**	**No**
	Masculinization	**Yes**	**No**
	Blood gonadotrophin abnormal	**Yes**	**No**
	Growth hormone abnormal	**Yes**	**No**
	Blood prolactin abnormal	**Yes**	**No**

	ACTH decreased	**Yes**	**No**
	ADH abnormal	**Yes**	**No**
	Glucose intolerance	**Yes**	**No**
	Hypoparathyroidism	**Yes**	**No**
	Hyperthyroidism	**Yes**	**No**
	Hypothyroidism	**Yes**	**No**
GASTROINTESTINAL			
	Anorexia	**Yes**	**No**
	Ascites	**Yes**	**No**
	Colitis	**Yes**	**No**
	Constipation	**Yes**	**No**
	Dehydration	**Yes**	**No**
	Dental prosthesis user	**Yes**	**No**
	Periodontal disease	**Yes**	**No**
	Tooth disorder	**Yes**	**No**
	Tooth development disorder	**Yes**	**No**
	Diarrhea	**Yes**	**No**
	Abdominal distension	**Yes**	**No**
	Dry mouth	**Yes**	**No**
	Dysphagia	**Yes**	**No**
	Enteritis	**Yes**	**No**
	Esophagitis	**Yes**	**No**

	Gastro-intestinal fistula	**Yes**	**No**
	Anal fistula	**Yes**	**No**
	Biliary fistula	**Yes**	**No**
	Colonic fistula	**Yes**	**No**
	Duodenal fistula	**Yes**	**No**
	Acquired tracheo-oesophageal fistula	**Yes**	**No**
	Gallbladder fistula	**Yes**	**No**
	Ileal fistula	**Yes**	**No**
	Jejunal fistula	**Yes**	**No**
	Oral cavity fistula	**Yes**	**No**
	Pancreatic fistula	**Yes**	**No**
	Fistula, Pharynx	**Yes**	**No**
	Rectal fistula	**Yes**	**No**
	Salivary gland fistula	**Yes**	**No**
	Fistula of small intestine	**Yes**	**No**
	Gastic fistula	**Yes**	**No**
	Flatulence	**Yes**	**No**
	Gastritis	**Yes**	**No**
	Gastrointestinal disorder	**Yes**	**No**
	Dyspepsia	**Yes**	**No**
	Hemorrhoids	**Yes**	**No**

	Ileus	**Yes**	**No**
	Fecal incontinence	**Yes**	**No**
	Biliary anastomotic leak	**Yes**	**No**
	Esophageal anastomotic leak	**Yes**	**No**
	Large intestinal anastomotic leak	**Yes**	**No**
	Anastomotic leak	**Yes**	**No**
	Pancreatic anastomotic leak	**Yes**	**No**
	Pharyngeal anastomotic leak	**Yes**	**No**
	Rectal anastomotic leak	**Yes**	**No**
	Small intestinal anastomotic leak	**Yes**	**No**
	Intestinal stoma leak	**Yes**	**No**
	Gastric anastomotic leak	**Yes**	**No**
	Malabsorption	**Yes**	**No**
	Anal exam abnormal	**Yes**	**No**
	Oesophagoscopy abnormal	**Yes**	**No**
	Endoscopy large bowel abnormal	**Yes**	**No**
	Laryngoscopy abnormal	**Yes**	**No**
	Ear, nose and throat examination abnormal	**Yes**	**No**
	Pharyngeal examination abnormal	**Yes**	**No**
	Proctoscopy abnormal	**Yes**	**No**

	Endoscopy small intestine abnormal	**Yes**	**No**
	Gastroscopy abnormal	**Yes**	**No**
	Tracheoscopy abnormal	**Yes**	**No**
	Anal mucositis	**Yes**	**No**
	Esophageal mucositis	**Yes**	**No**
	Large intestinal mucositis	**Yes**	**No**
	Laryngeal mucositis	**Yes**	**No**
	Mucositis oral	**Yes**	**No**
	Pharyngeal mucositis	**Yes**	**No**
	Rectal mucositis	**Yes**	**No**
	Small intestinal mucositis	**Yes**	**No**
	Gastric mucositis	**Yes**	**No**
	Tracheal mucositis	**Yes**	**No**
	Nausea	**Yes**	**No**
	Anal necrosis	**Yes**	**No**
	Intestinal necrosis	**Yes**	**No**
	Duodenal necrosis	**Yes**	**No**
	Esophageal necrosis	**Yes**	**No**
	Gallbladder necrosis	**Yes**	**No**
	Hepatic necrosis	**Yes**	**No**
	Ileal necrosis	**Yes**	**No**

	Jejunal necrosis	**Yes**	**No**
	Mouth necrosis	**Yes**	**No**
	Pancreatic necrosis	**Yes**	**No**
	Peritoneal necrosis	**Yes**	**No**
	Pharyngeal necrosis	**Yes**	**No**
	Rectal necrosis	**Yes**	**No**
	Small intestinal necrosis	**Yes**	**No**
	Gastrointestinal stoma necrosis	**Yes**	**No**
	Gastric necrosis	**Yes**	**No**
	Cecal obstruction	**Yes**	**No**
	Colonic obstruction	**Yes**	**No**
	Duodenal obstruction	**Yes**	**No**
	Esophageal obstruction	**Yes**	**No**
	Gallbladder obstruction	**Yes**	**No**
	Ileal obstruction	**Yes**	**No**
	Jejunal obstruction	**Yes**	**No**
	Rectal obstruction	**Yes**	**No**
	Small intestinal obstruction	**Yes**	**No**
	Intestinal stoma obstruction	**Yes**	**No**
	Obstruction gastric	**Yes**	**No**
	Appendicitis perforated	**Yes**	**No**
	Perforation bile duct	**Yes**	**No**

	Cecum perforation	**Yes**	**No**
	Colonic perforation	**Yes**	**No**
	Duodenal perforation	**Yes**	**No**
	Esophageal perforation	**Yes**	**No**
	Gallbladder perforation	**Yes**	**No**
	Ileal perforation	**Yes**	**No**
	Jejunal perforation	**Yes**	**No**
	Rectal perforation	**Yes**	**No**
	Small intestinal perforation	**Yes**	**No**
	Gastric perforation	**Yes**	**No**
	Proctitis	**Yes**	**No**
	Prolapse of intestinal stoma	**Yes**	**No**
	Salivary gland disorder	**Yes**	**No**
	Anal stenosis	**Yes**	**No**
	Bile duct stenosis	**Yes**	**No**
	Intestinal stenosis	**Yes**	**No**
	Colonic stenosis	**Yes**	**No**
	Duodenal stenosis	**Yes**	**No**
	Esophageal stenosis	**Yes**	**No**
	Ileal stenosis	**Yes**	**No**
	Jejunal stenosis	**Yes**	**No**
	Pancreatic duct stenosis	**Yes**	**No**

	Stricture/stenosis (including anastomotic), Pharynx	**Yes**	**No**
	Rectal stenosis	**Yes**	**No**
	Small intestinal stenosis	**Yes**	**No**
	Stenosis of gastrointestinal stoma	**Yes**	**No**
	Gastric stenosis	**Yes**	**No**
	Taste alteration	**Yes**	**No**
	Typhlitis	**Yes**	**No**
	Anal ulcer	**Yes**	**No**
	Cecal ulcer	**Yes**	**No**
	Colonic ulcer	**Yes**	**No**
	Duodenal ulcer	**Yes**	**No**
	Esophageal ulcer	**Yes**	**No**
	Ileal ulcer	**Yes**	**No**
	Jejunal ulcer	**Yes**	**No**
	Rectal ulcer	**Yes**	**No**
	Small intestine ulcer	**Yes**	**No**
	Stomal ulcer	**Yes**	**No**
	Gastric ulcer	**Yes**	**No**
	Vomiting	**Yes**	**No**
GROWTH AND DEVELOPMENT			
	Bone development abnormal	**Yes**	**No**

	Slipped femoral epiphysis	**Yes**	**No**
	Unequal limb length	**Yes**	**No**
	Kyphosis	**Yes**	**No**
	Developmental disturbance	**Yes**	**No**
	Developmental delay	**Yes**	**No**
	Delayed puberty	**Yes**	**No**
	Precocious puberty	**Yes**	**No**
	Short stature	**Yes**	**No**
HEMORRHAGE/BLEEDING			
	Hematoma	**Yes**	**No**
	Intracranial hemorrhage	**Yes**	**No**
	Intra-abdominal hemorrhage	**Yes**	**No**
	Anal hemorrhage	**Yes**	**No**
	Hemorrhage in bile duct	**Yes**	**No**
	Cecal hemorrhage	**Yes**	**No**
	Colonic hemorrhage	**Yes**	**No**
	Duodenal hemorrhage	**Yes**	**No**
	Esophageal hemorrhage	**Yes**	**No**
	Ileal hemorrhage	**Yes**	**No**
	Jejunal hemorrhage	**Yes**	**No**
	Hepatic hemorrhage	**Yes**	**No**
	Lower gastrointestinal hemorrhage	**Yes**	**No**

	Oral hemorrhage	**Yes**	**No**
	Pancreatic hemorrhage	**Yes**	**No**
	Peritoneal hemorrhage	**Yes**	**No**
	Rectal hemorrhage	**Yes**	**No**
	Intestinal stoma site bleeding	**Yes**	**No**
	Gastric hemorrhage	**Yes**	**No**
	Upper gastrointestinal hemorrhage	**Yes**	**No**
	Esophageal varices hemorrhage	**Yes**	**No**
	Hemorrhoidal hemorrhage	**Yes**	**No**
	Bladder hemorrhage	**Yes**	**No**
	Hematosalpinx	**Yes**	**No**
	Renal hemorrhage	**Yes**	**No**
	Ovarian hemorrhage	**Yes**	**No**
	Prostatic hemorrhage	**Yes**	**No**
	Retroperitoneal hemorrhage	**Yes**	**No**
	Spermatic cord hemorrhage	**Yes**	**No**
	Urostomy site bleeding	**Yes**	**No**
	Testicular hemorrhage	**Yes**	**No**
	Ureteric hemorrhage	**Yes**	**No**
	Urethral hemorrhage	**Yes**	**No**
	Hemorrhage urinary tract	**Yes**	**No**

	Uterine hemorrhage	**Yes**	**No**
	Vaginal hemorrhage	**Yes**	**No**
	Vas deferens hemorrhage	**Yes**	**No**
	Bronchopulmonary hemorrhage	**Yes**	**No**
	Bronchial hemorrhage	**Yes**	**No**
	Laryngeal hemorrhage	**Yes**	**No**
	Pulmonary hemorrhage	**Yes**	**No**
	Mediastinal hemorrhage	**Yes**	**No**
	Hemorrhage nasal	**Yes**	**No**
	Pharyngeal hemorrhage	**Yes**	**No**
	Pleural hemorrhage	**Yes**	**No**
	Respiratory tract hemorrhage	**Yes**	**No**
	Tracheostomy site bleeding	**Yes**	**No**
	Tracheal hemorrhage	**Yes**	**No**
	Hemorrhage	**Yes**	**No**
	Postoperative hemorrhage	**Yes**	**No**
	Petechiae	**Yes**	**No**
HEPATOBILIARY/ PANCREAS			
	Cholecystitis	**Yes**	**No**
	Hepatobiliary disease	**Yes**	**No**
	Hepatic failure	**Yes**	**No**

	Pancreatic enzymes decreased	**Yes**	**No**
	Pancreatitis	**Yes**	**No**
INFECTION			
	Febrile neutropenia	**Yes**	**No**
	Abdominal infection	**Yes**	**No**
	Anal infection	**Yes**	**No**
	Appendicitis	**Yes**	**No**
	Arteritis infective	**Yes**	**No**
	Biliary tract infection	**Yes**	**No**
	Bladder infection	**Yes**	**No**
	Sepsis	**Yes**	**No**
	Bone infection	**Yes**	**No**
	Encephalitis infection	**Yes**	**No**
	Encephalomyelitis infection	**Yes**	**No**
	Bronchitis	**Yes**	**No**
	Catheter related infection	**Yes**	**No**
	Cecal infection	**Yes**	**No**
	Cervicitis	**Yes**	**No**
	Infectious colitis	**Yes**	**No**
	Conjunctivitis infective	**Yes**	**No**
	Corneal infection	**Yes**	**No**
	Tooth infection	**Yes**	**No**

	Duodenal infection	**Yes**	**No**
	Esophageal infection	**Yes**	**No**
	Otitis externa	**Yes**	**No**
	Eye infection	**Yes**	**No**
	Salpingitis infection	**Yes**	**No**
	Device related infection	**Yes**	**No**
	Gallbladder infection	**Yes**	**No**
	Endocarditis infective	**Yes**	**No**
	Ileal infection	**Yes**	**No**
	Jejunal infection	**Yes**	**No**
	Joint infection	**Yes**	**No**
	Kidney infection	**Yes**	**No**
	Laryngitis	**Yes**	**No**
	Eye infection intraocular	**Yes**	**No**
	Lip infection	**Yes**	**No**
	Hepatic infection	**Yes**	**No**
	Pneumonia	**Yes**	**No**
	Lymph gland infection	**Yes**	**No**
	Mediastinal infection	**Yes**	**No**
	Infectious meningitis	**Yes**	**No**
	Otitis media	**Yes**	**No**
	Mucosal infection	**Yes**	**No**

	Infective myositis	**Yes**	**No**
	Infection	**Yes**	**No**
	Cranial nerve infection	**Yes**	**No**
	Peripheral nerve infection	**Yes**	**No**
	Rhinitis infective	**Yes**	**No**
	Gingival infection	**Yes**	**No**
	Pancreas infection	**Yes**	**No**
	Paranasal sinus infection	**Yes**	**No**
	Pelvic infection	**Yes**	**No**
	Penile infection	**Yes**	**No**
	Stoma site infection	**Yes**	**No**
	Peritoneal infection	**Yes**	**No**
	Pharyngitis	**Yes**	**No**
	Pleural infection	**Yes**	**No**
	Prostate infection	**Yes**	**No**
	Anorectal infection	**Yes**	**No**
	Salivary gland infection	**Yes**	**No**
	Scrotal infection	**Yes**	**No**
	Sinusitis	**Yes**	**No**
	Skin infection	**Yes**	**No**
	Small intestine infection	**Yes**	**No**
	Soft tissue infection	**Yes**	**No**

	Spinal cord infection	**Yes**	**No**
	Splenic infection	**Yes**	**No**
	Gastric infection	**Yes**	**No**
	Tracheitis	**Yes**	**No**
	Nail infection	**Yes**	**No**
	Upper aerodigestive tract infection	**Yes**	**No**
	Upper respiratory infection	**Yes**	**No**
	Ureteritis	**Yes**	**No**
	Urethral infection	**Yes**	**No**
	Urinary tract infection	**Yes**	**No**
	Uterine infection	**Yes**	**No**
	Vaginal infection	**Yes**	**No**
	Phlebitis infective	**Yes**	**No**
	Vulval infection	**Yes**	**No**
	Wound infection	**Yes**	**No**
	Vulvitis	**Yes**	**No**
	Opportunistic infection	**Yes**	**No**
	Viral hepatitis	**Yes**	**No**
LYMPHATICS			
	Lymph leakage	**Yes**	**No**
	Lymphedema	**Yes**	**No**
	Localized edema	**Yes**	**No**

	Edema limbs	**Yes**	**No**
	Localized edema	**Yes**	**No**
	Visceral edema	**Yes**	**No**
	Lymphatic disorder	**Yes**	**No**
	Fibrosis	**Yes**	**No**
	Lymphocele	**Yes**	**No**
	Lymphangitic streak	**Yes**	**No**
METABOLIC/LABORATORY			
	Alanine aminotransferase increased	**Yes**	**No**
	Aspartate aminotransferase increased	**Yes**	**No**
	Acidosis	**Yes**	**No**
	Hypoalbuminemia	**Yes**	**No**
	Alkaline phosphatase increased	**Yes**	**No**
	Alkalosis	**Yes**	**No**
	Amylase increased	**Yes**	**No**
	Blood bicarbonate decreased	**Yes**	**No**
	Hyperbilirubinemia	**Yes**	**No**
	Creatine phosphokinase increased	**Yes**	**No**
	Hypercalcemia	**Yes**	**No**
	Hypocalcemia	**Yes**	**No**

	Hypercholesterolemia	**Yes**	**No**
	Creatinine increased	**Yes**	**No**
	Gamma-glutamyltransferase increased	**Yes**	**No**
	Glomerular filtration rate decreased	**Yes**	**No**
	Hyperglycemia	**Yes**	**No**
	Hypoglycemia	**Yes**	**No**
	Hemoglobinuria	**Yes**	**No**
	Lipase increased	**Yes**	**No**
	Hypermagnesemia	**Yes**	**No**
	Hypomagnesemia	**Yes**	**No**
	Laboratory test abnormal	**Yes**	**No**
	Hypophosphatemia	**Yes**	**No**
	Hyperkalemia	**Yes**	**No**
	Hypokalemia	**Yes**	**No**
	Proteinuria	**Yes**	**No**
	Hypernatremia	**Yes**	**No**
	Hyponatremia	**Yes**	**No**
	Hypertriglyceridemia	**Yes**	**No**
	Hyperuricemia	**Yes**	**No**
MUSCULOSKELETAL/ SOFT TISSUE			
	Arthritis	**Yes**	**No**

	Scoliosis	**Yes**	**No**
	Joint range of motion decreased cervical spine	**Yes**	**No**
	Exostosis	**Yes**	**No**
	Gait abnormal	**Yes**	**No**
	Upper extremity dysfunction	**Yes**	**No**
	Superficial soft tissue fibrosis	**Yes**	**No**
	Fibrosis deep connective tissue	**Yes**	**No**
	Fracture	**Yes**	**No**
	Joint effusion	**Yes**	**No**
	Joint disorder	**Yes**	**No**
	Device complication	**Yes**	**No**
	Joint range of motion decreased lumbar spine	**Yes**	**No**
	Extraocular muscle disorder	**Yes**	**No**
	Muscle weakness lower limb	**Yes**	**No**
	Muscle weakness upper limb	**Yes**	**No**
	Facial muscle weakness	**Yes**	**No**
	Muscle weakness left-sided	**Yes**	**No**
	Eye muscle weakness	**Yes**	**No**
	Pelvic floor muscle weakness	**Yes**	**No**
	Muscle weakness right-sided	**Yes**	**No**

	Muscle weakness trunk	**Yes**	**No**
	Muscle weakness	**Yes**	**No**
	Musculoskeletal deformity	**Yes**	**No**
	Musculoskeletal disorder	**Yes**	**No**
	Myositis	**Yes**	**No**
	Osteonecrosis	**Yes**	**No**
	Osteoporosis	**Yes**	**No**
	Seroma	**Yes**	**No**
	Abdominal soft tissue necrosis	**Yes**	**No**
	Soft tissue necrosis lower limb	**Yes**	**No**
	Soft tissue necrosis upper limb	**Yes**	**No**
	Head soft tissue necrosis	**Yes**	**No**
	Neck soft tissue necrosis	**Yes**	**No**
	Pelvic soft tissue necrosis	**Yes**	**No**
	Chest wall necrosis	**Yes**	**No**
	Trismus	**Yes**	**No**
NEUROLOGY			
	Apnea	**Yes**	**No**
	Arachnoiditis	**Yes**	**No**
	Ataxia	**Yes**	**No**
	Radiculitis brachial	**Yes**	**No**

	Ischemia cerebrovascular	**Yes**	**No**
	Central nervous system necrosis	**Yes**	**No**
	Cognitive disturbance	**Yes**	**No**
	Confusion	**Yes**	**No**
	Dizziness	**Yes**	**No**
	Encephalopathy	**Yes**	**No**
	Extrapyramidal disorder	**Yes**	**No**
	Hydrocephalus	**Yes**	**No**
	Irritability	**Yes**	**No**
	Recurrent laryngeal nerve palsy	**Yes**	**No**
	Cerebrospinal fluid leakage	**Yes**	**No**
	Leukoencephalopathy	**Yes**	**No**
	Memory impairment	**Yes**	**No**
	Mental status changes	**Yes**	**No**
	Agitation	**Yes**	**No**
	Anxiety	**Yes**	**No**
	Depression	**Yes**	**No**
	Euphoria	**Yes**	**No**
	Myelitis	**Yes**	**No**
	Neurological disorder NOS	**Yes**	**No**
	Olfactory nerve disorder	**Yes**	**No**

	Optic nerve disorder	**Yes**	**No**
	Oculomotor nerve disorder	**Yes**	**No**
	IVth nerve disorder	**Yes**	**No**
	Glossopharyngeal nerve disorder	**Yes**	**No**
	Trigeminal nerve disorder	**Yes**	**No**
	Abducens nerve disorder	**Yes**	**No**
	Facial nerve disorder	**Yes**	**No**
	Acoustic nerve disorder NOS	**Yes**	**No**
	Vagus nerve disorder	**Yes**	**No**
	Accessory nerve disorder	**Yes**	**No**
	Hypoglossal nerve disorder	**Yes**	**No**
	Peripheral motor neuropathy	**Yes**	**No**
	Peripheral sensory neuropathy	**Yes**	**No**
	Personality change	**Yes**	**No**
	Phrenic nerve paralysis	**Yes**	**No**
	Psychosis	**Yes**	**No**
	Pyramidal tract syndrome	**Yes**	**No**
	Seizure	**Yes**	**No**
	Depressed level of consciousness	**Yes**	**No**
	Speech disorder	**Yes**	**No**
	Syncope	**Yes**	**No**

	Tremor	**Yes**	**No**
OCULAR/VISUAL			
	Cataract	**Yes**	**No**
	Dry eye syndrome	**Yes**	**No**
	Eyelid function disorder	**Yes**	**No**
	Glaucoma	**Yes**	**No**
	Keratitis	**Yes**	**No**
	Night blindness	**Yes**	**No**
	Nystagmus	**Yes**	**No**
	Conjunctival disorder	**Yes**	**No**
	Eye disorder	**Yes**	**No**
	Diplopia	**Yes**	**No**
	Optic nerve edema	**Yes**	**No**
	Proptosis	**Yes**	**No**
	Retinal detachment	**Yes**	**No**
	Retinopathy	**Yes**	**No**
	Scleral disorder	**Yes**	**No**
	Uveitis	**Yes**	**No**
	Vision blurred	**Yes**	**No**
	Flashing vision	**Yes**	**No**
	Photophobia	**Yes**	**No**
	Vitreous hemorrhage	**Yes**	**No**

	Watering eyes	**Yes**	**No**
PAIN			
	Abdominal pain	**Yes**	**No**
	Anal pain	**Yes**	**No**
	Back pain	**Yes**	**No**
	Bladder pain	**Yes**	**No**
	Bone pain	**Yes**	**No**
	Breast pain	**Yes**	**No**
	Buttock pain	**Yes**	**No**
	Cardiac pain	**Yes**	**No**
	Chest wall pain	**Yes**	**No**
	Chest pain	**Yes**	**No**
	Toothache	**Yes**	**No**
	Esophageal pain	**Yes**	**No**
	External ear pain	**Yes**	**No**
	Pain in extremity	**Yes**	**No**
	Eye pain	**Yes**	**No**
	Facial pain	**Yes**	**No**
	Gallbladder pain	**Yes**	**No**
	Headache	**Yes**	**No**
	Gastrointestinal pain	**Yes**	**No**
	Joint pain	**Yes**	**No**

	Kidney pain	**Yes**	**No**
	Laryngeal pain	**Yes**	**No**
	Lip pain	**Yes**	**No**
	Hepatic pain	**Yes**	**No**
	Lymph node pain	**Yes**	**No**
	Ear pain	**Yes**	**No**
	Myalgia	**Yes**	**No**
	Neck pain	**Yes**	**No**
	Neuralgia	**Yes**	**No**
	Oral pain	**Yes**	**No**
	Gingival pain	**Yes**	**No**
	Ovulation pain	**Yes**	**No**
	Pain	**Yes**	**No**
	Pelvic pain	**Yes**	**No**
	Penile pain	**Yes**	**No**
	Pericardial pain	**Yes**	**No**
	Perineal pain	**Yes**	**No**
	Peritoneal pain	**Yes**	**No**
	Phantom pain	**Yes**	**No**
	Pleuritic pain	**Yes**	**No**
	Prostatic pain	**Yes**	**No**
	Rectal pain	**Yes**	**No**

	Scalp pain	**Yes**	**No**
	Scrotal pain	**Yes**	**No**
	Sinus pain	**Yes**	**No**
	Pain of skin	**Yes**	**No**
	Stomach pain	**Yes**	**No**
	Testicular pain	**Yes**	**No**
	Pharyngolaryngeal pain	**Yes**	**No**
	Tumor pain	**Yes**	**No**
	Urethral pain	**Yes**	**No**
	Uterine pain	**Yes**	**No**
	Vaginal pain	**Yes**	**No**
	Pain	**Yes**	**No**
PULMONARY/ UPPER RESPIRATORY			
	Adult respiratory distress syndrome	**Yes**	**No**
	Aspiration	**Yes**	**No**
	Atelectasis	**Yes**	**No**
	Bronchospasm	**Yes**	**No**
	Carbon monoxide diffusing capacity decreased	**Yes**	**No**
	Chylothorax	**Yes**	**No**
	Cough	**Yes**	**No**
	Dyspnea	**Yes**	**No**

	Laryngeal edema	**Yes**	**No**
	Forced expiratory volume decreased	**Yes**	**No**
	Bronchial fistula	**Yes**	**No**
	Laryngeal fistula	**Yes**	**No**
	Pulmonary fistula	**Yes**	**No**
	Oral cavity fistula	**Yes**	**No**
	Pharyngeal fistula	**Yes**	**No**
	Pleural fistula	**Yes**	**No**
	Tracheal fistula	**Yes**	**No**
	Hiccough	**Yes**	**No**
	Hypoxia	**Yes**	**No**
	Nasal congestion	**Yes**	**No**
	Bronchial obstruction	**Yes**	**No**
	Laryngeal obstruction	**Yes**	**No**
	Pharyngeal stenosis	**Yes**	**No**
	Tracheal obstruction	**Yes**	**No**
	Pleural effusion	**Yes**	**No**
	Pneumonitis	**Yes**	**No**
	Pneumothorax	**Yes**	**No**
	Postoperative thoracic procedure complication	**Yes**	**No**

	Prolonged intubation after pulmonary resection (>24 hrs after surgery)	**Yes**	**No**
	Pulmonary fibrosis	**Yes**	**No**
	Respiratory disorder	**Yes**	**No**
	Vital capacity decreased	**Yes**	**No**
	Voice alteration	**Yes**	**No**
RENAL/GENITOURINARY			
	Bladder spasm	**Yes**	**No**
	Cystitis	**Yes**	**No**
	Vesical fistula	**Yes**	**No**
	Female genital tract fistula	**Yes**	**No**
	Renal pelvis fistula	**Yes**	**No**
	Ureteric fistula	**Yes**	**No**
	Urethral fistula	**Yes**	**No**
	Uterine fistula	**Yes**	**No**
	Vaginal fistula	**Yes**	**No**
	Urinary incontinence	**Yes**	**No**
	Bladder anastomotic leak	**Yes**	**No**
	Fallopian tube anastomotic leak	**Yes**	**No**
	Kidney anastomotic leak	**Yes**	**No**
	Spermatic cord anastomotic leak	**Yes**	**No**

	Urostomy leak	**Yes**	**No**
	Ureteric anastomotic leak	**Yes**	**No**
	Urethral anastomotic leak	**Yes**	**No**
	Uterine anastomotic leak	**Yes**	**No**
	Vaginal anastomotic leak	**Yes**	**No**
	Vas deferens anastomotic leak	**Yes**	**No**
	Bladder obstruction	**Yes**	**No**
	Fallopian tube obstruction	**Yes**	**No**
	Prostatic obstruction	**Yes**	**No**
	Spermatic cord obstruction	**Yes**	**No**
	Urostomy obstruction	**Yes**	**No**
	Testicular obstruction	**Yes**	**No**
	Ureteric obstruction	**Yes**	**No**
	Urethral obstruction	**Yes**	**No**
	Uterine obstruction	**Yes**	**No**
	Vaginal obstruction	**Yes**	**No**
	Vas deferens obstruction	**Yes**	**No**
	Bladder perforation	**Yes**	**No**
	Fallopian tube perforation	**Yes**	**No**
	Kidney perforation	**Yes**	**No**
	Ovarian rupture	**Yes**	**No**
	Prostatic perforation	**Yes**	**No**

	Spermatic cord perforation	**Yes**	**No**
	Urostomy perforation	**Yes**	**No**
	Testicular perforation	**Yes**	**No**
	Ureteric perforation	**Yes**	**No**
	Urethral perforation	**Yes**	**No**
	Uterine perforation	**Yes**	**No**
	Vaginal perforation	**Yes**	**No**
	Vas deferens perforation	**Yes**	**No**
	Prolapse of urostomy	**Yes**	**No**
	Renal failure	**Yes**	**No**
	Urogenital disorder	**Yes**	**No**
	Bladder stenosis	**Yes**	**No**
	Fallopian tube stenosis	**Yes**	**No**
	Prostatic disorder	**Yes**	**No**
	Spermatic cord stenosis	**Yes**	**No**
	Urostomy stenosis	**Yes**	**No**
	Testicular stricture/stenosis	**Yes**	**No**
	Ureteric stenosis	**Yes**	**No**
	Urethral stricture	**Yes**	**No**
	Uterine stenosis	**Yes**	**No**
	Vaginal stricture	**Yes**	**No**
	Vas deferens stenosis	**Yes**	**No**

	Renal tubular disorder	**Yes**	**No**
	Urinary frequency	**Yes**	**No**
	Urinary retention	**Yes**	**No**
	Urine discoloration	**Yes**	**No**
SECONDARY MALIGNANCY			
	Treatment related secondary malignancy	**Yes**	**No**
SEXUAL/REPRODUCTIVE FUNCTION			
	Lactation disorder	**Yes**	**No**
	Nipple deformity	**Yes**	**No**
	Breast hypoplasia	**Yes**	**No**
	Ejaculation disorder	**Yes**	**No**
	Erectile dysfunction	**Yes**	**No**
	Gynecomastia	**Yes**	**No**
	Infertility	**Yes**	**No**
	Irregular menstruation	**Yes**	**No**
	Libido decreased	**Yes**	**No**
	Orgasm abnormal	**Yes**	**No**
	Reproductive tract disorder	**Yes**	**No**
	Vaginal discharge	**Yes**	**No**
	Vaginal dryness	**Yes**	**No**

	Vaginal mucositis	**Yes**	**No**
	Vaginal atresia	**Yes**	**No**
	Vaginal inflammation	**Yes**	**No**
SYNDROMES			
	Retinoic acid syndrome	**Yes**	**No**
	Alcohol intolerance	**Yes**	**No**
	Cytokine release syndrome	**Yes**	**No**
	Flu-like symptoms	**Yes**	**No**
	Ill-defined disorder	**Yes**	**No**
	Tumor flare	**Yes**	**No**
	Tumor lysis syndrome	**Yes**	**No**
VASCULAR			
	Capillary leak syndrome	**Yes**	**No**
	Peripheral ischemia	**Yes**	**No**
	Phlebitis superficial	**Yes**	**No**
	Portal hypertension	**Yes**	**No**
	Vascular access complication	**Yes**	**No**
	Thrombosis	**Yes**	**No**
	Vascular disorder	**Yes**	**No**
	Aortic injury	**Yes**	**No**
	Injury to carotid artery	**Yes**	**No**

	Arterial injury - Extremity-lower	**Yes**	**No**
	Arterial injury - Extremity-upper	**Yes**	**No**
	Arterial injury	**Yes**	**No**
	Arterial injury - Visceral	**Yes**	**No**
	Venous injury - Extremity-lower	**Yes**	**No**
	Venous injury - Extremity-upper	**Yes**	**No**
	Injury to inferior vena cava	**Yes**	**No**
	Injury to jugular vein	**Yes**	**No**
	Venous injury	**Yes**	**No**
	Injury to superior vena cava	**Yes**	**No**
	Venous injury - Viscera	**Yes**	**No**
	Visceral arterial ischemia	**Yes**	**No**

Appendix 28

NHS Lothian –
University Hospitals Division

Department of Pharmacy
Royal Infirmary of Edinburgh
51 Little France Crescent
Old Dalkeith Road
EDINBURGH
EH16 4SA

Telephone 0131 242 2919
Fax 0131 242 2925
E-mail: melinda.cuthbert@luht.scot.nhs.uk

Your Ref:
Our Ref: crossfire/mphil/nominal group/letter 2

Certificate No: FS 31228

Dear Colleague

Pre-nominal group meeting materials to develop criteria for Yellow Card reporting in oncology patients receiving chemotherapy

Thank you for agreeing to participate in the above meeting to assist me in developing standards to operationalise the classification of serious oncology ADRs and to develop proposed criteria for Yellow Card reporting in oncology patients receiving chemotherapy.

As you are aware not all of the ADRs, which meet the criteria for reporting, get reported via the Yellow Card Scheme however. There are numerous contributing factors to this under-reporting but the major reason is that there are too many adverse reactions (which meet the Yellow Card Schemes criteria for reporting) seen in oncology to report them all. As a result it is important that criteria are developed to ensure that appropriate serious and/or unknown ADRs do not go unreported in oncology, which could compromise patient safety.

I enclose background information and the NCI Common Terminology for Cancer Adverse Events (version 3) for your information; also enclosed are the following for your completion:

1) A list of possible criteria and scenarios identified for oncology ADRs reporting from a recent questionnaire. Please indicate your level of agreement as directed.

2) A complete list of mapped MedDRA terminology for all CTCAE terms. You will need to indicate whether you consider the term to be 'serious' in oncology; and if 'yes' then should it be considered for inclusion in list of 'serious' ADRs which should be considered for reporting via the Yellow Card Scheme. There is also a comment field, in case you wish to make any suggestions for changes/additions as well at this time. I enclose an example sheet of how to complete.

I would be most grateful if you could complete the two items and return to me by the latest of one week before the scheduled meeting (still to be confirmed). I enclose a Freepost envelope for return of the latter two items. Also can I please ask that if you have not replied with your availability to the alternative dates circulated that you do so now.

A summary of the responses will be available for discussion at the meeting to be confirmed in September, where the participants will be asked to agree final proposed standards and criteria for reporting ADRs via the Yellow Card Scheme in oncology.

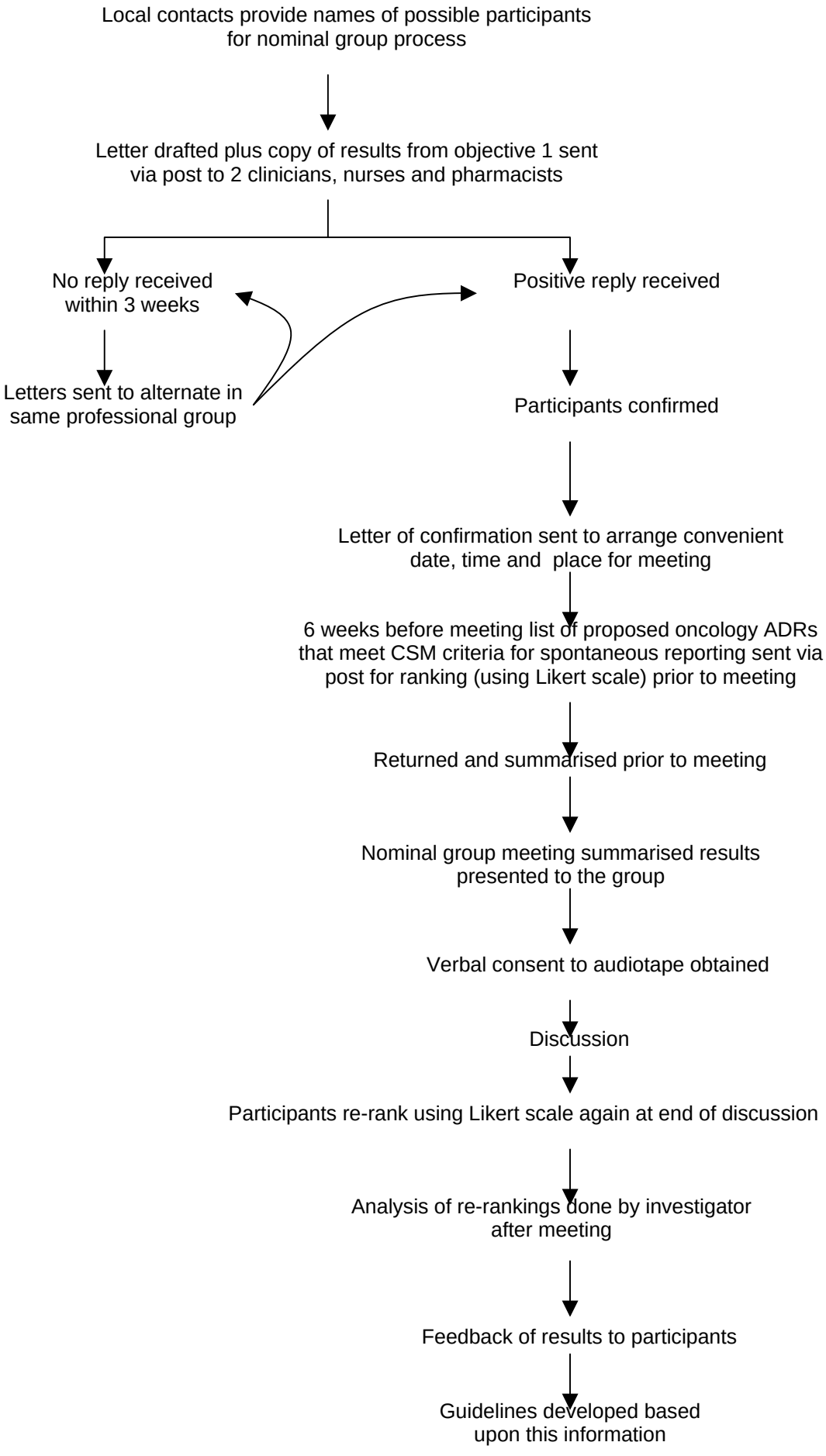
Please contact me via telephone on 0131 242 2917 or 0791 888 9003 or e-mail (melinda.cuthbert@luht.scot.nhs.uk) if you have any questions. I thank for your participation and look forward to seeing you at the meeting.

Yours Sincerely

Melinda Cuthbert
Principal Pharmacist

Appendix 29

Objective 3: To develop standards to operationalise the classification of serious ADRs in cancer chemotherapy patients for spontaneous ADR reporting.



Appendix 30

From: Bailey, Alex
Sent: 30 June 2008 09:58
To: Cuthbert, Melinda
Subject: RE: ethics

Dear Melinda,

Looking at the protocol for part III, I can advise you that this does not require review by an NHS REC as it is a service evaluation.

Regards,

Alex

Alex Bailey
Deaconess House
148 Pleasance
Edinburgh
EH9 9RS
Tel: 0131 536 9050

From: Cuthbert, Melinda
Sent: 04 June 2008 13:30
To: Bailey, Alex
Cc: 'jamwicks@hotmail.com'
Subject: ethics

Dear Alex

Thank you for this e-mail. I am delighted to say the least so I can proceed with piloting the questionnaire now! Can I also check on the next stage of my protocol at this point as well and whether ethics approval would be required? The next part is the nominal group process to come up with criteria for which oncology ADRs should be reported. I thank you in anticipation for your decision on this.

Kind regards
Melinda Cuthbert

Appendix 31

Lower Level Terms that received pre-nominal group consensus on serious classification and reporting via the Yellow Card

Lower Level Terms not classed as serious and should not be considered for reporting via the Yellow Card Scheme

Allergic rhinitis	Dry mouth	Upper respiratory infection
Hearing test abnormal	Dysphagia	Urethral infection
External ear inflammation	Esophagitis	Urinary tract infection
Middle ear inflammation	Flatulence	Uterine infection
Tinnitus	Dyspepsia	Vaginal infection
Hemoglobin decreased	Hemorrhoids	Vulval infection
Palpitations	Phlebitis superficial	Vulvitis
General symptom	Salivary gland disorder	Lymphedema
Fatigue	Taste alteration	Localized edema
Fever	Vomiting	Edema limbs
Insomnia	Catheter related infection	Lymphatic disorder
Obesity	Conjunctivitis infective	Gamma-glutamyltransferase increased
Body odor	Corneal infection	Muscle weakness lower limb
Chills	Tooth infection	Muscle weakness upper limb
Sweating	Duodenal infection	Facial muscle weakness
Weight gain	Esophageal infection	Eye muscle weakness
Weight loss	Otitis externa	Pelvic floor muscle weakness
Atrophy skin	Eye infection	Muscle weakness trunk
Fat atrophy	Salpingitis infection	Apnea
Bruising	Ileal infection	Dizziness
Skin disorder	Jejunal infection	Irritability
Dry skin	Kidney infection	Memory impairment
Flushing	Laryngitis	Euphoria
Alopecia	Lip infection	Olfactory nerve disorder
Skin hyperpigmentation	Pneumonia	Tremor
Skin hypopigmentation	Lymph gland infection	Dry eye syndrome
Skin induration	Otitis media	Eyelid function disorder
Injection site reaction	Mucosal infection	Conjunctival disorder
Nail disorder	Rhinitis infective	Diplopia
Photosensitivity	Gingival infection	Flashing vision
Pruritus	Paranasal sinus infection	Photophobia
Acne	Pelvic infection	Watering eyes
Skin striae	Penile infection	Abdominal pain
Telangiectasia	Stoma site infection	Anal pain
Urticaria	Pharyngitis	Back pain
Wound dehiscence	Prostate infection	Bladder pain
Hot flashes	Anorectal infection	Bone pain
Glucose intolerance	Salivary gland infection	Breast pain
Constipation	Scrotal infection	Buttock pain
Dehydration	Sinusitis	Chest wall pain
Dental prosthesis user	Skin infection	Toothache
Periodontal disease	Small intestine infection	Esophageal pain
Tooth disorder	Nail infection	Nasal congestion
Tooth development disorder	Upper aerodigestive tract infection	Voice alteration
		Pancreas infection

Abdominal distension	infection	Hiccough
External ear pain	Pericardial pain	Bladder spasm
Pain in extremity	Perineal pain	Cystitis
Eye pain	Peritoneal pain	Renal tubular disorder
Facial pain	Phantom pain	Urine discoloration
Gallbladder pain	Pleuritic pain	Nipple deformity
Headache	Prostatic pain	Breast hypoplasia
Gastrointestinal pain	Rectal pain	Gynecomastia
Joint pain	Scalp pain	Irregular menstruation
Kidney pain	Scrotal pain	Libido decreased
Laryngeal pain	Sinus pain	Orgasm abnormal
Lip pain	Pain of skin	Vaginal discharge
Ear pain	Stomach pain	Vaginal dryness
Neck pain	Testicular pain	Alcohol intolerance
Oral pain	Pharyngolaryngeal pain	Flu-like symptoms
Gingival pain	Tumor pain	Ill-defined disorder
Ovulation pain	Urethral pain	
Pain	Uterine pain	
Pelvic pain	Vaginal pain	
Penile pain	Pain	
	Cough	

Lower Level Terms classed as serious and should be considered for reporting via the Yellow Card Scheme

Hearing loss	Gastro-intestinal fistula	Jejunal perforation
Hemolysis	Anal necrosis	Rectal perforation
Myelodysplasia	Intestinal necrosis	Small intestinal perforation
Spleen disorder	Duodenal necrosis	Gastric perforation
Electrocardiogram QTc interval prolonged	Esophageal necrosis	Duodenal ulcer
Atrial fibrillation	Gallbladder necrosis	Esophageal ulcer
Ventricular fibrillation	Hepatic necrosis	Gastric ulcer
Myocardial ischemia	Ileal necrosis	Bone development abnormal
Cardiac troponin I increased	Jejunal necrosis	Slipped femoral epiphysis
Cardiac troponin T increased	Mouth necrosis	Unequal limb length
Cardiopulmonary arrest	Pancreatic necrosis	Kyphosis
Left ventricular failure	Peritoneal necrosis	Developmental disturbance
Pulmonary hypertension	Pharyngeal necrosis	Developmental delay
Restrictive cardiomyopathy	Rectal necrosis	Delayed puberty
Cor pulmonale	Small intestinal necrosis	Precocious puberty
Cardiac valve disease	Gastrointestinal stoma necrosis	Short stature
Coagulopathy	Gastric necrosis	Intracranial hemorrhage
Disseminated intravascular coagulation	Appendicitis perforated	Intra-abdominal hemorrhage
Death	Perforation bile duct	Anal hemorrhage
Multi-organ failure	Cecum perforation	Hemorrhage in bile duct
Sudden death	Colonic perforation	Cecal hemorrhage
Thermal burn	Duodenal perforation	Colonic hemorrhage
Erythema multiforme	Esophageal perforation	Duodenal hemorrhage

Erythema multiforme	Esophageal perforation	Duodenal hemorrhage
Skin ulceration	Gallbladder perforation	Esophageal hemorrhage
Adrenal insufficiency	Ileal perforation	Ileal hemorrhage
	Oculomotor nerve disorder	Leukoencephalopathy
Jejunal hemorrhage	Phrenic nerve paralysis	Neurological disorder NOS
Hepatic hemorrhage	Seizure	Optic nerve disorder
Lower gastrointestinal hemorrhage	Retinal detachment	Visceral arterial ischemia
Pancreatic hemorrhage	Cardiac pain	
Peritoneal hemorrhage	Chest pain	
Rectal hemorrhage	Adult respiratory distress syndrome	
Gastric hemorrhage	Bronchial fistula	
Upper gastrointestinal hemorrhage	Laryngeal fistula	
Esophageal varices hemorrhage	Pulmonary fistula	
Bladder hemorrhage	Oral cavity fistula	
Renal hemorrhage	Pharyngeal fistula	
Ovarian hemorrhage	Pleural fistula	
Prostatic hemorrhage	Tracheal fistula	
Retroperitoneal hemorrhage	Pneumothorax	
Ureteric hemorrhage	Pulmonary fibrosis	
Urethral hemorrhage	Vesical fistula	
Hemorrhage urinary tract	Female genital tract fistula	
Uterine hemorrhage	Renal pelvis fistula	
Vaginal hemorrhage	Ureteric fistula	
Tracheal hemorrhage	Urethral fistula	
Hemorrhage	Uterine fistula	
Hepatic failure	Vaginal fistula	
Pancreatitis	Testicular obstruction	
Bone infection	Urethral obstruction	
Encephalitis infection	Bladder perforation	
Encephalomyelitis infection	Fallopian tube perforation	
Endocarditis infective	Kidney perforation	
Spinal cord infection	Ovarian rupture	
Scoliosis	Prostatic perforation	
Joint range of motion decreased cervical spine	Spermatic cord perforation	
Fibrosis deep connective tissue	Urostomy perforation	
Musculoskeletal deformity	Testicular perforation	
Osteonecrosis	Ureteric perforation	
Abdominal soft tissue necrosis	Urethral perforation	
Soft tissue necrosis lower limb	Uterine perforation	
Soft tissue necrosis upper limb	Vaginal perforation	
Head soft tissue necrosis	Vas deferens perforation	
Neck soft tissue necrosis	Renal failure	
Pelvic soft tissue necrosis	Treatment related 2^{o} malignancy	
Chest wall necrosis	Thrombosis	
Arachnoiditis	Aortic injury	
Ischemia cerebrovascular	Injury to carotid artery	
Central nervous system necrosis	Injury to inferior vena cava	
Encephalopathy	Injury to jugular vein	
Hydrocephalus	Venous injury	
Recurrent laryngeal nerve palsy	Injury to superior vena cava	
Cerebrospinal fluid leakage	Venous injury - Viscera	

Appendix 32

Hypersensitivity
Immune system disorder
Autoimmune disorder
Serum sickness
Ear disorder
Bone marrow hypocellular
CD4 lymphocytes decreased
Haptoglobin decreased
Iron increased
Leukopenia
Lymphopenia
Neutrophil count decreased
Platelet count decreased
Arrhythmia
Atrioventricular block first degree
Mobitz type I
Mobitz (type) II atrioventricular block
Atrioventricular block complete
Asystole
Conduction disorder
Sick sinus syndrome
Stokes-Adams syndrome
Wolff-Parkinson-White syndrome
Atrial flutter
Atrial tachycardia
Nodal arrhythmia
Sinus arrhythmia
Sinus bradycardia
Sinus tachycardia
Arrhythmia supraventricular
Supraventricular extrasystoles
Supraventricular tachycardia
Syncope vasovagal
Ventricular bigeminy
Rhythm idioventricular
Premature ventricular contractions
Torsade de pointes
Ventricular trigeminy
Ventricular arrhythmia
Ventricular flutter
Ventricular tachycardia
Cardiac disorder
Hypertension
Hypotension
Diastolic dysfunction
Myocarditis
Anal ulcer
Cecal ulcer
Colonic ulcer
Ileal ulcer
Jejunal ulcer
Rectal ulcer
Small intestine ulcer
Stomal ulcer
Hematoma
Oral hemorrhage
Intestinal stoma site bleeding
Pericardial effusion
Pericarditis
Fibrinogen decreased
INR increased
Activated partial thromboplastin time prolonged
Thrombotic microangiopathy
Endoscopy of large bowel abnormal
Cheilitis
Rash desquamating
Radiation recall reaction (dermatologic)
Dermatitis radiation
Hand-and-foot syndrome
Decubitus ulcer
Cushingoid
Endocrine disorder
Feminization
Masculinization
Blood gonadotrophin abnormal
Growth hormone abnormal
Blood prolactin abnormal
ACTH decreased
ADH abnormal
Hypoparathyroidism
Hyperthyroidism
Hypothyroidism
Anorexia
Ascites
Diarrhea
Enteritis
Gastritis
Gastrointestinal disorder
Fecal incontinence
Biliary anastomotic leak
Esophageal anastomotic leak
Large intestinal anastomotic leak
Anastomotic leak
Pancreatic anastomotic leak
Pharyngeal anastomotic leak
Rectal anastomotic leak
Small intestinal anastomotic leak
Intestinal stoma leak
Gastric anastomotic leak
Malabsorption
Anal exam abnormal
Oesophagoscopy abnormal
Peritoneal infection
Pleural infection
Soft tissue infection
Splenic infection
Gastric infection
Tracheitis
Ureteritis
Phlebitis infective
Wound infection
Opportunistic infection
Visceral edema
Fibrosis
Laryngoscopy abnormal
Ear, nose and throat examination abno
Pharyngeal examination abnormal
Proctoscopy abnormal
Endoscopy small intestine abnormal
Gastroscopy abnormal
Tracheoscopy abnormal
Anal mucositis
Esophageal mucositis
Large intestinal mucositis
Laryngeal mucositis
Mucositis oral
Pharyngeal mucositis
Rectal mucositis
Small intestinal mucositis
Gastric mucositis
Tracheal mucositis
Nausea
Cecal obstruction
Colonic obstruction
Duodenal obstruction
Esophageal obstruction
Gallbladder obstruction
Ileal obstruction
Jejunal obstruction
Rectal obstruction
Small intestinal obstruction
Intestinal stoma obstruction
Obstruction gastric
Proctitis
Prolapse of intestinal stoma
Anal stenosis
Bile duct stenosis
Intestinal stenosis
Colonic stenosis
Duodenal stenosis
Esophageal stenosis
Ileal stenosis
Jejunal stenosis
Pancreatic duct stenosis
Stricture/stenosis (including anastomoti
Rectal stenosis
Small intestinal stenosis
Stenosis of gastrointestinal stoma
Gastric stenosis
Typhlitis
Joint effusion
Joint disorder
Device complication
Joint range of motion decreased lumba
Extraocular muscle disorder
Muscle weakness left-sided
Muscle weakness right-sided
Muscle weakness
Musculoskeletal disorder
Myositis
Osteoporosis
Seroma

Hemorrhoidal hemorrhage
Hematosalpinx
Spermatic cord hemorrhage
Urostomy site bleeding
Testicular hemorrhage
Vas deferens hemorrhage
Bronchopulmonary hemorrhage
Bronchial hemorrhage
Laryngeal hemorrhage
Pulmonary hemorrhage
Mediastinal hemorrhage
Hemorrhage nasal
Pharyngeal hemorrhage
Pleural hemorrhage
Respiratory tract hemorrhage
Tracheostomy site bleeding
Postoperative hemorrhage
Petechiae
Cholecystitis
Hepatobiliary disease
Pancreatic enzymes decreased
Colitis, infectious (e.g., Clostridium difficile)
Abdominal infection
Anal infection
Appendicitis
Arteritis infective
Biliary tract infection
Bladder infection
Bronchitis
Cecal infection
Cervicitis
Infectious colitis
Device related infection
Gallbladder infection
Eye infection intraocular
Hepatic infection
Mediastinal infection
Infective myositis
Infection
Uveitis
Vision blurred
Vitreous hemorrhage
Myalgia
Neuralgia
Aspiration
Atelectasis
Bronchospasm
Carbon monoxide diffusing capacity decreased
Chylothorax
Dyspnea
Laryngeal edema
Forced expiratory volume decreased
Hypoxia
Bronchial obstruction
Laryngeal obstruction
Pharyngeal stenosis
Tracheal obstruction
Vaginal obstruction
Vas deferens obstruction
Prolapse of urostomy
Urogenital disorder
Bladder stenosis
Fallopian tube stenosis
Prostatic disorder
Spermatic cord stenosis
Urostomy stenosis
Testicular stricture/stenosis
Ureteric stenosis
Urethral stricture
Uterine stenosis
Rectal fistula
Salivary gland fistula
Fistula of small intestine
Gastic fistula
Ileus
Febrile neutropenia
Oral cavity fistula
Pancreatic fistula
Fistula, Pharynx
Kidney anastomotic leak
Spermatic cord anastomotic leak
Urostomy leak
Ureteric anastomotic leak
Urethral anastomotic leak
Uterine anastomotic leak
Vaginal anastomotic leak
Vas deferens anastomotic leak
Bladder obstruction
Fallopian tube obstruction
Prostatic obstruction
Spermatic cord obstruction
Urostomy obstruction
Ureteric obstruction
Lymphocele
Lymphangitic streak
Alanine aminotransferase increased
Aspartate aminotransferase increased
Acidosis
Hypoalbuminemia
Alkaline phosphatase increased
Alkalosis
Amylase increased
Blood bicarbonate decreased
Hyperbilirubinemia
Creatine phosphokinase increased
Hypercalcemia
Hypocalcemia
Hypercholesterolemia
Creatinine increased
Glomerular filtration rate decreased
Hyperglycemia
Hypoglycemia
Hemoglobinuria
Lipase increased
Trismus
Ataxia
Radiculitis brachial
Cognitive disturbance
Confusion
Extrapyramidal disorder
Mental status changes
Agitation
Anxiety
Depression
Myelitis
IVth nerve disorder
Glossopharyngeal nerve disorder
Trigeminal nerve disorder
Abducens nerve disorder
Facial nerve disorder
Acoustic nerve disorder NOS
Vagus nerve disorder
Accessory nerve disorder
Hypoglossal nerve disorder
Peripheral motor neuropathy
Peripheral sensory neuropathy
Personality change
Psychosis
Pyramidal tract syndrome
Depressed level of consciousness
Speech disorder
Syncope
Cataract
Glaucoma
Keratitis
Night blindness
Nystagmus
Eye disorder
Optic nerve edema
Proptosis
Retinopathy
Sepsis
Joint infection
Renal tubular disorder
Vaginal stricture
Vas deferens stenosis
Urinary frequency
Urinary retention
Lactation disorder
Ejaculation disorder
Erectile dysfunction
Infertility
Reproductive tract disorder
Vaginal mucositis
Vaginal atresia
Vaginal inflammation
Retinoic acid syndrome
Cytokine release syndrome
Tumor flare

Pleural effusion
Pneumonitis
Postoperative thoracic procedure complication
Prolonged intubation after pulmonary resection (>24 hrs after surgery)
Respiratory disorder
Vital capacity decreased
Urinary incontinence
Bladder anastomotic leak
Fallopian tube anastomotic leak
Vasculitis
Blood disorder
Disease progression
Colitis
Anal fistula
Biliary fistula
Colonic fistula
Duodenal fistula
Acquired tracheo-oesophageal fistula
Gallbladder fistula
Ileal fistula

Hypermagnesemia
Hypomagnesemia
Laboratory test abnormal
Hypophosphatemia
Hyperkalemia
Hypokalemia
Proteinuria
Hypernatremia
Hyponatremia
Hypertriglyceridemia
Hyperuricemia
Arthritis
Exostosis
Gait abnormal
Upper extremity dysfunction
Superficial soft tissue fibrosis
Jejunal fistula

Tumor lysis syndrome
Capillary leak syndrome
Peripheral ischemia
Portal hypertension
Vascular access complication
Vascular disorder
Arterial injury - Extremity-lower
Arterial injury - Extremity-upper
Arterial injury
Arterial injury - Visceral
Venous injury - Extremity-lower
Venous injury - Extremity-upper
Lymph node pain

Infectious meningitis
Cranial nerve infection
Peripheral nerve infection
Viral hepatitis
Lymph leakage
Hepatic pain

Appendix 33

Nominal Group decisions on Lower Level Terms with no prior consensus on seriousness or reporting via the Yellow Card Scheme

Colour Legend of Nominal Group meeting decisions
Serious but do not report =
Not serious & do not report =
Serious & report =

Hypersensitivity	Pericardial effusion	Laryngoscopy abnormal
Immune system disorder	Pericarditis	Ear, nose and throat examination
Autoimmune disorder	Fibrinogen decreased	Pharyngeal examination abnorma
Serum sickness	INR increased	Proctoscopy abnormal
Ear disorder	Activated partial thromboplastin time prolonged	Endoscopy small intestine abnorm
Bone marrow hypocellular	Thrombotic microangiopathy	Gastroscopy abnormal
CD4 lymphocytes decreased	Endoscopy of large bowel abnormal	Tracheoscopy abnormal
Haptoglobin decreased	Cheilitis	Anal mucositis
Iron increased	Rash desquamating	Esophageal mucositis
Leukopenia	Radiation recall reaction (dermatologic)	Large intestinal mucositis
Lymphopenia	Dermatitis radiation	Laryngeal mucositis
Neutrophil count decreased	Hand-and-foot syndrome	Mucositis oral
Platelet count decreased	Decubitus ulcer	Pharyngeal mucositis
Arrhythmia	Cushingoid	Rectal mucositis
Atrioventricular block first degree	Endocrine disorder	Small intestinal mucositis
Mobitz type I	Feminization	Gastric mucositis
Mobitz (type) II atrioventricular block	Masculinization	Tracheal mucositis
Atrioventricular block complete	Blood gonadotrophin abnormal	Nausea
Asystole	Growth hormone abnormal	Cecal obstruction
Conduction disorder	Blood prolactin abnormal	Colonic obstruction
Sick sinus syndrome	ACTH decreased	Duodenal obstruction
Stokes-Adams syndrome	ADH abnormal	Esophageal obstruction
Wolff-Parkinson-White syndrome	Hypoparathyroidism	Gallbladder obstruction
Atrial flutter	Hyperthyroidism	Ileal obstruction
Atrial tachycardia	Hypothyroidism	Jejunal obstruction
Nodal arrhythmia	Anorexia	Rectal obstruction
Sinus arrhythmia	Ascites	Small intestinal obstruction
Sinus bradycardia	Diarrhea	Intestinal stoma obstruction
Sinus tachycardia	Enteritis	Obstruction gastric
Arrhythmia supraventricular	Gastritis	Proctitis
Supraventricular extrasystoles	Gastrointestinal disorder	Prolapse of intestinal stoma
Supraventricular tachycardia	Fecal incontinence	Anal stenosis
Syncope vasovagal	Biliary anastomotic leak	Bile duct stenosis
Ventricular bigeminy	Esophageal anastomotic leak	Intestinal stenosis
Rhythm idioventricular	Large intestinal anastomotic leak	Colonic stenosis
Premature ventricular contractions	Anastomotic leak	Duodenal stenosis
Ventricular trigeminy	Pancreatic anastomotic leak	Esophageal stenosis
Ventricular arrhythmia	Pharyngeal anastomotic leak	Ileal stenosis
Ventricular flutter	Rectal anastomotic leak	Jejunal stenosis
Ventricular tachycardia	Small intestinal anastomotic leak	Pancreatic duct stenosis
Cardiac disorder	Intestinal stoma leak	Stricture/stenosis, Pharynx

Hypertension
Hypotension
Diastolic dysfunction
Myocarditis
Anal ulcer
Cecal ulcer
Colonic ulcer
Ileal ulcer
Jejunal ulcer
Rectal ulcer
Small intestine ulcer
Stomal ulcer
Hematoma
Oral hemorrhage
Intestinal stoma site bleeding
Hemorrhoidal hemorrhage
Hematosalpinx
Spermatic cord hemorrhage
Urostomy site bleeding
Testicular hemorrhage
Vas deferens hemorrhage
Bronchopulmonary hemorrhage
Bronchial hemorrhage
Laryngeal hemorrhage
Pulmonary hemorrhage
Mediastinal hemorrhage
Hemorrhage nasal
Pharyngeal hemorrhage
Pleural hemorrhage
Respiratory tract hemorrhage
Tracheostomy site bleeding
Postoperative hemorrhage
Petechiae
Cholecystitis
Hepatobiliary disease
Pancreatic enzymes decreased
Colitis, infectious (e.g., Clostridium difficile)
Abdominal infection
Anal infection
Appendicitis
Arteritis infective
Biliary tract infection
Bladder infection
Bronchitis
Cecal infection
Cervicitis
Infectious colitis
Device related infection
Gallbladder infection
Eye infection intraocular
Gastric anastomotic leak
Malabsorption
Anal exam abnormal
Oesophagoscopy abnormal
Peritoneal infection
Pleural infection
Soft tissue infection
Splenic infection
Gastric infection
Tracheitis
Ureteritis
Phlebitis infective
Wound infection
Opportunistic infection
Visceral edema
Fibrosis
Lymphocele
Lymphangitic streak
Alanine aminotransferase increased
Aspartate aminotransferase increased
Acidosis
Hypoalbuminemia
Alkaline phosphatase increased
Alkalosis
Amylase increased
Blood bicarbonate decreased
Hyperbilirubinemia
Creatine phosphokinase increased
Hypercalcemia
Hypocalcemia
Hypercholesterolemia
Creatinine increased
Glomerular filtration rate decreased
Hyperglycemia
Hypoglycemia
Hemoglobinuria
Lipase increased
Hypermagnesemia
Hypomagnesemia
Laboratory test abnormal
Hypophosphatemia
Hyperkalemia
Hypokalemia
Proteinuria
Hypernatremia
Hyponatremia
Hypertriglyceridemia
Hyperuricemia
Arthritis
Exostosis
Rectal stenosis
Small intestinal stenosis
Stenosis of gastrointestinal stoma
Gastric stenosis
Typhlitis
Joint effusion
Joint disorder
Device complication
Joint range of motion decreased lumbar spine
Extraocular muscle disorder
Muscle weakness left-sided
Muscle weakness right-sided
Muscle weakness
Musculoskeletal disorder
Myositis
Osteoporosis
Seroma
Trismus
Ataxia
Radiculitis brachial
Cognitive disturbance
Confusion
Extrapyramidal disorder
Mental status changes
Agitation
Anxiety
Depression
Myelitis
IVth nerve disorder
Glossopharyngeal nerve disorder
Trigeminal nerve disorder
Abducens nerve disorder
Facial nerve disorder
Acoustic nerve disorder NOS
Vagus nerve disorder
Accessory nerve disorder
Hypoglossal nerve disorder
Peripheral motor neuropathy
Peripheral sensory neuropathy
Personality change
Psychosis
Pyramidal tract syndrome
Depressed level of consciousness
Speech disorder
Syncope
Cataract
Glaucoma
Keratitis
Night blindness
Nystagmus

Hepatic infection
Mediastinal infection
Infective myositis
Infection
Uveitis
Vision blurred
Vitreous hemorrhage
Myalgia
Neuralgia
Aspiration
Atelectasis
Bronchospasm
Carbon monoxide diffusing capacity decreased
Chylothorax
Dyspnea
Laryngeal edema
Forced expiratory volume decreased
Hypoxia
Bronchial obstruction
Laryngeal obstruction
Pharyngeal stenosis
Tracheal obstruction
Pleural effusion
Pneumonitis
Postoperative thoracic procedure complication
Prolonged intubation after pulmonary resection (>24 hrs after surgery)
Respiratory disorder
Vital capacity decreased
Urinary incontinence
Bladder anastomotic leak
Fallopian tube anastomotic leak
Vasculitis
Blood disorder
Disease progression
Colitis
Anal fistula
Biliary fistula
Colonic fistula
Duodenal fistula
Acquired tracheo-oesophageal fistula
Gallbladder fistula
Ileal fistula
Jejunal fistula
Oral cavity fistula
Pancreatic fistula
Fistula, Pharynx
Kidney anastomotic leak
Spermatic cord anastomotic leak
Urostomy leak
Ureteric anastomotic leak
Urethral anastomotic leak
Uterine anastomotic leak
Vaginal anastomotic leak
Vas deferens anastomotic leak
Bladder obstruction
Fallopian tube obstruction
Prostatic obstruction
Spermatic cord obstruction
Urostomy obstruction
Ureteric obstruction
Uterine obstruction
Vaginal obstruction
Vas deferens obstruction
Prolapse of urostomy
Urogenital disorder
Bladder stenosis
Fallopian tube stenosis
Prostatic disorder
Spermatic cord stenosis
Urostomy stenosis
Testicular stricture/stenosis
Ureteric stenosis
Urethral stricture
Uterine stenosis
Rectal fistula
Salivary gland fistula
Fistula of small intestine
Gastic fistula
Ileus
Febrile neutropenia
Gait abnormal
Upper extremity dysfunction
Superficial soft tissue fibrosis
Fracture
Scleral disorder
Joint infection
Renal tubular disorder
Vaginal stricture
Vas deferens stenosis
Urinary frequency
Urinary retention
Lactation disorder
Ejaculation disorder
Erectile dysfunction
Infertility
Reproductive tract disorder
Vaginal mucositis
Vaginal atresia
Vaginal inflammation
Retinoic acid syndrome
Cytokine release syndrome
Tumor flare
Tumor lysis syndrome
Capillary leak syndrome
Peripheral ischemia
Portal hypertension
Vascular access complication
Vascular disorder
Arterial injury - Extremity-lower
Arterial injury - Extremity-upper
Arterial injury
Arterial injury - Visceral
Venous injury - Extremity-lower
Venous injury - Extremity-upper
Lymph node pain
Infectious meningitis
Cranial nerve infection
Peripheral nerve infection
Viral hepatitis
Lymph leakage
Hepatic pain
Eye disorder
Optic nerve edema
Proptosis
Retinopathy

Appendix 34

MedDRA LLT CTEP Term	AE Supraordinate Term	Select AE
Autoimmune disorder	Autoimmune reaction	
Serum sickness	Serum sickness	
Vasculitis	Vasculitis	
Hearing loss	Hearing: patients without baseline audiogram and not enrolled in a monitoring program	
Hemolysis	Hemolysis (e.g., immune hemolytic anemia, drug-related hemolysis)	
Myelodysplasia	Myelodysplasia	
Spleen disorder	Splenic function	
Arrhythmia	Cardiac Arrhythmia - Other (Specify, __)	
Atrioventricular block first degree	Conduction abnormality/atrioventricular heart block	AV Block-First degree
Mobitz type I	Conduction abnormality/atrioventricular heart block	AV Block-Second degree Mobitz Type I (Wenckebach)
Mobitz (type) II atrioventricular block	Conduction abnormality/atrioventricular heart block	AV Block-Second degree Mobitz Type II
Atrioventricular block complete	Conduction abnormality/atrioventricular heart block	AV Block-Third degree (Complete AV block)
Asystole	Conduction abnormality/atrioventricular heart block	Asystole
Conduction disorder	Conduction abnormality/atrioventricular heart block	Conduction abnormality NOS
Sick sinus syndrome	Conduction abnormality/atrioventricular heart block	Sick Sinus Syndrome
Stokes-Adams syndrome	Conduction abnormality/atrioventricular heart block	Stokes-Adams Syndrome
Wolff-Parkinson-White syndrome	Conduction abnormality/atrioventricular heart block	Wolff-Parkinson-White Syndrome
Palpitations	Palpitations	
Electrocardiogram QTc interval prolonged	Prolonged QTc interval	
Atrial fibrillation	Supraventricular and nodal arrhythmia	Atrial fibrillation
Atrial tachycardia	Supraventricular and nodal arrhythmia	Atrial tachycardia/Paroxysmal Atrial Tachycardia
Nodal arrhythmia	Supraventricular and nodal arrhythmia	Nodal/Junctional
Sinus arrhythmia	Supraventricular and nodal arrhythmia	Sinus arrhythmia
Arrhythmia supraventricular	Supraventricular and nodal arrhythmia	Supraventricular arrhythmia NOS
Supraventricular extrasystoles	Supraventricular and nodal arrhythmia	Supraventricular extrasystoles '(Premature Atrial Contractions; Premature Nodal/Junctional Contractions)
Supraventricular tachycardia	Supraventricular and nodal arrhythmia	Supraventricular tachycardia
Ventricular bigeminy	Ventricular arrhythmia	Bigeminy
Rhythm idioventricular	Ventricular arrhythmia	Idioventricular rhythm
Torsade de pointes	Ventricular arrhythmia	Torsade de pointes
Ventricular trigeminy	Ventricular arrhythmia	Trigeminy
Ventricular arrhythmia	Ventricular arrhythmia	Ventricular arrhythmia NOS
Ventricular fibrillation	Ventricular arrhythmia	Ventricular fibrillation
Ventricular flutter	Ventricular arrhythmia	Ventricular flutter
Ventricular tachycardia	Ventricular arrhythmia	Ventricular tachycardia
Myocardial ischemia	Cardiac ischemia/infarction	
Cardiac troponin I increased	Cardiac troponin I (cTnI)	
Cardiac troponin T increased	Cardiac troponin T (cTnT)	

Cardiopulmonary arrest	Cardiopulmonary arrest, cause unknown (non-fatal)	
Hypertension	Hypertension	
Hypotension	Hypotension	
Left ventricular failure	Left ventricular systolic dysfunction	
Myocarditis	Myocarditis	
Pericardial effusion	Pericardial effusion (non-malignant)	
Pericarditis	Pericarditis	
Pulmonary hypertension	Pulmonary hypertension	
Restrictive cardiomyopathy	Restrictive cardiomyopathy	
Cor pulmonale	Right ventricular dysfunction (cor pulmonale)	
Cardiac valve disease	Valvular heart disease	
Coagulopathy	Coagulation - Other (Specify, __)	
Disseminated intravascular coagulation	DIC (disseminated intravascular coagulation)	
Death	Death not associated with CTCAE term	Death NOS
Multi-organ failure	Death not associated with CTCAE term	Multi-organ failure
Sudden death	Death not associated with CTCAE term	Sudden death
Thermal burn	Burn	
Erythema multiforme	Rash: erythema multiforme (e.g., Stevens-Johnson syndrome, toxic epidermal necrolysis)	
Hand-and-foot syndrome	Rash: hand-foot skin reaction	
Skin ulceration	Ulceration	
Adrenal insufficiency	Adrenal insufficiency	
Hypoparathyroidism	Parathyroid function, low (hypoparathyroidism)	
Hyperthyroidism	Thyroid function, high (hyperthyroidism, thyrotoxicosis)	
Hypothyroidism	Thyroid function, low (hypothyroidism)	
Ascites	Ascites (non-malignant)	
Colitis	Colitis	
Gastro-intestinal fistula	Fistula, GI	Abdomen NOS
Anal fistula	Fistula, GI	Anus
Biliary fistula	Fistula, GI	Biliary tree
Colonic fistula	Fistula, GI	Colon/cecum/appendix
Duodenal fistula	Fistula, GI	Duodenum
Acquired tracheo-oesophageal fistula	Fistula, GI	Esophagus
Gallbladder fistula	Fistula, GI	Gallbladder
Ileal fistula	Fistula, GI	Ileum
Jejunal fistula	Fistula, GI	Jejunum
Oral cavity fistula	Fistula, GI	Oral cavity
Pancreatic fistula	Fistula, GI	Pancreas
Fistula, Pharynx	Fistula, GI	Pharynx
Rectal fistula	Fistula, GI	Rectum

Salivary gland fistula	Fistula, GI	Salivary gland
Fistula of small intestine	Fistula, GI	Small bowel NOS
Gastic fistula	Fistula, GI	Stomach
Ileus	Ileus, GI (functional obstruction of bowel , i.e., neuroconstipation)	
Anal necrosis	Necrosis, GI	Anus
Intestinal necrosis	Necrosis, GI	Colon/cecum/appendix
Duodenal necrosis	Necrosis, GI	Duodenum
Esophageal necrosis	Necrosis, GI	Esophagus
Gallbladder necrosis	Necrosis, GI	Gallbladder
Hepatic necrosis	Necrosis, GI	Hepatic
Ileal necrosis	Necrosis, GI	Ileum
Jejunal necrosis	Necrosis, GI	Jejunum
Mouth necrosis	Necrosis, GI	Oral
Pancreatic necrosis	Necrosis, GI	Pancreas
Peritoneal necrosis	Necrosis, GI	Peritoneal cavity
Pharyngeal necrosis	Necrosis, GI	Pharynx
Rectal necrosis	Necrosis, GI	Rectum
Small intestinal necrosis	Necrosis, GI	Small bowel NOS
Gastrointestinal stoma necrosis	Necrosis, GI	Stoma
Gastric necrosis	Necrosis, GI	Stomach
Cecal obstruction	Obstruction, GI	Cecum
Colonic obstruction	Obstruction, GI	Colon
Duodenal obstruction	Obstruction, GI	Duodenum
Esophageal obstruction	Obstruction, GI	Esophagus
Gallbladder obstruction	Obstruction, GI	Gallbladder
Ileal obstruction	Obstruction, GI	Ileum
Jejunal obstruction	Obstruction, GI	Jejunum
Rectal obstruction	Obstruction, GI	Rectum
Small intestinal obstruction	Obstruction, GI	Small bowel NOS
Intestinal stoma obstruction	Obstruction, GI	Stoma
Obstruction gastric	Obstruction, GI	Stomach
Appendicitis perforated	Perforation, GI	Appendix
Perforation bile duct	Perforation, GI	Biliary tree
Cecum perforation	Perforation, GI	Cecum
Colonic perforation	Perforation, GI	Colon
Duodenal perforation	Perforation, GI	Duodenum
Esophageal perforation	Perforation, GI	Esophagus
Gallbladder perforation	Perforation, GI	Gallbladder
Ileal perforation	Perforation, GI	Ileum
Jejunal perforation	Perforation, GI	Jejunum
Rectal perforation	Perforation, GI	Rectum

Small intestinal perforation	Perforation, GI	Small bowel NOS
Gastric perforation	Perforation, GI	Stomach
Anal stenosis	Stricture/stenosis (including anastomotic), GI	Anus
Bile duct stenosis	Stricture/stenosis (including anastomotic), GI	Biliary tree
Intestinal stenosis	Stricture/stenosis (including anastomotic), GI	Cecum
Colonic stenosis	Stricture/stenosis (including anastomotic), GI	Colon
Duodenal stenosis	Stricture/stenosis (including anastomotic), GI	Duodenum
Esophageal stenosis	Stricture/stenosis (including anastomotic), GI	Esophagus
Ileal stenosis	Stricture/stenosis (including anastomotic), GI	Ileum
Jejunal stenosis	Stricture/stenosis (including anastomotic), GI	Jejunum
Pancreatic duct stenosis	Stricture/stenosis (including anastomotic), GI	Pancreas/pancreatic duct
Stricture/stenosis (including anastomotic), Pharynx	Stricture/stenosis (including anastomotic), GI	Pharynx
Rectal stenosis	Stricture/stenosis (including anastomotic), GI	Rectum
Small intestinal stenosis	Stricture/stenosis (including anastomotic), GI	Small bowel NOS
Stenosis of gastrointestinal stoma	Stricture/stenosis (including anastomotic), GI	Stoma
Gastric stenosis	Stricture/stenosis (including anastomotic), GI	Stomach
Typhlitis	Typhlitis (cecal inflammation)	
Anal ulcer	Ulcer, GI	Anus
Cecal ulcer	Ulcer, GI	Cecum
Colonic ulcer	Ulcer, GI	Colon
Duodenal ulcer	Ulcer, GI	Duodenum
Esophageal ulcer	Ulcer, GI	Esophagus
Ileal ulcer	Ulcer, GI	Ileum
Jejunal ulcer	Ulcer, GI	Jejunum
Rectal ulcer	Ulcer, GI	Rectum
Small intestine ulcer	Ulcer, GI	Small bowel NOS
Stomal ulcer	Ulcer, GI	Stoma
Gastric ulcer	Ulcer, GI	Stomach
Bone development abnormal	Bone age (alteration in bone age)	
Slipped femoral epiphysis	Bone growth: femoral head; slipped capital femoral epiphysis	
Unequal limb length	Bone growth:limb length discrepancy	
Kyphosis	Bone growth:spine kyphosis/lordosis	
Developmental disturbance	Growth and Development - Other (Specify, __)	
Developmental delay	Growth velocity (reduction in growth velocity)	
Delayed puberty	Puberty (delayed)	
Precocious puberty	Puberty (precocious)	
Short stature	Short stature	
Intracranial hemorrhage	Hemorrhage, CNS	
Intra-abdominal hemorrhage	Hemorrhage, GI	Abdomen NOS
Anal hemorrhage	Hemorrhage, GI	Anus

Hemorrhage in bile duct	Hemorrhage, GI	Biliary tree
Cecal hemorrhage	Hemorrhage, GI	Cecum/appendix
Colonic hemorrhage	Hemorrhage, GI	Colon
Duodenal hemorrhage	Hemorrhage, GI	Duodenum
Esophageal hemorrhage	Hemorrhage, GI	Esophagus
Ileal hemorrhage	Hemorrhage, GI	Ileum
Jejunal hemorrhage	Hemorrhage, GI	Jejunum
Hepatic hemorrhage	Hemorrhage, GI	Liver
Lower gastrointestinal hemorrhage	Hemorrhage, GI	Lower GI NOS
Pancreatic hemorrhage	Hemorrhage, GI	Pancreas
Peritoneal hemorrhage	Hemorrhage, GI	Peritoneal cavity
Rectal hemorrhage	Hemorrhage, GI	Rectum
Gastric hemorrhage	Hemorrhage, GI	Stomach
Upper gastrointestinal hemorrhage	Hemorrhage, GI	Upper GI NOS
Esophageal varices hemorrhage	Hemorrhage, GI	Varices (esophageal)
Bladder hemorrhage	Hemorrhage, GU	Bladder
Hematosalpinx	Hemorrhage, GU	Fallopian tube
Renal hemorrhage	Hemorrhage, GU	Kidney
Ovarian hemorrhage	Hemorrhage, GU	Ovary
Prostatic hemorrhage	Hemorrhage, GU	Prostate
Retroperitoneal hemorrhage	Hemorrhage, GU	Retroperitoneum
Spermatic cord hemorrhage	Hemorrhage, GU	Spermatic cord
Testicular hemorrhage	Hemorrhage, GU	Testes
Ureteric hemorrhage	Hemorrhage, GU	Ureter
Urethral hemorrhage	Hemorrhage, GU	Urethra
Hemorrhage urinary tract	Hemorrhage, GU	Urinary NOS
Uterine hemorrhage	Hemorrhage, GU	Uterus
Vaginal hemorrhage	Hemorrhage, GU	Vagina
Vas deferens hemorrhage	Hemorrhage, GU	Vas deferens
Bronchopulmonary hemorrhage	Hemorrhage, pulmonary/upper respiratory	Bronchopulmonary NOS
Bronchial hemorrhage	Hemorrhage, pulmonary/upper respiratory	Bronchus
Laryngeal hemorrhage	Hemorrhage, pulmonary/upper respiratory	Larynx
Pulmonary hemorrhage	Hemorrhage, pulmonary/upper respiratory	Lung
Mediastinal hemorrhage	Hemorrhage, pulmonary/upper respiratory	Mediastinum
Hemorrhage nasal	Hemorrhage, pulmonary/upper respiratory	Nose
Pharyngeal hemorrhage	Hemorrhage, pulmonary/upper respiratory	Pharynx
Pleural hemorrhage	Hemorrhage, pulmonary/upper respiratory	Pleura
Respiratory tract hemorrhage	Hemorrhage, pulmonary/upper respiratory	Respiratory tract NOS
Tracheal hemorrhage	Hemorrhage, pulmonary/upper respiratory	Trachea
Hemorrhage	Hemorrhage/Bleeding - Other (Specify, __)	
Hepatobiliary disease	Hepatobiliary/Pancreas - Other (Specify, __)	
Hepatic failure	Liver dysfunction/failure (clinical)	

Pancreatitis	Pancreatitis	
Arteritis infective	Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10e9/L);	Artery
	Infection with normal ANC or Grade 1 or 2 neutrophils;	Artery
	Infection with unknown ANC	Artery
Bone infection	Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10e9/L);	Bone (osteomyelitis)
	Infection with normal ANC or Grade 1 or 2 neutrophils;	Bone (osteomyelitis)
	Infection with unknown ANC	Bone (osteomyelitis)
Encephalitis infection	Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10e9/L);	Brain (encephalitis, infectious)
	Infection with normal ANC or Grade 1 or 2 neutrophils;	Brain (encephalitis, infectious)
	Infection with unknown ANC	Brain (encephalitis, infectious)
Encephalomyelitis infection	Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10e9/L);	Brain + Spinal cord (encephalomyelitis)
	Infection with normal ANC or Grade 1 or 2 neutrophils;	Brain + Spinal cord (encephalomyelitis)
	Infection with unknown ANC	Brain + Spinal cord (encephalomyelitis)
Infectious colitis	Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10e9/L);	Colon
	Infection with normal ANC or Grade 1 or 2 neutrophils;	Colon
	Infection with unknown ANC	Colon
Endocarditis infective	Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10e9/L)	Heart (endocarditis)
	Infection with normal ANC or Grade 1 or 2 neutrophils;	Heart (endocarditis)
	Infection with unknown ANC	Heart (endocarditis)
Joint infection	Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10e9/L)	Joint
	Infection with normal ANC or Grade 1 or 2 neutrophils;	Joint
	Infection with unknown ANC	Joint
Eye infection intraocular	Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10e9/L)	Lens
	Infection with normal ANC or Grade 1 or 2 neutrophils;	Lens
	Infection with unknown ANC	Lens
Infectious meningitis	Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10e9/L)	Meninges (meningitis)
	Infection with normal ANC or Grade 1 or 2 neutrophils;	Meninges (meningitis)
	Infection with unknown ANC	Meninges (meningitis)
Cranial nerve infection	Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10e9/L)	Nerve-cranial
	Infection with normal ANC or Grade 1 or 2 neutrophils;	Nerve-cranial
	Infection with unknown ANC	Nerve-cranial
Peripheral nerve infection	Infection (documented clinically or microbiologically)	Nerve-peripheral

	with Grade 3 or 4 neutrophils (ANC <1.0 x 10e9/L)	
	Infection with normal ANC or Grade 1 or 2 neutrophils;	Nerve-peripheral
	Infection with unknown ANC	Nerve-peripheral
Spinal cord infection	Infection (documented clinically or microbiologically)	Spinal cord (myelitis)
	with Grade 3 or 4 neutrophils (ANC <1.0 x 10e9/L)	
	Infection with normal ANC or Grade 1 or 2 neutrophils;	Spinal cord (myelitis)
	Infection with unknown ANC	Spinal cord (myelitis)
Viral hepatitis	Viral hepatitis	
Visceral edema	Edema:viscera	
Arthritis	Arthritis (non-septic)	
Scoliosis	Bone: spine-scoliosis	
Joint range of motion decreased cervical spine	Cervical spine-range of motion	
Fibrosis deep connective tissue	Fibrosis-deep connective tissue	
Joint range of motion decreased lumbar spine	Lumbar spine-range of motion	
Muscle weakness left-sided	Muscle weakness, generalized or specific area (not due to neuropathy)	Left-sided
Muscle weakness right-sided	Muscle weakness, generalized or specific area (not due to neuropathy)	Right-sided
Musculoskeletal deformity	Muscular/skeletal hypoplasia	
Osteonecrosis	Osteonecrosis (avascular necrosis)	
Abdominal soft tissue necrosis	Soft tissue necrosis	Abdomen
Soft tissue necrosis lower limb	Soft tissue necrosis	Extremity-lower
Soft tissue necrosis upper limb	Soft tissue necrosis	Extremity-upper
Head soft tissue necrosis	Soft tissue necrosis	Head
Neck soft tissue necrosis	Soft tissue necrosis	Neck
Pelvic soft tissue necrosis	Soft tissue necrosis	Pelvic
Chest wall necrosis	Soft tissue necrosis	Thorax
Arachnoiditis	Arachnoiditis/meningismus/radiculitis	
Ataxia	Ataxia (incoordination)	
Ischemia cerebrovascular	CNS cerebrovascular ischemia	
Central nervous system necrosis	CNS necrosis/cystic progression	
Encephalopathy	Encephalopathy	
Hydrocephalus	Hydrocephalus	
Recurrent laryngeal nerve palsy	Laryngeal nerve dysfunction	
Cerebrospinal fluid leakage	Leak, cerebrospinal fluid (CSF)	
Leukoencephalopathy	Leukoencephalopathy (radiographic findings)	
Neurological disorder NOS	Neurology - Other (Specify, __)	
Optic nerve disorder	Neuropathy: cranial	CN II Vision
Oculomotor nerve disorder	Neuropathy: cranial	CN III Pupil, upper eyelid, extra ocular movements
Vagus nerve disorder	Neuropathy: cranial	CN X Motor-palate; pharynx, larynx

Accessory nerve disorder	Neuropathy: cranial	CN XI Motor-sternomastoid and trapezius
Phrenic nerve paralysis	Phrenic nerve dysfunction	
Psychosis	Psychosis (hallucinations/delusions)	
Pyramidal tract syndrome	Pyramidal tract dysfunction (e.g., increased tone, hyperreflexia, positive Babinski, decreased fine motor coordination)	
Seizure	Seizure	
Depressed level of consciousness	Somnolence/depressed level of consciousness	
Speech disorder	Speech impairment (e.g., dysphasia or aphasia)	
Optic nerve edema	Optic disc edema	
Retinal detachment	Retinal detachment	
Retinopathy	Retinopathy	
Vitreous hemorrhage	Vitreous hemorrhage	
Cardiac pain	Pain	Cardiac/heart
Chest pain	Pain	Chest/thorax NOS
Adult respiratory distress syndrome	Adult Respiratory Distress Syndrome (ARDS)	
Chylothorax	Chylothorax	
Bronchial fistula	Fistula, pulmonary/upper respiratory	Bronchus
Laryngeal fistula	Fistula, pulmonary/upper respiratory	Larynx
Pulmonary fistula	Fistula, pulmonary/upper respiratory	Lung
Oral cavity fistula	Fistula, pulmonary/upper respiratory	Oral cavity
Pharyngeal fistula	Fistula, pulmonary/upper respiratory	Pharynx
Pleural fistula	Fistula, pulmonary/upper respiratory	Pleura
Tracheal fistula	Fistula, pulmonary/upper respiratory	Trachea
Laryngeal obstruction	Obstruction/stenosis of airway	Larynx
Pharyngeal stenosis	Obstruction/stenosis of airway	Pharynx
Tracheal obstruction	Obstruction/stenosis of airway	Trachea
Pneumonitis	Pneumonitis/pulmonary infiltrates	
Pneumothorax	Pneumothorax	
Pulmonary fibrosis	Pulmonary fibrosis (radiographic changes)	
Vesical fistula	Fistula, GU	Bladder
Female genital tract fistula	Fistula, GU	Genital tract-female
Renal pelvis fistula	Fistula, GU	Kidney
Ureteric fistula	Fistula, GU	Ureter
Urethral fistula	Fistula, GU	Urethra
Uterine fistula	Fistula, GU	Uterus
Vaginal fistula	Fistula, GU	Vagina
Bladder obstruction	Obstruction, GU	Bladder
Fallopian tube obstruction	Obstruction, GU	Fallopian tube
Prostatic obstruction	Obstruction, GU	Prostate
Spermatic cord obstruction	Obstruction, GU	Spermatic cord
Urostomy obstruction	Obstruction, GU	Stoma

Testicular obstruction	Obstruction, GU	Testes
Ureteric obstruction	Obstruction, GU	Ureter
Urethral obstruction	Obstruction, GU	Urethra
Uterine obstruction	Obstruction, GU	Uterus
Vaginal obstruction	Obstruction, GU	Vagina
Vas deferens obstruction	Obstruction, GU	Vas deferens
Bladder perforation	Perforation, GU	Bladder
Fallopian tube perforation	Perforation, GU	Fallopian tube
Kidney perforation	Perforation, GU	Kidney
Ovarian rupture	Perforation, GU	Ovary
Prostatic perforation	Perforation, GU	Prostate
Spermatic cord perforation	Perforation, GU	Spermatic cord
Urostomy perforation	Perforation, GU	Stoma
Testicular perforation	Perforation, GU	Testes
Ureteric perforation	Perforation, GU	Ureter
Urethral perforation	Perforation, GU	Urethra
Uterine perforation	Perforation, GU	Uterus
Vaginal perforation	Perforation, GU	Vagina
Vas deferens perforation	Perforation, GU	Vas deferens
Renal failure	Renal failure	
Bladder stenosis	Stricture/stenosis (including anastomotic), GU	Bladder
Fallopian tube stenosis	Stricture/stenosis (including anastomotic), GU	Fallopian tube
Spermatic cord stenosis	Stricture/stenosis (including anastomotic), GU	Spermatic cord
Urostomy stenosis	Stricture/stenosis (including anastomotic), GU	Stoma
Testicular stricture/stenosis	Stricture/stenosis (including anastomotic), GU	Testes
Ureteric stenosis	Stricture/stenosis (including anastomotic), GU	Ureter
Urethral stricture	Stricture/stenosis (including anastomotic), GU	Urethra
Uterine stenosis	Stricture/stenosis (including anastomotic), GU	Uterus
Vaginal stricture	Stricture/stenosis (including anastomotic), GU	Vagina
Vas deferens stenosis	Stricture/stenosis (including anastomotic), GU	Vas deferens
Treatment related secondary malignancy	Secondary Malignancy - possibly related to cancer treatment (Specify, __)	
Vaginal atresia	Vaginal stenosis/length	
Retinoic acid syndrome	Retinoic acid syndrome	
Cytokine release syndrome	Cytokine release syndrome/acute infusion reaction	
Tumor lysis syndrome	Tumor lysis syndrome	
Capillary leak syndrome	Acute vascular leak syndrome	
Portal hypertension	Portal vein flow	
Thrombosis	Thrombosis/thrombus/embolism	
Aortic injury	Vessel injury-artery	Aorta
Injury to carotid artery	Vessel injury-artery	Carotid

Injury to inferior vena cava	Vessel injury-vein	IVC
Injury to jugular vein	Vessel injury-vein	Jugular
Venous injury	Vessel injury-vein	Other NOS
Injury to superior vena cava	Vessel injury-vein	SVC
Venous injury - Viscera	Vessel injury-vein	Viscera
Visceral arterial ischemia	Visceral arterial ischemia (non-myocardial)	