



Evaluating the clinical management of paediatric patients with cancer

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Table of contents

Copy right declaration.....	I
Acknowledgements	II
List of publications, presentations, and other contributions:	III
Table of contents	V
Table of figures	X
Table of tables	XI
Abbreviations.....	XII
Abstract.....	XV
Chapter 1 Introduction to paediatric cancer	1
1.1 General definitions	2
1.2 Cancer development and cancer-contributory factors.....	2
1.2.1 Cancer development.....	2
1.2.2 Genetic factors.....	3
1.2.3 Other (Non-genetic) factors.....	3
1.3 Epidemiology of paediatric cancer	5
1.4 Classification of paediatric cancer	8
1.5 Contribution of pharmacological approaches in the management of paediatric cancer and potential side effects	11
1.5.1 Systemic anti-cancer therapy (SACT)	11
1.5.2 Medicines for supportive care	12
1.6 Common cancer-relevant symptoms and treatment-associated side effects..	12
Chapter 2 Thesis rationale, aims, and objectives.....	16
2.1 Thesis rationale	17
2.2 Thesis aims and objectives	18
Chapter 3 The use of medicines for the management of haematological malignancies in paediatric populations: an international scoping review of observational studies	20
3.1 Introduction	21
3.2 Aim.....	22
3.3 Research question	22
3.4 Methods	22
3.4.1 Scoping review as a chosen method.....	23
3.4.2 Eligibility criteria	23
3.4.3 Search strategy.....	24
3.4.4 Study selection	25

3.4.5 Data extraction.....	26
3.4.6 Data synthesis and presentation	26
3.4.7 Critical appraisal of the included articles	26
3.5 Results	27
3.5.1 Studies characteristics	27
3.5.2 Data sources and settings.....	30
3.5.3 Oncological medicines (systemic anti-cancer therapy (SACT)) ± corticosteroids for the management of paediatric haematological malignancies	30
3.5.3.1 Oncological medicines for newly diagnosed patients	36
3.5.3.1.1 Acute lymphoblastic leukaemia (ALL)	36
3.5.3.1.2 Acute myeloid leukaemia (AML).....	37
3.5.3.1.3 Chronic myelogenous leukaemia (CML)	37
3.5.3.1.4 Hodgkin's lymphoma (HL).....	37
3.5.3.1.5 Non-Hodgkin lymphomas (NHL)	38
3.5.3.2 Refractory /relapsed (r/r) cases	38
3.5.3.3 Haematopoietic Stem Cell Transplantation (HSCT).....	39
3.5.4 Non-oncological medicines (supplementary medicines) to support the management of paediatric haematological malignancies	40
3.5.5 Other highlighted aspects	48
3.5.5.1 The prescribers	48
3.5.5.2 Dosing and patient characteristics	48
3.5.5.3 Drug licencing	50
3.5.5.4 Concurrent radiotherapy	50
3.5.5.5 Ethical approval and consent form in the collected articles.....	50
3.5.6 Results of critical appraisal assessment.....	51
3.5.7 The main reported limitations of the included studies.....	51
3.6 Discussion.....	52
3.6.1 Systemic anti-cancer therapy (SACT) ± corticosteroids	52
3.6.2 Non-oncological medicines	56
3.6.3 Other highlighted aspects	57
3.6.4 Limitations and strengths of the scoping review	58
3.7 Conclusion	58
Chapter 4 Overview of Scottish paediatric oncology care.....	60

4.1 The national vision for paediatric oncology (The cancer strategy for children and young people in Scotland 2021–2026)	62
4.2 Paediatric oncology treatment in Scotland.....	64
4.3 Overview of the oncology centres for paediatric patients with cancer in Scotland	65
4.4 Overview of the prescribers and their competencies in Scotland	68
Chapter 5 Guidance for prescribing supplementary medicines for three clinical indications in paediatric oncology patients within Scottish oncology wards: A document analysis-based study.....	70
5.1 Introduction	71
5.2 Aim and Objectives	72
5.3 Definitions	73
5.4 Methods	73
5.4.1 Document analysis as a chosen method.....	73
5.4.2 Inclusion and exclusion criteria	74
5.4.3 Data collection	75
5.4.4 Data management	75
5.4.5 Data extraction.....	76
5.4.6 Data analysis	76
5.5 Rigour and trustworthiness.....	77
5.6 Research team and reflexivity	78
5.7 Ethical considerations	78
5.8 Patient and public involvement.....	78
5.9 Results	78
5.9.1 Characteristics and description of identified documents.....	78
5.9.1.1 Document type-specific description	79
5.9.2 The content of identified documents	80
5.9.2.1 Document-type specific content.....	81
5.9.2.2 Content-specific highlights on medicines of interest	82
5.9.3 Recommended medicines and treatment lines in identified documents...	82
5.10 Discussion.....	97
5.10.1 Multiple potential documents to inform prescribing in the three areas ...	97
5.10.2 Missing content in identified documents.....	98
5.10.3 Heterogeneity in the recommended doses	98
5.10.4 Medicines in the identified documents.....	99
5.10.5 Recommendations to improve the prescribing practice	99

5.10.6 Strengths and Limitations.....	100
5.11 Conclusions.....	100
Chapter 6 Prescriber’s experiences on the use of information sources for prescribing three groups of supportive care medicines: A single-centre qualitative interview study	102
6.1 Introduction	103
6.2 Aim and Objectives	104
6.3 Study setting	104
6.4 Methods	104
6.4.1 Study design.....	105
6.4.1.1 Semi-structured interview as a chosen method to collect data (research instrument).....	105
6.4.2 Study participants	105
6.4.2.1 Inclusion and exclusion criteria.....	105
6.4.2.2 Sample strategy	106
6.4.3 Development of research materials.....	106
6.4.3.1 Preparation of Participant Information Sheet (PIS) and consent form	106
6.4.3.2 Development of the pre-interview questionnaire.....	107
6.4.3.3 Development of the interview guide (interview schedule)	107
6.4.3.3.1 Usability test (A pre-piloting test).....	110
6.4.3.3.2 Piloting.....	110
6.4.3.4 Preparation of invitation email template	111
6.4.4 Recruitment methods.....	111
6.4.5 Data collection	111
6.4.5.1 Data management.....	112
6.4.6 Data analysis	112
6.5 Rigour and robustness of the study	114
6.6 Research team and reflexivity	114
6.7 Ethical and regulatory considerations	115
6.7.1 Ethical approval	115
6.7.2 Additional required regulatory documents	115
6.8 Patient and public involvement.....	115
6.9 Results	116
6.9.1 Participant demographics (Baseline characteristics).....	116

6.9.2 Responses of participants to questions regarding used information sources in the pre-interview questionnaire	116
6.9.3 Themes and subthemes	116
6.10 Discussion.....	140
6.10.1 Recommendations to improve prescribing practice	142
6.10.2 Strengths and Limitations.....	143
6.11 Conclusions.....	143
Chapter 7 Reflections on challenges associated with conducting PhD research in paediatric oncology.....	145
7.1 Obstacles to conducting a cohort study	146
7.2 Obstacles to conducting a qualitative study exploring prescriber's behaviour	148
7.3 Research in paediatric oncology area in Scotland: An experience from the inside	150
Chapter 8 General discussion	152
8.1 Overview of key findings.....	153
8.2 Discussion of key findings	154
8.3 Implications for practice.....	157
8.4 Recommendations for future work	158
8.5 Strengths and limitations	160
8.6 Final conclusion	160
Appendices	187
Supplementary information for Chapter 3 (Appendix1)	188
Supplementary information for Chapter 5 (Appendix 2)	236
Supplementary information for Chapter 6 (Appendix 3)	286

Table of figures

Figure 1.1 Global estimates of age-standardised incidence rates of all childhood cancers for males and females, 2022	6
Figure 1.2 Global estimates of age-standardised mortality rates of all childhood cancers for males and females, 2022	7
Figure 1.3 Children aged 0-14: Microscopically Verified Cancer ¹ diagnoses by Year of Diagnosis, Scotland, 2012-2021, observed (Kaplan-Meier) survival (%) at 1 year following diagnosis, with 95% confidence intervals	8
Figure 3.1 PRISMA-ScR flowchart of the conducted search	28
Figure 4.1 Structure of the NHS in Scotland.	61
Figure 4.2 Principal and POSCU in Scotland	67
Figure 4.3 Competencies of prescribers according to Royal Pharmaceutical Society-developed framework	69
Figure 5.1 Steps of data analysis	77
Figure 5.2 The recommended medicines for the three indications	83
Figure 6.1 Types of information sources across the three clinical area	119
Figure 6.2 The information sources used to support prescribing across the three clinical areas	120
Figure 6.3 The information sources used to support prescribing by profession	122
Figure 6.4 The way of using information sources to prescribe three groups of medicines.	124
Figure 7.1 Record linkage overview – cohort identification and selected datasets	147

Table of tables

Table 1.1 Staging in lymphomas.....	10
Table 3.1 Deviations from the pre-defined protocol.....	23
Table 3.2 Inclusion and exclusion criteria	24
Table 3.3 Geographical distribution of the studies.....	29
Table 3.4 The number of studies on each haematological malignancy subcategory	31
Table 3.5 The identified agents of conventional chemotherapy.....	32
Table 3.6 The identified corticosteroids for the management of haematological malignancies.....	34
Table 3.7 Other forms of systemic anticancer therapy and their applications	35
Table 3.8 Myeloablative conditioning regimens for Haematopoietic Stem Cell Transplantation.....	40
Table 3.9 Supplementary medicines for paediatric patients with haematological malignancies.....	42
Table 3.10 Dosing and impact of patient characteristics	49
Table 3.11 Summary of critical appraisal scores	51
Table 4.1 Information on childhood cancer-specialised centres in Scotland.....	66
Table 5.1 Inclusion and exclusion criteria	74
Table 5.2 Raw data for extraction	76
Table 5.3 The clinical indications of the recommended anti-emetics according to the documents	85
Table 5.4 The clinical indication of the recommended anti-emetics for chemotherapy-induced nausea and vomiting (CINV) according to the documents	87
Table 5.5 Treatment lines of CINV for patients with cancer aged >6 months with regard to regional documents	90
Table 5.6 Treatment lines of CINV for patients with cancer aged <6 months with the regard to regional documents	93
Table 5.7 The clinical indications of the recommended medicines for the management of TLS.....	96
Table 6.1 Inclusion and exclusion criteria for the qualitative study	105
Table 6.2 Analysis stages of the interview data	113
Table 6.3 Actions to ensure rigour and robustness	114
Table 6.4 The themes and subthemes of the study.....	117
Table 6.5 Illustrative quotes from prescribers in the three clinical areas.....	121
Table 6.6 Reasons for using regional Standard Operating procedures	125
Table 6.7 Collated information from children with cancer	128
Table 6.8 The subthemes of the third theme (challenges and potential challenges while using available information sources).....	135

Abbreviations

6-MP	Mercaptopurine
ABVD	Doxorubicin hydrochloride (Adriamycin), bleomycin, vinblastine sulphate, dacarbazine
ADTC	Area Drug and Therapeutic Committee
AHPs	Allied health professionals
ALL	Acute lymphoblastic leukaemia
AML	Acute myeloid leukaemia
APL	Acute promyelocytic leukaemia
ASCO	American Society of Clinical Oncology
BBB	Blood-brain barrier
BFM	Berlin-Frankfurt-Münster
BL	Burkitt's lymphomas
BNF	British National Formulary
BNFC	British National Formulary for Children
BSA	Body surface area
CAMHS	Child and Adolescent Mental Health Services
CARDA	Checklist for Assessment and Reporting of Document Analysis
CCLG	Children's Cancer and Leukaemia Group
CEPAS	Chemotherapy Electronic Prescribing and Administration Systems
CHAS	Children's Hospices across Scotland
CHI	Community Health Index
CINV	Chemotherapy-induced nausea and vomiting
CKS	Clinical Knowledge Summaries
CLL	Chronic lymphocytic leukaemia
CMG	Clinical management guideline
CML	Chronic myelogenous leukaemia
CMP	Clinical management pathway
CNS	Central nervous system
COPDAC	Cyclophosphamide, vincristine, prednisolone, dacarbazine
COPP	Cyclophosphamide, vincristine, procarbazine, prednisone/ prednisolone
COREQ	Consolidated Criteria for Reporting Qualitative Research
COVID	Coronavirus disease
CSF	Cerebrospinal fluid
CT	Computed tomography
CYPC	Children and young people with cancer
EAALs	Expanded activated autologous lymphocytes
EBV	Epstein–Barr virus
eDRIS	Electronic Data Research and Innovation Service
EMA	European Medicines Agency
FDA	Food and Drug Administration
FM	Faisal Madanat (PhD student)
G6PD	Glucose-6-phosphate dehydrogenase
G-CSF	Granulocyte colony stimulating factor

GGC	Greater Glasgow and Clyde
GPhC	General Pharmaceutical Council
GVHD	Graft-versus-host disease
HA	Hanan Abunimeh (PhD student)
HAART	Highly active antiretroviral therapy
HDI	Human development index
HEPMA	Hospital Electronic Prescribing and Medicines Administration
HIV	Human immunodeficiency virus
HL	Hodgkin's lymphoma
HS	Hisham Alshammari (PhD student)
HSC-PBPP	Public Benefit and Privacy Panel for Health and Social Care
HSCT	Haematopoietic Stem Cell Transplantation
ICCC	International Classification for Childhood Cancer
IFRT	Involved-field radiation therapy
IOP	Intraocular pressure
IRAC	International Agency for Research on Cancer
IRAS	Integrated Research Application System
JB	Joanna Briggs Institute
LS	Louise Summers (Pharmacist)
m²	Meter square
MD	Medical doctor
MDRO	Multidrug-resistant organisms
MDT	Multidisciplinary team
MeSH	Medical Subject Headings
MHRA	Medicines and Healthcare products Regulatory Agency
MTX	Methotrexate
NCI	National Cancer Institute
NEWT	National Electronic Library for Medicines
NHL	Non-Hodgkin lymphomas
NHS	National Health Service
NICE	National Institute for Health and Care
NRS	National Register of Scotland
NW	Natalie Weir (Second supervisor)
OEPA	Vincristine, etoposide, prednisolone/ prednisone, doxorubicin
OID	Organisation Information Document
P	Participant
PBSC	Peripheral blood stem cell
PCC	Population, Concept, Context
PCP	Pneumocystis pneumonia
Ph+ ALL	Philadelphia chromosome-positive acute lymphoblastic leukaemia
PHRG	Pharmacoepidemiology and Healthcare Research Group
PHS	Public Health Scotland
PICO	Problem/Population, Intervention, Comparison, Outcome
PIS	Participant Information Sheet
PIS	Prescribing Information System

POSCU	Paediatric Oncology Shared Care Units
PRISMA-ScR	Systematic Reviews and Meta-analysis Extension for Scoping Reviews
PRN	Pro re nata
R/R	Refractory/relapsed
RA	Rahaf Alkhlaifat (PhD student, primary researcher)
RPS	Royal Pharmaceutical Society
SACT	Systemic anti-cancer therapy
SEER	Surveillance, epidemiology, and end results
SIPBS	Pharmacy and Biomedical Science
SmPC	Summary of Product Characteristics
SOPs	Standard Operating Procedures
TBI	Total body irradiation
TDF	Theoretical Domains Framework
TKI	Tyrosine kinase inhibitor
TLS	Tumour lysis syndrome
TM	Tanja Mueller (First supervisor)
TYA	Teenage, and young adult
UFH	Unfractionated heparin
UK	United Kingdom
US	United States
VBVP	Vinblastine, bleomycin, VP16 (etoposide), prednisone
WBC	White blood cells
WHO	World Health Organization

Abstract

Introduction: Cancer causes death in children internationally. Given the complexity of including children in research, little is known about medicine-based interventions (key therapies for the management of cancer), nor the information sources that guide the prescribing. This project aimed to enhance the understanding of medicine-based interventions worldwide and to explore the use of prescribing-guiding information sources in the area of paediatric oncology in Scotland.

Methods: Data were collected by three methods: a scoping review (2013-2023) on medicine-based interventions for paediatric patients with haematological malignancies internationally; a document analysis to explore Scotland-wide prescribing-guiding documents for cancer-related indications (i.e. emesis, tumour lysis syndrome, and *Pneumocystis* pneumonia prophylaxis); and interviews to elicit experiences of prescribers on prescribing-guiding information sources in the largest paediatric Scottish oncology centre.

Results: The scoping review identified 82 publications, reporting on 50 systemic anticancer therapy (SACT) agents $\pm$ corticosteroids and 74 supportive care medicines to manage paediatric haematological malignancies. The multi-drug therapeutic plans of non-novel SACT agents were commonly used. A range of documents with varied coverage of information (e.g. drug dispensing) on the medicines of interest were identified. The recruited prescribers confirmed the use of evidence-based documents throughout the prescribing process across the areas of interest, and discussed the availability of multiple information sources to support prescribing. The experiences of recruited prescribers provided a wide overview of information sources to support prescribing and confirmed the use of evidence-based information throughout the process. The challenges participants faced were mainly relevant to the content of information sources (e.g. lack of dose banding).

Conclusion: The complexity of treatments for paediatric haematological malignancies was evident, thereby confirming the burden on children and prescribers. Diverse documents/information sources were integrated in the process of prescribing in the areas of interest. The high use of evidence-based documents in routine practice may reflect the safety and effectiveness of medicine-based interventions.

Chapter 1 Introduction to paediatric cancer

This introductory chapter contains six sections. The sections provide a brief introduction to cancer, starting from the definition of cancer and common relevant terms, followed by potential contributory factors (i.e. genetic and non-genetic factors) in paediatric cancer and summarising the reported international, British, and Scottish paediatric epidemiological data, and ending with some background on the medicine-based treatment and common symptoms as well as side effects.

1.1 General definitions

Cases with cancer were recorded, for the first time, in the ancient Egyptian era hundreds of years ago (1). Linguistically, cancer is derived from the Latin word “cancer” which means crab that tightly clasps onto the targeted prey. It also stemmed from the Greek root *karkinos* that refers to the malignant tumour (2, 3). Medically, this term defines an abnormal growth of cells; the resultant abnormal cells can transfer from where they grew to other parts of body to start the invasive growth again (3). Neoplasm is defined as an uncontrolled growth of cells resulting in formation of a mass (i.e. benign or malignant mass) (3). The “benign” and “malignancy” terms can be used to differentiate and define this disease (4). The term “benign” relates to non-harmful accumulation of cells with regular boundaries (4). However, “malignancy” describes an accumulation of abnormal cancerous cells that are able to invade other parts of body after migrating through blood or networks of the lymphatic system (metastasis) (5). The term “tumour” is used interchangeably with the term “neoplasm” to describe the abnormal growth of cells (6). Cancer cells can originate from almost any organ or tissue in the human body (7). The originating of cancerous cells from epithelial tissues and connective tissues forms types of cancer that are called carcinomas and sarcomas, respectively (7, 8).

1.2 Cancer development and cancer-contributory factors

1.2.1 Cancer development

The transformation from normal cells to cancerous cells results from an imbalance in the regulatory pathways of the cell cycle in form of accumulated mutations and/or deactivation of certain cellular constituents (9). As a result, cells fail to differentiate into normal cells. These undifferentiated cells proliferate aggressively. Further, they demonstrate low sensitivity to administered medicines and resistance to the programmed-cell death (apoptosis) (9).

Currently, the exact instigating causes of most paediatric cancers are not well understood (10). However, the literature has addressed some potential associations between paediatric cancer and certain factors.

1.2.2 Genetic factors

The abnormalities that contribute to the development of paediatric cancers occur at the level of gene or chromosome. Any mutation in proto-oncogene families (e.g. protein kinases and growth factors) potentiate permeant production of growth factors and proliferating signals (9). Also, the inactivation of tumour suppressor genes, which regulate the extent of cell growth and division, causes uncontrollable proliferation (11, 12). The joining of two different genes from different chromosomes, called chromosomal translocation, contributes to cancer pathogenesis by production of proteins with oncogenic impact (13, 14).

Genetic syndromes and conditions might be linked with certain types of cancer. Contrary to their counterparts, children with an extra chromosome (Down's syndrome) are highly susceptible to the onset of leukaemia. Apart from that, this chromosomal abnormality does not lead to the development of solid tumours (15). Interestingly, children with Down syndrome may develop symptomless transient myeloproliferative disorder before transition to leukaemia (16).

1.2.3 Other (Non-genetic) factors

Maternal and children's lifestyles, environmental agents, and other interventions might be attributable to paediatric diseases and syndromes. However, their contributions to the emergence of paediatric cancer are unclear. Robust causal studies to ascertain the exact roles of non-genetic factors are required (17). This subsection sheds light on the available studies and reviews on non-genetic factors.

Certain maternal habits potentially have an impact on the development of paediatric malignancies. A systematic review (2023) demonstrated the negative association between maternal healthy diet involving high portions of fruits and development of leukaemia (18). A recent meta-analysis (until May 2023) indicated the connection between the risk of paediatric cancer and mother's pre- and post- natal consumption of alcohol (19). Paternal smoking increased the risk of certain types of paediatric cancer (e.g. acute lymphoblastic leukaemia (ALL)) based on two meta-analyses published in 2019 (20) and 2020 (21). On the other hand, there was no clear link

between maternal smoking habits and incidence of paediatric cancer based on the former meta-analysis (20). A meta-analysis and an international pooled analysis, conducted in 2014 (22) and 2018 (23), respectively, reported the potential risk of coffee intake during pregnancy on the development of ALL.

Although the contributory mechanisms are unknown, children-related factors such as birth weight could contribute to a number of malignancies such as ALL and central nervous system (CNS) malignancies (24-26). It is worth noting that both high and low weight can be concerning in this regard (27, 28). An analysis of surveillance, epidemiology, and end results (SEER) data from the United States (US) over a period of 15 years showed that males were more at risk of developing cancer than females (29). A meta-analysis found no significant evidence to support the relationship between premature birth and paediatric cancer (30).

Children, in contrast to adults, tend to be more negatively affected by ionising radiation, since the period of childhood is characterised by physical maturation and development of body systems (31). Exposure to ionising radiation is associated with initiation of leukaemia among children surviving the atomic bombs in Japan (32, 33). This radiation is also involved in the emergence of paediatric thyroid tumours, in addition to many other solid tumours (34, 35). The use of computed tomography (CT) scan for diagnosis is an emerging concern among practitioners because of its possible linkage with cancer development in children (36). Radiotherapy is an integral part of the management of many cancers in children but the potential emergence of secondary malignancies would be the cost of inappropriate involvement of such modality (37-39). Solar ultraviolet radiation combining with other factors (e.g. high birth weight (40)) can provoke some types of cancer such as melanoma, squamous cell carcinoma, and basal cell carcinoma in children despite the rarity of such cancer types in this population (40-42). Intermittent patterns of exposure to solar radiation showed a relationship with melanoma and basal cell carcinoma (41). In contrast, long-periods of cumulative exposure might be combined with the pathogenic mechanisms of squamous cell carcinoma (41).

Regarding air pollution, it is vital to underline the potential relationship between paediatric cancer and air pollution. It has been illustrated by two meta-analyses, one searching articles up to 2019 and the another including articles between 1987 and 2014, that exposure to benzene might attribute to the development of leukaemia (43,

44). A recent Danish case-control study suggested that air pollution could be part of the development of Non-Hodgkin lymphomas (NHL) in children (45). A previous Brazilian study revealed that nitrogen dioxide could cause cancer in children because of possible correlation with Hodgkin's lymphoma (HL) (46). On top of that, exposure to ambient outdoor pollutants during pregnancy period might predispose paediatric cancer later (47, 48). Regarding nuclear pollution, it has been found that the risk of developing cancer is approximately doubled in individuals under five years who live within a five-km radius of nuclear power stations (49). It is also crucial to consider the relationship between exposure to pesticides and the development of some diseases. Generally speaking, individuals can be exposed to pesticides unintentionally since the use of these agents is likely to occur in parks, gardens, agricultural areas, and even in houses through planting indoor plants. In a recent meta-analysis, the exposure to pesticides during the periconceptional period could augment the hazard of developing neuroblastoma. The carcinogenic danger of exposure to these agents is also proven during gestation (50).

It is evident that infectious microorganisms (e.g. viruses) have a role in the pathogenesis of certain paediatric malignancies. The International Agency for Research on Cancer (IRAC) lists the human immunodeficiency virus (HIV) and the Epstein–Barr virus (EBV) as onco-viruses (51).

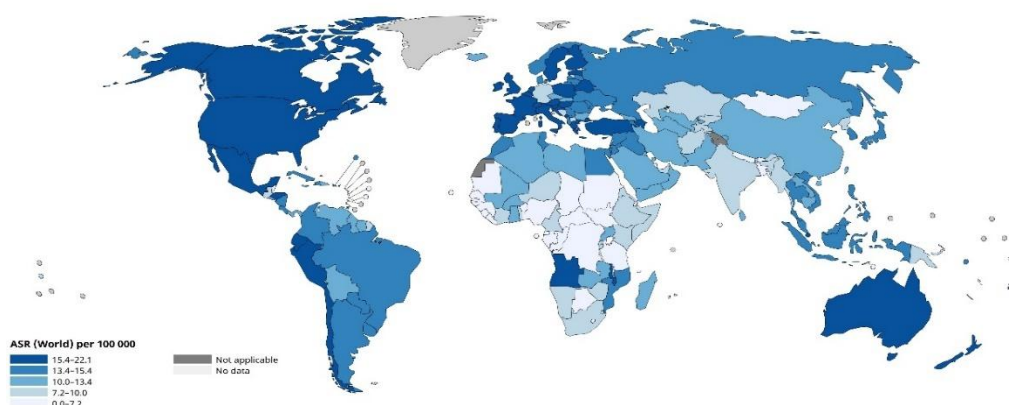
A Dutch study, involving children who had undergone organ transplantation over a 20-year period, showed the association between solid organ transplantation and risk of paediatric cancer. The cumulative incidence of cancer reached 41% (52). The onco-risk of kidney transplantation, in particular, was confirmed by a study conducted in the US (53).

1.3 Epidemiology of paediatric cancer

On a global scale, the estimated number of new cases among paediatric populations over the next three decades (2020-2050) is 13.7 million (54). The incidence of childhood cancer is higher in countries with high human development index (HDI), countries that are marked by the high achievements in the areas of knowledge (education level), health (life longevity), and living standards (55), compared to low-ranked HDI countries. The reason behind this variation might be due to under-diagnosis and under-reporting of paediatric cancer in low-ranked HDI countries (56). Figure 1.1 displays the international range of age-standardised incidence rates of

cancer for both genders in 2022. The accessibility of cancer treatment services, well-trained medical staff, and continuous improvement of the provided care in developed countries, wealthy countries that are characterised by the high level of industrialisation and high average income (57), promote high cure rates (> 80%). On the other hand, the reported cure rate is < 30% in developing countries (56, 58). A simulation-based analysis of paediatric cancer survival considering multiple clinical and epidemiologic factors has demonstrated that the 5-year survival estimate of childhood cancer is 37.4% worldwide (59). Leukaemia, lymphomas, brain cancer, and certain types of solid cancers including Wilms tumours and neuroblastoma are more common among paediatric populations (56). Although leukaemia is still the main diagnosed type of cancer among children, CNS malignancies are linked to more cancer-related death cases across the world (60). Leukaemia and CNS malignancies accounted for 132,194 deaths among patients < 19 years in 2019 (61). Figure 1.2 highlights the mortality rate of childhood cancer across the world in 2022.

Age-Standardized Rate (World) per 100 000, Incidence, Both sexes, age [0-19], in 2022
All cancers



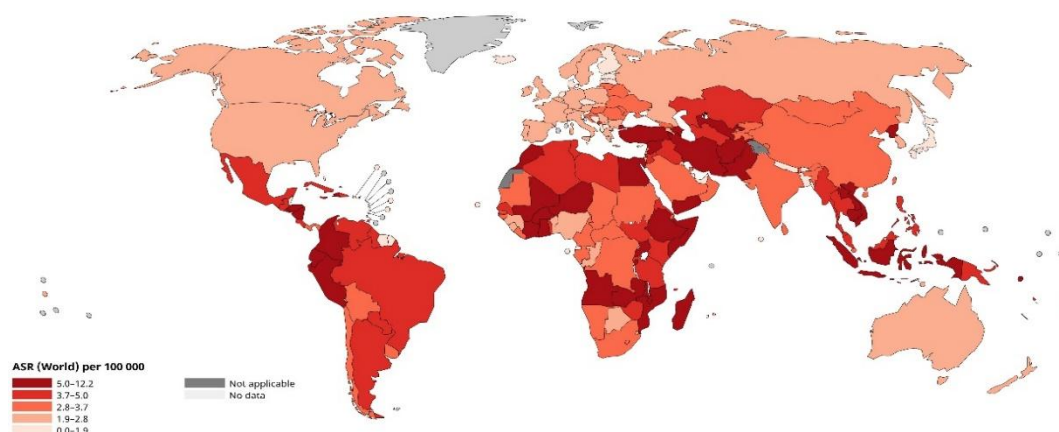
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Figure 1.1 Global estimates of age-standardised incidence rates of all childhood cancers for males and females, 2022

NB: Figure taken from World Health Organization, CC BY-NC-SA 3.0 IGO (62).



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for Research on Cancer
World Health
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Figure 1.2 Global estimates of age-standardised mortality rates of all childhood cancers for males and females, 2022

NB: Figure taken from World Health Organization, CC BY-NC-SA 3.0 IGO (63).

Cancer affects about 1,900 British children each year who are aged 0-14 years (64). Data from 2017 to 2019 showed that cancer was more common among boys than girls (64). The incidence rate of childhood cancer was the highest under the age of five compared to other paediatric ages for both boys and girls, taking into account the potential differences in incidence rates between different types of childhood cancer (64). More than 80 percent of British children with cancer live five years and more (65); for example, the duration of survival was five years and more, between 2012 and 2016, for 84% of British children who were diagnosed with cancer (64). In the UK, approximately 220 children die from cancer per year (64). Although leukaemia is the most common cancer in this age group, there is a higher death rate of cancers associated with the CNS and intracranial malignancies in the United Kingdom (UK) including Scotland (64). The mortality rate of cancer in children has been stable for both genders from 2017 to 2019 (64).

Scottish data corresponding to the period from 2012 to 2021 showed that 1,344 patients aged 14 years or younger were diagnosed with cancer (66). The most diagnosed type of cancer in Scottish children is leukaemia followed by brain and CNS malignancies (66). Little fluctuation in the number of reported cases has been noticed over 10-year period (Figure 1.3) (66). Regarding survival rates, Scotland generally had high survival rates of 84.7% (95% CI: 81.0% to 87.8%) between 2016 and 2020

(66). Scotland recorded 180 death cases from childhood cancer between 2012 and 2021. However, the reported death in the first year after diagnosis in cancer cases is twofold higher in children compared to young patients aged between 15 and 24 years (66).

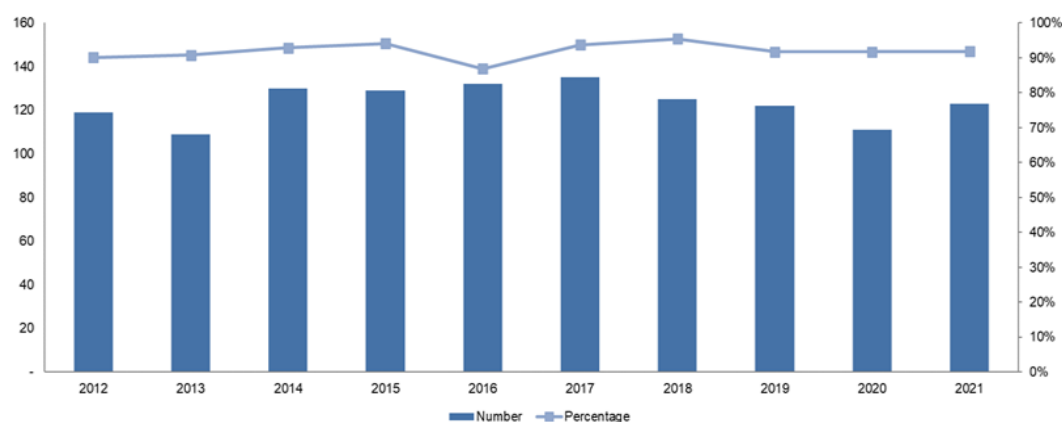


Figure 1.3 Children aged 0-14: Microscopically Verified Cancer¹ diagnoses by Year of Diagnosis, Scotland, 2012-2021, observed (Kaplan-Meier) survival (%) at 1 year following diagnosis, with 95% confidence intervals

NB: Figure taken from Public Health Scotland, Open Government Licence v3.0 (66).

1.4 Classification of paediatric cancer

Generally, disease classification guides clinicians in disease diagnosis and implementation of effective treatment plans. Any classification of paediatric malignancies should consider the high heterogeneity of these malignancies, in addition to lower percentage of paediatric patients diagnosed with cancer in comparison to adult patients (67). The International Classification for Childhood Cancer (ICCC) has been developed relying on the morphological traits of various malignancies and sites of these malignancies (68, 69). The latest published version (2017) classifies paediatric malignancies into twelve groups, namely: (a) leukaemia, myeloproliferative and myelodysplastic diseases, (b) lymphomas and reticuloendothelial neoplasms, (c) CNS and miscellaneous intracranial and intraspinal neoplasms, (d) neuroblastoma and other peripheral nervous cell tumours, (e) retinoblastoma, (f) renal tumours, (g) hepatic tumours, (h) malignant bone tumours, (i) soft tissue and other extrasosseous sarcomas, (g) germ cell tumours, trophoblastic tumours, and neoplasms of gonads, (k) other malignant epithelial neoplasms and malignant melanomas, (l) other and unspecified malignant neoplasms (69).

The inaugural World Health Organization (WHO) system classifies paediatric malignancies into four groups: leukaemia and lymphomas, soft-tissue and bone tumours, other solid tumours, and CNS tumours. Examination of malignancies at molecular level with the traditional morphological traits have shaped the classification of paediatric malignancies in this system (70).

Staging (i.e. identifying the extent of tumour growth across the body) of paediatric malignancies is also still challenging (71). Staging informs the treatment decision for these malignancies and assists with the measurement of the treatment outcomes. However, novel technologies enhance the scaling (staging) of malignancies by predicting the biological and clinical behaviour and addressing biomarkers of malignancies, especially for solid tumours (71). The use of the term “stage” is somewhat inconvenient in certain cases (i.e. leukaemia). In leukaemia, cancer eventually spreads throughout the body (72). Other considerations need to be accounted for to describe the behaviour of these cases and to stratify patients into risk groups (71).

▲ **Stratification of haematological malignancies**

Leukaemia stems from the formation of abnormal malignant cells resulting in the disturbance of innate biological operations (e.g. blood clotting and coagulation). In children, the acute form of leukaemia develops more frequently compared to the chronic form of this disease. Acute leukaemia is subcategorised into ALL and acute myeloid leukaemia (AML). The chronic form accounts for a lower number of cases and is subcategorised into two subcategories: chronic lymphocytic leukaemia (CLL) and chronic myelogenous leukaemia (CML) (73).

Risk stratification is a tool to adjust ALL treatment based on several attributes such as patient characteristics (74), detection of abnormal cytogenetics like Philadelphia chromosome (75), results of laboratory tests (74), and response to treatment (74). Patient characteristics such as gender and age are essential attributes; for example, the severity of ALL is higher for infants and children aged > 10 compared to other ages (75). The confirmation of CNS involvement is a high-risk trait and increases the risk of poor prognosis (75, 76). This confirmation is established by several means (e.g. microscopical identification of leukemic cells in the cerebrospinal fluid) (75). The results of laboratory tests also inform the stratification (e.g. the level of white blood cells (WBC)). Moreover, the way patients respond to the initial treatment influences

subsequent interventions (75). Such early evaluation enhances the accuracy of the stratification (77). The stratification of ALL risk slightly varies among the stratification systems. For instance, the National Cancer Institute (NCI) stratification system encompasses standard, high, and very high risk groups whereas the Berlin-Frankfurt-Münster (BFM) stratification system encompasses standard, intermediate, and high risk groups (78).

For AML, the risk stratification systems vary, but AML is generally divided into three sub-categories (i.e. low- or standard-, intermediate-, and high- risk) based on the detected genetic aberrations and the initial response to therapy (79).

Previously, three phases (i.e. chronic, accelerated, and blast) were used to classify CML. The recent version of the WHO classification removed the accelerated phase from the classification system (80).

Lymphoma represents a group of lymphatic tissue-originated malignancies derived from B lymphocytes, T lymphocytes, and natural killer cells (81). This miscellaneous group could be classified on the basis of many considerations, but typically comprises two classes: HL and NHL (82). Table 1.1 illustrates the stages of lymphoma and the considerations of staging.

Table 1.1 Staging in lymphomas

Staging	Hodgkin's lymphoma	Non-Hodgkin lymphomas
Stages	I, II, III, IV (83)	I, II, III, IV (84)
Consideration for staging	Involved lymph nodes (83)	Involved lymph nodes (84)
	Number of involved sites (83)	Involvement of central nervous system and bone marrow (84)
	Dissemination of the malignant cells (extra nodal dissemination) (83)	Dissemination of the malignant cells (84)
Suffix	-A: Refers to the absence of symptoms in the presented cases (83)	-X: Refers to the size of swelling lymph (> 1/3 of intrathoracic diameter (81).
	-X: Refers to the size of swelling lymph (> 1/3 of intrathoracic diameter (83)	-B: Refers to the presence of B symptoms (e.g. fever) (81)
	-B: Refers to the presence of B symptoms (e.g. fever) (83)	-E: Refers to the presence of bulk status where the diameter of tumour is > 10 cm (81)
	-E: Refers to the presence of bulk status where the diameter of tumour is > 10 cm (83, 85)	

In the inaugural WHO system, subtypes of leukaemia and lymphoma are grouped under three headings (i.e. myeloid neoplasms, lymphoid neoplasms, and HL) (70).

1.5 Contribution of pharmacological approaches in the management of paediatric cancer and potential side effects

Pharmacological approaches are key approaches in the management of cancer. The management of cancer, however, can also involve other approaches such as radiotherapy or surgery (86).

The pharmacological approach entails two groups of medicines: oncological medicines (systemic anti-cancer therapy (SACT)) and non-oncological medicines (medicines for supportive care).

1.5.1 Systemic anti-cancer therapy (SACT)

SACT encompasses treatment options such as conventional chemotherapy, or immunotherapy and targeted therapy used to treat, mitigate, delay, or prevent the growth of cancer (87).

The involvement of conventional chemotherapy in paediatric oncology started in the 1950s (88). Conventional chemotherapy includes cytotoxic anti-cancer agents that induce the death of normal and cancer cells through different underlying mechanisms of action (89). Agents with similar mechanisms form a specific category such as anti-metabolites (cytarabine, etc) and antimicrotubular agents (vincristine, etc) (90). In general, conventional chemotherapy is given in accordance with multi-drug protocols (89).

The 2000s marked the era of introducing targeted therapy and immunotherapy for children (91, 92). Targeted therapy targets distinct body moieties (e.g. enzymes), thereby interrupting the intracellular pathways of cancer infiltration, which consequently reduces the damage of normal cells (e.g. tyrosine kinase inhibitor (TKI)) (93). Immunotherapy, on the other hand, boosts and enhances the response of the patient's immune system to some diseases including cancer (94).

1.5.2 Medicines for supportive care

Supportive care refers to a range of treatment approaches aimed to manage harmful consequences from the disease itself (cancer) or the treatment of the disease. It complements the management of patients diagnosed with cancer including blood cancers (95). Notably, the areas covered by supportive care are very broad (96) in terms of used interventions, disease stage, and involved stakeholders including health professionals (95). The supportive care should be adaptable with the integration of new therapeutic interventions which might convey new side effects (95). The medicines for supportive care are given to mitigate the emerging symptoms and side effects or to improve patient's quality of life or to manage any other cancer-adjuvant indication rather than stopping the infiltration of cancer cells (95, 96).

1.6 Common cancer-relevant symptoms and treatment-associated side effects

Symptoms refer to the physical or mental features that develop from certain illnesses (indicating certain health conditions) or occur due to changing of existing normal conditions (97). On the other hand, side effects are treatment-induced effects that potentially develop alongside the beneficial effects of administering treatment (98). Side effects and symptoms can emerge from any part of the body (99). Side effects and symptoms may overlap; side effects might be symptomatic (100). It is evident that the type of malignancy interferes in the developing of symptoms and side effects (e.g. patients with haematological malignancies experience invasive fungal infection more than those with solid malignancies (101)).

All treatment approaches that are mentioned in section 1.5.1 have the tendency to instigate distressing side effects over the course of the disease. Markedly, the development of undesirable side effects is more common for conventional chemotherapy (102). The risk of some side effects can be aggravated by presence of others; for instance, the risk of infections increases with the existence of mucositis (103).

Symptoms, commonly develop in clusters (simultaneous development of two or more related symptom), e.g. nausea and anorexia (104, 105). Different patient-relevant aspects influence the experience of symptom development in paediatric patients (e.g. age (105), sex (105), ethnicity (4), and genetic factors (105)); for instance, the

development of severe symptoms in case of Hispanic ethnicity is low compared to other ethnic backgrounds (105).

The followings are some of common potential side effects and symptoms:

⤴ **Febrile neutropenia**

One of the most common complications among children with cancer is infections (103). Bacterial, fungal, and viral infections may develop (106). Exposure to cytotoxic regimens, hospitalisation, and a weakened immune system compromise patient status (107). The development of infections could be associated with febrile neutropenia, a concept that refers to low count of absolute neutrophils in particular. The definition of febrile neutropenia (i.e. in terms of in thresholds of absolute neutrophils and body temperature) varies across settings globally (103). Infections increase the morbidity and mortality in children with cancer (108). Moreover, severe febrile neutropenia necessitates the reduction of conventional chemotherapy doses which may promote cancer recurrence (109).

⤴ ***Pneumocystis pneumonia (PCP)***

Pneumocystis pneumonia (PCP) is defined as a pulmonary infection that is caused by fungus in immunosuppressed hosts like paediatric patients with cancer. The emergence of this infection is more frequent in patients with leukaemia and lymphoma and patients with solid tumours who are exposed to chemotherapy (110). Immunosuppressant treatment and malignancies increase the colonisation of *Pneumocystis* in younger hosts (111).

⤴ **Graft-versus-host disease (GVHD)**

Graft-versus-host disease (GVHD) is a clinical condition resulting from the insertion of external T cells into the host (human body) following Hematopoietic Stem Cell Transplantation (HSCT) (112). The exact pathogenesis of GVHD is still unknown (103). Conditioning regimens (especially intense regimens such as myeloablative regimens) can cause tissue injury which then leads to GVHD (112). GVHD can have many consequences, including gland abnormalities (113) and liver complications (114).

⤴ **Nausea and vomiting**

Nausea (sensation of feeling sick (115)) and vomiting are developed due to different causes in the context of paediatric oncology:

- ✦ Chemotherapy-induced nausea and vomiting (CINV): CINV is common, the frequency of developing the respective side effect ranges from 1% to 10% of users (116), and results from the stimulation of the area postrema by certain anti-cancer agents (117). Awareness of emetogenicity of specific regimens/ anticancer agents can allow health care professionals to predict the severity of nausea and vomiting.
- ✦ Opioid-induced nausea and vomiting: Opioids might be used to manage developing pain. Nausea is induced through several mechanisms including stimulating of area postrema (118). Antiemetics are reserved for high-risk patients (e.g. patients with a history of severe opioid-induced nausea and vomiting).
- ✦ Radiotherapy-induced nausea and vomiting: Receiving radiotherapy can induce nausea and vomiting. Inflammatory radiation-free radicals indirectly provoke medullary vomiting centre, causing nausea and vomiting (119). The severity of episodes is linked with aspects such as the area of exposure to radiotherapy and radiotherapy pertaining characteristics (e.g. site of exposure and dosing) (120). Because radiotherapy-induced nausea and vomiting is often confounded with CINV, it may be misdiagnosed (121).
- ✦ Anticipatory nausea and vomiting: Anticipatory nausea and vomiting occur due to the interaction between the patient and stimuli at the place of receiving the treatment (e.g. clinics), for example the smell, light, or even the white uniform of practitioners (122).
- ✦ Nausea and vomiting can also be caused by the cancer directly, e.g. lymphoma (123) and brain and kidney tumours (28).
- ✦ Nausea and vomiting associated with raised intrathecal pressure: Different aetiologies elevate the intracranial pressure such as brain tumour, cytotoxic oedema, low cerebrospinal fluid (CSF) flow, and haemorrhage in the skull vault (124). The raised pressure compresses area postrema and triggers nausea and vomiting (125).

If nausea and vomiting have been unmanaged, they will be responsible for numerous negative outcomes (e.g. dehydration (31), weight loss (31), and impaired quality of life (126)).

✦ **Tumour lysis syndrome (TLS)**

Tumour lysis syndrome (TLS) is a serious onco-metabolic disorder that occurs because of the substantial destruction (lysis) of cancer cells (127). The lysis of cells

eventually elevates the level of certain components in the serum (i.e. uric acid, phosphorus, and potassium), and lowers calcium levels. Consequently, patients may suffer from life-threatening conditions such as renal failure and arrhythmia (127). TLS mainly emerges in patients with high turnover tumours (e.g. most haematological malignancies (127) and advanced stages of solid malignancies (128)). Provided that TLS is a metabolic condition, any metabolic abnormality (e.g. acidosis) could aggravate the tumour lysis. Other aspects including tumour-specific aspects (e.g. tumour mass) and anti-cancer treatment-relevant aspects (sensitivity to treatment) can affect the development of this syndrome (127).

The side effects described above could be considered as early negative effects. However, treatment can induce late and long-term negative effects for paediatric survivors (e.g. infertility (129)). Paediatric cancer survivors (up to 75%) suffer from at least one toxic complication pertaining to treatment or cancer, which undoubtedly raises concern and demand for continual follow-up for this population (130). Sustained follow-up accelerates diagnosis and management of any late negative side effect, thereby enhancing survivors' quality of life (130).

Chapter 2 Thesis rationale, aims, and objectives

2.1 Thesis rationale

On a global scale, the estimated number of new cases with cancer among individuals aged < 19 years is 400,000 annually (131, 132). The incidence patterns of paediatric cancers are varied worldwide; for instance, Figure 1.2 in Chapter 1 illustrates that the age-standardised incidence rates of paediatric cancers for both sexes in 2022 was generally higher in Europe and North America compared to other parts of world (133). According to the WHO, cancer is a leading cause of death among children (134). Moreover, the traumatic experiences of cancer (135) place children at risk of multifaceted repercussions (i.e. physical, emotional, cognitive, and psychological) (136).

As highlighted in Chapter 1, pharmacological management is fundamental in the management of paediatric cancers. However, several challenges arise throughout the pharmacological management of children: (a) insufficient paediatric-specific evidence on medicine use (137); (b) the relative lack of approved medicines for paediatric indications (138); (c) different pharmacokinetic responses to the administered treatments among children; (d) the lack of age-appropriate medicine formulations for children (139); and (e) the ethical considerations treatment may pose because children generally rely on their guardians and families for making decisions (140). The aforementioned challenges complicate the process of prescribing medicines in medical practice.

Medical practice continues to evolve with the contributions of state-of-the-art technologies, emerging models/concepts of the management of diseases/symptoms, and the expansion of knowledge (141). In addition to its rapidly evolving nature, medical practice involves various stakeholders such as patients and healthcare providers (142). Arising issues that are relevant to the stakeholders may impact the medical practice and probably require them to adapt different tools and resources to make healthcare decisions. Research studies should not only capture the treatment patterns/treatment outcomes but also explore the afore-considered steps in the decision-making process to prescribe medicines in the fast-evolving and multi-stakeholder medical practice.

The provision of appropriate, safe, and effective care to children with cancer is not only supported by the approval of pioneering cancer-targeted medicines. It requires

information to be readily available to inform the decision-making process of prescribing medicines, with information acquired from various sources. Health care practitioners, including prescribers, use their clinical reasoning skills to make and support prescribing decisions. Actively practising of the clinical reasoning within medical practice promotes patients' safety (143, 144). Information collection from relevant sources is an integral part of the 8-step clinical reasoning cycle to reach decisions on the treatments (143). The literature has shown that the interpretation of the available information, including medicine-relevant information, influences the selection between treatments (143, 145). Therefore, the information sources from where information originates may serve as a key facilitator and aid for prescribing.

Taken together, knowledge gaps exist regarding the usual pharmacological treatments of paediatric cancers across the globe, and with respect to the practice of using information sources to guide prescribing workflows within Scottish paediatric oncology setting. This is despite the potential burden of prescribing for children with cancer in modern medical practice. An in-depth understanding of previous publications on drug-based management and of information sources for prescribing is required to address these aforementioned gaps. This understanding will, therefore, have scope to improve clinical practice, inform local policies, and tailor evidence-based sources.

2.2 Thesis aims and objectives

Aims

This thesis aimed at systematically examining the empirical evidence on pharmacological interventions for the management of paediatric haematological malignancies in a global context. These malignancies are the most common paediatric malignancies (146) considering the established heterogeneity of paediatric malignancies (147). The second aim was to generate new evidence on the available information sources and how they are used to support the prescribing of medicines for emesis, TLS, and PCP prophylaxis in the Scotland and challenges arising throughout this process. The primary focus on the aforementioned health issues was because these issues were informed by National Health Service (NHS) practitioners, thereby reflecting their needs and priorities.

Objectives

1. To identify the pharmacological management to treat paediatric haematological malignancies internationally, which encompasses
 - ⤴ oncological medicines (SACT),
 - ⤴ and non-oncological medicines (supportive care medicines) (Chapter 3).
2. To identify the guiding information sources potentially used to prescribe medicines in the aforementioned critical areas corresponding to supportive care within the three Scottish paediatric oncology centres, by investigating
 - ⤴ medicine-relevant content within these information sources,
 - ⤴ and recommended medicines and treatment lines of the three indications (Chapter 5).
3. To describe the practice of using available prescribing-guiding information sources and the challenges posed by prescribing based on these sources in the three areas of interest (Chapter 6).

Chapter 3 The use of medicines for the management of haematological malignancies in paediatric populations: an international scoping review of observational studies

3.1 Introduction

Haematopoiesis is a vital internal process for both the production and differentiation of diverse cells. Haematopoiesis involves multiple stages of renewing hematopoietic stem cells and creating myeloid and lymphoid progenitors which are the precursors of human cells such as blood cells (148, 149). This process is highly controlled to ensure the continuous replenishing of the human body with normal cells (148, 149). However, any disturbance of this process, irrespective of the stage, could lead to the occurrence of several disorders and diseases, including haematological malignancies. Haematological malignancies mainly encompass leukaemia and lymphomas, depending on the affected types of cells/lineages (148, 149).

As mentioned in Chapter 1, different approaches can be implemented to manage this disease. The use of medicines, the pharmacological approach, is established in the treatment of paediatric patients diagnosed with haematological malignancies (150, 151). Contrary to adult patients, the number of approved SACT agents for the treatment of children is low due to the lower incidence of childhood cancer compared to adulthood cancer (152). Further, the low number of approved medicines for children might be attributed to preclusion of children from clinical trials (153), and the low number of paediatric-specific trials (154). With respect to regulatory bodies, the European Medicines Agency (EMA) approves a lower number of medicines for paediatric patients compared to the US Food and Drug Administration (FDA) (155). For example, imatinib (for treatment of CML) was approved by FDA and EMA to treat patients who carry ABL1 gene, whereas arsenic acid (for acute promyelocytic leukaemia (APL)) was approved in paediatric patients by the FDA only (156). The Medicines and Healthcare products Regulatory Agency (MHRA), the independent regulatory body of licensing of medicines in the UK, approved a lower number of medicines compared to FDA and EMA (157). Moreover, the licencing status of medicines varies across countries (158).

Overall, information about the use of medicines (e.g. labelled indication) in the paediatric field is sparse (159). Although clinical trials provide significant evidence on the efficacy and safety of medicines to treat different diseases (160), their strict inclusion and exclusion criteria might not reflect real-world everyday practice. Therefore, observational studies may provide better empirical evidence on medicine

use (160). No previous systematic reviews or scoping reviews have described the pharmacological management of paediatric haematological malignancies in practice across the world. Hence, conducting an international scoping review would be useful to provide a broad overview of the current literature on drug utilisation in the area of paediatric cancer.

3.2 Aim

This scoping review aimed to comprehensively explore the real-world use of SACT and supportive medicines in the management of paediatric haematological malignancies.

3.3 Research question

What SACT and supportive medicines have been used for the treatment or management of the paediatric populations who are diagnosed with haematological malignancies in clinical practice worldwide?

3.4 Methods

The methodology was in accordance with the Joanna Briggs Institute (JBI) recommendations; the Preferred Reporting Items for Systematic Reviews and Meta-analysis Extension for Scoping Reviews (PRISMA-ScR) have guided the reporting (161) (Table S3.17, Appendix 1). A priori scoping review protocol was developed and registered on the University of Strathclyde's Pure platform to make it publicly accessible (162). Some deviations from the protocol occurred for practical reasons, including the search period; an extension of the upper limit of paediatric patients age to be < 19 years; and the exclusion of other non-haematological paediatric cancers. Table 3.1 provides the full details. No funding was required to conduct this review.

Table 3.1 Deviations from the pre-defined protocol

The original (previous) scope	The deviation / Current scope	Explanation
Including paediatric patients <18	Including paediatric patients <19	According to a global survey, the mean of upper cut-off of paediatric age exceeded 18 in many countries over the last two decades (163).
Including all types of cancer	Including haematological malignancies only	Because of time limitation and the heterogeneity of different types of paediatric cancer, the review included literature on the most common types of paediatric cancers worldwide which are haematological types-leukaemia and lymphomas (146).

3.4.1 Scoping review as a chosen method

Conducting a scoping review is the most appropriate means to map out all available literature on a particular topic (164). Medicine use in paediatric oncology is not fully identified and understood. Existing empirical evidence on medicine use in paediatric oncology can be identified and examined with the aid of a scoping review. Scoping reviews acknowledge undisclosed research gaps in the field of interest as well. Another benefit of conducting scoping reviews is that they can inform clinical practice / policies (164). Additionally, a scoping review is fundamental for formulating further specific problem/population, intervention, comparison, outcome (PICO) questions for future systematic reviews (164).

3.4.2 Eligibility criteria

English publications from January 2013 to February 2023 were retrieved from relevant bibliographical databases. The review included observational studies because these studies simulate the real-world care provided for patients in the relevant clinical settings, and thereby reflecting the actual practice without strict monitoring and highly controlled parameters. The restriction on the year of publication was due to unmanageable number of hits when the search started from inception and this timeframe was considered sufficient to provide an up-to-date overview. The details of the inclusion and exclusion criteria are illustrated in Table 3.2.

Table 3.2 Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Population P	
Studies involving children and adolescents aged <19 years old who were diagnosed with a haematological malignancy	Studies solely involving adults with haematological malignancies Studies involving children and adolescents aged <19 years old who were diagnosed with malignancies other than haematological
Concept C	
The treatment of haematological malignancy itself or other clinical indications (i.e. supportive care for relevant ailments) using medicines)	Focus on other treatment approaches such as radiotherapy and surgery
Context C	
No geographical limitations Treatment in clinical practice	None
Source of evidence	
Observational studies (e.g. cohort and cross-sectional studies), providing that these studies reflected the routine practice	⬆ Intervention studies (e.g. randomised controlled trials) ⬆ Case series ⬆ Case reports ⬆ Secondary/Tertiary studies (e.g. systematic reviews) ⬆ Conferences abstracts ⬆ Opinions ⬆ Commentaries

NB: The criteria were set according to Population, Concept, and Context (PCC) framework (165).

3.4.3 Search strategy

The search strategy was developed using the key terms and synonyms of:

- ⬆ The populations of interest (i.e. paediatric populations)
- ⬆ The intervention (i.e. use of medicines)
- ⬆ The studied disease (i.e. haematological malignancy)
- ⬆ The excluded study designs

Appropriate combining of three Boolean operators (i.e. “AND”, “OR”, and “NOT”) was applied in the construction of the search strategies for the selected databases. Key terms of the excluded study designs and the Boolean operator “NOT” were used to exclude articles that referred to the type of study in the titles using relevant keywords. Search strategies were tailored assuming the variation of the used controlled or standardised headings among databases. These headings were MeSH (Medical Subject Headings) for PubMed database and Emtree for Embase database. The final developed search strategies (Table S3.1, Appendix 1) were reviewed by TM and NW. The search was conducted on the three electronic databases PubMed (Medline), Embase, and Scopus because these datasets indexed articles relevant to the medical field in February 2023. The in-built search filters were applied to limit publication year, language, and species. Then, the search results from the selected databases were exported to Covidence (42).

Besides using the Google search engine, four sources of grey literature (MedRxiv, Google Scholar, Open Grey, and ProQuest Dissertations) were also searched for additional articles using basic and common relevant terms (e.g. children, cancer, and medicines).

3.4.4 Study selection

Identified articles from the three aforementioned databases went through two stages of examination on Covidence before inclusion. Covidence automatically removed duplicates from the imported articles, with an additional manual option of removing duplicates within this software. In the first stage, titles and abstracts of identified articles were examined in accordance with the inclusion criteria. The identified articles from the former stage underwent a second stage of screening (full text). Ten percent of articles were screened (title and abstract/full text) by both RA (primary reviewer) and another researcher (HA or FM) independently. Any disagreement was resolved by discussion. It has been established that agreement percentage above 80% is adequate (166).

A manual search of reference lists of articles included in this study was conducted to supplement the search strategy.

RA contacted authors in case of inaccessibility of the full text of studies via email twice, with a one-month gap between emails, between July 2023 and December 2023.

ResearchGate was an additional approach to contact authors for the full texts. Furthermore, RA also searched for email addresses of authors online if the email addresses were not provided for contact in the abstracts of the studies. Eventually, inaccessible articles were excluded.

3.4.5 Data extraction

After the two screening stages, articles proceeded to the stage of extraction. The data were extracted from the articles based on a customized table (Microsoft Excel spreadsheet) of the relevant information. The relevant information included the following: the author name, study-related information (i.e. publication year, country of study, aim(s) of the study, source of data, study design, sample size, and clinical settings), disease-related information (i.e. malignancy category, subcategory, risk stratification), patient-related information (i.e. demographics), medicine-related information (i.e. doses, routes of administration, treatment duration, and indication), concurrent radiotherapy, the prescriber, the state of licencing, and the considerations of ethical approval/informed consents (Table S3.2, Appendix 1). The final data extraction template was developed after piloting with 30% of studies. The data extraction of 10% of articles was done independently by FM (validation of data extraction). Discussions were held whenever inconsistencies were encountered to obtain agreement.

3.4.6 Data synthesis and presentation

Narrative synthesis was utilised to summarise data in this review. Data were grouped and clustered on the basis of types of therapy and other main headings (167). Tables were another form to present and summarise the findings of this review. Some publications focused on various areas (e.g. the treatment of more than one malignancy or complication).

3.4.7 Critical appraisal of the included articles

The retrieved articles were individually appraised against relevant JBI critical appraisal tools (checklists) (168) to evaluate their methodological quality (169). Tools consist of questions to evaluate the study design (e.g. clear description of population(s) of interest), study conduct (e.g. dealing with confounding factors), and analysis of data (e.g. the use of appropriate statistical methods). The JBI critical appraisal tools were applied in this review because these tools are widely used to

appraise the quality of research articles (169). The number of the assessing criteria were eleven and eight for cohort and cross-sectional study designs, respectively. Criteria were assessed as followings; “Yes” =1, “No”, “Unclear”, and “Not applicable” =0. The critical assessment of 10% of articles was also done independently by FM.

3.5 Results

3.5.1 Studies characteristics

The PRISMA-ScR flow chart is shown in Figure 3.1. The agreement percentages of the 10% validation at title and abstract screening, full-text screening, and data extraction stages were 87%, 88%, and 86%, respectively. The agreement percentage of the 10% validation at the critical appraisal stage was 78%. From an initial number of 11,899 hits, 82 articles were eligible for inclusion and proceeded to data extraction. Articles were excluded whenever they did not completely meet the inclusion criteria after the thorough reviewing of the full text, for example articles with wrong study design (e.g., clinical trials, RCTs, or clinical pharmacokinetic studies) were excluded. The number of studies that exemplified the medicine-based management for leukaemia and lymphomas was 49 (59.8%) and 29 (35.4%), respectively. Additionally, four studies (4.9%) considered both malignancies in their explorations.

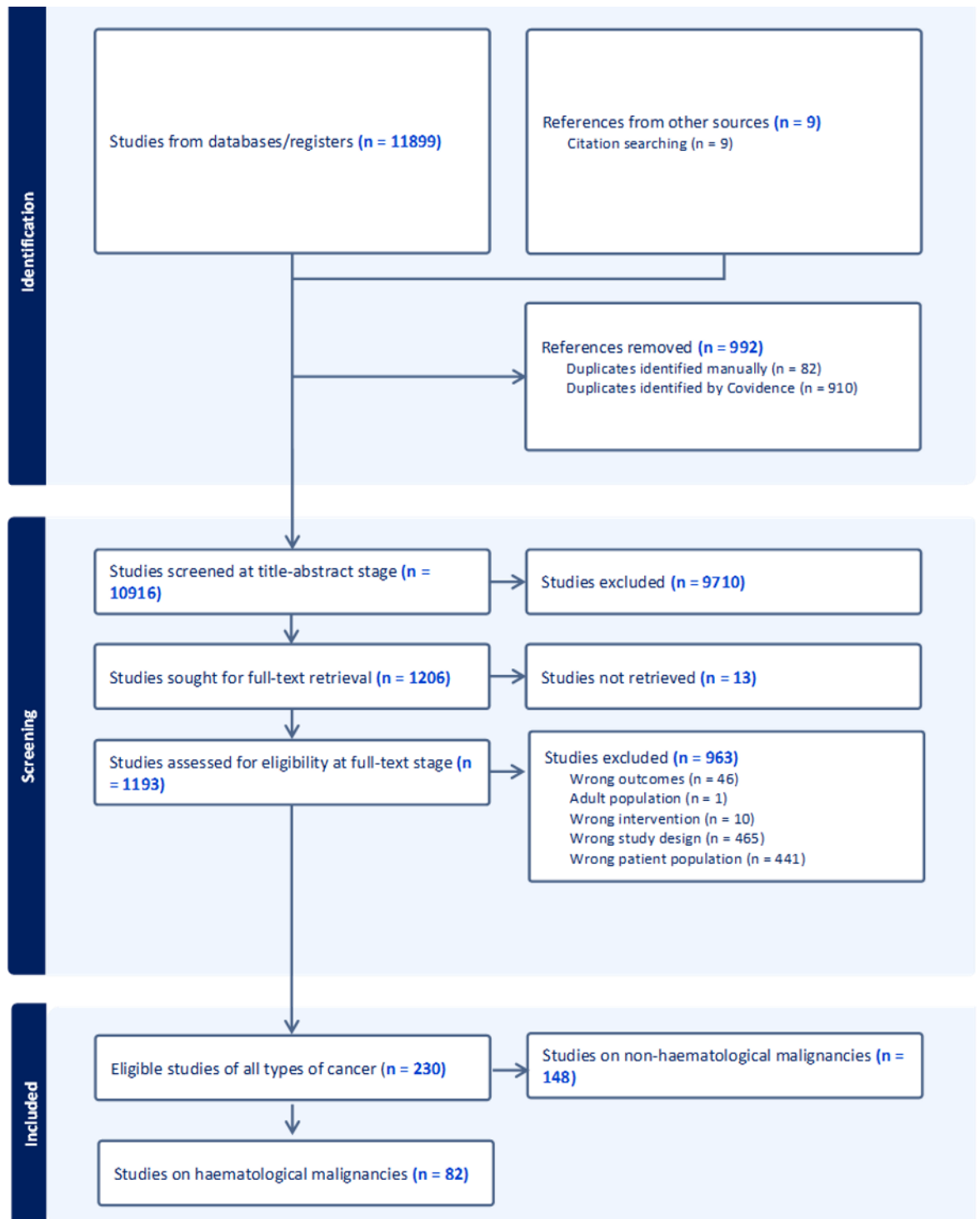


Figure 3.1 PRISMA-ScR flowchart of the conducted search

This international scoping review retrieved literature from all continents except Australia (Table 3.3). The highest number of observational studies were conducted in medical institutions located in Asia. The number of the retrieved studies from Europe and Americas were 13 (15.9%) and 12 (14.6%), respectively. Twelve studies (14.6%)

were performed in Middle Eastern countries. Five studies (6.1%) were set in Africa. The remainders (n=2, 2.4%) recruited patients from more than one country.

Table 3.3 Geographical distribution of the studies

Region	Number of studies (%)
Asia	38 (46.3%)
India	13 (15.9%)
China	7 (8.5%)
Pakistan	7 (8.5%)
Japan	5 (6.1%)
Korea	1 (1.2%)
Philippine	1 (1.2%)
Tanzania	1 (1.2%)
Taiwan	1 (1.2%)
Thailand	1 (1.2%)
Singapore	1 (1.2%)
Europe	13 (15.9%)
Turkey	7 (8.5%)
France	2 (2.4%)
Finland	1 (1.2%)
Italy	1 (1.2%)
Poland	1 (1.2%)
Spain	1 (1.2%)
Americas	12 (14.6%)
United States	4 (4.9%)
Canada	3 (3.7%)
Brazil	3 (3.7%)
Mexico	1 (1.2%)
Nicaragua	1 (1.2%)
Middle East / Gulf Region	12 (14.6%)
Egypt	5 (6.1%)
Saudi Arabia	3 (3.7%)
Jordan	1 (1.2%)
Iran	1 (1.2%)
Iraq	1 (1.2%)
Oman	1 (1.2%)
Africa	5 (6.1%)
Kenya	3 (3.9%)
South Africa	2 (2.4%)
Australasia	0 (0.0%)

The vast majority of the identified studies were cohort studies (n = 80, 97.6%). Two cross-sectional studies were reported among the identified articles (2.4%) (170, 171) (Table S3.3, Appendix 1). Most of the identified articles were published between 2016-2021. Overall, 12,556 paediatric patients were included in the 82 studies; the lowest number of included paediatric patients was 14 in two studies (172, 173) whereas the highest was 1415 (174).

All studies but seven (8.5%) (173, 175-180) reported the gender of the included patients. In 66 out of the 75 studies that reported on gender, the majority of patients were male (51%-90%). The ethnicity of the included paediatric patients was reported in three studies (3.7%) (181-183).

3.5.2 Data sources and settings

Tertiary health care settings were the most common clinical settings (n=80, 97.6%) (171-250). The outpatient settings of hospitals were also documented (n=5, 6.1%) (170, 194, 198, 218, 251). Authors of nine studies (11.0%) explicitly stated the residential areas, namely urban and rural areas, of the included patients in their studies (174, 179, 190, 196, 201, 205, 211, 229, 241). One study (1.2%) highlighted the inclusion of patients from rural residential areas of the country (Nicaragua) (240).

Medical records were the source of data in 44 studies (53.7%) (170, 171, 174, 175, 177-179, 181-184, 189-192, 194, 195, 197-200, 202-204, 208, 211, 215, 217, 218, 222-225, 227-229, 232, 233, 235, 239, 241, 242, 246, 251). The data were also abstracted from databases (registries) in some studies (n= 12, 14.6%) (173, 180, 185, 187, 188, 193, 196, 207, 213, 220, 233, 238). The authors of one study illustrated the use of a clinical database (193). The remainder provided insufficient information regarding the type of database (e.g. clinical or administrative). Primary data were collected in five studies (6.1%) using clinical data collection forms (201, 212, 228, 232, 240).

The characteristics of each individual study are outlined in Table S3.3, Appendix 1.

3.5.3 Oncological medicines (systemic anti-cancer therapy (SACT)) ± corticosteroids for the management of paediatric haematological malignancies

The medicine-based management of paediatric patients with haematological malignancies was described in 71 studies (Table 3.4). All studies except five (178, 179, 185, 194, 212) reported the use of SACT ± corticosteroids for one subcategory of haematological malignancies (Table 3.4).

Table 3.4 The number of studies on each haematological malignancy subcategory

Treatment indication	Number of studies / Total number of studies
Acute lymphoblastic leukaemia	(n=30/82, 36.6%) (170, 173-175, 179, 185, 192, 197, 201, 203, 206, 207, 209, 212, 214, 219, 220, 227, 228, 233, 235, 236, 238-242, 244, 245, 247)
Acute myeloid leukaemia	(n=14/82, 17.1%) (179, 180, 183, 185, 187, 211-213, 215, 217, 222, 226, 232, 237)
Chronic myelogenous leukaemia	(n=2/82, 2.4%) (172, 176)
Hodgkin's lymphoma	(n=14/82, 17.1%) (177, 182, 190, 196, 199, 204, 210, 216, 218, 224, 231, 248, 249, 251)
Non-Hodgkin lymphomas	(n=17/82, 20.7%) (171, 184, 186, 189, 191, 193-195, 205, 208, 216, 221, 223, 225, 229, 230, 234)

Thirty-nine studies (47.6%) documented the names of adapted or adopted treatment protocols (clinical trial protocols) (e.g. BFM, Chinese Children's Leukaemia Group, and UK-ALL) (170, 174, 178-180, 183, 184, 186, 189, 191-193, 195-197, 201, 203, 206-208, 214, 219-221, 225, 227, 228, 230, 231, 233-236, 239-242, 245, 247) (Table S3.4, Appendix 1). Combinations of medicines were used to manage the paediatric haematological malignancies. The therapeutic combinations mainly consisted of conventional chemotherapy agents (Table 3.5). Corticosteroids were also incorporated into these combinations to manage certain haematological malignancies (Table 3.6). In this review, the duration of treatment was mentioned in ten studies (12.2%) (172, 174, 179, 186, 197, 239-242, 245). Eight out of the ten studies were studies on the management of ALL (172, 174, 179, 186, 197, 239-242, 245), with a range of treatment duration from 96 to 169 weeks.

Table 3.5 The identified agents of conventional chemotherapy

Conventional chemotherapy agent	Acute lymphoblastic leukaemia			Acute myeloid leukaemia			Chronic myelogenous leukaemia	Hodgkin's lymphoma			Non-Hodgkin lymphomas		
	New cases	Refractory/ relapsed cases	Haematopoietic Stem Cell Transplantation	New cases	Refractory/ relapsed cases	Haematopoietic Stem Cell Transplantation	New cases	New cases	Refractory/ relapsed cases	Haematopoietic Stem Cell Transplantation	New cases	Refractory/ relapsed cases	Haematopoietic Stem Cell Transplantation
Alkylating agents													
Bendamustine										X			X
Busulfan			X			X							
Carboplatin						X		X			X		
Carmustine										X			X
Chlorambucil								X					
Cisplatin									X				
Cyclophosphamide	X	X		X		X		X		X	X		X
Dacarbazine			X					X					
Ifosfamide	X							X	X				X
Mechlorethamine								X					
Melphalan						X				X			
Nimustine			X			X				X			X
Procarbazine								X					
Thiotepa						X							

Treosulfan			X										
Antimetabolites													
Cytarabine	X	X		X	X	X			X		X		
Fludarabine		X		X	X	X							
Gemcitabine			X						X				
Hydroxyurea							X				X		
Mercaptopurine	X			X							X	X	
Methotrexate	X			X		X					X	X	
Thioguanine	X		X	X							X		
Miscellaneous													
Amsacrine				X									
Arsenic trioxide					X								
Asparaginase	X			X							X		
Harringtonine				X									
Mitoguazone								X					
Omacetaxine				X									
Tretinoin				X	X								
Mitotic inhibitors													
Etoposide	X			X		X		X	X	X	X		X
Teniposide	X		X										X
Vinblastine								X			X	X	
Vincristine	X							X			X	X	
Vindesine	X												
Vinorelbine								X	X				
Antibiotics/ antineoplastics													
Bleomycin								X			X		
Daunorubicin	X			X							X		
Doxorubicin	X			X		X		X			X	X	
Idarubicin		X		X									
Mitoxantrone				X									

Tetrahydropyrany Adriamycin						X							
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NB= X indicates the use of this agent for the respective situation.

Table 3.6 The identified corticosteroids for the management of haematological malignancies

Conventional chemotherapy agent	Acute lymphoblastic leukaemia			Acute myeloid leukaemia			Chronic myelogenous	Hodgkin' s lymphoma			Non-Hodgkin lymphomas		
	New cases	Refractory/ relapsed cases	Haematopoietic Stem Cell	New cases	Refractory/ relapsed cases	Haematopoietic Stem Cell	New cases	New cases	Refractory/ relapsed cases	Haematopoietic Stem Cell	New cases	Refractory/ relapsed cases	Haematopoietic Stem Cell
Dexamethasone	X								X		X		
Hydrocortisone	X			X							X		
Methylprednisolone sodium succinate									X				
Prednisolone	X				X			X	X		X		
Prednisone	X							X			X		

NB= X indicates the use of this agent for the respective situation.

Other SACT agents were prescribed in certain contexts. Table 3.7 describes the indications for prescribing SACT agents other than conventional chemotherapy.

Table 3.7 Other forms of systemic anticancer therapy and their applications

Management of refractory /relapsed cases	Other systemic anticancer therapy agents	Details
	Tisagenlecleucel	Tisagenlecleucel (Chimeric Antigen Receptor T-cell therapy) was used to treat refractory / relapsed cases with acute lymphoblastic leukaemia (173).
	Blinatumomab	Blinatumomab was administered before tisagenlecleucel (173).
	Inotuzumab	Inotuzumab was administered before tisagenlecleucel (173).
	Brentuximab vedotin	The use of brentuximab vedotin was documented in refractory / relapsed cases with Hodgkin's lymphoma (224).
Management of other cases	Expanded activated autologous lymphocytes	The involvement of expanded activated autologous lymphocytes was reported for a group of patients with acute myeloid leukaemia (222).
	Imatinib	Imatinib was utilised for the management of chronic myelogenous leukaemia (172, 176) and Philadelphia chromosome-positive acute lymphoblastic leukaemia (239).
	Dasatinib	Dasatinib had a role if the management of chronic myelogenous leukaemia cases with imatinib resulted in unsatisfied outcomes (treatment failure) (176).
	Nilotinib	Nilotinib had a role if the management of chronic myelogenous leukaemia cases with imatinib resulted in unsatisfied outcomes (treatment failure) (176).
	Rituximab	Rituximab was use for Burkitt's lymphomas at stage IV that involved central nervous system (225), B-cell lymphoma cases with observed involvement of kidneys and jaw (184), and for post-transplant Burkitt's lymphomas (223).

SACT was delivered to paediatric patients with haematological malignancies through invasive (i.e. intravenous, intrathecal, intramuscular, and subcutaneous) and non-invasive routes (i.e. oral) (Table S3.5, Appendix 1). Invasive routes of administration were the predominant routes of administration for SACT agents. SACT could be administered intravenously in a rapid push or in an infusion manner. The duration of administering infusions ranged from half an hour - 36 hours (183, 212, 217, 233, 247). It was noticed that certain SACT agents were infused over different periods of time (e.g. cytarabine (183, 212, 233, 247)) (Table S3.6, Appendix 1). The findings illustrated that corticosteroids could be administered intravenously, intrathecally, and orally (Table S3.5, Appendix 1).

3.5.3.1 Oncological medicines for newly diagnosed patients

3.5.3.1.1 Acute lymphoblastic leukaemia (ALL)

SACT + corticosteroids had been administered to treat newly diagnosed paediatric patients with ALL ((Table 3.5) and (Table 3.6)) in line with the institution's protocols. All ALL-treatment protocols started with induction and ended with maintenance phases. In-between phases varied amidst the retrieved observational studies. In-between phases were intensification or consolidation phases, interim maintenance, which were presented in some protocols, and CNS-directed phase with intrathecal therapy. The combinations of SACT + corticosteroids at each phase were different across studies. Compared to other ALL studies, eight studies (9.8%) reported the given SACT + corticosteroids for the management of patients with ALL during induction (203, 206, 207, 214, 219, 220, 235) or maintenance (170) phase. The doses of the SACT+ corticosteroids at each stage are displayed in Table S3.7, Appendix 1. Each risk group received a specific combination of SACT+ corticosteroids with the highest treatment intensity for patients with high risk (n=11, 13.4%) (174, 179, 197, 206, 207, 219, 227, 233, 235, 236, 247). The administered intensive blocks for high-risk patients including etoposide and vindesine were noticed in the studies from Turkey and China.

Salami and colleagues pointed out that imatinib was used along with other SACT agents and corticosteroids for the entire treatment duration (from induction to maintenance) (239).

3.5.3.1.2 Acute myeloid leukaemia (AML)

Studies on paediatric AML generally addressed the exposure to SACT in two-phase frameworks (induction and consolidation phases). Two studies (2.4%), conducted in Brazil and Singapore, illustrated the treatment of specific populations of AML. Patients with Down's syndrome were less intensively treated by administering cytarabine, daunorubicin, and etoposide (183, 211). Sutiman et al. documented the addition of mitoxantrone if patients had no complete remission (183). The doses of SACT± corticosteroids are displayed in Table S3.8, Appendix 1.

Zhang et al. illustrated the combination of biological therapy (expanded activated autologous lymphocytes (EAALs)) and conventional chemotherapy (222).

3.5.3.1.3 Chronic myelogenous leukaemia (CML)

The lowest number of SACT agents for the empirical treatment of haematological malignancies was identified for the chronic phase of CML. Hydroxyurea was also prescribed prior to initiation of imatinib. The stated clinical indication for giving hydroxyurea in the treatment of paediatric patients with CML was hyperleukocytosis ($WBC > 50 \times 10^9 /L$) (176). The doses of SACT are displayed in Table S3.9, Appendix 1.

3.5.3.1.4 Hodgkin's lymphoma (HL)

Four SACT agents were combined to form the standard four-medicine regimen for HL treatment, which were doxorubicin hydrochloride (Adriamycin), bleomycin, vinblastine, and dacarbazine (ABVD) across geographically different settings (174, 179, 192, 206, 214, 220, 227, 233, 235, 240-242, 245, 247). Irrespective of the diagnosed stage, this regimen was implemented to treat classic HL (197, 201, 203, 207, 219, 236) or all HL subtypes including classic HL (174, 179, 201, 207, 219, 227). Switching to distinct regimens other than the ABVD regimen was documented as well (Table S3.10, Appendix 1). It is worth mentioning that therapeutic plans also combined two regimens (each regimen could be composed of 3-5 SACT agents ± corticosteroids) for the management of cases with HL (182, 196, 210, 231, 248, 251). The doses of SACT are displayed in Table S3.11, Appendix 1.

3.5.3.1.5 Non-Hodgkin lymphomas (NHL)

Most studies (n=11, 13.4%) on NHL showed the following of specific treatment protocols consisting of SACT + corticosteroids to manage patients with NHL (184, 186, 189, 191, 193, 195, 208, 221, 225, 230, 234) (Table S3.12, Appendix 1). In four studies (4.9%), each risk group received specific combinations (184, 186, 208, 234).

Specific considerations were taken while treating specific lymphoma subtypes (e.g. being infected with HIV (184) or *Plasmodium falciparum* malaria and EBV (191)). The therapeutic plan of the endemic type of Burkitt's lymphomas (BL), a type of BL associated with the widespread presence of other epidemic diseases (e.g. malaria), during induction and consolidation phases was reliant on five medicines: cyclophosphamide, vincristine, doxorubicin, prednisone, and methotrexate (MTX) (191). Development of B-cell lymphomas including BL had been shown among some patients with HIV (184). In comparison to HIV-diagnosed cases with lymphoma, the intensity of the pharmacological treatment was higher for HIV-free cases (184).

Regimens could be combinations of two forms of anti-cancer agents, such as a combination of rituximab and conventional chemotherapy agents. Patients with stage IV of BL that involved the CNS received conventional chemotherapy, corticosteroids, and rituximab (225). Despite its rarity, the diagnosis with BL following solid-organ transplants was also reported in one study (1.2%). Rituximab was the mainstay in most of the considered regimens; it could be administered as monotherapy or part of the combination regimens (223).

3.5.3.2 Refractory /relapsed (r/r) cases

Relapsed cases are patients who do not show response to the treatment $\geq$ six months post-treatment initiation, whilst refractory cases show unresponsiveness before approaching the cut-off of six months (252). Ten studies (12.2%) illustrated the pharmacological treatment of r/r cases: two studies (2.4%) on ALL (173, 212), two studies (2.4%) on AML (180, 212), four studies (4.9%) on HL (177, 190, 218, 224), and two studies (2.4%) on NHL (171, 221). Table 3.5 shows different SACT agents to manage r/r cases. Regimens were mainly composed of one (173) or more SACT agents (171, 177, 180, 190, 212, 218, 221, 224). For HL, these regimens were called "salvage regimens" (177, 190, 218, 224) and contained corticosteroids (Table S3.13,

Appendix 1). One study reported that monotherapy for r/r NHL cases was prescribed along with celecoxib, a nonsteroidal anti-inflammatory drug (NSAID). The doses of SACT± corticosteroids are displayed in Table S3.14, Appendix 1.

3.5.3.3 Haematopoietic Stem Cell Transplantation (HSCT)

Eleven studies (13.4%) illustrated the myeloablative conditioning regimens of SACT prior to treating with allogenic (185, 187, 188, 209, 217, 238, 244) or autologous (177, 213, 216, 218) HSCT (Table 3.8). Busulfan-based regimens were used to prepare paediatric patients for allogenic (185, 187, 188, 209, 217, 244) or autologous HSCT (213, 218). Non-busulfan conditioning regimens were treosulfan-based (238) and nitrosourea-based (177, 216) conditioning regimens. Treosulfan-based conditioning treatment were used to prepare patients for allogenic HSCT, whereas nitrosourea-based triple regimens were used to prepare patients for autologous HSCT. The transplantation also involved prescribing of cyclophosphamide and etoposide with other supplementary medicines for peripheral blood stem cell (PBSC) mobilisation (216). The doses of SACT are displayed in Table S3.15, Appendix 1.

Table 3.8 Myeloablative conditioning regimens for Haematopoietic Stem Cell Transplantation

Conditioning regimen	Haematological malignancies subcategories	Number of studies / Total number of studies
(Busulfan - Cyclophosphamide)	Acute lymphoblastic leukaemia (185, 209), Acute myeloid leukaemia (185, 187, 188)	(4/82) (185, 187, 188, 209)
(Busulfan - Fludarabine - Thiotepa)	Acute lymphoblastic leukaemia (244)	(1/82) (244)
(Busulfan- Cyclophosphamide- Melphalan)	Acute myeloid leukaemia (217)	(1/82) (217)
(Busulfan - Etoposide)	Acute lymphoblastic leukaemia (185), Acute myeloid leukaemia (185)	(1/82) (185)
(Busulfan - Melphalan)	Acute lymphoblastic leukaemia (185), Acute myeloid leukaemia (185, 188, 213)	(1/82) (185, 188, 213)
(Busulfan - Cytarabine -Etoposide)	Acute myeloid leukaemia (213)	(1/82) (213)
(Treosulfan - Cyclophosphamide - Fludarabine - Melphalan -Thiotepa)	Acute lymphoblastic leukaemia (238)	(1/82) (238)
(Nimustine - Etoposide - Cyclophosphamide)	Hodgkin's lymphoma (216), Non-Hodgkin lymphomas (216)	(1/82) (216)
(Carmustine - Etoposide - Cyclophosphamide)	Hodgkin's lymphoma (216), Non-Hodgkin lymphomas (216)	(1/82) (216)
(Carmustine - Etoposide - Melphalan - Cytarabine)	Hodgkin's lymphoma (177, 218), Non-Hodgkin lymphomas (177)	(2/82) (177, 218)

3.5.4 Non-oncological medicines (supplementary medicines) to support the management of paediatric haematological malignancies

In total 34 studies (41.5%) reported the use of supplementary medicines for paediatric patients with leukaemia (174-176, 178, 179, 181, 183, 187, 188, 194, 197, 198, 200-203, 209, 211, 212, 215, 217, 219, 226, 232, 233, 235, 237-239, 241, 243, 244, 246, 250), and 14 (17.1%) studies documented the supplementary medicines given for paediatric patients with lymphomas (171, 177, 178, 184, 193, 194, 200, 208, 216, 218, 223, 225, 234, 250).

Some studies described the routes of delivering supplementary medicines, including the use of oral (171, 193, 202, 212, 232-234, 239, 243), intravenous (178, 193, 202, 212, 215, 234, 239, 243), subcutaneous (193, 212, 226), inhaled (215), topical (171), and ophthalmic (250) formulations to manage the developing side effects and symptoms.

Seventy-four supplementary medicines were identified in this review (Table 3.9). The management of infections (i.e. PCP prophylaxis (174, 179, 193, 197, 201, 202, 208, 209, 212, 215, 219, 232, 234, 239, 241), prophylaxis and treatment of fungal infections (171, 174, 177, 178, 193, 216, 225, 233, 234, 239), and prophylaxis in the state of febrile neutropenia (175, 179, 209, 211, 212, 237, 239, 243) and afebrile neutropenia (243)) were the most common indications for prescribing supplementary medicines among studies in this review. Respiratory infections in particular were the most documented indication for administering antibiotics (16/82, 19.5%) (171, 174, 179, 193, 197, 201, 202, 208, 209, 212, 215, 219, 232, 234, 239, 241). Other frequently documented clinical indications were management of SACT-induced toxicity (171, 193, 211, 212, 215-218, 237, 243, 246) and GVHD prophylaxis accompanying HSCT (187, 188, 209, 217, 238, 239, 244).

Each supplementary medicine, except midazolam, was applied for a specific clinical complication. One or combinations of supplementary medicines could be prescribed in the area of supportive care. The use of a combination of supplementary medicines was markedly noted in prophylaxis against febrile neutropenia.

Table 3.9 Supplementary medicines for paediatric patients with haematological malignancies

Supplementary medicine	Number of studies on leukaemia that document the use of this medicine / Total number of studies	Number of studies on lymphomas that document the use of this medicine / Total number of studies	Notes
Prophylaxis during neutropenia			
Cefuroxime	(1/82) (243)	None	
Ceftazidime	(2/82) (212, 246)	None	One study mentioned the use of the third generation of cephalosporin without specifying the agents (237).
Cefepime	(2/82) (215, 246)	None	
Cefaperazon-sulbactam	(1/82) (246)	None	
Carbapenem	(2/82) (215, 246)	None	
Meropenem	(1/82) (217)	None	
Piperacillin/ Tazobactam	(3/82) (212, 215, 217)	None	
Amikacin	(2/82) (243, 246)	None	Three studies mentioned the use of aminoglycosides without specifying the agents (215, 217, 237).
Gentamicin	(1/82) (212)	None	
Teicoplanin	(2/82) (217, 246)	None	Teicoplanin was an exclusive option for the second-line treatment of neutropenia (246).
Vancomycin	(3/82) (211, 215, 217)	None	Vancomycin whenever clinical instability or infections caused by multidrug-resistant organisms, which were resistant to at least two classes of antibiotics, were documented (215).
Ciprofloxacin	(2/82) (211, 243)	None	Receiving ciprofloxacin was reported in cases with afebrile neutropenia (243).

Amphotericin B	(2/82) (212, 217)	None	The involvement of amphotericin B in the antibiotic regimen was linked to persistent fever > 3-5 days (212).
Caspofungin	(1/82) (212)	None	The involvement of caspofungin in the antibiotic regimen was linked to persistent fever > 3-5 days (212).
Pulmonary infections			
Amoxicillin clavulanate	(1/82) (171)	None	
Prophylaxis against Pneumocystis			
Cotrimoxazole	(12/82) (174, 179, 197, 201, 202, 209, 212, 215, 219, 232, 239, 241)	(3/82) (193, 208, 234)	
Dapsone	(2/82) (202, 215)	None	Dapsone was the selected choice for normal levels of glucose-6-phosphate dehydrogenase (202).
Pentamidine	(2/82) (202, 215)	None	Pentamidine was infused in the context of glucose-6-phosphate dehydrogenase deficiency (202).
Atovaquone	(1/82) (202)	None	
Prevention of fungus-induced infections			
Fluconazole	(3/82) (175, 211, 239)	None	
Voriconazole	(3/82) (212, 237, 243)	None	
Itraconazole	(1/82) (212)	None	
Micafungin	(1/82) (243)	None	The coincidence of voriconazole and vincristine during treatment of acute lymphoblastic leukaemia was avoided by prescribing micafungin (243).
Treatment of fungus-induced infections			
Ketoconazole	(2/82) (179, 237)	None	
Amphotericin B	(2/82) (179, 237)	None	
Oral candidiasis			
Nystatin	None	(1/82) (171)	
Tinea capitis			

Clotrimazole	None	(1/82) (171)	
Human immunodeficiency virus management			
Stavudine-Lamivudine-Efavirenz); Highly Active Antiretroviral Therapy	None	(1/82) (184)	Highly Active Antiretroviral Therapy was given for human immunodeficiency virus-diagnosed cases.
Cytomegalovirus treatment			
Ganciclovir	(1/82) (239)	None	
Herpes virus prophylaxis			
Aciclovir	(1/82) (209)	None	Prophylactic aciclovir was used prior Haematopoietic Stem Cell Transplantation (209).
Chicken pox management			
Aciclovir	None	(1/82) (171)	
Calamine	None	(1/82) (171)	
Neutropenia			
Granulocyte colony stimulating factor	(3/82) (183, 212, 226)	(4/82) (171, 193, 216, 218)	
Tumour lysis syndrome			
Allopurinol	(6/82) (174, 179, 200, 217, 232, 241)	(1/82) (200)	
Febuxostat	(1/82) (200)	(1/82) (200)	
Rasburicase	(1/82) (200)	(1/82) (200)	
Antidotes for systemic anti-cancer therapy-induced toxicity			
Methotrexate-induced toxicity			
Folinic acid (Leucovorin)	(4/82) (174, 178, 233, 239)	(4/82) (178, 193, 225, 234)	
Ifosfamide-induced toxicity			
Mesna	None	(3/82) (171, 177, 234)	
Prophylaxis against lung toxicity			
Methylprednisolone	None	(1/82) (216)	

Haematopoietic Stem Cell Transplantation supportive care			
Graft-versus-host disease prophylaxis			
Methotrexate	(7/82) (187, 188, 209, 217, 238, 239, 244)	None	Graft-versus-host disease prophylaxis was usually dual course of methotrexate and cyclosporin or tacrolimus (187, 188, 209, 217, 238, 239, 244). Methotrexate in this regard supported the stem cell transplantation.
Cyclosporin	(7/82) (187, 188, 209, 217, 238, 239, 244)	None	
Tacrolimus	(7/82) (187, 188, 209, 217, 238, 239, 244)	None	
Mycophenolate mofetil	(1/82) (238)	None	
Prevention of Haematopoietic Stem Cell Transplantation rejection			
Antithymocyte globulin	(3/82) (187, 209, 244)		Antithymocyte globulin was considered in two situations; when the donor was either other related /unrelated to the recipient and when human leukocyte antigen between donor and recipient was mismatched (209, 244).
Peripheral blood stem cell mobilisation			
Plerixafor	None	(1/82) (216)	
Thrombotic events			
Unfractionated heparin	(1/82) (181)	None	The ninth edition of antithrombotic therapy and prevention of thrombosis was the reference for dosing (41).
Enoxaparin	(1/82) (181)	None	
Tinzaparin	(1/82) (181)	None	
Low fibrinogen level			
Fresh frozen plasma	None	(1/82) (235)	
Pain			
Paracetamol	None	(1/82) (171)	
Ibuprofen	None	(1/82) (171)	
Diclofenac	None	(1/82) (171)	

Morphine	None	(1/82) (171)	
Tramadol	None	(1/82) (171)	
Dihydrocodeine	None	(1/82) (171)	
Sedoanalgesia			
Midazolam	(1/82) (194)	(1/82) (194)	
Ketamine	(1/82) (194)	(1/82) (194)	
Insomnia			
Midazolam	None	(1/82) (171)	
Busulfan-induced seizures			
Phenytoin	(1/82) (209)	None	
Steroid-induced hypertension			
Amlodipine	(1/82) (203)	None	
Enalapril	(1/82) (203)	None	
Labetalol	(1/82) (203)	None	
Steroid-induced glaucoma			
Latanoprost	(1/82) (250)	(1/82) (250)	
Ripasudil hydrochloride hydrate	(1/82) (250)	(1/82) (250)	Carbonic inhibitors and hyperosmotic agents were given for cases with intraocular pressure > 30 mmHg.
Timolol maleate	(1/82) (250)	(1/82) (250)	Carbonic inhibitors and hyperosmotic agents were given for cases with intraocular pressure > 30 mmHg.
Emesis			
Dexamethasone	(1/82) (198)	(1/82) (171)	This medicine was specifically used for chemotherapy-induced nausea and vomiting in patients with leukaemia (198).
Dimenhydrinate	(1/82) (198)	None	This medicine was specifically used for chemotherapy-induced nausea and vomiting in patients with leukaemia (198).
Granisetron	(1/82) (198)	(1/82) (171)	This medicine was specifically used for chemotherapy-induced nausea and vomiting in patients with leukaemia (198).
Metoclopramide	None	(1/82) (171)	
Ondansetron	(1/82) (198)	(1/82) (171)	This medicine was specifically used for chemotherapy-induced nausea and vomiting in patients with leukaemia (198).
Mucositis			

Miconazole	None	(1/82) (171)	Betadine (Povidone-iodine) was also considered (171).
Anorexia			
Multivitamin syrup	None	(1/82) (171)	
Constipation			
Lactulose	None	(1/82) (171)	
Diarrhoea			
Loperamide	None	(1/82) (171)	
Zinc sulphate	None	(1/82) (171)	
Hyperacidity			
Omeprazole	None	(1/82) (171)	
Esomeprazole	None	(1/82) (171)	
Ulgel	None	(1/82) (171)	

3.5.5 Other highlighted aspects

3.5.5.1 The prescribers

Only ten studies (12.2%) (174, 176, 182, 187, 188, 198, 200, 204, 223, 226) clarified the type of prescribers for medicines. Physicians (medical prescribers) were the authorised prescribers for SACT (174, 176, 182, 187, 204, 223, 226). For supportive care, physicians (188, 200) and the “clinical team” (198) took the responsibility of prescribing supplementary medicines for the paediatric patients. The members of the clinical team in the latter study were unidentified (198).

3.5.5.2 Dosing and patient characteristics

Table 3.10 outlines the impact of patient characteristics on dosing. Dosing of oncological and non-oncological medicines was tailored based on body surface area (BSA), weight, and age. BSA was extensively used for dosing of SACT agents.

Table 3.10 Dosing and impact of patient characteristics

Patient characteristics	Details	Number of studies / Total number of studies
SACT and corticosteroids		
Body surface area	Dosing of systemic anti-cancer therapy agents was based on patient's surface area. Dosing of corticosteroids at certain treatment phases was based on surface area.	(49/82) (170-172, 174, 176, 177, 179, 180, 183, 184, 186, 187, 191-197, 199, 201, 205, 206, 208-210, 214, 216-222, 225-227, 229, 230, 232-234, 238-242, 245, 247)
Weight	Dosing of certain systemic anti-cancer therapy agents was based on patient's weight in specific contexts.	(8/82) (173, 176, 180, 187, 188, 209, 234, 238)
Age	Each age or age band had specific dose for intrathecal therapy	(14/82) (174, 193, 194, 201, 206, 214, 221, 229, 230, 232-234, 240, 241)
Supplementary medicines		
Body surface area	Dosing of folinic acid (174, 178, 193, 225, 234) and mesna (234) Dosing of G-CSF (193, 212, 216, 226) Dosing of allopurinol (174, 200) Dosing of ciprofloxacin (243) Dosing of co-trimoxazole (202)	(11/82) (174, 178, 193, 200, 202, 212, 216, 225, 226, 234, 243)
Weight	Dosing of voriconazole (212, 243), fluconazole (175), itraconazole (212), and micafungin (243) Dosing of granulocyte colony stimulating factor (193, 216, 226) Dosing of allopurinol (200, 232) and rasburicase (200) Dosing of methylprednisolone for SACT toxicity (216) Dosing of cefepime (215) Dosing of antithrombin (181) Dosing of dapsone and pentamidine (202)	(11/82) (175, 181, 193, 200, 202, 212, 215, 216, 226, 232, 243)
Age	Each group of patients has specific dosing for folinic acid (233)	(1/82) (233)

3.5.5.3 Drug licencing

In comparison to the majority of the studies, three studies (3.7%) referred to the use of licensed drugs (168, 171, 238). Tisagenlecleucel was approved by the FDA for r/r ALL cases (173). The approval of imatinib provides an alternative to HSCT in paediatric patients who have CML (176). Micafungin, on the other hand, was approved across Europe for the prevention of fungal invasion in paediatric patients whenever performing HSCT is expected. It is also an approved option for persistent neutropenia (10 days and more) (243). No information on off-label and unlicensed use of medicines had been reported in the included studies.

3.5.5.4 Concurrent radiotherapy

Radiotherapy was also integrated into the therapeutic pharmacological plans for paediatric patients with haematological malignancies. Total body irradiation (TBI) was one of the utilised radiotherapy modalities in NHL (189), Philadelphia chromosome-positive acute lymphoblastic leukaemia (Ph+ ALL) (239), AML (183), or for all malignancies except HL (194). In HSCT, it formed the basis of TBI-based conditioning regimens (187, 188, 213, 244). Involved-field radiation therapy (IFRT) was used for patients with HL in eleven studies (13.4%) (182, 190, 196, 199, 204, 210, 224, 231, 248, 249, 251). IFRT was mainly given in conjugation with ABVD (182, 190, 199, 204, 210, 224, 248, 249, 251). The implantation of IFRT was for all patients (190, 204, 210) or for cases with bulk status (190, 204, 210), or for those with either partial response (251) or r/r response (224). Radiotherapy was mentioned in one study (1.2%) (218) without any specifications. Local irradiation was also used in one study (1.2%) on HSCT (216). Application of cranial irradiation was seen in twelve studies (14.6%) on ALL (197, 201, 227, 233, 241, 242, 245, 247), NHL (186, 189, 230), and haematological malignancies (194). Cranial irradiation was mostly directed for patients with CNS disease (186, 197, 201, 227, 233, 241, 242, 245, 247) or patients with T-cell subcategory (197, 227, 241, 242, 245, 247).

3.5.5.5 Ethical approval and consent form in the collected articles

Obtaining approval from the relevant boards and committees to conduct the studies was documented in 62 studies (75.6%) (170-173, 176-179, 181-191, 193-234, 251). Informed consent forms were also requested before the extraction of patients' data

for scientific research purposes according to 19 studies (23.2%) (170, 192, 196, 198, 200, 202, 206, 211, 214, 217, 219, 222, 226, 228, 229, 232, 235, 240, 243).

3.5.6 Results of critical appraisal assessment

The scores of the quality assessment ranged from one to seven (Table 3.11). Fifty-seven studies (69.5%) had quality score between 2 to 5. It was noted that the strategies to address incomplete follow-up were mostly unclear (score=0) across the included studies. The final synthesis included all studies given that results of critical appraisal of scoping review's studies are not a prerequisite for their inclusion in the data analysis (165). Table S3.16, Appendix 1 provides the full details. Critical appraisal of articles depends on the reviewers' judgments (253) and judgments can be subjective (254); this may explain the low agreement percent of the 10% validation at this stage.

Table 3.11 Summary of critical appraisal scores

Score	1	2	3	4	5	6	7
Number of cohort studies (n=80)	8 (9.8%)	10 (12.2%)	13 (15.9%)	13 (15.9%)	21 (25.6%)	8 (9.8%)	7 (8.5%)
Number of cross-sectional studies (n=2)						1 (1.2%)	1 (1.2%)

NB: Low score for the critical appraisal suggests low quality of the relevant study and reflects high risk of bias, and vice versa.

3.5.7 The main reported limitations of the included studies

According to the authors of the included articles, the retrospective design of studies (34, 41.5%) (171, 173, 175, 178, 181, 185-188, 196, 199, 202-204, 211, 213, 215, 216, 218-223, 230-235, 238, 242, 247, 251) and the low number of recruited patients (n=22, 26.8%) (173, 177, 178, 183, 186, 191, 193, 195, 197, 200, 211, 215, 216, 218, 219, 222, 230, 232-234, 239, 249) were the two main limitations of the conducted studies.

3.6 Discussion

To the best of my knowledge, this is the first comprehensive review of the pharmacological treatment of paediatric haematological malignancies in routine practice from the perspective of observational investigations. The scope of this review was not confined to medicines administered to stop or mitigate the abnormal infiltrations of cancer cells; it also delineated the medicine-based management of other symptoms and side effects. Seventy-four supplementary medicines, 50 SACT agents, and five corticosteroids were reported by the present work. SACT agents of different cytotoxic mechanisms with or without corticosteroids were utilised to manage paediatric haematological malignancies. Each malignancy was managed by different combinations of SACT $\pm$ corticosteroids, according to the review findings. Combining medicines might slow the drug-induced resistance (255) and decrease the doses of drugs without mitigating the efficacy (256). The latter action may reduce the risk of undesired drug-related toxicity (256).

Interestingly, the highest number of included observation-based studies belonged to institutions located in Asia. With regard to number of studies, India was at the forefront. The low number of trials on paediatric oncology in Asia (257) might explain the interest of the researchers in conducting non-interventional studies to describe the applied treatment for Asian paediatric populations with cancer. The focus on conducting interventional trials rather than observational studies to examine the medicine use in paediatric cancers (258) probably explains the lower observational research in Western countries compared to Eastern countries (i.e. Asian countries) in this review. The male predominance in the majority of studies was documented. This trend is, perhaps, due to higher estimated 5-year prevalence of lymphoma and leukaemia in male children (259).

3.6.1 Systemic anti-cancer therapy (SACT) $\pm$ corticosteroids

SACT was primarily administered invasively (e.g. intravenously and intrathecally). Through the intravenous route of administration, SACT could be delivered directly to the circulatory system and therefore promotes rapid actions (260). The intrathecal administration of SACT overcomes the semi-permeability of the blood-brain barrier (BBB) and ensures the delivery of medicines to the CNS with limited systemic toxicity (261). The invasive administration of SACT $\pm$ corticosteroids might demand skilful

staffs and extra sterility precautions (262) and instigate inconvenience (261). It would be valuable to investigate the drawbacks of delivering SACT agents to children with haematological malignancies, focusing on potential concerns of children and needs of healthcare providers.

Conventional chemotherapy was the mainstay of the management of paediatric haematological malignancies worldwide. This finding is in accordance with the literature which stressed the indispensable role of the conventional chemotherapy in paediatric oncology area (263). Unexpectedly, the use of other SACT forms such as Chimeric Antigen Receptor T-cell therapy (CAR-T) and targeted therapy was less common compared to conventional chemotherapy in this review. Certain factors such as licencing regulations influenced the prescribing of other SACT forms. The drug licencing of tisagenlecleucel by the relevant regulatory body supported its use for r/r cases within clinical practice (173). Yet, the rationale of utilising brentuximab for r/r cases was not stated by the authors (224). The use of imatinib – a TKI – for CML and Ph+ ALL can be explained by the presence of an abnormal mutation, Philadelphia chromosome, that provokes the production of different variants of the same aberrant kinase in these malignancies. Of note, the promising outcomes of prescribing EAALs for other tumours (i.e. solid tumours) and financial status of patient's family promoted their application for haematological malignancies (222). This review showed the limited use of other SACT forms for r/r cases in haematology. In contrast to these findings, the involvement of other SACT forms is relatively more common in the treatment of r/r cases with various solid malignancies, according to a systematic review published in 2022 (264).

The review highlighted that prescribers favoured an intensive treatment approach, consisting of several phases, for the management of paediatric ALL. The augmented therapeutic effect of using combinations of SACT in treatment phases has been documented approximately six decades ago (265). The application of therapeutic combinations in a few phases ensures the cumulative recovery by the elimination of any residual leukemic cells. Notably, the improvement of survival has been documented in parallel with the application of this intensive approach. To cite an example, the 5-year survival has reached more than 80% for children treated with paediatric-specific protocols at the beginning of the 21st century (266).

In this review, protocols of previous clinical trials were the backbone of the given treatment. Studies from Asia instituted modified versions of clinical trial protocols (e.g. UK-ALL) to treat patients with ALL. Three Chinese institutions showed the use of a Chinese protocol to treat patients (192, 235, 236); one of these, for example, reported the omission of mercaptopurine (6-MP) which was administered along with MTX to consolidate the treatment and replacement of 6-MP with thioguanine compared to another (236). The justification of this practice was not mentioned by the authors (236). In India, modified versions of BFM and UK-ALL were followed. In one study, the institution had made some modifications on UK-ALL to “de-escalate” the treatment for all patients through reducing the number of treatment phases. This process of simplifying was done to reduce the predisposition of toxicity and maintain the effectiveness of treatment at the same time. The absence of enough supportive care to manage the potential toxicity of the original UK-ALL protocol prompted the institution to make these modifications (201). In Pakistan, studies used modified versions of BFM with varying doses of specific agents of SACT. The Iraq-based study showed the treatment of patients over a long period (17 years) and the adoption of modified versions of UK-ALL protocols. The earlier two protocols had only one difference in the dose of asparaginase. The latest version was, however, distinguished by a lower number of intensification phases and the absence of interim phases (174). In Europe, each of the identified Turkish studies in this review had shown following modified version BFM protocol. One of these showed the use of vincristine as an alternative to vindesine owing to its availability.

The SACT agents used for AML varied among institutions internationally and regionally. For example, the two Chinese studies published in 2020 and 2021 treated AML using different SACT agents. Although it was not the latest study (published in 2020), one of the aforementioned Chinese studies indicated the use of EAALs for some patients which was not reported in other AML-targeted studies globally. This might be because this type of treatment is generally directed to patients with solid tumours (222). The ultimate goal of incorporating EAALs in the treatment was to mitigate the incidence of relapse (222). Two induction regimens were adopted by the Chinese institution in the second study; the low-intensity induction was preferred in patients with other complications (e.g. infection) or to prevent the treatment dropout of patients because of socioeconomic reasons (226). The use of low-intensity treatment in Kenya aimed to reduce the emergent toxicity in the lack of optimal

supportive care (232). Another middle-income country (Pakistan) studied the possibility of omitting etoposide from the induction phase since it provided no additional benefits on survival based on the study's results (217).

The ABVD regimen served as the basis of the childhood HL treatment in our review. The use of vincristine, etoposide, prednisolone/prednisone, doxorubicin (OEPA) and cyclophosphamide, vincristine, prednisolone, dacarbazine (COPDAC) regimens was to overcome the long-term toxicities on body systems (e.g. cardiovascular), compared to the ABVD regimen (231). Similarly, the lower health complications of the vinblastine, bleomycin, VP16 (etoposide), prednisone (VBVP) regimen also supported its use for low risk groups (196). On the other hand, the latter study indicated following more intense treatment to treat a higher risk group (196). The use of cyclophosphamide, vincristine, procarbazine, prednisone/ prednisolone (COPP) was to intensify the provided treatment for patients with bulky disease (251). Cost and availability of SACT played a role in the determination of the used regimen according to an identified study from South Africa (182). The review illustrated the treatment of different variants of BL (endemic BL, immunodeficiency -associated BL, and post-transplant BL). Findings revealed that patients with these variants were treated differently. In Kenya, the low number of SACT agents in the treatment of epidemic BL might be due to the poor infrastructures to manage possible toxicities since the authors emphasised the importance of the appropriate dosing of SACT to diminish the impact of toxicities (191). It is worth mentioning that the endemic variant of BL is predominant among children residing in countries of equatorial Africa (191). The treatment of HIV-positive patients with BL was generally different because of the concern over toxicities of regimens given for HIV-negative patients with BL. However, the authors indicated the use of regimens given for HIV-negative patients in case of HIV diagnosis among patients with BL assuming no high toxicities or drug-drug interactions were expected. The latter practice was due to less effectiveness of the HIV-negative regimens for cases involving dissemination to other organs (184). According to post-transplant BL, the study demonstrated the heterogeneity of provided treatment for this variant of BL. The rationale for this variation, according to the authors, could not be specified since each institution had its own preferred treatment (223). To deeply understand the differences of the provided treatment for these three types of BL, further investigations are required.

3.6.2 Non-oncological medicines

This review identified a variety of troublesome complications secondary to cancer and/or its management. Thus, and in line with anticipations, the review's findings acknowledged various supplementary medicines. Supplementary medicines were used therapeutically and/or prophylactically to control the developing short- /long-term side effects and symptoms.

The findings on non-oncological medicines showed that the included studies (n=25, 30.5%) apparently focused on the pharmacological management of infections in paediatric haematological malignancies. Infections contribute to death in children with cancer including children who are diagnosed with haematological malignancies (267, 268). The review markedly highlighted the management of respiratory infections, perhaps due to the compromising of lung function through the treatment course of cancer (269). Broad-spectrum antibiotics were the empirical treatment for febrile neutropenia, according to the present review. The justification of using broad-spectrum antibiotics was indicated in one study (1.2%) and was the high-rate mortality of the developing infections (63). Among various antibiotic families, cephalosporins were the drug of choice to prevent febrile neutropenia. The presence of a range of options with broad coverage of bacteria (270), well tolerability (271), and low incidence of toxicity (272) might contribute to the selection of this family. Consistently, paediatric patients take cephalosporin prophylaxis in the course of other procedures, such as surgical procedures. Paediatric patients planned for surgery (e.g. cardio, genitourinary) primarily received cefazolin – a cephalosporin – (273-278) as a prophylactic antibiotic (273, 274). The use of fluoroquinolones was noticed in the context of afebrile neutropenia in form of ciprofloxacin. In fact, the safety profile of ciprofloxacin is better than other fluoroquinolones in the paediatric field (279). Infection with PCP was mitigated through the administration of co-trimoxazole or other alternatives (i.e. dapsone, pentamidine, and atovaquone) in two studies (2.4%) (202, 215). This is consistent with the findings of a recent review (2023) on PCP in children diagnosed with cancer (280). The underlying reason for the use of alternatives (i.e. dapsone) in this review was the development of cotrimoxazole-related ethnic neutropenia (202). Findings indicated that the prescription of triazoles (e.g. voriconazole and itraconazole) and echinocandins (e.g. caspofungin and micafungin) were higher in the clinical settings of high-income countries (i.e. Taiwan and Saudi

Arabia) (56, 89). A global survey published in 2021, intended to characterise the antifungal prescribing pattern in children (281), also documented the widespread use of triazoles in high-income countries. The survey also highlighted that fluconazole was the most-used antifungal agent for prophylactic purposes across the world, especially in low-income countries, in agreement with our findings. This review also summarised the provided medicines to mitigate the consequences of TLS. The selection between febuxostat and allopurinol, which belong to the same hypouricemic class, depended on the preference of the physician but no rationale was mentioned regarding the use of rasburicase (200). Prescribing rasburicase after previous exposure to allopurinol or febuxostat might be due to the inadequate response to these agents (282).

3.6.3 Other highlighted aspects

Other relevant information was extracted to provide further details on drug licencing, patient's characteristics that affected dosing, and prescribers.

Besides no statements on off-label use of medicines, there was a lack of statements regarding the licencing of medicines in the retrieved articles. A systematic review reported the prevalence of unlicensed use of medicines for children in the primary care setting (283). The literature also documented the off-label and unlicensed use of anti-cancer agents in paediatric oncology wards (284). Moreover, the off-label and unlicensed practice is prevalent while treating children and covers certain non-oncological medicines such as antibiotics and antiemetics (158). Future quantitative studies would be beneficial to examine and compare the extent of using licensed and unlicensed medicines within oncology facilities across the globe.

The doses of SACT agents were mainly tailored based on the body surface area of patients. This individualisation of doses is essential to attain the effectiveness without reaching the toxic level of anti-cancer agents, considering the low therapeutic index of agents such as chemotherapeutic agents (285). The decision-making in the cancer field might embody different healthcare professionals in what is called multidisciplinary teams (286). Physicians were in charge of prescribing medicines, although this was explicitly reported in only two studies (2.4%) in this review.

The majority of studies (n=62, 75.6%) had obtained approval from the relevant ethics committee to conduct these observational studies. In contrast, the number of studies

that had considered attaining consent forms from relevant stakeholders was low (n=19, 23.2%). Obtaining consent from children or their guardians builds trust and shows respect to participant's autonomy (287). Getting consent from the study participants also safeguards researchers from any legal repercussions (288). Aspects including following the ethical principles which regulate the conduction of observational studies targeting children in particular and the adherence to these principles worldwide might be valuable to investigate. Such investigations may add additional knowledge to the ethics field. Another interesting issue to investigate would be the age at which children could decide whether to participate in a scientific study or not.

3.6.4 Limitations and strengths of the scoping review

The three strengths of this review comprised: (a) capturing all medicines that were given to paediatric patients, which contributed to the holistic understanding of the area of interest and made this review comprehensive; (b) relying on a robust methodological framework which minimised researcher bias; and (c) placing no geographical limitations which provided a broad global scope. Contrarily, the review had a number of limitations. The main limitation was that this review did not aim to investigate treatment outcomes (e.g. survival outcomes) of prescribing oncological and non-oncological medicines, given that the aim of this review was to summarise the prescribed medicines considering time constraints. Another considerable limitation was the inclusion of the articles from the last ten years from the date of running the search on the selected electronic databases. However, the evidence will not have considerably changed, therefore findings remain of relevance. Additionally, the review excluded articles written in languages other than English because of limited translation resources. As a result, data of some relevant non-English articles might have been overlooked (language bias). Moreover, the exclusion of interventional studies limited the investigation in clinical trial settings where paediatric patients might receive treatment.

3.7 Conclusion

The main purpose of this scoping review was to reflect on the real-world pharmacological practice for children with haematological malignancies globally based on the synthesis of observational studies' findings. Combinations of oncological

and non-oncological medicines were required to tackle cancer and coexisting symptoms and side effects. The treatment of each paediatric haematological malignancy was not standardised across the world, perhaps due to reasons such as variance in the existing infrastructures of supportive care. In-depth knowledge regarding the medicine use in supportive care area was deficient, hence more research is required to explore the medicine-based interventions for conditions like busulfan-induced seizures in actual clinical practice.

Chapter 4 Overview of Scottish paediatric oncology care

This chapter is intended to give general insights on the nation-wide vision for the management of children with cancer and the current treatment basis in Scotland. Chapter 4 also provides a brief overview of the existing oncology centres and sheds light on types of prescribers and their roles. Therefore, this chapter gives some background on the context of Scottish paediatric oncology and, hence, the settings for the next two studies.

Approximately 8% of the UK's total population live in Scotland (5.5 million). Fourteen Scottish NHS health boards are accountable for improving citizens' health and delivering the required healthcare services. General taxes are the main funding source for the healthcare services in UK. Broadly speaking, the charge-free access to prevention, diagnosis, treatment, palliative care, and rehabilitation services is established "at the point of delivery" across UK. Figure 4.1 represents bodies that are involved in the provision of care Scotland-wide.

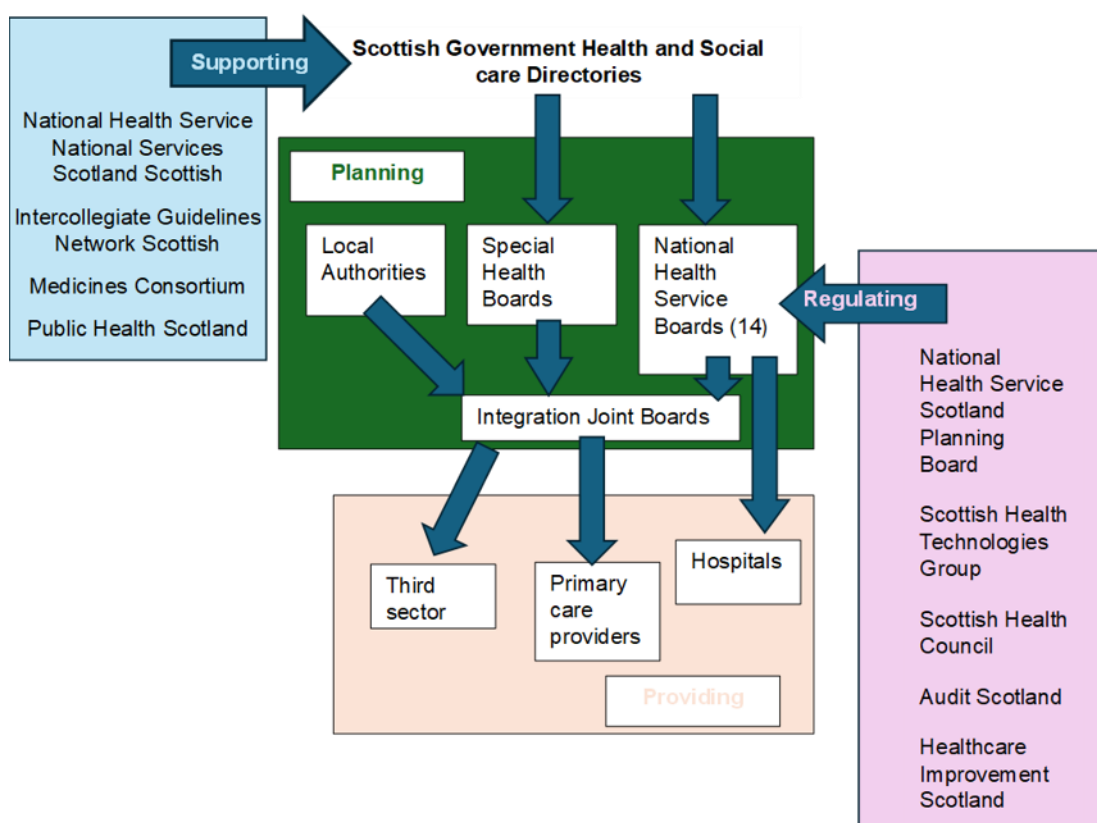


Figure 4.1 Structure of the NHS in Scotland.

NB: Information taken from (289, 290).

In relation to children-targeted programmes, networks, and services in Scotland, a child health programme is in place to ensure the provisioning of high-valued healthcare services not only to children but also to their guardians. This programme covers three children-relevant areas: (a) screening of specific health conditions; (b) immunisation of children; (c) health assessment, supporting parents, and health promotion along with responsible staff (291). Specific services or networks are also in place, supporting specific paediatric patients such as Child and Adolescent Mental Health Services (CAMHS) which supports patients (0-18 years) (292) who develop mental health conditions (293). Another example is the Managed Service Network for children and young people with cancer (CYPC) — established in 2011 (294). This national network facilitates inter- and intra- collaborations among NHS health boards and other institutions, in addition to achieving the vision of the Scottish government for providing patient-centred cancer services for paediatric populations (294).

4.1 The national vision for paediatric oncology (The cancer strategy for children and young people in Scotland 2021–2026)

The Scottish Government has taken strategic steps to improve the provision of care in the area of paediatric oncology over the past years. However, formulating the 2021-2026 Collaborative and Compassionate Cancer Care Strategy could be considered as a key milestone in this area. This scientific cancer strategy, managed by Managed Service Network, aims to improve the provided care for children, adolescent, and young adults with cancer. Some of the stated programmes in this strategy were part of the previous cancer plan (2016-2019). Services are intended to be safe, high-quality, and equitable. Authorities commit to implement the “Once for Scotland” strategy, which was launched post- coronavirus disease (COVID) (295), to achieve equity in the access to the treatment Scotland-wide. To deliver high-quality services, Managed Service Network emphasises the need of intertwining scientific evidence and clinical practice. Managed Service Network works in partnership with NHS health boards, multidisciplinary teams, patients/ their families, and third parties including educational institutions to ensure the provisioning of consistent and equitable care. Additionally, Managed Service Network also has contributions in clinical research with the purpose of improving the outcomes of Scotland-based childhood cancer treatment (296).

The 2021-2026 Scotland-wide strategy has set ten ambitions, contributing toward the provision of optimal care for paediatric patients with cancer in addition to enhancing their experiences (296):

1. Maximizing the improvement of treatment outcomes through employing of rigorous diagnosis and taking evidence-based treatment decision.
2. Delivering post-treatment care services (e.g. health surveillance and psychological care) to all paediatric patients.
3. Ensuring that paediatric patients are receiving treatment safely and consistently following the approved treatment protocols.
4. Establishing appropriate age-oriented cancer services especially for patients aged 16-25 and facilitating the transition from paediatric to adult care system (survivorship care).
5. Developing of inclusive leaderships with other bodies at all levels to provide long-lasting and high-quality services.
6. Integration of the supportive care services like rehabilitation, nutritional support, and reablement into the entire service system.
7. Integration of round-the-clock nationwide palliative care services into the entire service system.
8. Developing a skilful medical workforce and promoting the multidisciplinary approach to fulfil the needs of paediatric patients.
9. Promoting sustainable and equitable opportunities for learning, training, and education across the constituent country.
10. Securing paediatric patients against any potential inequity in the access to the implemented high-quality services.

Sixty-two actions were set to achieve the former ten ambitions; each action is undertaken by one or more responsible bodies/managers including NHS health board medical directors, Managed Service Network, Scottish Government, Public Health Scotland (PHS), NHS health board allied health professionals (AHPs) directors,

Managed Service Network CYPC AHP lead, NHS health board psychology directors, Managed Service Network CYPC lead pharmacists, Managed Service Network CYPC lead nurses, NHS health board nurse directors, Managed Service Network CYPC national network manager, Managed Service Network CYPC teenage, and young adult (TYA) clinical lead. About 53% of actions target services that covered both paediatric patients and young adults concurrently (296).

4.2 Paediatric oncology treatment in Scotland

Broadly, paediatric patients with cancer can receive treatment within established clinical trials, similar to paediatric patients in other high-income countries (58). Despite the encouragement of the Scottish Government to participate in relevant clinical trials, not all paediatric patients are treated within trial settings (296). The low motivation and fear of participation in the clinical trials might explain the reluctance of children or their parents to involve in these trials.

Applying consistent cancer treatment is essential in the Scottish settings (296). According to the 2021-2026 strategy, nationally approved treatment protocols are in place to support the treatment of paediatric patients. The treatment is also in accordance with agreed protocols in the UK, including protocols of the Children's Cancer and Leukaemia Group (CCLG) (296). CCLG is a dedicated charity that sets the highest standards to upgrade the offered treatment for children with cancer and underpin research in the paediatric cancer landscape in the UK and Ireland (297). Clinical trial protocols and CCLG protocols might substitute clinical management guideline (CMG) / clinical management pathway (CMP), a plan that delineates the treatment journey of the patient, in paediatric cancer care. CMG/CMP are detailed guidance from the screening of cancer to the post-treatment follow-up designed for the involved healthcare providers to manage cancer cases (298). The treatment protocols are not the only required information for the treatment; relevant clinical data, which is collected at pre-determined points through a patient's journey, is fundamental as well (298).

Safety in the delivery of treatment to paediatric patients is also considered. The safe delivery of treatment should comply with the national standards which include the use of the Chemotherapy Electronic Prescribing and Administration Systems (CEPAS) (Chemocare). CEPAS are systems to prescribe and approve the provided treatment (e.g. SACT) for patients with cancer, promoting prescribing in a safe manner.

Managed Service Network is working to establish a paediatric-specific CEPAS which would standardise the implemented practice Scotland-wide (296). Jointly with NHS National Services Scotland, Managed Service Network sets up a “Enhanced Cancer Registry” containing datasets on the diagnosis, treatment, and prognosis of children with cancer to support the outputs of research as well as practice and to promote the improvement of provided care (299).

Prescribing of SACT is performed through CEPAS in line with implemented policies. Paper-based prescriptions are rare in the Scottish settings and when used, prescriptions should follow policies and should be quickly accessible, when needed. All SACT prescriptions are verified by qualified registered pharmacists (296).

A published document from the cancer policy unit stated the development of regional and national guidelines and protocols on supportive treatments for indications such as emesis and TLS (298). CEPAS contains information on medicines of supportive care that can be administered along with SACT (300).

Conducting regular meetings during the course of a patient’s treatment set the ground for providing care in the paediatric oncology sector. The multidisciplinary team (MDT) is composed of clinical and non-clinical professionals including consultants, radiologists, specialised nurses, and social care professionals to manage cases with cancer. The decision for treatment is discussed within multidisciplinary meetings which are conducted regularly. In Scotland, eight types of multidisciplinary meetings are created to maintain the collaboration in assessing and treating cases with cancer. It could be regional or national, on a weekly or monthly basis. The type of the malignancy influences the frequency and level of meetings (e.g. national). Two types of the multidisciplinary meetings (i.e. relapse multidisciplinary meetings and multidisciplinary meetings of UK national advisory panels) involve practitioners from England and Northern Ireland in addition to practitioners from Scotland. Mortality and morbidity review meetings allow sharing of lessons learned and discussion of clinical cases with wider audiences of clinicians. Based on these peer-review meetings, suggestions for potential amendments to the recommended treatment can be made to improve practice (296). Practitioners in these meetings share examples of good practice and review the developing adverse effects their patients encountered at the respective centres. These shared experiences inform routine clinical practice (301).

4.3 Overview of the oncology centres for paediatric patients with cancer in Scotland

Twenty-one centres across the UK and Northern Ireland offer treatment for paediatric patients with cancer. Three out of these 21 centres are based in Scotland. Table 4.1 depicts some information on the three specialised centres in Scotland. The national authorities launched shared care centres across Scotland, and thus, paediatric patients can receive some treatment in units (clinics) at nearby local hospitals. The nearest specialised hospital guides the treatment in each unit. This mitigates the concerns over regularly having to travel long distances to receive the treatment. These units are called Paediatric Oncology Shared Care Units (POSCU) (302).

Table 4.1 Information on childhood cancer-specialised centres in Scotland

Principal centre name	Ward name	Served areas	Responsible health board
Glasgow Royal Hospital for Children	Ward 2A Schiehallion	East Dunbartonshire, East Renfrewshire, Glasgow City, Inverclyde, Renfrewshire, West Dunbartonshire,	National Health Service Greater Glasgow and Clyde
Edinburgh Royal Hospital for Children	Ward 2	South East Scotland, including Edinburgh, East Lothian, West Lothian, and Midlothian	National Health Service Lothian
Royal Aberdeen Children's Hospital	114	Tayside, Shetland, and Orkney Islands	National Health Service Grampian

NB: Information taken from (303-305).

Figure 4.2 shows POSCU and principal centres across Scotland. The care in POSCU is administered at three levels 1,2,3 (302, 306):

1. Level 1 (lower services): Patients who feel indisposed because of any health issue refer to level 1. This level offers services such as blood and platelet transfusions and services to mitigate treatment-related issues.
2. Level 2: This level provides the services of level 1 along with day-care chemotherapy.

3. Level 3 (higher services): This level provides the services of level 1 and 2. Patients can receive extended infusions of chemotherapy (24-hour infusion) and can stay overnight.

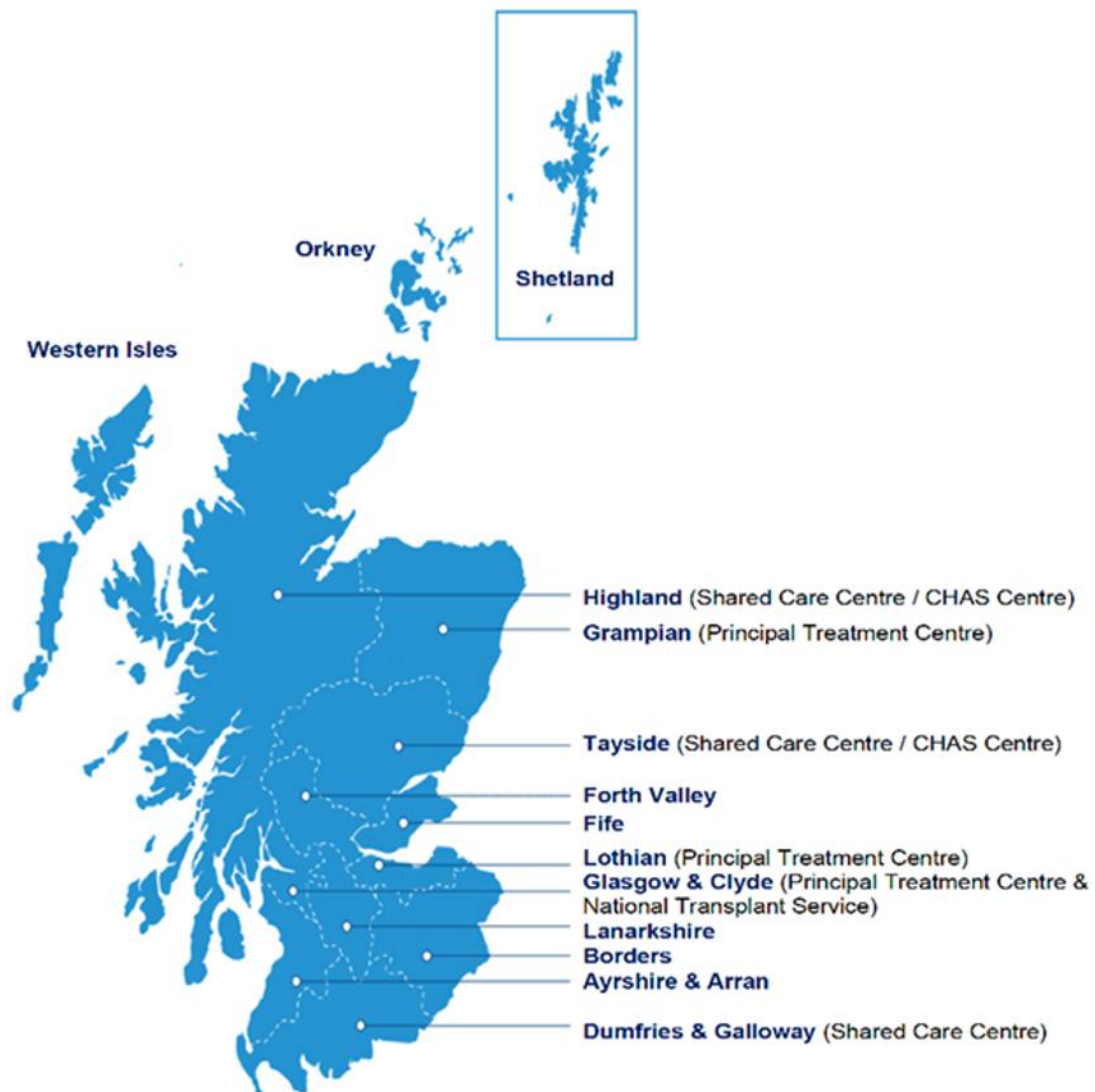


Figure 4.2 Principal and POSCU in Scotland

NB: Figure taken from Scottish Government, Open Government Licence v3.0 (296). POSCU= Paediatric Oncology Shared Care Units; CHAS = Children's Hospices across Scotland

Services of palliative and end of life care, respite (when a person other than the usual carer cares for the patient with cancer (307)), and hospice are operated by Children's Hospices across Scotland (CHAS) (296). National allograft stem cell transplant service is delivered to all ages, including children up to 18 years, in Glasgow (296, 308).

Overall, the staff involved in managing paediatric patients with cancer includes oncologists, haematologists, pharmacists, nurses, pathologists, dietitians, radiologists, radiographers, dietitians, psychologists, physiotherapists, and occupational therapists (302).

4.4 Overview of the prescribers and their competencies in Scotland

The majority of prescribers are physicians and dentists (309). In addition to their basic healthcare role, competent and well-trained pharmacists, nurses, and other practitioners (e.g. midwives and optometrists) are, however, eligible to prescribe medicines with the appropriate qualifications and within their area of expertise. Prescribing of medicines by pharmacists, nurses, etc. is known as non-medical prescribing. Non-medical prescribing can be classified as independent non-medical prescribing or supplementary non-medical prescribing. Independent prescribing of medicines involves both diagnosed and undiagnosed health conditions. Physicians and nurse/pharmacist prescribers can also prescribe controlled drugs and unlicensed medicines. In supplementary-type prescribing, the prescribing by non-medical prescribers is complemented by inputs from physicians/dentists. It worth noting that all pharmacists are independent prescribers in Scotland at present (309).

The prescribing role is an intrinsic part of the physician's and dentist's role. Meanwhile, being certified as an independent pharmacist prescriber requires holding a 4-year MPharm degree (310), completing the pharmacist independent prescriber course (310), and General Pharmaceutical Council (GPhC)-accredited registration (311). Recently, the MPharm curriculum has been amended to include courses on prescribing to support the learning process and to prepare MPharm students for prescribing roles (312). For nurse prescribers, registered nurses, who hold degree level (SCQF, level 9) at minimum (313), need to pass a V300 independent prescribing programme (314). This educational programme combines theoretical and practical learning modules (314).

On behalf of two bodies (i.e. National Institute for Health and Care (NICE) and Health Education England (309)), ten competencies (Figure 4.3) pertaining to two main domains form a framework developed by the Royal Pharmaceutical Society (RPS), the UK-wide professional association for pharmacy profession (315).

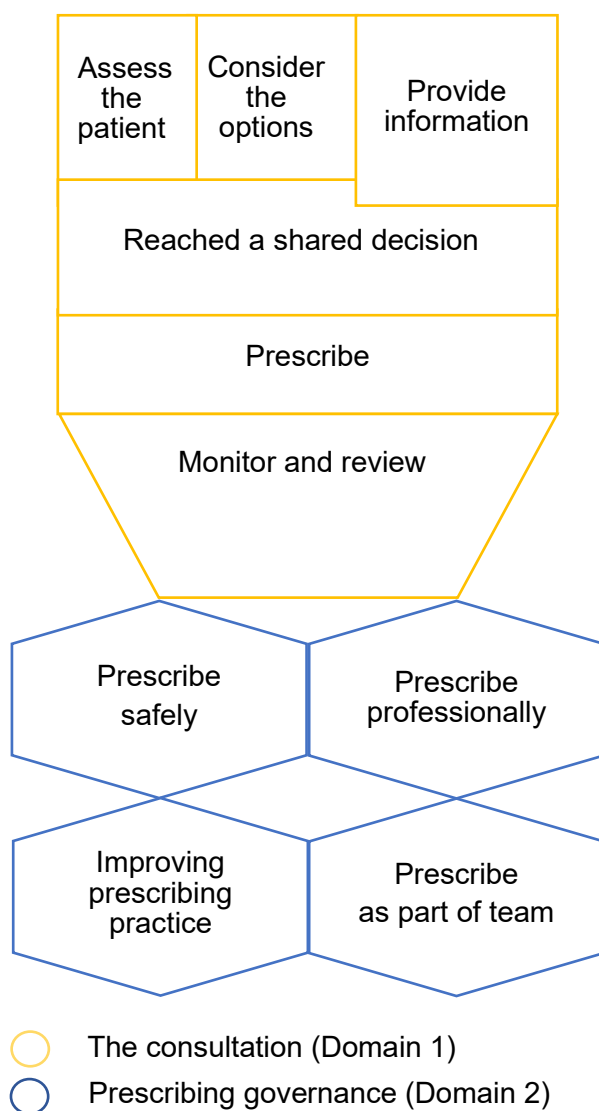


Figure 4.3 Competencies of prescribers according to Royal Pharmaceutical Society-developed framework

NB: Information taken from (309).

Competent prescribers for paediatric patients with cancer in the respective centres, following the 2021-2026 vision, are working to deliver high-quality care to patients in Scotland.

Chapter 5 Guidance for prescribing supplementary medicines for three clinical indications in paediatric oncology patients within Scottish oncology wards: A document analysis-based study

5.1 Introduction

Despite the improvement in survival of children with cancer over the past years, toxicities of novel (316, 317) and conventional (317) SACT agents are still concerning. Children with cancer who are exposed to the effective SACT agents can develop undesirable (negative) consequences along with desirable ones. The quality of life is impaired by the development of distressing side effects and symptoms (e.g. emesis) (318). Further, certain symptoms could hinder the physical development of children. For instance, nausea and vomiting are accompanied by decreasing in the patient's appetite which secondarily affects nutrition, and therefore may impede body development. The emerging toxicities increase the risk of morbidity (319) and mortality (e.g. infection-attributable mortality (318), TLS-attributable mortality (320), and SACT-attributable mortality (321)) in cases with cancer during the treatment course. Regarding the impact of toxicities on the implemented therapeutic plans, emerging toxicities (e.g. emesis) can trigger treatment cessation (318). In terms of treatment adherence, symptoms such as emesis might adversely affect the desire of children to continue the treatment (318). Without appropriate supportive care to diminish the impact of these toxicities, the health of paediatric patients can deteriorate.

Conditions (e.g. TLS and PCP) and symptoms (e.g. emesis) are critical health issues paediatric patients with cancer usually experience. Medicine-based interventions are required to prevent and/or treat such health issues.

Globally, it was estimated that emesis develops among up to 70% of children with cancer who are exposed to conventional chemotherapy (322). Emesis has a reported incidence of 54% in paediatric populations with haematological malignancies (320). Unfortunately, because of factors including inconsistency of adapted treatment and heterogeneity in populations with cancer, defining the incidence of TLS (323) in paediatric populations with cancer is insufficient. Generally, incidence of PCP is recorded at 43% prior to administering of prophylactic agents. The incidence of PCP in patients with ALL and NHL ranged between 22% and 45% (324).

The literature has underlined the significance of clinical information in the management of health conditions using medicines (325). Therefore, information sources are used to support the clinical decision making and prescribing process. The information sources for prescribing are constantly changing. For example, online

information sources have become part of prescribing practice of late (326). The used information varies globally due to differences in the acceptance of evidence and availability of sources (327). Considering the ongoing medical breakthroughs, and the subsequently generated medical knowledge, clinical practice is undoubtedly subject to change (328).

Cancer is the number one cause of deaths for children in Scotland (66). In addition, prescribing medicines for the management of diagnosed health conditions is a common intervention in NHS settings. This raises the demand for exploring the existing relevant documents (clinical guidelines, etc) used to support the prescribing in clinical practice. These documents potentially elicit information for the prescribing to support the delivery of high-quality care to patients. No study has previously described the potential documents/their content to prescribe medicines for the three aforementioned indications in Scotland. To my knowledge, there are also no previous studies that have explored this —specifically—in other countries.

5.2 Aim and Objectives

Aim

The aim of study was to explore the content of documents used to support the prescribing process for paediatric patients with cancer in Scotland. The focus of the study was directed toward three clinical indications, namely: emesis, TLS, and PCP prophylaxis.

Objectives

1. To identify documents potentially used in prescribing of medicines for paediatric patients with cancer in the three Scottish paediatric oncology centres for the treatment of the three aforementioned clinical indications.
2. To summarise the medicine-relevant content for the management of three indications in these documents.
3. To summarise the recommended pharmacological options to manage the three indications in Scottish oncology centres.

4. To identify the recommended first-, second-, and third- line treatment options to manage the three indications in Scottish oncology centres, if possible.

5.3 Definitions

Document is a broad, overarching term that describes sources containing information, including textual and audio-visual materials (329).

A drug formulary (drug list) is a directory of adopted medicines to manage health conditions in the therapeutic plans considering the private or public remuneration of these medicines (330, 331) . Drug formularies are updated regularly (332).

Clinical guidelines denote collections of evidence-informed recommendations on the potential choices to provide optimal care for a specific group of patients. The potential choices are evaluated considering the evidence on their harmful and beneficial effects on patient's health (333). Protocols are explicit schemes of relatively rigid instructions to manage a clinical condition or to conduct a research project (334). Accordingly, protocols and guidelines have the capability of reducing the variability of care given to patients with similar disease characteristics (334, 335).

The term "Standard Operating Procedures" (SOPs) in clinical practice reflects the regulatory procedures to guide clinical practitioners in executing specific clinical actions for each patient (336). Within clinical practice, it connects the evidence-based guidelines with real practice and accelerates the execution of required clinical actions (336).

5.4 Methods

The Checklist for Assessment and Reporting of Document Analysis (CARDA) (337) was the reporting guidance in this document analysis to ensure the reporting of results in a comprehensive way (Table S5.1, Appendix 2).

5.4.1 Document analysis as a chosen method

Document analysis is a method to review and investigate the available data in different electronic/printed documents (338). Document analysis is an iterative process of reading and interpreting of data (338).

Broad-covering (e.g. containing many scenarios) and exact (i.e. exact references and details of a particular area) data are provided in the documents (338). Furthermore, data within documents are “non-reactive” (338) (i.e. data do not react with surrounding circumstances through the process of data collection (339)) and stable (i.e. the presence of the researcher does not affect what is being investigated (338)).

Document analysis can be used to corroborate or verify the findings of other research studies. On the other hand, document analysis can be used as a “stand-alone” method to answer specific research questions on policies, organisations, and activities of interest or to generate new knowledge (338, 340).

In the present study, document analysis was the most appropriate approach because this approach provides the guidance for reviewing the existing written/textual evidence. The identification and characterisation of documents possibly used for guiding the prescribing of supplementary medicines, in turn, enhance the knowledge (338) on available documents/their content.

5.4.2 Inclusion and exclusion criteria

The final versions of existing (i.e. not created or written for the purpose of this study) evidence-based documents used in routine practice were analysed. Eligible documents to be reviewed were documents which were created to guide prescribing medicines for the three indications in paediatric oncology centres, and probably used in Scotland. Table 5.1 illustrates the inclusion and exclusion criteria of this study.

Table 5.1 Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Guidelines including treatment flow charts	Adult- or geriatric- specific information sources
Drug formularies	Newsletters
Standard Operating Procedures	Research studies
Relevant databases	Educational materials
Evidence-based summaries	Patient leaflets
Clinical protocols	Information sources specific to herbal medicines
	Information sources focusing on the prices of medicines
	Information sources focusing on health care services
	Stories on charity websites

5.4.3 Data collection

Data were collected through two approaches. The first approach was searching on Bing and Google to retrieve publicly available documents. The search was conducted using relevant terms and keywords by RA (Table S5.2, Appendix 2). It was conducted in September 2024 and re-run in February 2025. The second search was done to update the results of first search. Google is a search engine widely used across the world, including the UK (342). This search engine is open to all users to browse diverse sources on the searched topic (343). Bing, another search engine, was also searched because it is the default search engine for NHS health boards, and also a popular search engine in the UK. The individual websites of included NHS health boards were checked as well (Table S5.3, Appendix 2). The in-built search functionalities on the approached websites, links, and menus were used to search for further documents. Additionally, publicly unavailable documents were sought from the relevant NHS health boards (October 2024-January 2025). Contacts from centres were approached by TM to collect these documents. Follow-up emails were sent. NHS contacts were consulted to ascertain if there were additional uncollected documents prescribers usually use in the prescribing process. The reference lists of the retrieved documents were also reviewed to identify potential additional documents.

Assessing face validity (a pre-data collection test) to check the appearance, relevance, and accessibility of the instrument while measuring what is aimed to measure (344), usually done by experts or lay individuals (345), was considered. A list of potential documents was prepared and sent for validation to one of the practitioners in one of the included centres.

5.4.4 Data management

All publicly unavailable documents were stored in the University virtual cloud (OneDrive), a password-protected platform. Before analysis, the local unpublished documents were de-identified. The de-identification was done by removing the name of authors and respective organisation of the publicly unavailable documents. Each document in this study was assigned a specific number. This number was used in the

subsequent content analysis to refer to the document. No medicine-relevant content was redacted.

5.4.5 Data extraction

The categories of information to be extracted were developed in line with the process of rationale prescribing (346), ten principles of good prescribing (347), and the research questions. Additionally, the experiences of the research team members informed the extraction of the raw data. Table 5.2 illustrates the searched information (variables) for each medicine in each document and the reason behind searching for this information.

Table 5.2 Raw data for extraction

Information category	Reason
Dosage regimen (dose, interval, route of administration, and duration) Population of treatment Formulation(s) Drug dispensing Drug administration	These pieces of information are required to select medicines.
Monitoring measures	This piece of information is essential to know if the drug is working or not and to detect potential toxicities.
Precaution	Prescribers should be aware of any issue that might reduce the benefits and/or increase the risks of administering the selected medicine.
Drug allergy /Hypersensitivity	Prescribers should be aware of this information before prescribing medicine.
Response to toxicities	This piece of information is essential to know what to do if the treatment medicine-related problems occur.
Drug storage	Prescribers should consider medicine stability which is affected by the storage.
Drug disposal	Prescribers should be aware of the way to discard waste of medicines.

5.4.6 Data analysis

Figure 5.1 illustrates the steps that were followed to conduct the analysis; i.e. to characterise and group the collected documents, and to interpret the collected data. The main characteristics of the included documents were collated in a table. Documents were grouped based on clinical indication. Within each clinical indication,

documents were classified into one of three groups: international, national, and regional. The quality of documents was not evaluated.

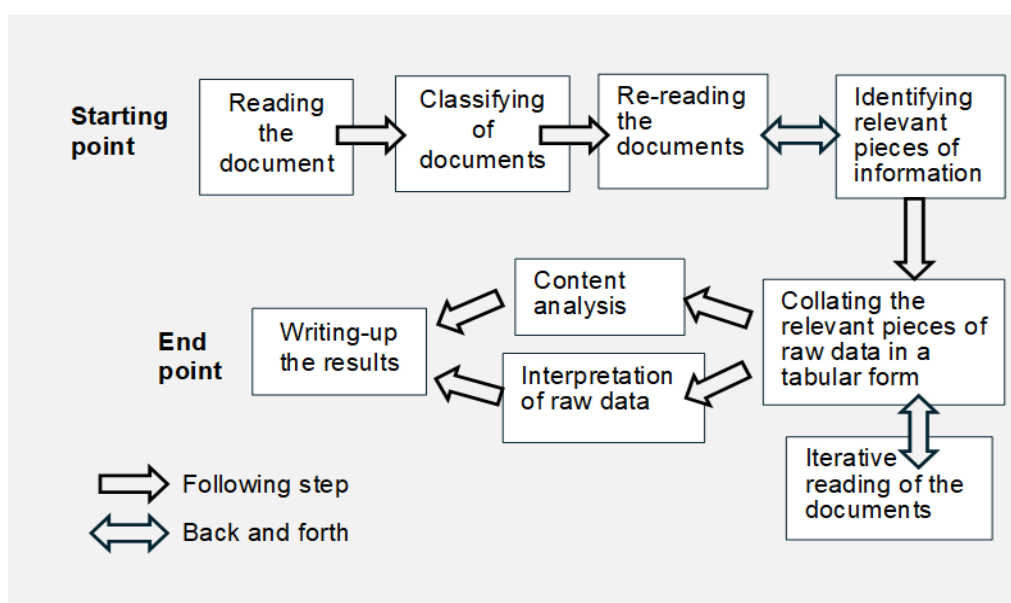


Figure 5.1 Steps of data analysis

The final tables of raw data were determined after familiarisation with the collected documents. Raw data in the collected sources was analysed using summative content analysis, guided by Hsieh and Shannon et al (348). After identifying the relevant content and collating the content in tabular form, the summative content analysis was applied. The summative content analysis involved counting the content of each category of medicine-relevant information of the respective medicine across documents. Afterword, the pattern was determined by highlighting the most and the least content identified across documents (348).

Information might be either fully or partially addressed; for example, the partial addressing of content on dosage regimen of a certain medicine means that for example the route of administration was not reported along with the recommended dose (Tables S5.4, S5.5, S5.6, Appendix 2).

5.5 Rigour and trustworthiness

The analysis was validated by a clinical practitioner LS, who routinely uses guidelines and formularies, to increase the rigour and trustworthiness and to decrease bias (349). The agreement level between RA and LS was 99.95%. Other approaches to

increase the trustworthiness and rigour were the debriefing discussions with TM and NW (350) and the use of the CARDA checklist.

5.6 Research team and reflexivity

As per the CARDA checklist, all members of the research team were pharmacists. RA was a doctoral student and held an MSc in Clinical Pharmacy whereas TM and NW were PhD holders and senior lecturers, and NW practiced as a community pharmacist. LS was a pharmacist at NHS Lothian. The research interests of team members included health policies/guidelines and health services in conjugation with the rationale use of medicines. Table S5.1, Appendix 2 provides more details.

5.7 Ethical considerations

Ethical approval was not applicable for this type of studies because – as outlined in section 5.4.2 – no human participants were involved, and no patient-relevant or sensitive data were collected in this study. The collected unpublished documents were de-identified by RA (5.4.4 section) given that some documents were publicly unavailable.

5.8 Patient and public involvement

Patients and the public were not recruited in this study. Further, this study did not contact patients/public or involve patient-specific data.

5.9 Results

5.9.1 Characteristics and description of identified documents

A total of 20 documents were identified at three governance levels (i.e. international (n=2), national (n=11), and regional (n=7)) (Table S5.7, Appendix 2). The documents consisted of seven clinical guidelines, six drug formularies, three SOPs, two evidence-based summaries, one database/book, and one previous clinical trial protocol. Documents targeted healthcare professionals including pharmacists, nurses, and physicians; however, two documents were developed for healthcare professionals working in specific settings (i.e. palliative care (document F) and primary care (document C)). Ten documents included guidance for the management of both adults and children whilst eight were children-specific. Nine documents were designed for

patients with cancer, of which two documents specified the types of cancer (i.e. solid malignancies (document S), specific types of haematological malignancies (document N)). The provisioning of documents to the target audience was done by one body or jointly (collaborations between two bodies or more). Professional bodies (e.g. RPS) were responsible for providing a third of the documents followed by NHS health boards which published a quarter of documents (Table S5.8, Appendix 2). Authors were mostly named in the regional documents, but these documents were de-identified. Authors were either individuals or group of individuals. The aim of developing the identified documents was not clearly specified in four documents. Most documents – excluding formularies and one SOP – included references. Citation was generally absent in the documents.

Table S5.7, Appendix 2 provides the individual characteristics of each document.

5.9.1.1 Document type-specific description

▲ Clinical guidelines (Documents J, K, M, O, Q, R, S)

The layouts of clinical guidelines across indications were generally different. The table of contents of guidelines was not highlighted in the beginning of most documents. Guidelines mostly included appendices. Interestingly, one national clinical guideline on PCP prophylaxis made specific recommendations for further research.

▲ Formularies (Documents A, B, F, G, H, I)

Although the British National Formulary (BNF) (document A) and the British National Formulary for Children (BNFC) (document B) had a similar layout, the layouts of regional formularies were different. Regional formularies were not fully synchronised with the regional guidelines with respect to medicines of interest.

▲ Standard Operating Procedures (Documents L, P, T)

The layouts of the identified SOPs were similar. Table of contents were absent in all SOPs. The identified SOPs mostly contained appendices. SOPs were the shortest documents.

5.9.2 The content of identified documents

All documents had missing medicine-relevant information on medicines of interest with varied extent. In certain documents, medicines of interest were not even mentioned. The most reported content was the recommended dose of medicines (n=104). Dosing of medicines of interest was mostly based on bands (ranges) across the identified documents, including age-band (i.e. age-bands were the most common bands), weight-band, or BSA-band (Table S5.9, Appendix 2). Even for the same medicine, more than one type of banding was presented for dosing across documents. For instance, dosing ondansetron, which was recommended for chemotherapy- and radiotherapy- induced emesis, was defined by age, weight, and BSA bands across documents. Apparently, not all documents defined the paediatric patients with bands (Table S5.9, Appendix 2). Further, doses were either fixed (regular) or individualised. Individualising of doses was achieved through multiplying doses by children's weight (kg) or BSA (meter square (m²)). The collected documents showed that the use of BSA in the calculation of doses was limited (Table S5.9, Appendix 2). Some documents also showed the shifting from individualisation of doses to prescribing fixed doses along with increasing age. The least frequently presented information for all medicines was on drug disposal (n=10), which was specifically mentioned in the Summary of Product Characteristics (SmPC).

Reviewing the documents identified a lack (e.g., limited information on drug storage) and some inconsistency (i.e., duration medicines administration) across documents. No document included all medicine-relevant information for all three groups of medicines. Limited information on drug storage (n=19) was highlighted for medicines across the documents. The recommended doses were inconsistent for one medicine prescribed for PCP prophylaxis, one for TLS, and eight for emesis between regional and national documents (Table S5.10, Appendix 2). Statements on the unlicensed use of some medicines or specific formulations were mainly mentioned in three documents (documents A, B, F). The addressed statements on unlicensed use of medicines could be for all children or for specific age groups (Table S5.11, Appendix 2). No conflicting information was shown for drug dispensing, monitoring measures, precautions, drug allergy, response to toxicities, and drug storage/disposal. Infrequent variation in the information of drug administration and drug duration was found for specific medicines. For example, in regional documents, cotrimoxazole was recommended for two days rather than three days.

5.9.2.1 Document-type specific content

▲ Clinical guidelines (Documents J, K, M, O, Q, R, S)

Clinical guidelines contained information on doses, dose banding, and routes of administration for most of the three groups of supplementary medicines (number of times this information documented for all medicines in the guidelines = 47). Clinical guidelines, regardless of the indication, contained more specific details on treatment duration whenever duration was reported. Content on precautions was present for specific medicines (e.g., aprepitant) from the three supportive care groups (number of times this information documented for the relevant medicines in the guidelines = 17). No content on drug allergy and hypersensitivity was reported.

▲ Formularies (Documents A, B, F, G, H, I)

The study demonstrated the obvious lack of medicine-relevant information in formularies. Formularies might be basic, containing information on available formulations at centres (i.e. regional formularies), or might cover further details (e.g. BNFC). The national documents (BNF (document A) and BNFC (document B)) did not name certain medications for the management of the conditions and symptoms of interest that were highlighted in other documents. Content on precaution for specific medicines from the three supportive care groups was present (number of times this information documented for the relevant medicines in formularies = 19).

▲ Standard Operating Procedures (Documents L, P, T)

SOPs included information on doses, dose banding, and routes of administration of most medicines studied in this study (number of times this information documented for all medicines in SOPs = 17). SOPs also highlighted more specific details on treatment duration in instances where treatment duration was reported. No content was present on drug allergy/hypersensitivity or response to toxicity.

▲ Summaries (Documents C, D)

The SmPC was the most comprehensive source of information with regard to medicine-relevant content for all indications. Whereas content on the drug disposal was specifically reported in SmPC (number of times this information documented for medicines in SmPC = 9), most information on the response to toxicity (number of

times this information documented for medicines in SmPC = 11) and drug storage (number of times this information documented for medicines in SmPC = 11) was provided by SmPC. For drug disposal, drug monographs in SmPC recommended the referral to local regulations regarding unused drug or drug waste. No specific details on steps to dispose medicines were offered by these monographs. Interestingly, the pharmaceutical brands of medicines for all indications were mentioned in SmPC. There was no paediatric-specific information about the use of medicines for the three health conditions in the Clinical Knowledge Summaries (CKS).

5.9.2.2 Content-specific highlights on medicines of interest

Information on drug dispensing (number of times this information documented = 48) and drug administration (number of times this information documented = 54) was highly reported for antiemetics. There were 40/48, 83.3% and 36/54, 66.7% mentions on the dispensing of antiemetics and administration of antiemetics, respectively. Limited information on drug dispensing and drug administration was documented for PCP medicines ((n=4/48, 8.3%) and (n=7/54, 13.0%)) and anti-TLS medicines ((n=4/48, 8.3%) and (n=11/54, 20.4%)). Of note, content on monitoring measures (number of times this information documented = 30) was highly reported for the two recommended medicines for TLS (number of times this information documented for the two medicines = 11/30, 36.6%) in TLS-guiding documents. Content on response to toxicities (number of times this information documented = 24) was reported for specific antiemetics (i.e. metoclopramide and chlorpromazine) (number of times this information documented for metoclopramide and chlorpromazine = 8/24, 33.3%).

5.9.3 Recommended medicines and treatment lines in identified documents

Figure 5.2 illustrates the list of recommended medicines and their number for the three clinical indications of interest. All medicines, except one, were not controlled drugs. The only controlled drug, drug that may cause addiction or may pose a risk of abuse, was nabilone (schedule 2). Drugs of schedule 2 are known for the high risk of abuse (351).

Emesis (15 recommended medicines)	<i>Pneumocystis</i> pneumonia prophylaxis (four recommended medicines)	Tumour lysis syndrome (two recommended medicines)
•Selective serotonin receptor (5-HT₃) 1- Granisetron 2- Ondansetron 3- Palonosetron •Anticholinergic 8- Hyoscine Hydrobromide •Neurokinin 1 receptor antagonist 4- Aprepitant 5- Fosaprepitant •Phenothiazine 6- Levomepromazine 7- Chlorpromazine •Antihistamine 9- Cyclizine •Atypical Antipsychotic 10- Olanzapine •Benzodiazepine 11- Lorazepam •Butyrophenone antipsychotic 12- Haloperidol •Cannabinoid 13- Nabilone •Corticosteroid 14- Dexamethasone •Dopamine antagonist 15- Metoclopramide	•Antiprotozoal 1- Atovaquone 2- Pentamidine •Sulfonamide/ Antifolate antibiotic 3- Co-Trimoxazole •Sulfone antibacterial 4- Dapsone	•Xanthine oxidase inhibitor 1- Allopurinol 2- Rasburicase

Figure 5.2 The recommended medicines for the three indications

The recommendations for emesis were intended to either treat diagnosed patients or prevent the development of emesis in at-risk cases. The study identified 15 antiemetics from eleven therapeutic classes for the management of emesis (Figure 5.2). The listed antiemetics varied among guidelines and SOPs at national and regional levels. For example, as illustrated in Table S5.4, Appendix 2, olanzapine and chlorpromazine were highlighted in only one national and one regional documents, respectively.

Table 5.3 illustrates, alphabetically, the clinical indications for medicines to manage emesis. Documents were largely focused on the management of emesis developed from chemotherapy. Limited information was provided to manage emesis developed from other stimuli such as opiate-induced emesis.

Table 5.4 defines the specific clinical indication for the pharmacological management in relation to CINV.

Table 5.3 The clinical indications of the recommended anti-emetics according to the documents

Anti-emetic (alphabetic- ascending order)	Medicine- induced N&V		Radiotherapy- induced nausea and vomiting	Anticipatory nausea and vomiting	Nausea and vomiting associated with raised intracranial pressure	Failure in the treatment	No information /No specific indication
	Chemotherapy- induced nausea and vomiting	Opiate- induced nausea and vomiting					
Aprepitant	B, D, E, F, I, K, L, M						A, C, G, H, J
Chlorpromazine	L						A, B, C, D, E, F, G, H, I, J, K
Cyclizine	M	K	K	M	K, M	F, L	A, B, C, D, E, G, H, I, J
Dexamethasone	F, J, K, L, M						A, B, C, D, E, G, H, I
Fosaprepitant	B, D, E, I, K, L, M						A, C, F, G, H
Granisetron	B, D, E, K, L, M						A, C, F, G, H, I, J
Haloperidol	L						A, B, C, D, E, F, G, H, I, G, K
Hyoscine Hydrobromide	K, L, M						A, B, C, D, E, F, G, H, I, J
Levomepromazine	K, L, M			L	M	L	A, B, C, D, E, F, G, H, I, J

Anti-emetic (alphabetic- ascending order)	Medicine- induced N&V		Radiotherapy- induced nausea and vomiting	Anticipatory nausea and vomiting	Nausea and vomiting associated with raised intracranial pressure	Failure in the treatment	No information /No specific indication
	Chemotherapy- induced nausea and vomiting	Opiate- induced nausea and vomiting					
Lorazepam	K, M		M	F, K, L, M			A, B, C, D, E, G, H, I, J
Metoclopramide	B, D, E, F, K, L, M					L	A, C, G, H, I, J
Nabilone	F, I, L, M			M		F, K	A, B, C, D, E, G, H, I, J
Olanzapine	K						A, B, C, D, E, F, G, H, J, L, M
Ondansetron	B, D, E, F, K, L, M		E, F				A, C, G, H, I, J
Palonosetron	D, E, K, L, M						A, B, C, F, G, H, I, J

NB: Letters refer to documents. A: British National Formulary (BNF), B: British National Formulary for Children (BNFC), C: Clinical Knowledge Summaries (CKS), D: Summary of product characteristics (SmPC), E: Martindale, F: Association for Paediatric Palliative Medicine (APPM) formulary, G: Regional formulary 1, H: Regional formulary 2, I : Regional formulary 3, J: International clinical guideline, K: Regional clinical guideline 1, L: Regional Standard Operating procedures (SOP), M: Regional clinical guideline 2.

Table 5.4 The clinical indication of the recommended anti-emetics for chemotherapy-induced nausea and vomiting (CINV) according to the documents

Anti-emetic (Alphabetic-ascending order)	Acute ¹	Acute ²	Delayed ¹	Delayed ²	Breakthrough Nausea and vomiting ¹	Refractory Chemotherapy-induced nausea and vomiting ¹	Nausea and vomiting associated with low emetic risk ²	Nausea and vomiting associated with moderately emetic risk ²	Nausea and vomiting associated with high emetic risk ²	Nausea and vomiting associated with very high emetic risk ²
	Chemotherapy-induced nausea and vomiting									
Aprepitant	K	M	K	M	K	K		B, D, E, F, I, K, M	B, D, E, F, I, K, L, M	K, L, M
Chlorpromazine										
Cyclizine					M	M				
Dexamethasone	K, M	J	K, M					L, M	F, J, L, M	L, M
Fosaprepitant	E, K		E, K					B, D, E, I	B, D, E, F, I, M	M
Granisetron	D, E, K, M									
Haloperidol										
Hyoscine Hydrobromide						K, M				
Levomepromazine	M		K, M		K, M	K, M, K, M		K, L, M	K, L, M	K, L, M
Lorazepam					K, M	K, M		M	M	M
Metoclopramide			M	B, D, E, F, K	M	K		M	L, M	L, M

Anti-emetic (Alphabetic- ascending order)	Acute ¹	Acute ²	Delayed ¹	Delayed ²	Breakthrough Nausea and vomiting ¹	Refractory Chemother apy- induced nausea and vomiting ¹	Nausea and vomiting associated with low emetic risk ²	Nausea and vomiting associated with moderately emetic risk ²	Nausea and vomiting associated with high emetic risk ²	Nausea and vomiting associated with very high emetic risk ²
Chemotherapy-induced nausea and vomiting										
Nabilone	M		K, M		M	K, L, M		K, M	K, M	K, M
Olanzapine	K		K		K			K	K	K
Ondansetron	M	K	M	K			K, L, M	K, L, M	K, L, M	I, J, K
Palonosetron	M	D, K	M	D, E, K	K, M	K, M		D, E, K, M	K, M	D, E, K, M

NB: Letters refer to documents. ¹ Medicines were administered to manage this type of emesis. ² Medicines were administered to prevent this type of emesis. A: British National Formulary (BNF), B: British National Formulary for Children (BNFC), C: Clinical Knowledge Summaries (CKS), D: Summary of product characteristics (SmPC), E: Martindale, F: Association for Paediatric Palliative Medicine (APPM) formulary, G: Regional formulary 1, H: Regional formulary 2, I : Regional formulary 3, J: International clinical guideline, K: Regional clinical guideline 1, L: Regional Standard Operating procedures (SOP), M: Regional clinical guideline 2.

Table 5.5 provides details on the treatment lines for the management of emesis with regard to emetogenicity of the received medicines in patients with cancer aged > 6 months. Table 5.6 provides aforementioned details for patients with cancer aged < 6 months. Texts of the estimated incidence of emesis (in %) of the emetogenicity categories (very high, high, moderate, low and minimal) were clearly included in the document of centre B. To cite an example, very high emetogenicity refers to regimens or medicines with emetogenic potential > 90%. As shown in Table 5.5 and Table 5.6, monotherapy was only recommended for cases with low emetogenicity. In all regional documents, no pharmacological intervention was recommended for minimal risk of emesis. Certain considerations were stated to inform the treatment of chemotherapy-induced emesis in patients with cancer such as child age. The recommendations on a regional level were not homogenous.

Table 5.5 Treatment lines of CINV for patients with cancer aged >6 months with regard to regional documents

Emetogenicity of provided anti-cancer therapy	Treatment lines	Centre AA	Centre BB	Centre CC
Very high	1 st line treatment ¹	Ondansetron + Dexamethasone ^{3,4} + Aprepitant OR Metoclopramide ⁵	Ondansetron + Dexamethasone ^{2,4,6} + Aprepitant ¹⁰ ± Levomepromazine	
	2 nd line treatment ^{1,9}	+ Levomepromazine	+ Levomepromazine Ondansetron ⇔ Palonosetron	
	3 rd line treatment ¹		+ Lorazepam OR Metoclopramide Administer granisetron as alternative 5 – HT3 receptor antagonist or nabilone ⁷	
High	1 st line treatment ¹	Ondansetron + Dexamethasone ^{3,4} OR	Ondansetron + Dexamethasone ^{2,4,6}	

Emetogenicity of provided anti-cancer therapy	Treatment lines	Centre AA	Centre BB	Centre CC
		Metoclopramide ⁵	+ Aprepitant ± Levomepromazine	
	2 nd line treatment ^{1,9}	+ Levomepromazine OR Aprepitant	+ Levomepromazine Ondansetron ↔ Palonosetron	
	3 rd line treatment ¹		+ Lorazepam OR Metoclopramide Consider granisetron as alternative 5 – HT3 receptor antagonist or nabilone ⁷	
Moderate	1 st line treatment ¹	Ondansetron ± Dexamethasone ^{3,4}	Ondansetron + Aprepitant ⁷ + Levomepromazine	
	2 nd line treatment ^{1,9}	+ Levomepromazine OR Dexamethasone ^{3,4}	+ Levomepromazine + Dexamethasone ^{2,4,6}	

Emetogenicity of provided anti-cancer therapy	Treatment lines	Centre AA	Centre BB	Centre CC
			Ondansetron ↔ Palonosetron	
	3 rd line treatment ¹		+ Lorazepam OR Metoclopramide Consider granisetron as alternative 5 – HT3 receptor antagonist or nabilone ⁷	
Low	1 st line treatment ¹	Ondansetron pro re nata	Ondansetron pro re nata	
	2 nd line treatment ^{1,9}	Ondansetron	Ondansetron	
	3 rd line treatment ¹			

NB: Centres AA, BB, CC are the three paediatric oncology centres. Centre C had no regional documents. ↔ indicates the change from ondansetron to palonosetron. ¹ Assuming no contradiction was documented to any of antiemetics; ² dexamethasone should be halved; ³ this antiemetic was not recommended for patients with leukaemia or lymphoma who received regimens included steroids; ⁴ this antiemetic was not recommended for the following groups: patients diagnosed with CNS tumours; patients receiving immunomodulatory therapy; patients receiving chemotherapy- or radiotherapy- based conditioning regimens; patients with prolonged profound neutropenia; ⁵ metoclopramide replaced dexamethasone or aprepitant in case of contradiction; ⁶ this antiemetic was not recommended for patients diagnosed brain tumour and osteosarcoma; ⁷ this medicine was added if patient was not on dexamethasone; ⁸ this intervention was applied for teenagers. ⁹ All the doses of medicines in the first line should be optimised. ¹⁰ Not given for patients with leukaemia or lymphoma who received ifosafamide-based therapeutic regimens. Pro re nata means as needed.

Table 5.6 Treatment lines of CINV for patients with cancer aged <6 months with the regard to regional documents

Emetogenicity of provided anti-cancer therapy	Treatment lines	Centre AA	Centre BB	Centre CC
Very high	1 st line treatment ¹	Ondansetron + Dexamethasone ^{3,4} + Levomepromazine	Ondansetron + Dexamethasone ^{4,6} ± Levomepromazine	
	2 nd line treatment ¹	-	+ Levomepromazine Ondansetron ↔ Palonosetron	
	3 rd line treatment ¹	-	+ Lorazepam OR Metoclopramide Consider granisetron as alternative 5 – HT3 receptor antagonist or nabilone ⁸	
High	1 st line treatment ¹	Same to patients > 6 months	Ondansetron + Dexamethasone ^{4,6} ± Levomepromazine	
	2 nd line treatment ¹		+ Levomepromazine Ondansetron	

Emetogenicity of provided anti-cancer therapy	Treatment lines	Centre AA	Centre BB	Centre CC
			↔ Palonosetron	
	3 rd line treatment ¹		+ Lorazepam OR Metoclopramide Consider granisetron as alternative 5 – HT3 receptor antagonist or nabilone ⁸	
Moderate	1 st line treatment ¹	Same to patients > 6 months	Ondansetron + Dexamethasone ^{4,6} ± Levomepromazine ³	
	2 nd line treatment ¹		Ondansetron ↔ Palonosetron± Levomepromazine [If not already on it]	
	3 rd line treatment ¹		+ Lorazepam OR Metoclopramide Consider granisetron as alternative 5 – HT3	

Emetogenicity of provided anti-cancer therapy	Treatment lines	Centre AA	Centre BB	Centre CC
			receptor antagonist or nabilone ⁸	
Low	1 st line treatment ¹	Same to patients > 6 months	Same to options for >6 month	
	2 nd line treatment ¹			
	3 rd line treatment ¹			

NB: Centres AA, BB, CC are the three paediatric oncology centres. Centre C had no regional documents. ⇔ indicates the change from ondansetron to palonosetron. ¹ Assuming no contradiction was documented to any of antiemetics; ² dexamethasone should be halved; ³ this antiemetic was not recommended for patients with leukaemia or lymphoma who received regimens included steroids; ⁴ this antiemetic was not recommended for the following groups: patients diagnosed with CNS tumours; patients receiving immunomodulatory therapy; patients receiving chemotherapy- or radiotherapy- based conditioning regimens; patients with prolonged profound neutropenia; ⁵ metoclopramide replaced dexamethasone or aprepitant in case of contradiction; ⁶ this antiemetic was not recommended for patients diagnosed brain tumour and osteosarcoma; ⁷ this medicine was added if patient was not on dexamethasone: ⁸ this intervention was applied for teenagers. ⁹ All the doses of medicines in the first line should be optimised.

Regarding PCP prophylaxis, the first line medication was co-trimoxazole. The use of one of the alternatives was recommended when the first line is intolerable. The selection of the alternative, according to documents, was done on a case-by-case basis considering the preference of the patient and the treating prescriber.

Recommendations were stated for the prevention and treatment of TLS. There were only two options for prophylaxis, one of which was also indicated for treatment of established TLS. The dual therapy of allopurinol and rasburicase should be avoided according to all documents. Table 5.7 illustrates the clinical indication (if reported) in documents. Whereas allopurinol was preferred for mild cases, rasburicase was preferred for high-risk cases. There was no content on the management of refractory cases of TLS.

Table 5.7 The clinical indications of the recommended medicines for the management of TLS

Medicine	No information	Prophylaxis for			Treatment
		mild to moderate risk cases	high-risk cases	Without specification	
Allopurinol	A, C, F, G, H, I	P		B, D, N, O, Q, R	D, E
Rasburicase	A, B, C, F, G, H		I, N, O, P, Q, R	D, E	D, E, I, O, P, Q, R

NB: Letters refer to documents. A: British National Formulary (BNF), B: British National Formulary for Children (BNFC), C: Clinical Knowledge Summaries (CKS), D: Summary of product characteristics (SmPC), E: Martindale, F: Association for Paediatric Palliative Medicine (APPM) formulary, G: Regional formulary 1, H: Regional formulary 2, I : Regional formulary 3, N: National clinical trial protocol, O: National clinical guideline, P: Regional Standard Operating procedures (SOP), Q: Regional clinical guideline 1, R: Regional clinical guideline 2, S: Regional clinical guideline 3, T: Regional Standard Operating procedures (SOP).

5.10 Discussion

The study is the first, to my knowledge, to investigate documents that might serve prescribers, who prescribe medicines for emesis with various stimuli, TLS, and PCP prophylaxis, in the context of paediatric cancer. The key highlights of this study: (a) potential prescribing-guiding documents were not limited to clinical guidelines; (b) the lack of reporting of certain statements such as statements on unlicensed use of medicines was noticed in all documents and the lack of reporting the use of certain medicines for the indications of interest in the identified documents; (c) the medicine-relevant content, except for doses, was broadly consistent, although inconsistency in the recommended doses between regional and national documents was shown particularly for antiemetics; and (d) the recommended pharmacological therapies for emesis were more complicated (i.e. regimens were more complicated) than that for TLS and PCP prophylaxis.

5.10.1 Multiple potential documents to inform prescribing in the three areas

The present study identified various potential documents to inform the prescribing for the clinical indications of interest. Interestingly, the practice of considering different sources is accepted and encouraged. The General Medical Council, which regulates the activities of physicians in the UK, stated that physicians who are in charge of prescribing should be familiar with BNF and BNFC and should consider nation-wide guidelines (352). Two reasons may explain the identification of various documents to inform clinical practice in this study (i.e. fast-updating process of documents and variable adopted regional recommendations). Information relevant to medicines is prone to evolving on a regular basis on account of perpetual advancements in the drug development landscape (353). Documents such as clinical guidelines are updated accordingly along with the emergence of new evidence (354). Hence, many documents may be created or modified, assuming the potential variations in the updating frequency, to provide the recent updates on pharmacological recommendations. Regionally, the development/updating of recommendations is informed by the available medicines/formulations on-site which may contribute to the development of many regional documents. In each NHS health board, the adoption of medicines is affected by the decision of the local Area Drug and Therapeutic Committee (ADTC) after obtaining acceptance from the Scottish Medicines

Consortium (355). Having multiple documents might provide the practitioners with multiple options at hand to support the prescribing practice. However, RA believes that unifying clinical guidelines and SOPs for the management of symptoms and health conditions of interest, at least across Scotland, would further facilitate the task of prescribing. Prescribing for children is already complex and burdensome on prescribers due to the overload of information etc. that might exist, thus improvements in the provision of prescribing documents might be valuable. These improvements may indirectly enhance the provision of high-quality and equitable care for children.

5.10.2 Missing content in identified documents

Missing information on certain medicines or certain aspects was present across documents. The absence of information on medicines of interest in CKS might be because these summaries were targeted towards healthcare professionals in the primary care settings (356). The British National Formulary for Children often suggested following local relevant protocols for certain medicines (e.g. rasburicase (357)) instead of providing prescribers with guiding information. In cases, the SmPC explained the lack of information by scarcity of evidence on clinical efficacy (e.g. atovaquone (358)). Regional formularies might be mainly developed for the prescribers to be familiar with available medicines/formulations and to provide options for therapeutic substitutions. As a consequence, a dearth of information on medicines was available in the regional formularies. According to the documents included in this study, not all medicines and their formulations were licensed for use in children. Generally, regional documents did not explicitly provide guidance on unlicensed use of medicines in this study. This finding confirmed the results of a cross-sectional study (2022) involving paediatric guidelines (359). The absence of written recommendations on the unlicensed use of medicines regionally may reflect one of two circumstances: (a) prescribers prescribe all medicines in a licensed way, (b) or they prescribe certain medicines in an unlicensed way without written references within regional documents. Future investigations may confirm the pattern of prescribing medicines and determine the degree of unlicensed use of medicines in paediatric Scottish care facilities.

5.10.3 Heterogeneity in the recommended doses

Study findings elucidated heterogeneity in the recommended doses of certain medicines, mostly for emesis. In line with the findings, an expert-led analysis from Germany (2023) on documents for the management of febrile neutropenia showed

variations in terms of recommended doses and other issues between national and regional documents (360). Different reasons might contribute to this heterogeneity: (a) limited paediatric data might make some institutions extrapolate dosing information for children from adult information using different models and calculations, resulting in heterogeneity in the recommended doses; (b) the adjustment of doses considering the regional practice or consensus might be linked to the variation in doses among institutions; and (c) the varied genetic profiles of paediatric populations might support making changes on doses to reduce the toxicities of medicines and to enhance their effectiveness. However, findings of the present study showed the inconsistency in the method of calculating the recommended doses, which likely contributed to this heterogeneity. Further in-depth studies could explore whether variations are necessary or appropriate for prescribing appropriately, taking into account that variations without supporting evidence might negatively impact the quality of care provided in clinical practice (361).

5.10.4 Medicines in the identified documents

Interestingly, medicines from many different therapeutic classes were recommended for emesis. This research covered emesis developed from any stimulus which might explain this wide range of classes. Anti-emetics were prescribed in combinations for CINV, in line with American Society of Clinical Oncology (ASCO) guidelines (362). High prevalence of CINV might contribute to the substantial focus on this type across documents. The treatment of CINV was different across regions. In line with our findings, authors of a review reported that there is no standardisation of the treatment of CINV in children (318). Same options for TLS were recommended across guidelines. A variation in the guidelines on TLS for children (e.g. some consider rasburicase in the TLS management) was reported in a study conducted to understand the management of TLS in the US (363). Notably, the study revealed information on nabilone, the only controlled drug reported in this study, that might reflect its use in the paediatric oncology wards which requires additional cautions. It is noteworthy to highlight that not all prescribers prescribe controlled medicines in Scotland (355).

5.10.5 Recommendations to improve the prescribing practice

Establishing a forum between regulatory bodies of national formularies and NHS practitioners including prescribers would meet practitioner's needs regarding

medicine-relevant information. This action would be of significance since regulatory bodies would have the opportunity to address and understand the needs and priorities of prescribers across the UK. The content on radiotherapy- and opiate- induced emesis was less reported compared to CINV, according to the findings. It would be of importance to consolidate the guidance on the management of these non-CINV emesis given that these kinds of emesis can develop as discussed in Chapter 1, by providing more textual evidence on the management of these types.

5.10.6 Strengths and Limitations

The major strength of this study lies in the inclusion of published and unpublished documents. Further, the search for publicly available documents was done on two search engines. Additionally, assuring the face validity of the potential documents was also a potential strength. The validation of data extraction and continuous debriefing with TM and NW represented a strength in this study.

Selectivity bias might arise provided that the adoption of specific documents is affected by the institution's principles and policies (338). The study only focused on medicine-relevant information that might reinforce the prescribing decisions of medicines. This might not give information on other forms of supportive care interventions. For example, hydration is an integral part of TLS management. Moreover, sources for disease diagnosis were out of scope of this study. Apart from that, the study was not intended to judge the accuracy of information since all information included in the retrieved documents is assumed to be evidence-based. Further, the recommendations were not graded or evaluated using appropriate tools such as the AGREE II instrument. The study explores the available documents, but this does not necessarily indicate that all these are used to guide the prescribing decisions in routine practice.

5.11 Conclusions

This study provides insights into the nature and content of available documents for prescribing in three critical areas of supportive care. These insights enhance the understanding of the respective guidance in the areas of interest which was not limited to one type of document (e.g., clinical guideline). The complexity of treatment regimens for emesis compared to TLS and PCP prophylaxis might require the use of other types of information sources to consolidate the process of prescribing. Variation

in the recommended doses was apparent for specific medicines but the appropriateness of this was unclear. Future quantitative studies focusing on the prescribing of medicines of interest and relevant treatment outcomes across Scotland would determine the appropriateness of this variation and may audit the prescribing practice. Various documents might support prescribers in Scottish paediatric oncology wards, which may complicate the prescribing if prescribers refer to all these documents throughout prescribing cascades. It would be valuable in future studies to explore how these documents are used in the Scottish clinical practice.

**Chapter 6 Prescriber's experiences
on the use of information sources
for prescribing three groups of
supportive care medicines: A
single-centre qualitative interview
study**

6.1 Introduction

Prescribing is defined as a decision-making process of determining and naming treatment for the management of health conditions what treatment to prescribe (364). The availability of adequate and accurate information is required for the decision-making process that leads to the prescribing of safe and effective medicines (365). A recent consultation paper (2024) published by the Scottish Government indicated that prescribing decisions should generally be made based on robust clinical evidence (366). The previous study (Chapter 5) identified various evidence-based sources at national and regional levels for the three clinical indications of interest: emesis, PCP prophylaxis, and TLS. The identified sources contained varied statements that could inform the prescribing for the three clinical indications. It was also stated in the aforementioned governmental paper that prescribing is made with respect to a number of considerations (i.e. medicine effectiveness, medicine safety, and medicine cost-effectiveness) (366). Relatedly, the impact of medicines on the environment is increasingly considered in Scotland (367). In parallel, having “sufficient information” about patients is an essential requirement for prescribing (368). Hence, prescribing is not a straightforward process but involves the interpretation of various information sources, influential factors, and patient-related information.

Medical practice, where prescribers practice prescribing, is changing rapidly aligning with the increasing pace of approval of novel medicines (328), such as palonosetron (an antiemetic used in CINV in adults and children) (369), and the rapid generation of medical information (370). Additionally, shifting to the digitalisation of information (371) revolutionises medical practice provided that this improves workflows within health institutions and connects different health institutions. In Scotland, a variety of actions have been implemented to digitalise the healthcare services and thereby enhancing the sharing of information (372). For instance, Hospital Electronic Prescribing and Medicines Administration (HEPMA), a national electronic system, which also provides information including information on medicines, doses, and associated alerts which can guide healthcare providers in the Scottish health settings (373). The rapid generation of medical information increases the information overload on practitioners (370) whereas the digitalisation of systems may be associated with cognitive burden (374). Previous research acknowledges the lack of understanding the use of at-hand information sources by prescribers (375). Considering the complexity of prescribing and the rapid change of medical practice, little is known

about how available information sources are used to prescribe medicines in the context of the indications of interest. The previous analysis explored the available information sources for prescribers without exploration of what is actually used in practice (Chapter 5). No available data exists on the used information sources and challenges encountered in prescribing medicines for emesis, TLS, and PCP prophylaxis within Scottish paediatric oncology area at present. This study corroborates the use of documents for prescribing medicines (Chapter 5), and enhances the knowledge of the use of various information sources for prescribing medicines in routine practice by identifying additional sources to obtain the information to support prescribing.

6.2 Aim and Objectives

Aim

The study explored experiences from Scottish clinical practice regarding the use of information sources to guide the prescribing of supplementary medicines for emesis, TLS, and PCP prophylaxis in paediatric patients with cancer.

Objectives

1. To describe the use of information sources for the purpose of prescribing medicines for emesis, TLS, and PCP prophylaxis in a Scottish paediatric cancer ward.
2. To understand the challenges of using available information sources in prescribing these medicines for paediatric patients with cancer.

6.3 Study setting

Participants were recruited from the Glasgow Royal Hospital for Children within NHS GGC because obtaining ethical approval for this study could not be possible in a timely manner from the other two centres in Scotland. Details about this setting are presented in Chapter 4.

6.4 Methods

The study's aim / objectives were co-conceptualised with practitioners in the NHS. The 32-standard Consolidated Criteria for Reporting Qualitative Research (COREQ)

(376) was applied to ensure the quality of reporting the findings in a comprehensive and clear manner. Table S6.1, Appendix 3 provides the details of COREQ criteria.

6.4.1 Study design

A qualitative design based on individual semi-structured interviews was chosen to answer the research questions of this study. The interviews were conducted between July 2025 and September 2025.

6.4.1.1 Semi-structured interview as a chosen method to collect data (research instrument)

One-to-one interviews, including semi-structured interviews, are well-known tools to collect in-depth qualitative data about individual's perspectives and experiences (377). Semi-structured interviews are more flexible; interviewees (informants) can describe the topic for discussion more openly, compared to structured interviews (378). Unstructured interviews are extremely flexible; however, these interviews may not be suitable to elaborate the required information about the topic of interest since this type of interview allows the collection of general information on certain topic rather than specific information from interviewees (379).

6.4.2 Study participants

6.4.2.1 Inclusion and exclusion criteria

To determine the eligibility of the candidates, a set of inclusion and exclusion criteria were applied (Table 6.1).

Table 6.1 Inclusion and exclusion criteria for the qualitative study

Inclusion criteria	Exclusion criteria
Being prescribers (i.e. medical prescribers or non-medical prescribers).	Having no experience in routine clinical care e.g. experience limited only to clinical trials.
Are working in Glasgow Royal Hospital for Children within National Health Service Glasgow and Clyde.	Are not prescribers / actively prescribing.
Making prescribing decisions of supplementary medicines for paediatric patients with cancer irrespective to the duration of experience.	

6.4.2.2 Sample strategy

Purposive sampling was employed for the selection of participants because the study targeted specific prescribers. This allowed the recruitment of experienced participants with rich knowledge about the investigated area (i.e. paediatric oncology) (380). Prescribers were also purposively recruited with a maximum variation (i.e. experience, age, ethnicity, main profession, and gender) to obtain relatively varied insights into the decision-making process (381). The rules and guidelines to determine the sample size for interview-based studies are varied (382). It has been reported in the literature that five to 11 participants would be enough to generate adequate thematic saturation (80%) (383) when redundancy of collected data is established (384). On the other hand, it was stated that two to ten participants are suitable to attain the redundancy of data on human experiences (385). Another important aspect with regard to sample size is the information power (386). Whenever the aim of the study is narrow, the targeted participants have specific characteristic, the interviewing is in-depth and the analysis does not aim to explore the whole situation, the sample size tends to be small (386). Since this study included one centre and targeted a niche area, six to eight prescribers were considered adequate to provide an overview of experiences in the use of information sources for prescribing, which was also realistic given the sample size of the target population. If saturation was not attained, it would be acknowledged as a limitation.

6.4.3 Development of research materials

Before recruiting the relevant prescribers and conducting the interviews (collecting of data), the following steps were done:

- ✦ Preparation of Participant Information Sheet (PIS) and consent form
- ✦ Development of the pre-interview questionnaire
- ✦ Development of the interview guide
- ✦ Preparation of invitation email template

6.4.3.1 Preparation of Participant Information Sheet (PIS) and consent form

A PIS (Figure S6.1, Appendix 3) was developed to provide a description of the study, its aim, the role of participants and their rights, besides the contact details of the research team. A consent form was developed to gain the written consent from the

participants. Templates of the two former documents were adapted from the University of Strathclyde's relevant templates. The PIS and consent form were checked (face validity) (345) by TM, NW, and a senior research administrator at NHS GGC. The PIS, along with the consent form, was inserted prior to the screening part in the digital pre-interview questionnaire and attached with the invitation email. Every participant received the PIS and consent form.

6.4.3.2 Development of the pre-interview questionnaire

The questionnaire was developed on Qualtrics (387) to screen potential participants, collect information on participants (e.g. gender, ethnicity, and age), and to get an overview of what kind of information sources the potential participants used in their practice. It contained multiple-choice questions and open-ended questions. Completing the screening question was a pre-requisite for proceeding to the other questions. The screening question was on whether candidates were prescribers of medicines to manage emesis, TLS, or PCP prevention within paediatric oncology area in Scotland. The potential participants were asked to provide their names and email addresses then they were asked about gender, ethnicity, profession, and working settings to describe the variation in the sample. Certain questions (i.e. age, gender (identity), and ethnicity) were not compulsory to answer. The questionnaire stated that the collected contact information would be required to contact participants. The final part contained three questions on the information sources participants used in the areas of interest.

The questionnaire was checked by a number of researchers to assess the appearance of the questionnaire, clarity of its content (i.e. linguistically and grammatically), and the logical flow of the created sections. The researchers were TM, NW, and four colleagues from the Pharmacoepidemiology and Healthcare Research Group (PHRG) at the University of Strathclyde. All had experience in creating surveys and formulating survey questions.

6.4.3.3 Development of the interview guide (interview schedule)

The study's interview guide was developed by RA based on input from a pharmacist and reviewed by TM, NW, and a senior research administrator at NHS GGC prior to usability test and piloting. In the introductory section of the interview guide, two general questions about the years of experience and prescribing qualifications were included to stimulate the conversation. The two general questions helped to

contextualise the discussion between RA and the participant and measured the level of enthusiasm of the participant. Then, the questions were more contextualised to meet the study's objectives. The interview guide (*Italic font*) was composed of three sections, each section focusing on one clinical indication:

Ice breaker questions:

How many years have you been prescribing supplementary medicines for paediatric patients with cancer? Any specific prescribing qualifications?

Then

We are going to talk about the information sources you use in prescribing medicines for emesis.

1. *You selected a range of information sources to prescribe medicines for emesis; can you tell me how you decide which information source to use?*
 - a. *Prompt: Does patients' age or other patient-related considerations influence the used information sources?*
 - b. *Prompt: Other considerations such as prescribers' preferences*
 - c. *Prompt: Emesis types and severity*
2. *What other information sources, if any, you may use to prescribe medicines for emesis?*
 - a. *Prompt: Others e.g. human sources: other prescribers, peers*
 - b. *Prompt: Electronic systems*
3. *Please tell me how you use the sources, you mentioned, to prescribe anti-emetics.*
 - a. *Probe: Is there any specific order to follow while using these sources?*
4. *Based on your experience, what are the challenges, if any, while using prescribing information sources to manage emesis in paediatric cancer?*
 - a. *Prompt: Accessibility*
 - b. *Prompt: Time to prescribe using these sources*
 - c. *Prompt: Conflicting information*

We are going to talk about the used information sources in prescribing medicines for tumour lysis syndrome.

5. *You selected a range of information sources to prescribe medicines for tumour lysis syndrome; can you tell me how you decide which information source to use?*

- a. *Prompt: Does patients' age or other patient-related considerations influence the used information sources?*
- b. *Prompt: Other considerations such as prescribers' preferences*
- 6. What other information sources, if any, you may use to prescribe medicines for tumour lysis syndrome?
 - a. *Prompt: Others e.g. human sources: other prescribers, peers*
 - b. *Prompt: Electronic system*
- 7. Please tell me how you use the sources, you mentioned, to prescribe anti-tumour lysis medicines.
 - a. *Probe: Is there any specific order to follow while using these sources?*
- 8. Based on your experience, what are the challenges of using these sources to manage tumour lysis in paediatric cancer?
 - a. *Prompt: Source-relevant limitations*
 - b. *Prompt: Accessibility*
 - c. *Prompt: Time to prescribe using these sources*

We are going to talk about the used information sources in prescribing medicines for PCP prophylaxis.

- 9. You selected a range of information sources to prescribe medicines for PCP prophylaxis; can you tell me how you decide which information source to use?
 - a. *Prompt: Does patients' age or other patient-related considerations influence the used information sources?*
 - b. *Prompt: Other considerations such as prescribers' preferences*
- 10. What other information sources, if any, you may use to prescribe medicines for PCP prophylaxis?
 - a. *Prompt: Others e.g. human sources: other prescribers, peers*
 - b. *Prompt: electronic systems*
- 11. Please tell me how you use the sources, you mentioned, to prescribe PCP prophylaxis you mentioned.
 - a. *Probe: Is there any specific order to follow while using these sources?*
- 12. Based on your experience, what are the challenges of using information sources to prevent PCP in paediatric cancer?
 - a. *Prompt: Source-relevant limitations*
 - b. *Prompt: Accessibility*
 - c. *Prompt: Time to prescribe using these sources*

Ending the interview

13. Is there anything else you would like to add? Any final thoughts?

The questions of the interview guide were open-ended questions to maximise the opportunity for participants to express their experiences, elaborate their thoughts, and to understand the process of using information sources (388), accompanied by some prompts, if required. Prompts were informed by the piloting interview.

6.4.3.3.1 Usability test (A pre-piloting test)

A usability test was applied to refine the interview guide (version 1) and to ensure its consistency and simplicity of language. This test prevented the overlooking of any issue relevant to the language and consistency by conducting an interview with a practitioner in another area, which further increased the rigour of the interview guide. The interview was conducted with a pharmacist who works at one of the Scottish NHS boards and uses evidence-based documents regularly. Accordingly, this was considered a preparatory testing as the pharmacist does not specialise in the clinical areas of paediatric oncology before piloting. This was intentional to allow for usability testing without reducing the sample size of the targeted population (i.e. prescribers for paediatric patients at NHS GGC) and affording the research the opportunity for further interview technique practice.

6.4.3.3.2 Piloting

Piloting qualitative studies, including interview-based studies, increases the validity and reliability of studies, and consequently improves their quality (389). Testing the questions of the developed interview guide ensures the ability of the research instrument (e.g. interview) to gather in-depth data from participants (389). One voluntary online pilot interview was conducted with a lead pharmacist, working in in-patient and outpatient paediatric oncology/haematology settings at a hospital in Wales, who has similar characteristics to the participants of our study (390). The pilot interview may not be included in the final analysis; therefore, piloting was done with a prescriber in another centre to ensure that the final sample size of eligible prescribers was not reduced. The interview guide (V1) was used in the pilot interview. This interview tested the need for modifying or reframing the questions included in the interview guide (V1). The interview also tested how long it took to conduct the interview. NW joined the meeting to observe the conversation and observe the

interviewing skills of RA. After piloting, additional prompts were added to the interview guide.

6.4.3.4 Preparation of invitation email template

The invitation email template (Figure S6.2, Appendix 3) was prepared by RA and checked by TM and NW for clarity and appropriateness before sending to the collaborator, a lead pharmacist in NHS GGC, who was the collaborator/gatekeeper in this study. The number of prescribers for paediatric patients with cancer at this site was 26, as informed by the collaborator. The collaborator was not excluded from the recruitment.

6.4.4 Recruitment methods

Three approaches were used to approach participants:

1. A gatekeeper at the targeted NHS health board. The invitation email template was sent to the research collaborator (pharmacist lead) to pass the invitation to the targeted participants along with consent form and PIS (passive recruitment strategy (391)). The collaborator sent the invitation to 26 prescribers.
2. Inviting participants through professional organisation (i.e. RPS) via their newsletters and forums (passive recruitment strategy (391)).
3. Snowballing techniques (392) (active recruitment strategy (391)).

Recruitment lasted from July 2025 to 15th November 2025. Participants who were interested in participating could email RA directly or complete the online questionnaire. Giving informed consent to voluntarily participate in the study was part of the recruitment stage. Further, the participant had to complete the questionnaire before conducting the interview.

6.4.5 Data collection

RA – a trained female researcher on qualitative methods and postgraduate student – conducted the interviews (section 6.4.1.1) online through MS Teams in a quiet place without distraction at a time convenient for the participants and RA. The option of face-to-face interviews was also offered to participants if more convenient, to be located in their workplaces (hospitals). The interviews were conducted in the English

language. RA introduced herself and reminded the participants of the study's aims before proceeding to the interview questions. RA used a printed checklist of the interview guide to ensure covering all topics of the study during data gathering (393). The same interview guide was used for all interviews to maintain consistency during collecting of data. The interviews were recorded by the aid of MS Teams. No field notes were used. However, RA created a file including relevant information about the interviews (e.g. date of interview, time, ...) and shared it with TM and NW via the University cloud storage (OneDrive).

6.4.5.1 Data management

All raw data (i.e., transcripts and MS Teams recordings) were stored safely on OneDrive which is password-protected. Access to data was limited to the research team only (i.e. RA, TM, NW, and HS). The interviews were anonymised (removing the identifiers) by RA. The names and the demographic information were stored separately after assigning a study ID to each interview. MS Teams recordings were automatically saved on the University cloud storage. MS Teams has an inbuilt functionality to generate transcripts of the conducted interviews (meetings); the details regarding transcriptions are documented in section 6.4.6.

Data (i.e., transcripts and MS Teams recordings) will be stored until the completion of RA's PhD and publishing of a peer-reviewed research paper then it will be deleted permanently. No paper-based documents of analysis were generated.

6.4.6 Data analysis

After transcription, inductive thematic analysis was used to analyse the interview data because this study investigated areas that have not previously explored. Further, the use of inductive analysis reduces the bias that deductive analysis with pre-existing expectations may entail. In inductive thematic analysis, themes emerge from the data that originated from interviewees (394) — prescribers in this instance. Thus, prescriber's perspectives can be represented without the interference of pre-defined hypothesis. The framework method (395) — a well-known systematic approach to analyse interview data — guided the inductive analysis of the interview data (Table 6.2). The interview data were analysed in the NVivo software (396) after uploading the checked anonymised transcripts into NVivo. NVivo facilitated the organisation and sorting of the interview data. Data analysis and data collection were conducted concurrently. HS validated 10% of the total number of transcripts.

Table 6.2 Analysis stages of the interview data

Stage number	Analysis stage	Description
Stage 1	Transcription	RA re-listened to the audio of recordings and reviewed (edited) the transcripts meticulously. This ensured the accuracy of MS Teams-generated transcripts. RA modified the layout of the transcripts by changing the line spacing, numbering the lines, and adding page numbers to the transcripts. HS relistened to 10% of recording, reviewed the transcripts, and did the transcription independently.
Stage 2	Familiarisation	RA read the transcripts multiple times and re-listened to the recorded audio files to be familiar with the entire set of data.
Stage 3	Generation of codes	Line-by-line identification of any related codes was done by RA. The codebook was created in NVivo and included a brief description of each code. HS identified codes, created a code book, and provided a brief description of each code independently (codes were very similar (number of agreements/ (number of agreements + number of disagreements) (98%)).
Stage 4	Building the analytical framework	The research team met frequently to review/reword codes, name each code appropriately, and check how codes were fitting together within each category (clusters of codes). The consensus on the final framework was reached after a series of discussions based on the aim of the study and following the coding of the last transcript.
Stage 5	Applying of analytical frameworks	The final framework was applied for all transcripts.
Stage 6	Charting interview data	An NVivo-aided abstracting of “voluminous” interview data into a developed matrix (spreadsheet) of rows (representing participants) and columns (representing codes).
Stage 7	Interpretation of data	Several discussions among members of the research team were conducted throughout the whole analysis process to interpret data.

In addition, summative content analysis (348) was used to quantify the number of information sources and perceived challenges across the three clinical areas. This analysis supported the descriptive nature of this study by transparently highlighting the number of each information source and challenge.

6.5 Rigour and robustness of the study

Credibility, dependability, transferability, and confirmability of the study were verified through the following actions to ensure the rigour and robustness of the study. Table 6.3 illustrates the measured criteria (397) and conducted actions.

Table 6.3 Actions to ensure rigour and robustness

Criteria	The action
Credibility– This criterion indicates the integrity while carrying out the research, which enhances the trust in the results (397).	⤴ Continuous de-briefing with TM and NW. Additionally, generating objective findings – unaffected by researcher's preferences – was taken into account through the reflections on the data analysis. ⤴ Reporting and interpretation of conflicting data and opposite perspectives (negative case analysis).
Dependability– This criterion indicates that results can be similar if the study is repeated (results are stable over time) (397).	⤴ Application of the tailored interview guide. ⤴ The study reported the use of NVivo software to organise codes. ⤴ Adapting of Consolidated Criteria for Reporting Qualitative Research checklist to report the findings.
Transferability– This criterion indicates the extent of transferability of the results to other settings (397).	⤴ The details of method and sampling were documented. ⤴ Efforts to maximise the engagement of participants throughout the data collection phase (the use of three recruitment approaches).
Confirmability– This criterion indicates that results were drawn from the research's original data (generated data) (397).	⤴ The collection of data was monitored by TM and NW who were not involved in the collection of data. ⤴ Interviews were recorded and transcripts were checked multiple times. ⤴ The interview data (the raw data) were continually compared with the emerged codes and themes. ⤴ Cross-linking between findings and direct quotes (a verification of data interpretation).

6.6 Research team and reflexivity

As per the COREQ checklist, all members of research team were pharmacists and had experience in qualitative methods. RA and HS were doctoral students and held MSc in Clinical Pharmacy whereas TM and NW were PhD holders and senior lecturers, and NW practiced as a community pharmacist. No prior relationship had been established between RA and the participants. The research interests of the

research team members included health policies/guidelines, health services, and the rationale use of medicines. Table S6.1, Appendix 3 provides the full details.

6.7 Ethical and regulatory considerations

6.7.1 Ethical approval

Ethical approval was gained from the Strathclyde Institute of Pharmacy and Biomedical Science (SIPBS) in December 2024. The approval from NHS GGC was granted in May 2025. Participants obtained the consent form from the gatekeeper or RA. All participants provided electronically signed consent forms to RA in advance of the interviews. The study assured that data were anonymised for publication purposes.

6.7.2 Additional required regulatory documents

An Integrated Research Application System (IRAS) form was prepared by RA, reviewed by TM, and submitted through the IRAS platform <https://www.myresearchproject.org.uk/>, a national online platform to submit requests to conduct UK-based social and healthcare research projects. Other documents, specifically Organisation Information Document (OID) and other forms (e.g. research passport form), were prepared by RA, reviewed by TM, and submitted along with the IRAS form. OID was required to provide the needed information to set the agreements between participating NHS organisations and other organisations, such as educational organisations.

6.8 Patient and public involvement

Patients and the public were not recruited in this study. Further, this study did not contact patients/public or involved patient-specific data. The non-engagement of patients and the public was because this study aimed to explore the use of information sources from the prescriber's side not from the patient's side. Further, the study did not aim to evaluate the use of medicines for paediatric patients with cancer which involves collecting patient-relevant data.

6.9 Results

6.9.1 Participant demographics (Baseline characteristics)

All participants were recruited via the gatekeeper. Ten participants completed the questionnaire; one candidate was not eligible for the study, and one potential participant did not respond to emails sent after completion of the questionnaire. The reason for not responding was unknown. Eight participants from different age groups with experience ranging from eight months to 18 years were interviewed online. The participants had various ethnic background and worked within different clinical settings. Most participants were women. The participants might be identified because of the small number of participants. Therefore, the details of the characteristics of participants are not provided. The average duration of interviews was 48 ± 6 minutes.

6.9.2 Responses of participants to questions regarding used information sources in the pre-interview questionnaire

Participants highlighted a number of information sources by completing the pre-interview questionnaire. The number of documentary information sources were

- ▲ seven for emesis (i.e., national guidance (CCLG) (n=8), SOPs (n=7), BNFC (n=7), regional formulary (n=5), literature (n=2), BNF (n=1), and Scottish Medicines Consortium (n=1)),
- ▲ six for PCP prophylaxis (i.e., SOPs (n=6), treatment protocols (n=6), BNFC (n=6), regional formulary (n=5), adult guidance (n=1), and BNF (n=1)),
- ▲ six for TLS (i.e., treatment protocol (n=6), BNFC (n=5), SOPs (n=4), BNF (n=2), regional formulary (n=2), and national guidelines (n=1)).

The responses to “others” option, which allowed participants to add other information sources, were group chat for prescribing anti-emetics and anti-TLS medicines (n=1), human information source (i.e., consultant) (n=1) for prescribing *Pneumocystis* pneumonia prophylactic medicines and anti-TLS medicines, and experience for prescribing antiemetics (n=1).

6.9.3 Themes and subthemes

The combined interview data identified three themes and ten subthemes. Table 6.4 provides the themes and subthemes of the data. The quotes (*Italic font*) by

participants were identified as follows: (*P (participant) along with an identification number, health profession, subject of talking*). The [note:] within quotes denotes added notes by the coder for clarification.

Table 6.4 The themes and subthemes of the study

Theme number	Theme title	Subthemes
Theme 1	Information sources used	Subtheme 1.1: Humans, documents, and experiences as information sources
		Subtheme 1.2: Variable use of information sources across the three clinical areas
		Subtheme 1.3: Variable use of information sources by health profession
Theme 2	Contextualising identified information sources: Articulated experiences	Subtheme 2.1: Standardised practice of using available information sources
		Subtheme 2.2: Embracing multidisciplinary communication during prescribing
		Subtheme 2.3: Multifactorial influences on selecting information sources
		Subtheme 2.4: Effective use of digitalised systems in local setting
Theme 3	Challenges and potential challenges while using available information sources	Subtheme 3.1: Information source-level challenges
		Subtheme 3.2: Personal-level challenges
		Subtheme 3.3: System-level challenges (Infrastructure-level challenges)

Theme 1: Information sources used

This theme outlined the different types of information sources according to perspectives of prescribers. It also denoted the used information sources in each of the three supportive care areas and the information sources for medical doctor(s) (MDs) and pharmacists. Three subthemes belonged to this theme.

Subtheme 1.1: Humans, documents, and experiences as information sources

The analysis identified 31 information sources used by the participants within interview data (Figure 6.1). Information sources can inform prescribing directly in specific patient scenarios or inform their prescribing practices more generally (e.g. from learning at a conference). Further, specific information sources, such as national guidelines and research literature, were also used to create local documents for prescribing. The identified information sources could be divided into three types:

1. human sources: *"...our pharmacy technicians are really good because they'll know what formulations you can quarter, which ones you can't, etcetera."* (P4, pharmacist, talking about PCP prophylaxis);
2. documents: *"...then consult the BNFC on the correct dose."* (P7, MD, talking about TLS);
3. experiential and practice-based information sources: *"I think the conferences are important source of information even for emesis because you see a nursing presentation, medical presentation on the approach to anti-emetic in the outpatient. I think it's a big source of information that changes the practice."* (P2, MD, talking about emesis).

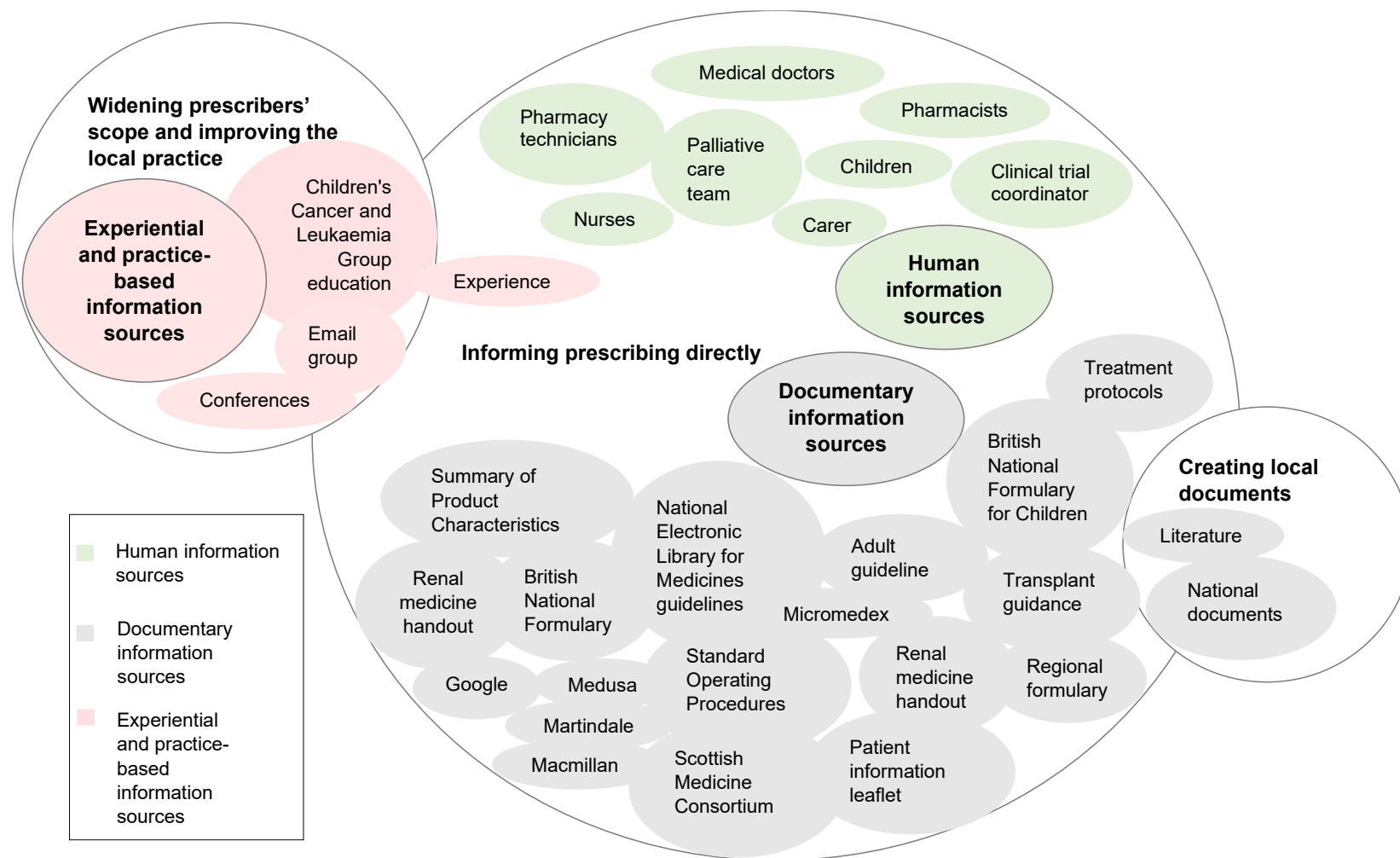


Figure 6.1 Types of information sources across the three clinical area

Subtheme 1.2: Variable use of information sources across the three clinical areas

This subtheme highlighted relative variability in information sources to be used across the three clinical areas. The highest number of existing information sources was relevant to emesis. Figure 6.2 presents areas of divergence and convergence in information sources between the three clinical indications. Table 6.5 provides some illustrative quotes.

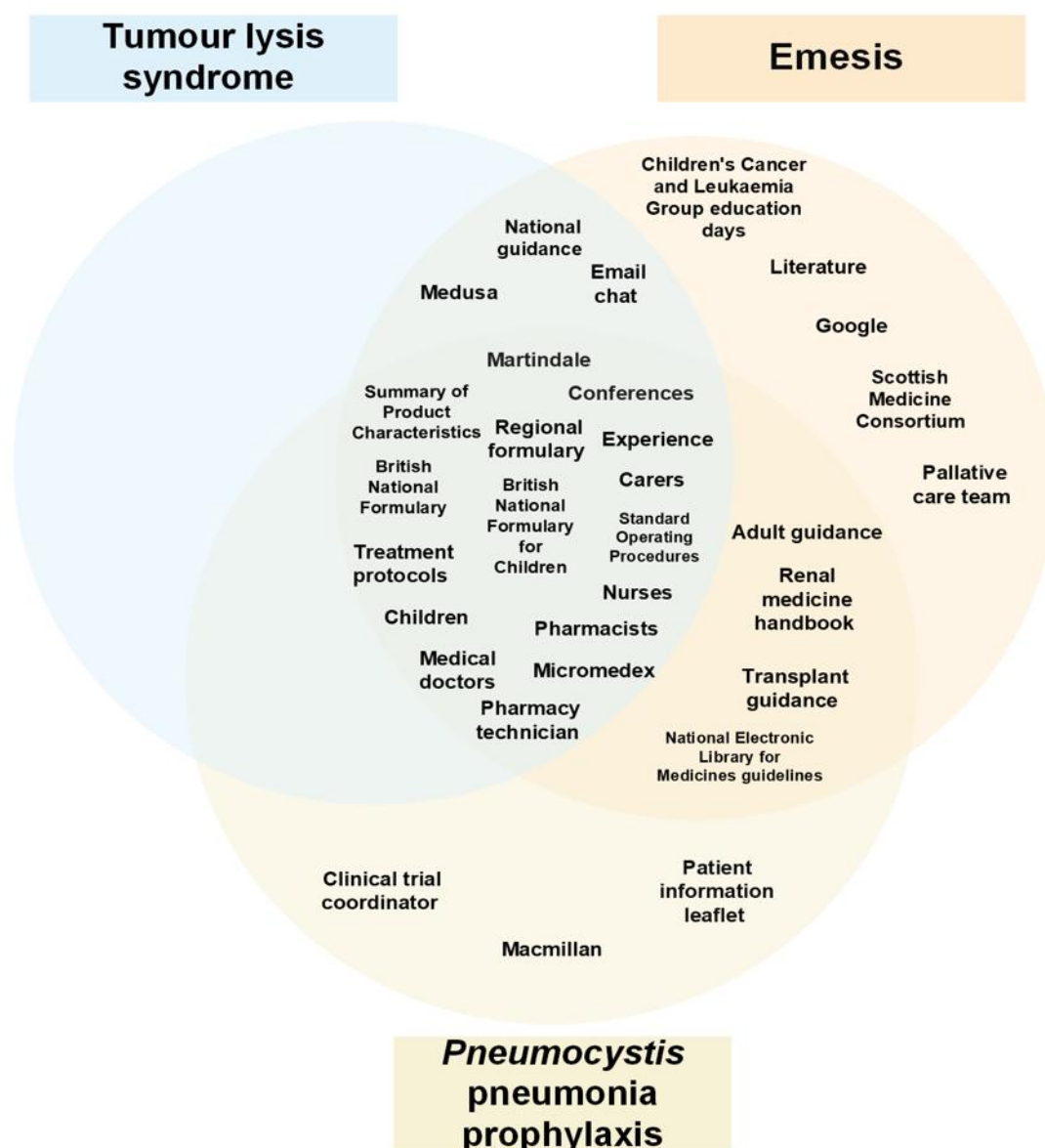


Figure 6.2 The information sources used to support prescribing across the three clinical areas

Table 6.5 Illustrative quotes from prescribers in the three clinical areas

Information source	Illustrative quotes
Emesis	
Palliative care	<i>“But if we were going into a kind of difficult to control symptoms and territory, I probably would be actually physically speaking to the palliative care team” (P7, Medical doctor, talking about emesis)</i>
<i>Pneumocystis pneumonia</i> prophylaxis	
Patient information leaflet	<i>“So that’s looking at the SPC or the patient information leaflet and seeing whether or not we can manipulate the tablets to do that.” (P4, pharmacist, talking about PCP)</i>
Emesis and <i>Pneumocystis pneumonia</i> prophylaxis	
Adult guidance	<i>“We have used adult policies because if you want to get pentamidine nebulized, we can’t deliver that within the paediatric hospital because of the facilities.” (P1, Pharmacists, talking about emesis)</i>
Emesis and tumour lysis syndrome	
Email chat	<i>“But also, we have an e-mail chat where a group chat where if we have any issues and in actual fact, I did put a query out about anti-emetics very recently.” (P1, pharmacist, talking about emesis)</i>
All indications	
Regional formulary	<i>“So, the drug formulary within the health board would influence your choice of drug. So, I suppose that’s an information source.” (P1, pharmacist, talking about all indications)</i>

NB: Quotes (Italic font) are followed by an identifier; the elements of the identifier are elucidated in section 6.9.3.

Subtheme 1.3: Variable use of information sources by health profession

This subtheme illustrated the information sources with regard to participant’s health profession. It reflected that certain information sources were used by MD prescribers but not by pharmacist prescribers and vice versa. Figure 6.3 presents areas of divergence and convergence in information sources between MD prescribers and pharmacist prescribers. Table 6.5 provides some illustrative quotes.

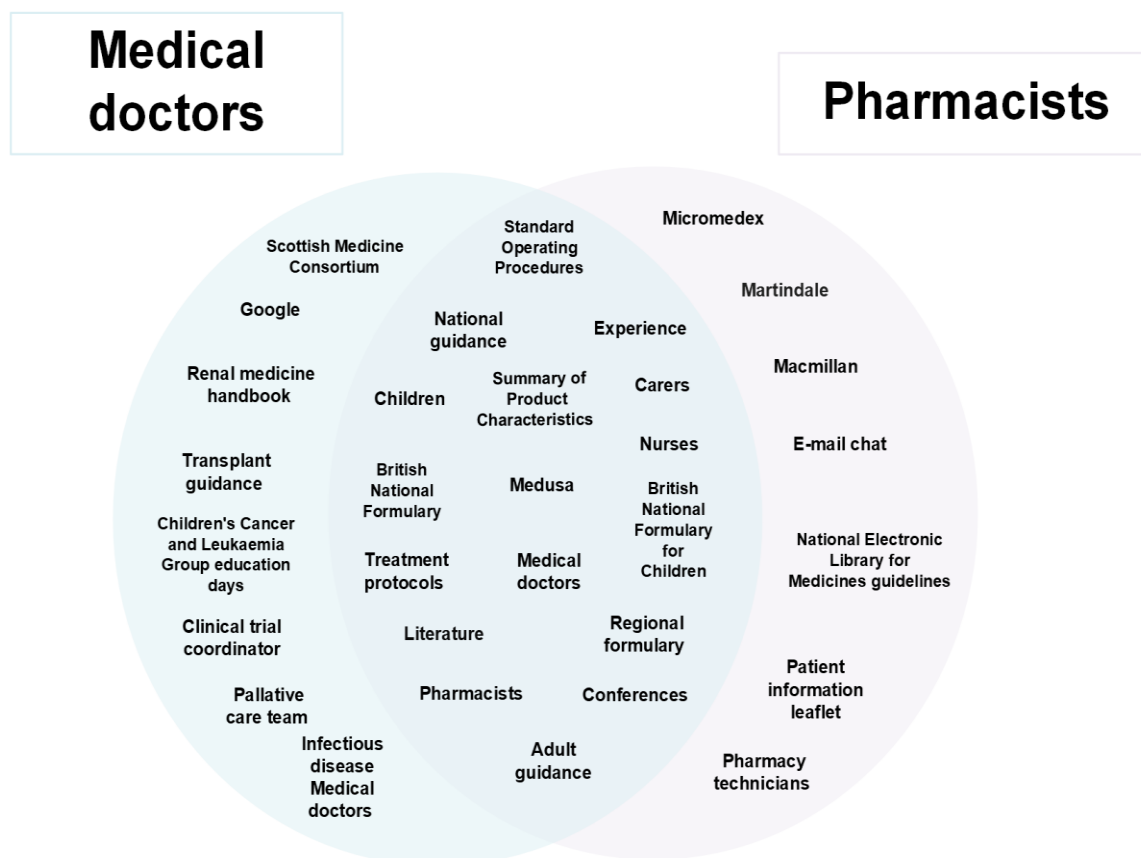


Figure 6.3 The information sources used to support prescribing by profession

Theme 2: Contextualising identified information sources: Articulated experiences

This theme denoted how prescribers used the identified information sources to prescribe three groups of medicines for paediatric patients with cancer practically. It also described the contributing factors that some participants explicitly stated to opt for certain information sources. Further, this theme outlined the effective role of digitalised healthcare systems/software on-site.

Subtheme 2.1: Standardised practice of using available information sources

Across the three clinical areas, regional SOPs were perceived as optimal information sources. Figure 6.4 depicts the main prescribing information sources for the management of emesis, TLS, and prevention of PCP and highlights the use of other information sources when needed. Five reasons to use regional SOPs were identified (i.e. standardisation of practice, comprehensiveness, easy-to-use source, regular updating, and informing prescribers what to do). Table 6.6 illustrates the perceived

reasons behind the primary use of regional SOPs using regional SOPs primarily. The comprehensiveness and standardisation of practice were the most common reasons for adherence to the regional SOPs, but other reasons related to their ease of use, the fact that they were updated often, and that they offered useful step-by-step guidance on clinical procedures. Several participants, across the three clinical areas, derived initial information from SOPs *“...the first would be the SOP, second would be kind of, I guess treatment protocols if they have a particular way of prescribing supportive care for TLS” (P6, MD, talking about TLS).*

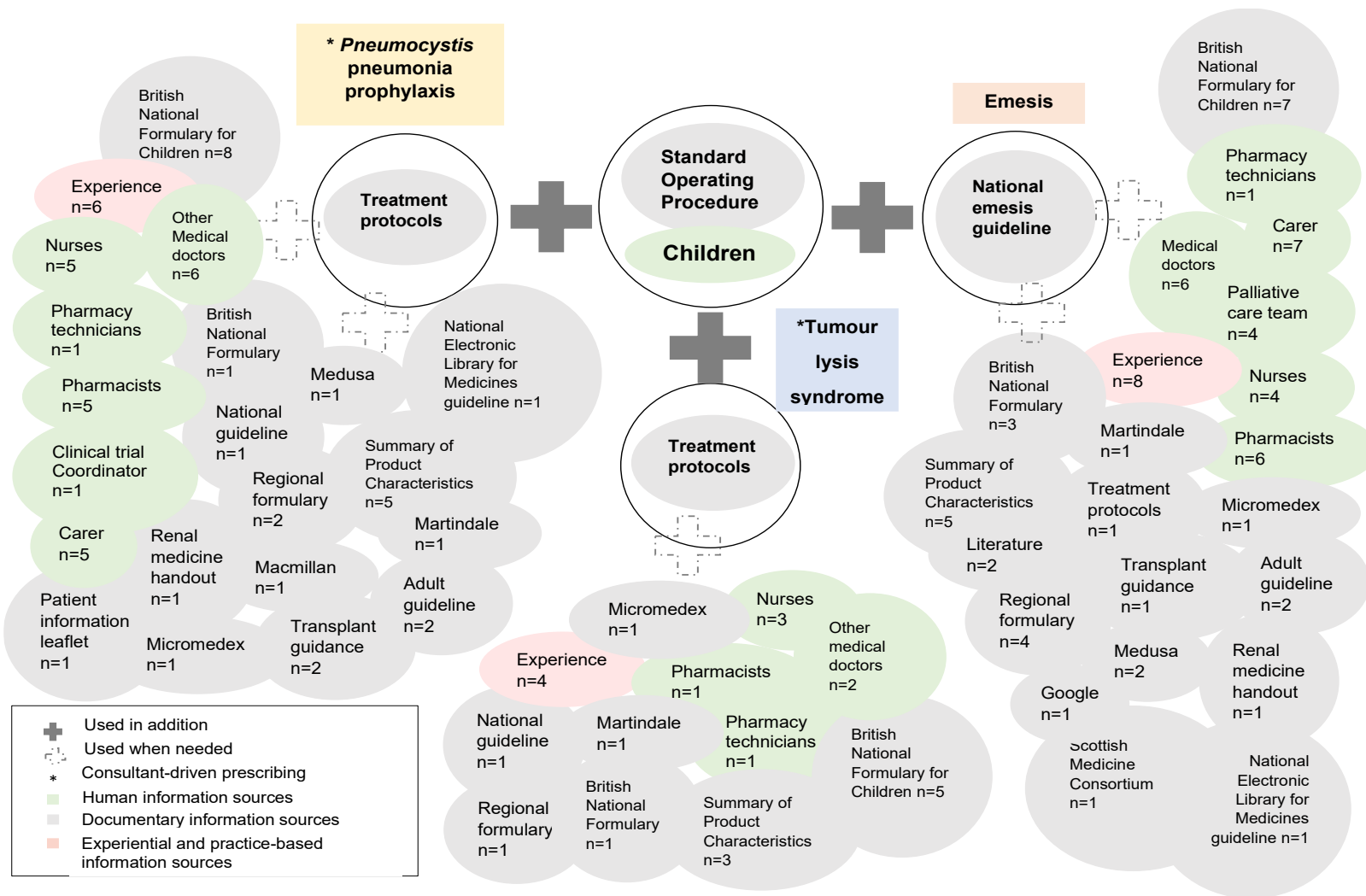


Figure 6.4 The way of using information sources to prescribe three groups of medicines.

Table 6.6 Reasons for using regional Standard Operating procedures

Reason	Emesis	<i>Pneumocystis pneumonia</i> prophylaxis	Tumour lysis syndrome
Standardisation of practice	<i>"Just to standardise practice, just to make sure that's what's been ratified and approved for the health board." (P4, pharmacist, talking about emesis)</i>	<i>"We know that we've looked at it as a group of local clinicians and agreed that that's the right thing to do for our patient population." (P5, medical doctor, talking about PCP prophylaxis)</i>	<i>"Again, for exactly the same reason I said for the anti-emetics that we have looked at this as a group and feel that this is most appropriate for our patient group." (P5, medical doctor, talking about TLS)</i>
Comprehensiveness	<i>"I would only use our standard operating procedure. Obviously if that fails at first treatment, we're going back to standard operating procedure and we're looking at second line choices because there's second line choices within that SOP." (P1, pharmacist, talking about emesis)</i>	<i>"You shouldn't have to go and look for other information anywhere because your SOP should be comprehensive." (P1, pharmacist, talking about PCP prophylaxis)</i>	<i>"So, number 1 it's our, it's our SOP. That's what I use because that's because it's quite thorough..." (P6, medical doctor, talking about TLS)</i>
Easy-to-use source	-	<i>"Yes, and it's often the easiest and quickest." (P7, medical doctor, talking about PCP prophylaxis)</i>	<i>"So, that's my preference because that's where I see the information black and white" (P2, medical doctor, talking about TLS)</i>
Regular updating	<i>"It's because the guidelines get updated from time to time." (P2, medical doctor, talking about emesis)</i>	<i>"I think you would use your own SOPs [note: Standard Operating Procedures] because they should be reviewed every two years, so they should be up to date." (P1, pharmacist, talking about PCP prophylaxis)</i>	-

Reason	Emesis	<i>Pneumocystis pneumonia</i> prophylaxis	Tumour lysis syndrome
Informing prescribers what to do	<i>“SOP [note: Standard Operating Procedure] will have a kind of standard operating about this is what we're going to do in reality because it's been prepared by pharmacists and then signed off by the medical staff...” (P3, pharmacist, talking about emesis)</i>	-	-

NB: Quotes (*Italic font*) are followed by an identifier; the elements of the identifier are elucidated in section 6.9.3.

All participants emphasised the involvement of paediatric patients as information sources during prescribing cascades to individualise the treatment across the three clinical areas. Table 6.7 presents more objective cues (i.e. biomarkers and medical history) and the more subjective cues (i.e. patient's preference and symptoms) information which was collated from paediatric patients. Patient characteristics such as ethnicity were also considered as described by participants.

Table 6.7 Collated information from children with cancer

Collected information/ patient characteristics	Emesis	<i>Pneumocystis pneumonia</i> prophylaxis	Tumour lysis syndrome
Preference	<i>"...they'll be individual preference with anything. So, here will be individualised the patient based on needs." (P3, pharmacist, talking about emesis)</i>	<i>"...whether they took liquids, whether they preferred tablets. So, there would be information. There are two different preparations of cotrimoxazole, so you probably don't know this, but one's banana, one's strawberry..." (P1, pharmacist, talking about PCP prophylaxis)</i>	<i>"They might say I really didn't like the allopurinol because it's not nice at all as a solution, so a patient might ask to switch to tablet version, but I probably wouldn't expect much more from their side." (P7, medical doctor, talking about TLS)</i>
Symptoms/Biomarkers	<i>"Are they very, very constipated? Don't use your ondansetron so much. Let's try a short course of metoclopramide, which is a prokinetic. If it's like nausea and vomiting, that is also associated with diarrhoea." (P4, pharmacist, talking about emesis)</i>	<i>"You would use dapsone. Generally, you need to have an adequate G6PD [note: Glucose-6-phosphate dehydrogenase] level, so that needs to be checked first before you can change, and we have seen some methemoglobinemia with dapsone." (P1, pharmacist, talking about PCP prophylaxis)</i>	<i>"I'll rely on their bloods, et cetera. I'll have a wee look at the urate." (P4, pharmacist, talking about TLS)</i>
Medical history	<i>"I go in to see a child who is vomiting, and they tell me I've used cyclizine before. I struggled a lot... I struggled a lot... That's not the right thing for me. So, I think for me, looking at that child and that family, the best information source still becomes what their</i>	<i>"Always children and their guidance, their carers are always information because they tell you about their behaviour. Had they responded to previous PCP prophylaxis?" (P2, medical doctor, talking about PCP prophylaxis)</i>	-

Collected information/ patient characteristics	Emesis	<i>Pneumocystis pneumonia</i> prophylaxis	Tumour lysis syndrome
	<i>body has adapted the pharmacokinetically and in the past and they say, oh, that's not the right thing" (P2, medical doctor, talking about emesis)</i>		
Patient characteristics	<i>"So, there will be a little bit of can I change in doses and things like that, depending on people's age, weight and things like that" (P7, medical doctor, talking about emesis)</i>	<i>"And in certain skin colours you might choose not to give dapsone because it's difficult to see blue lips." (P1, pharmacist, talking about PCP prophylaxis)</i>	<i>"And then, yeah, for us, obviously we're checking their G6PD [note: Glucose-6-phosphate dehydrogenase], we're checking to see, oh, what's the ethnicity?" (P2, medical doctor, talking about TLS)</i>

NB: Quotes (*Italic font*) are followed by an identifier; the elements of the identifier are elucidated in section 6.9.3.

Most participants indicated the consultant-led prescribing process for the management of TLS *“I think it's something that's very much driven by doctors on our site.”* (P4, pharmacist, talking about TLS) and prevention of PCP *“...you would use consultants as a first line field for whatever reason you would with you would agree with the consultant what second line was going to be...”* (P1, pharmacist, talking about PCP prophylaxis).

Input from consultants were considered to initiate a switch between allopurinol and rasburicase: *“It would usually involve a conversation with the consultant if I think that they needed to escalate to rasburicase or if they were if the consultant thought that they were high risk and wanted him to start automatically on rasburicase, I wouldn't be doing that without telling somebody.”* (P8, MD, talking about TLS). A junior pharmacist explicitly reported that their role in the prescribing area of TLS was limited.

Most participants commented that cancer-relevant treatment protocols guided prescribers by offering information on whether pharmacological intervention was indicated for TLS and PCP prophylaxis or not *“So also looking at what the protocol guideline is because there's some that say that you don't need to do PCP prophylaxis.”* (P4, pharmacist, talking about PCP prophylaxis).

Subtheme 2.2: Embracing multidisciplinary communication during prescribing

It was stated by several participants, mostly in the area of emesis, that fellow healthcare providers including prescribers were working as a team, especially in the management of challenging cases: *“In multidisciplinary team meetings, we use nursing, medical and pharmacy colleagues to help and obviously would seek advice from pharmacy colleagues when we have problematic cases.”* (P5, MD, talking about emesis). A few participants stated the role of the team for problematic cases with TLS *“I would say for example that if I was unsure whether this person definitely was indicated to receive TLS treatment, I say it was a rare condition and it wasn't explicitly described in the guideline. There may be a discussion between medical staff, pharmacy staff, nursing staff, whether route and look at their urate and consider actually giving it.”* (P3, pharmacist, talking about TLS) and regarding PCP prophylaxis *“So even in the MDT [note: multidisciplinary team] you may get a state say this is the best way to go with your prophylaxis, but this is the best way. Are you given a*

prophylactic agent that can also cover other agents? There is certain PCP prophylaxis that can cover for Toxoplasma.” (P2, MD, talking about PCP prophylaxis).

Most participants indicated the collation of specific information occasionally from certain profession/team across the three clinical areas. Prescribers might return to MDs or nurses searching for practical information on patients for the management of emesis and prevention of PCP. Pharmacists/ pharmacy technicians offered medicine-relevant information for prescribers. For information regarding the time of administering prophylaxis and the best route of drug administration, nurses were commonly consulted. Other specialists (i.e. infectious disease MDs) and specialist team (i.e. palliative care team) were perceived as informants for PCP prophylaxis and management of emesis, respectively. Table S6.2, Appendix 3 presents the illustrative quotes for each profession/team.

Subtheme 2.3: Multifactorial influences on selecting information sources

This subtheme described four contributing factors to the selection of information sources based on the perspectives of participants.

Age of paediatric patients (older and younger age)

Many participants stated that older patients age (paediatric patients >16 years) might lead them to use adult-relevant information source(s) if the main information sources do not provide needed information. Participants cited this factor more for emesis. According to many participants, the BNF could be used for paediatric patients > 16 years *“Only if I’m dealing with an adult sized patient, the default. So, if I have 100 Kilo 16-year-old, I’ll be double checking the doses in BNF and not BNFC.” (P8, MD, talking about emesis).* A few participants said that adult guidance might be used if the needed information was not present in paediatric-relevant information sources for PCP prophylaxis or emesis *“...but if we had a teenager and what where we are first line treatment was hadn’t have been as successful as we’d hoped. I may then have a look at the adult guidance just to check” (P1, pharmacist, talking about PCP prophylaxis).* For younger ages, a participant mentioned that younger ages might encourage her to use other documentary information sources for emesis *“If somebody’s particularly young. So, I did have a patient recently who was only seven months old who had epilepsy, was on carbamazepine, which caused a lot of interactions with stuff, and I ended up having to use a whole variety of resources” (P4, pharmacist, talking about*

emesis). However, another participant may refer to pharmacists who would support the prescribing for these ages *“I wouldn't worry about age though if they're not falling into one of my easy dose bandings for the little babies, I would always be checking with pharmacy for the dose.”* (P8, MD, talking about emesis).

Type of emesis

To seek additional information, a participant indicated referring to the literature. *“In particular, delayed emesis has been problematic in several of my patients recently, so for that in particular, I've been seeking additional information from the CCLG guidelines or from papers and journals.”* (P5, MD, talking about emesis).

Personal preference

Participants reported that their personal preference did not influence their use of regionally approved documents. Many participants preferred returning to the national guidance for emesis *“just because it's easier to access would just be the CCLG. It's a PDF quite easy to access document, so yeah, that's just preference. Purely on practicalities”* (P3, pharmacist, talking about emesis). A national guideline was a preferred option by a participant for TLS. The BNFC was also favourable by a few participants for emesis and by a participant for TLS. Pharmacists were the preferred information source for a participant in the area of emesis.

Prescribing setting

The prescribing setting may lead prescribers to use BNFC more than other information sources for emesis and PCP prophylaxis, as expressed by a participant *“I will say that yeah because for me in the outpatient, I've mainly seen patients with leukaemia. So yes, in the outpatient I'm heavily in tune with BNFC because SPC because that's probably a bit higher niche and complicated for the inpatient...”* (P2, MD, talking about emesis).

Subtheme 2.4: Effective use of digitalised systems in local setting

Many participants nominated one or more digitalised systems namely, Chemocare, Q-pulse (a system where practitioners could have access to documents), and HEPMA, that streamline the prescribing process. Chemocare prompted many participants to prescribe medicines especially for the management of chemotherapy-

induced emesis *“How I figure out how emetogenic something is by looking at what's being built on Chemocare. So, all the courses that have been built and the pharmacist that build; [.....] and [.....] will write down how emetogenic it is and that gives me an idea of how many antiemetics I should be prescribing.”* (P4, pharmacist, talking about emesis) and helped with the monitoring of medicines toxicities *“It's a [note: Chemocare] vehicle to prescribe and it's also it helps you as a counter check. Sometimes, it reminds you to say you're given too much of a dose, you prescribe a dose. It limits you to say, oh this is cut, this surface area has to be checked.”* (P2, MD, talking about emesis). It was highlighted by some participants that Chemocare could generate the recommended doses for PCP prophylaxis along with the entry of the required patient parameters. Further, many participants indicated that Q-pulse could be considered as a vehicle of documents *“all the SOPs are stored on Q-pulse, so that's how we access our SOPs.”* (P6, MD, talking about). For emesis, HEPMA could remind prescribers of any potential drug interaction, according to a few participants *“It [note: HEPMA] reminds you that you are prescribing a medicine that has got a drug interaction.”* (P2, MD, talking about emesis).

Theme 3: Challenges and potential challenges while using available information sources

This theme described the perspectives of prescribers for children with cancer regarding the challenges they faced when prescribing using available information sources. It also addressed potential challenges that they or other colleagues might face. Three subthemes belonged to this theme; all subthemes were reported by participants across the three areas.

Subtheme 3.1: Information source-level challenges

The lack of dose banding information, in particular, on certain medicines in the national documents was highlighted by participants primarily in the areas of emesis (n=4) and PCP prophylaxis (n=2) *“Occasionally they [note: BNFC] don't have the dose for a particular age group...”* (P6, MD, talking about emesis). A few participants stated the lack of dosing information on PCP prophylaxis (n=2) and TLS (n=2) in cancer treatment protocols *“So, a lot of the guidelines won't necessarily talk about it in kind of specifics. The patients that are on trials or studies, most of them, certainly the altogether trial will say refer to local guidance.”* (P7, MD, talking about TLS). Issues

including “rare” heterogeneity (n=2) and conflict (n=1) with regard to information between documents were mentioned in the area of emesis.

Some participants had raised concern over the length of cancer treatment protocols primarily in the area of PCP prophylaxis (n=4) *“I think the information is there usually the issue with trying to put specific treatment protocols is that it can be buried under, you know, many pages of protocol information so it can be quite hard to find that information for my treatment protocol.”* (P6, MD, talking about PCP prophylaxis).

Subtheme 3.2: Personal-level challenges

Based on the perspectives of participants, other prescribers might be unfamiliar with the available information sources that were related to TLS (n=3) and PCP prophylaxis (n=1) *“I can imagine other prescribers may not be so familiar with where all the information sources are...”* (P1, pharmacist, talking about PCP prophylaxis). A few participants stated other challenges including the challenges of other prescribers in reviewing the literature on emesis (n=1) and disagreement between consultants and guidelines in the area of PCP prophylaxis (n=1).

Subtheme 3.3: System-level challenges (Infrastructure-level challenges)

Across the three areas, internet unavailability may pose challenges while prescribing, if occurred *“The only thing that I would struggle with is if we had like our Wi-Fi go down, then I think it would be a bit challenging because everything is basically electronic.”* (P4, pharmacist, talking about PCP prophylaxis).

The inaccessibility to certain information sources were mentioned by a few participants and were represented by the inaccessibility to renal information handouts and other regional protocols/SOPs for the management of emesis (n=1) and prevention of PCP (n=1), respectively.

Table 6.8 elucidates the three subthemes with the aid of relevant illustrative quotes across the three clinical indications.

Table 6.8 The subthemes of the third theme (challenges and potential challenges while using available information sources)

Subtheme	Emesis	<i>Pneumocystis pneumonia</i> prophylaxis	Tumour lysis syndrome
Subtheme 3.1: Information source-level challenges	A lack of dose banding information for certain medicines in the national documents (n=4): <i>"Occasionally they [note: BNFC] don't have the dose for a particular age group..."</i> (P6, Medical doctor, talking about emesis)	A lack of dose banding information for certain medicines in the national documents (n=2): <i>"I suppose it's dose banded co-trimoxazole and dapsone for most of all our PCP prophylaxis. You may not find that in BNFC that way."</i> (P2, Medical doctor, talking about PCP prophylaxis) A lack of dosing information in treatment protocols (n=2): <i>"Generally, I find the treatment guidelines that the first step doesn't stipulate any dosing. Just say follow local practise, but then we have an SOP for local practise. So yeah, they get most treatment guidelines don't include dosing for PCP prophylaxis from my experience."</i> (P3, pharmacist, talking about PCP prophylaxis) A lack of information on the alternatives for PCP prophylaxis (n=1): <i>"I feel that there are challenges is when you're seeking alternative if they've not tolerated the first line Septrin [note: a brand name for co-trimoxazole] and or they've had a reaction and you're</i>	A lack of clear information on dosing in the national documents (n=2): <i>"like I said, I think in BNFC it just says see specialty guidelines. So, you just need to go find the SOP, but I can get to that."</i> (P8, Medical doctor, talking about TLS) A lack of dosing information in treatment protocols (n=2): <i>"So, a lot of the guidelines won't necessarily talk about it in kind of specifics. The patients that are on trials or studies, most of them, certainly the altogether trial will say refer to local guidance."</i> (P7, Medical doctor, talking about TLS)

Subtheme	Emesis	<i>Pneumocystis pneumonia</i> prophylaxis	Tumour lysis syndrome
		<i>seeking alternatives, that would takes a little bit of time to identify what's the best formulation and drug to give for reactions or sensitivity." (P5, Medical doctor, talking about PCP prophylaxis)</i> The length of treatment protocols (n=4): <i>"I think the information is there usually the issue with trying to put specific treatment protocols is that it can be buried under, you know, many pages of protocol information so it can be quite hard to find that information for my treatment protocol." (P6, Medical doctor, talking about PCP prophylaxis)</i>	The length of treatment protocols (n=1): <i>"Like protocol specific treatment guidelines, those are a nightmare. You need to find the index and find which section to go to." (P8, Medical doctor, talking about TLS)</i> The length of regional SOP ^a (n=1): <i>"You don't want people to be on a night</i>

Subtheme	Emesis	<i>Pneumocystis pneumonia</i> prophylaxis	Tumour lysis syndrome
	Infrequent heterogeneity between regional and national documents (n=2): "...for dosing information we do have like a local sheet. That's call antiemetic dosing on it. We do have like the BNF for children, but that can sometimes be a wee bit different." (P4, pharmacist, talking about emesis) Potential conflicting information between treatment protocols and SOPs (n=1): "Apart from maybe things that are stipulated in the treatment guideline that are contraindicated for that type of cancer, these things might		<i>shift at 12 midnight who are covering the whole of the hospital and you're asking them to read the guideline for the department...you don't want somebody at the middle of the night at 12:00 because he wants to prescribe rasburicase or allopurinol. He has to open the guidelines for tumour lysis and start reading it when he has to tend to almost 100 patients in the hospital. I think that I'm just expressing all my worrying about the people at the middle of the night when I'm not there."</i> (P2, Medical doctor, talking about TLS)

Subtheme	Emesis	<i>Pneumocystis pneumonia</i> prophylaxis	Tumour lysis syndrome
	<i>contradict what would be kind of standard antiemetics you would choose based on the emetogenic potential of the chemotherapy, but you might tend to want to avoid them. So, for example, steroids, dexamethasone might be avoided and some CNS tumours and types of leukaemia</i> (P3, pharmacist, talking about emesis)		
Subtheme 3.2: Personal level-challenges	Reviewing the literature ^a (n=1): <i>"Looking at the literature review may be a bit more challenging for some prescribers."</i> (P1, pharmacist, talking about emesis)	Familiarity with the available information sources ^a (n=1): <i>"I can imagine other prescribers may not be so familiar with where all the information sources are..."</i> (P1, pharmacist, talking about PCP prophylaxis) Disagreement between consultants and guidelines (n=1): <i>"I would say the biggest challenge is if you have a</i>	Familiarity with the available information sources ^a (n=3): <i>"For others who have maybe not familiar with those protocols and might take them a bit longer if it's a brand-new protocol"</i> (P3, pharmacist, talking about TLS)

Subtheme	Emesis	<i>Pneumocystis pneumonia</i> prophylaxis	Tumour lysis syndrome
		<i>consultant who's not agreeing with the treatment guideline and then just making sure that you suss out their reason and document it clearly of why they're not wanting" (P8, Medical doctor, talking about PCP prophylaxis)</i>	
Subtheme 3.3: System-level challenges	Internet cut ^b (n=1): <i>"...what is challenging is if you can't access that information, if the Internet goes down..." (P6, Medical doctor, talking about emesis)</i> Inaccessibility to renal information handouts (n=1): <i>"Some of them [note: information sources] I don't have access to, but I know there's a renal medicine handbook for complex situations" (P2, Medical doctor, talking about emesis)</i>	Internet cut ^b (n=3): <i>"The only thing that I would struggle with is if we had like our Wi-Fi go down, then I think it would be a bit challenging because everything is basically electronic." (P4, pharmacist, talking about PCP prophylaxis)</i> Inaccessibility to other regional SOPs and protocols (n=1): <i>"I don't use their specific information resources just because of time constraints and I don't fully understand depending on all the different health boards, I don't have access to their information resources." (P4, pharmacist, talking about PCP prophylaxis)</i>	Internet cut ^b (n=1): <i>"...if we don't have our computer access, the world shuts down." (P5, Medical doctor, talking about TLS)</i>

NB: Quotes (*Italic font*) are followed by an identifier; the elements of the identifier are elucidated in section 6.9.3.^a A challenge that others might face from the perspectives of participants; ^b A potential challenge that participants might face.

6.10 Discussion

The findings of this interview study illustrated the diversity of applied information sources to support prescribing in a Scottish paediatric oncology ward. The discussions with participants revealed the standardised practice of using available information sources in the daily clinical practice of the study's investigated areas. It also showed that prescribers had good adherence to locally agreed-upon documents, along with proactive involvements of healthcare providers and children with cancer and/or their characteristics across the three clinical indications. A handful of challenges, such as the lack of dose banding information on certain medicines, have been reflected by participants, mostly at the information source-level.

The study documented a range of used evidence-driven information sources which may imply the prioritising of evidence-based prescribing in this centre. The WHO stresses that it is essential to provide high-quality care to manage diseases (398). Evidence-based practice corroborates the provision of high-quality care and prevents any unwarranted variations in the provided care (399). Furthermore, the application of evidence-based practice may promote benefits for the clinical institutions; it cuts avoidable costs by reducing the admission rates and saving resources (400). Additionally, evidence-based practice increases the likelihood of desirable treatment outcomes for patients (400). SOPs were listed as information sources in this qualitative study in tune with many examples of UK-based studies (401-403) in the literature. In line with our findings, the BNF/BNFC is commonly used among healthcare providers in the UK (404). Tertiary literature was not frequently listed as information source by participants in this study compared to a study from Sweden (2024) (405). A cross-sectional study from Saudi Arabia (2022) (406), targeting prescribers including paediatric prescribers, reported the predominant use of electronic databases, such as Up-to-date, which were less reported by our participants. Commercial information sources (e.g. medical sales representatives) had no role in supplying information to the included participants which may help limit the use of biased information in clinical practice (407). The observed divergence in information sources between MD prescribers and pharmacist prescribers was potentially due to different duties and scope of knowledge of each profession. The discrete and embedded (408) quotes from participants in this study on PCP prophylaxis and TLS which indicated the prescribing in these areas was standard and self-explanatory (e.g. there were only two standard medicines for TLS), which may

justify the diversity and relatively higher number of information sources to prescribe antiemetics compared to the other two groups of medicines.

The present study showed that prescribers were aware of how they prescribed medicines for children with cancer through relying primarily on evidence-based information sources, local ones in particular. Similar to our findings, a study interviewed prescribers working in eleven hospitals located in the UK highlighted the primary use of local documents during prescribing of antibiotics (409). Unlike our findings, a Swedish study (2024) on head injury guidelines, a critical clinical area, found that the local guidelines were less used in comparison to other information sources (405). A previous survey-based study that targeted the Scottish primary care settings also does not align with our findings. It reported that the BNFC, prescriber's experience, and previous prescribing notes were the main information sources for prescribers (410). This difference might be because paediatric oncology area is different and more challenging than primary care. Generally, this suggests that the use of information sources is highly dependent on the clinical area of interest, which may have implications for prescribers entering into new areas of clinical practice.

The role of MDT and interprofessional/interpersonal communications (i.e. prescriber-prescriber, healthcare provider-prescriber, and child-prescriber discussions) were highlighted by participants. MDT communications in the realm of paediatric cancer bring several benefits, including enhancing the collection of information about patients and adherence to evidence-based practice. Moreover, working in an MDT improves the cooperation and relationships among fellow healthcare providers (411). Good communication between healthcare providers and children and/or their families fosters improvement in treatment outcomes and increases levels of patient satisfaction during the course of treatment (412). Additionally, the results indicated that prescribers considered paediatric patient's preferences, as described by two previous studies (413, 414). This showed the respect towards children-centred care (415). Another qualitative study (416) and a mixed method analysis (414) incorporated patients' characteristics and/or symptoms when prescribing antibiotics for conjunctivitis (416) and antidepressants (414), respectively. The findings from this study may imply the efforts of the respective centre to create an environment that supported collaborations and empowered communications between diverse practitioners. It also might imply that practitioners supported the idea of effective communication while providing care for children with cancer.

The lack of dosing information on certain medicines – mainly in national formularies (BNF/BNFC) – was highlighted by some participants. Authors of a recent review reported the lack of paediatric-relevant data regarding the dosing of antibiotics and suggested that pharmaceutical manufactures hold the responsibility for this (417). Consistent with our findings on treatment protocols, a study from Tanzania reported the lack of adequate information about supportive care medicines in cancer-relevant treatment protocols (418). The burdensome length of certain documentary information sources was reported by many participants. Clinical guidelines length (i.e. number of pages) is one of the measures to consider while optimising the development of guidelines (419). Furthermore, the length of clinical guidelines is an influential criterion in the adaptation of these evidence-based documents in practice (333). The low number of accessibility challenges may imply the efforts to align with a “single source of truth” vision which emphasises the importance of the provision of accessible medicine-relevant information (420). No participants in the present study mentioned any challenges corresponding to the document’s format, layout, or textual wording. A Swedish cross-sectional survey (2024) discussing the use of head injury clinical guidelines for children highlighted that an easy-to-navigate layout might increase the adherence to clinical guidelines (i.e. evidence-based information sources) (405). Practically speaking, there is no healthcare service without limitations, research should be done to identify potential challenges and to suggest some interventions to improve the implementation of the relevant service.

6.10.1 Recommendations to improve prescribing practice

In routine care, prescribers refer to many clinical guidelines, thus, the development of short summaries of the clinical guidelines by the relevant organisations is likely to further support the prescribing cascades especially for night-shift prescribers. The study also advocates increasing the accessibility to sources that might not be easily accessible such as renal information sources which can be used to adjust the therapeutic plans for patients with impaired kidney function. The accessibility to all information sources may further improve the clinical workflows and potentially save prescriber’s time. Increasing the accessibility to regional clinical guidelines/SOPs between centres may be beneficial. Such action may ensure the safe and effective transfer for children who transfer from one centre to another, if this happened. The role of pharmacy technicians might need more recognition when it comes to the development of regional documents considering the valuable knowledge these

practitioners acquire through practising in this critical clinical area. The development of regional documents taking into account the knowledge of all relevant practitioners might further foster the application and rigour of these documents.

6.10.2 Strengths and Limitations

The key strength of this study was that this is the first study, to my knowledge, to capture a range of prescribers' experiences in utilising information sources to prescribe three groups of medicines for paediatric patients with cancer. The study also generated in-depth information. Another strength was that the sample was diverse when it comes to age, ethnicity, and years of experience. Further, the participants were recruited from the largest paediatric oncology centre in Scotland (421). The limitations were: (a) all participants were recruited from one centre; the findings cannot be generalised and as a result this may impact the transferability. Several attempts had been made to get the approval from the other two centres, but the process for getting the approval was complex for both centres ; (b) the participant number were modest, yet it should be acknowledged that the sample size was small, with 31% of prescribers for children in Glasgow Royal Hospital for Children were recruited; (c) data were collected until the point that it was unlikely to yield new data, and clear conclusions were attained. The definition of data saturation may not have been achieved according to certain sampling guidelines (e.g. the guideline that recommends recruiting ten interviews with a stopping criterion of three interviews (422)); (d) no nurse prescribers showed willingness to participate, possibly because of their busy schedules. Therefore, no nurse prescribers were interviewed, and their insights were missed in this study; and (e) the female gender was predominant in the recruited sample. The predominance of the female gender may be explained by the predominance of female staff in the healthcare workforce in Scotland (423).

6.11 Conclusions

The study provides insights into some experiences from prescribers working in the largest paediatric oncology centre in Scotland. The study revealed the dynamic, hierarchical, evidence-driven practice of using information sources in one Scottish paediatric centre. It identified the information sources of importance to guide prescribers for children with cancer in three clinical areas. Further, it showed how the information sources were contextualised in routine clinical practice. The supportive role of digitalised systems was highlighted by a number of prescribers. The lack of

dosing information for some medicines in the national formularies was challenging for some participants.

Chapter 7 Reflections on challenges associated with conducting PhD research in paediatric oncology

Carrying out this PhD research project in the area of paediatric oncology was challenging. The direction of my PhD research project has dramatically changed due to logistical constraints and limited resources. This reflective discourse illustrates some of the obstacles I faced throughout the PhD marathon, and highlights two research areas I initially planned to explore.

7.1 Obstacles to conducting a cohort study

In April 2023, I started preparing drafts of a study protocol and Public Benefit and Privacy Panel for Health and Social Care (HSC-PBPP) application form to investigate the prescribing of oncological (SACT) and non-oncological (supportive care) medicines to paediatric patients (<16 years) with cancer in Scotland. This work was expected to exemplify the Scottish experience in the management of paediatric cancers over the past ten years in clinical practice. The outlined objectives were:

1. To describe the prescribing of SACT and non-oncological medicines for paediatric patients diagnosed with cancer in Scotland, and the changes that have occurred in prescribing patterns over a ten-year period.
2. To describe the demographical and clinical characteristics of paediatric patients with cancer in Scotland.
3. To describe the magnitude of using off-label and licensed medicines for the management of different types of paediatric cancer.
4. To analyse the outcomes of the applied therapeutic regimens for the management of paediatric cancers.

The study was intended to be a multi-centre retrospective cohort study. The cohort was to be identified from the CEPAS and linked with Scottish Morbidity Records SMR06 (Cancer Registry), SMR01 (inpatient hospital episodes), Prescribing Information System (PIS), and National Register of Scotland (NRS). Data linkage of datasets of interests was expected to be facilitated through a unique patient reference used in Scotland (the Community Health Index (CHI) number), and provided through the Electronic Data Research and Innovation Service (eDRIS) (424) (Figure 7.1). The access to the extracted pseudonymised data was planned to be through the Scottish Safe Haven network (<https://www.researchdata.scot/work-and-impact/current-projects/scottish-safe-haven-network/>).

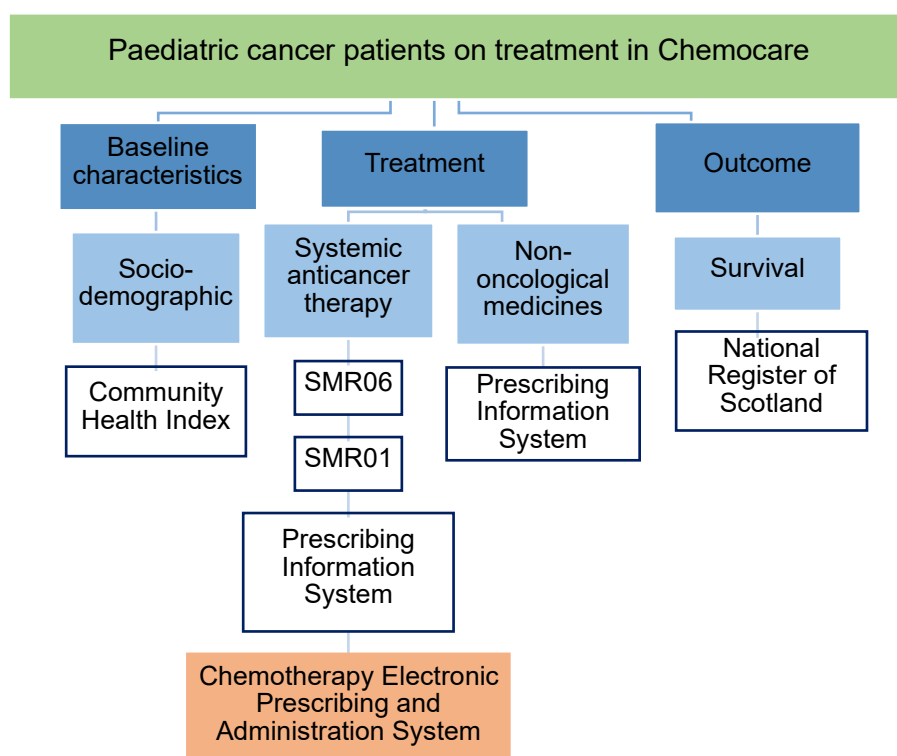


Figure 7.1 Record linkage overview – cohort identification and selected datasets

The plan was to cover the period from 01/01/2014 until the latest available date. The study protocol outlined the study cohort, exposure of interest, and outcomes of interest. The HSC-PBPP form provided details on the included Scottish oncology centres that are outlined in Chapter 4, research-ethics considerations, regulatory context, data processing and protection, dissemination of research outputs, as well as retention and disposal of data. The drafts of the study protocol and HSC-PBPP form were reviewed by TM. In December 2023, TM was informed that data on SACT prescribing for paediatric populations were not accessible for research purposes. Without having the data on SACT prescribing, conducting the analysis was not possible. It was disappointing given that other types of data were collected and digitalised within the relevant national databases (e.g. the datasets on birth date were stored in CHI). Additionally, the data on SACT prescribing for adults were available for research purposes, and it had not been pointed out that the respective paediatric data were not available for research projects at the stage of developing the protocol of my study. The inaccessibility to paediatric-relevant data might reflect the protective culture of NHS community when it came to the research studies that were related to children. An investigation has been recently initiated by the Scottish Government over

concerns regarding the prescribing of antibiotics for children in one of the clinical institutions (425). Such public concerns might make clinical institutions hesitant to provide data for the research studies targeting paediatric patients. This had significant implications for this research study and PhD thus, but – most importantly – has significant implications for the paediatric oncology populations. The limited access to data promoted me to explore the prescribing area from another facet (section 7.2).

7.2 Obstacles to conducting a qualitative study exploring prescriber's behaviour

In February 2024, I started writing a protocol for an interview-based study titled “Unearthing behavioural determinants of prescribers for paediatric patients with haematological malignancies in Scottish hospitals: A qualitative study supported by the Theoretical Domains Framework (TDF)”.

The scoping review (Chapter 3) found a wide variety of medicines prescribed to manage the paediatric haematological malignancies. Given that the behaviour of prescribers could affect prescribing (426, 427), it was essential to understand how prescriber's behaviour influence drug prescribing to explain the way care is provided to patients, and to enhance the quality of prescribing by formulating further robust policies (427-429). Theories to explore the multifarious influential factors pertaining to a process or phenomenon of interest enable researchers to generate new knowledge that guides the development of new interventions (430). TDF condensed 33 theories and 128 constructs to describe the determinants of human behaviours including healthcare providers, the role of surrounding environmental (contextual) factors, and other influencing factors. The domains of this framework involve affective, cognitive, and social factors, besides determining the influence of the other stakeholders (431). The TDF was chosen to support the development of the interview guide and the data analysis.

The theory-supported study aimed to attaining in-depth understanding of the dynamic process of the prescribing of oncological (SACT) and non-oncological medicines for the treatment of paediatric patients <19 years with haematological malignancies in the three Scottish paediatric oncology centres (Chapter 4). It would have explored thoughts, beliefs, and experiences of the recruited medical and non-medical prescribers. In addition to examining the role of contextual factors, this study would

have investigated the influence of other stakeholders, such as patients and patient's families or guardians who take part in the prescribing decision process, from the perspectives of the prescribers. The outlined objectives were:

1. To identify prescriber-related factors that govern prescribing of SACT for paediatric patients with haematological malignancies in Scotland.
2. To identify prescriber-related factors that govern the prescribing of non-oncological medicines for paediatric patients with haematological malignancies.
3. To identify the contribution of patients' parents, patients, and other stakeholders such as peers in the process of prescribing SACT from the perspectives of prescribers.
4. To identify the contribution of patients' parents, patients, and other stakeholders such as peers in the process of prescribing non-oncological medicines from the perspectives of prescribers.
5. To uncover the role of external/contextual factors in the process of prescribing SACT derived from the perspectives of prescribers.
6. To uncover the role of external/contextual factors in the process of prescribing non-oncological medicines derived from the perspectives of prescribers.

Data were expected to be collected via semi-structured interviews. The draft of the interview guide was developed in line with a rigorous framework (TDF) which would have reinforced the credibility of the study. Additionally, this would have guaranteed the coverage of all relevant theory-informed domains in the data generation phase (432). Inductive and TDF-driven deductive analyses were expected to be used to analyse data in this study. This is because the analysis of data by deductive analysis only might overlook potential non-TDF data (433).

The study protocol and ethical approval form were prepared and reviewed by TM and NW in May 2024. The study was supposed to be conducted from July 2024 to May 2025. Sadly, we (myself, TM, and NW) had a meeting with NHS practitioners who did not support the idea of this research. The support and permission of NHS practitioners were crucial to carry out this study to support engagement and recruitment. Conducting a research study without considering the needs and priorities of

practitioners might make it difficult to influence practitioners and to translate the findings of the research studies into clinical practice. As a result, no practical value would be added to improve the clinical practice. The findings of a qualitative (434) and a quantitative study (435) exploring the reasons of the limited participation of paediatricians or paediatric practitioners in the research from Australia (434) and Americas (435) may provide explanations of the discouragement with regard to participation in qualitative studies such as the one initially proposed. Previous negative experiences on participation in research may discourage practitioners from taking part in any future studies (434). The lack of time (434, 435) by practitioners may contribute to the limited interest in research participation. Moreover, practitioners need to priorities their tasks and some may consider the engagement in research as an off-task activity (434). A mixed method study from Ireland on the engagement of practitioners in cancer research highlighted the fear of judgment and concerns over discussing sensitive topics as barriers to the engagement in the research (436). The area of paediatric cancer might be a sensitive area to openly discuss with practitioners because shedding light on this area may disclose experiences with patients that are sometimes linked to death (437). Fear of judgment and the sensitivity of the topic, consequently, may further explain the reluctance of practitioners to involve in this study. The reluctance to conduct this study might confirm the distress of conducting research studies that focus on the prescribing for children in Scotland from different facets.

7.3 Research in paediatric oncology area in Scotland: An experience from the inside

From my point of view as a researcher, conducting research studies that focused on the use of medicines in the Scottish paediatric cancer setting was discomforting. I experienced exhaustion and frustration since I had to re-strategise the PhD project twice considering the available resources. All challenges posed while I was concurrently working on the scoping review (Chapter 3). Nevertheless, this experience enriched my knowledge regarding the developing of protocols, expanded my understanding on the respective methods, concepts, and frameworks, and helped me to sharpen resilience and tenacity, which are fundamental to keep moving in the research field.

Forums between the academic bodies and relevant Scottish health institutions, perhaps, will further facilitate carrying out research in the complex areas (e.g. paediatric cancer area) for the researchers at different research stages. Further, these kinds of forums may perhaps bridge the researcher-practitioner gap and improve the engagement of practitioners in research as participants and co-researchers. The engagement of practitioners in research undoubtedly contributes to the improvement of medical practice and patient outcomes (438).

Chapter 8 General discussion

This chapter summarises the findings of the individual studies conducted throughout this project. It also includes the general discussion followed by the understanding of phenomenon of interest (the use of prescribing-informing information sources) by the triangulation of findings presented in Chapters 5 and 6. In addition, this chapter highlights potential implications on prescribing practice, potential future research, and suggested measures to improve prescribing practice. Then, the final part of this chapter provides a summary of the strengths and limitations of this PhD project and a final conclusion.

8.1 Overview of key findings

This thesis investigates paediatric oncology practice from two facets: (a) observation-based publications on the treatments of paediatric haematological malignancies worldwide; (b) investigation of available prescribing-informed documents in three supportive care areas for prescribers in the Scottish routine practice and the use of these documents and other information sources in the largest paediatric oncology centre.

The international scoping review consisting of 82 observational studies (2013-2023) from three databases showed the utilisation of multi-drug therapeutic plans of SACT± corticosteroids for the management of paediatric haematological malignancies. The evidence from this review indicated that the role of non-novel SACT (i.e. conventional chemotherapy) was more prominent compared to novel SACT (e.g. tisagenlecleucel) in everyday management of paediatric haematological malignancies. The therapeutic plans varied among haematological malignancies (lymphomas and leukaemia) globally. Further, different combinations of SACT ± corticosteroids were used to treat the same malignancies across clinical institutions. Supportive care medicines (e.g. antibiotics, anti-TLS, and granulocyte colony stimulating factor (G-CSF)) were a pivotal part of the provided treatments to manage the developing health complications in paediatric patients. The evidence on novel supportive care medicines such as isavuconazole was very limited. Some of the clinical indications (e.g. depression and anxiety) in the landscape of paediatric haematological malignancies for which medicines may be used were not covered in the identified studies, thus the pharmacological treatments for these indications were not explored.

The second part of this project explored prescribing-informing information sources comprising documents that were used in specific supportive care areas (i.e. emesis,

TLS, and PCP prophylaxis) by two methods (i.e. document analysis and semi-structured interviews). The document analysis-based study of Scotland-wide documents that probably guide prescribing in the aforementioned areas identified 20 diverse documents, mainly national and regional documents. The identified documents for the three clinical indications were not limited to clinical guidelines. The medicine-relevant content of medicines in the three areas was identified (e.g. recommended dose) in these documents. The extent of the provision of medicine-relevant content was different among documents. In other words, the depth of the identified documents regarding medicine-relevant content varied. The recommended dose of medicines was the most documented medicine-relevant content in these documents for the three indications. The variation in medicine-relevant information was noticed for the recommended dose of medicines such as lorazepam. The number of recommended medicines for emesis was the highest compared to the other two indications. The interview-based study recruited prescribers from the largest paediatric oncology centre in Scotland and captured the wide picture of the use of information sources in clinical practice in the three areas of interest. Three themes were identified: the first theme delineated the types of information sources to be used in the three areas by MD and pharmacist prescribers; the second theme elaborated on the use of information sources in the context of prescribing (the interview-based study discovered a high degree of adherence to evidence-based information sources among participants in the prescribing areas of three critical clinical indications); and the third theme identified the challenges that may arise while using information sources in everyday practice. Based on the perspectives of prescribers, challenges that were relevant to information sources were more often mentioned compared to personal and infrastructure-relevant challenges.

8.2 Discussion of key findings

The multi-method research design, where two or more studies with different methods are conducted in one project (439), was used to explore the topic of prescribing-informed information sources (part 2). The triangulation of findings of two or more studies increases the validity of the conclusions through the convergence of findings (440). Additionally, further insights could be gained from the triangulation of findings of more than one study (441). Hence, the confidence in the attaining findings is increased (442).

The document analysis-based study delineated documents (written information sources) that were potentially used for prescribing in the areas of interest. However, the interview-based study explored the information sources from another aspect (a pragmatic aspect). It elaborated the firsthand experiences of using available information sources including SOPs, clinical guideline, formularies. Accordingly, the interview-based study verified and supplemented the findings of the document analysis-based study and vice versa, providing a comprehensive understanding of the information sources for prescribing in the areas of interest. The hybrid of semi-structured interviews and document analysis data indicated that different types of documents can guide the prescribing of the three groups of supportive care medicines.

The role of regional documents for the three clinical indications was more prominent within the included setting, although the reviewing of documents showed that the number of national documents was relatively higher than the number of regional documents. The only exception was the national document for emesis (CCLG) that had a key role in prescribing anti-emetics. SOPs were primarily used by prescribers in the three areas rather than sources such as product summaries (SmPC). The interview-based study showed that comprehensiveness was one of the common reasons of adapting SOPs, while the document analysis outlined that SOPs contained adequate information with regard to dosing, route of administration, and formulations for children. The reluctance of participants to provide examples when it came to the lack or heterogeneity of the information in need was observed. However, the perspectives of some prescribers explicitly verified the findings of the document analysis regarding the lack of information on dose banding for cotrimoxazole (PCP prophylactic), aprepitant (antiemetic), and levomepromazine (antiemetic) for the indications of interest in the BNFC. The perceptions on the lack of clear information on rasburicase (anti-TLS medicine) in the BNF/BNFC were corroborated by the results of the document analysis-based study. Even though it was stated infrequently, the heterogeneity in dosing of two medicines between national and regional documents was confirmed by the findings of the two studies. The mentioned examples of heterogeneity were levomepromazine and aprepitant (antiemetics). In relation to integration of new information, the interview data interrelated intangible information sources such as experience and other information such as humans. The identification of these sources would not have been possible by the document analysis-based study

alone due to the nature of document studies, which are inherently conducted to review written information sources.

The understanding of drug-based treatments for the most common paediatric malignancies in routine clinical care was limited before reviewing the literature through conducting the scoping review. A universal overview of varied multi-drug regimens for different haematological malignancies was provided by the scoping review (part 1), which also showed the prescribing of a variety of supportive care medicines throughout the course of treatment. No studies have been identified from Scotland about medicines prescribed for paediatric patients with haematological malignancies, which means that no knowledge was acquired on the pharmacological anti-cancer and supportive care therapies of haematological malignancies in the context of Scotland. However, the scoping review outlined the use of co-trimoxazole, pentamidine, dapsone, and atovaquone in routine care which were also identified as recommended options in the PCP prophylaxis-guiding documents in the context of Scotland. Moreover, the review's findings on the anti-emetics used and anti-TLS medicines were in accordance with the recommended medicines listed in the Scotland-wide emesis- and TLS- guiding documents but with two exceptions. The use of febuxostat for TLS was reported in a study from Japan (200) included in the scoping review but was not recommended in the identified documents of the document analysis-based study, showcasing international variations on medication use and pharmacological recommendations. Likewise, dimenhydrinate was mentioned as an option for the management of CINV in a study from Canada (198) but was not outlined by the recommendations of the Scottish guidance. The prescribing of a wide range of medicines in supportive care area for infections, TLS etc. was expected because of the possibility of the development of many symptoms and side effects in children. However, it was anticipated to identify a higher use of novel anticancer therapy for paediatric haematological malignancies, given that novel anticancer medicines are continuously developed and approved to improve the care provided to patients.

The document analysis and interview studies (part 2) closed the knowledge gap pertaining to information sources for prescribing and their actual use in Scotland. New insights into the diversity of available information sources and challenges while using these information sources have been added to the evidence base. It was evident that prescribers may not have to refer to all information sources to prescribe medicines of interest which was anticipated taking into account the potential overload of information

throughout prescribing and the need to make quick treatment decisions. However, the diversity and availability of evidence-based documents may further catalyse the use of these evidence-based documents while practising. As in any practice, challenges were encountered; some may be inevitable, such as the length of documents, and some could be mitigated or controlled, for instance, internet unavailability can be controlled by the presence of relevant round-the-clock support teams which may provide back-up systems or connections for emergency situations and perform regular maintenance

8.3 Implications for practice

The project may have practical implications for prescribing practice at meso and macro levels. At meso level, the interview-based study fostered the awareness of encountering obstacles prescribers might face. It may be important to inform policy developers and other stakeholders about these obstacles to minimise them, thereby further enhancing the prescribing task. The interview-based study showed that information sources such as practitioners, including pharmacy technicians, were hidden information sources. Therefore, their involvement in the development of regional documents would make these documents more comprehensive and useable. Further, such involvement may empower practitioners such as pharmacy technicians to become more active in the provision of optimal drug-based interventions. Additionally, the findings in this project indicated that the concept of multidisciplinary team could be implemented in routine practice of a complex clinical area. The multidisciplinary work facilitates the exchange of knowledge and information among practitioners and provides the support within paediatric oncology care facilitates. This evidence may support the transferability of multidisciplinary team concept to other paediatric-relevant wards (e.g. neonatal intensive care) and other paediatric oncology settings in other countries. At macro level, the document analysis-based and interview-based studies showed the lack of certain information such as dispensing information for PCP prophylactic medicines in the national formularies which may inform the revision of the existing sources to make them more comprehensive. Finally, the wide variety of medicines paediatric patients with haematological malignancies were exposed to may urge the stakeholders to further examine the safety of administering medicines. This may be one of the actions to mitigate the health complications throughout the course of treatment.

8.4 Recommendations for future work

As highlighted in section 8.1, this project added new empirical evidence on the pharmacological management of paediatric patients with haematological malignancies and on the available documents for prescribers in Scotland, in addition to information sources that were used by prescribers in the largest paediatric oncology centre and the challenges they may face. However, other relevant aspects still need further explorations.

A cross-sectional study to describe the prescribing of SACT and supportive care medicines for children with cancer in Scotland would be the initial step to get an overview of prescribing practice in Scotland. This will undoubtedly support the audit efforts to improve the care provided for children and will provide underpinning context for other quantitative studies. The provision of high-quality and equitable in Scotland might be difficult to attain if the prescribing practice for children with cancer is not fully understood.

The scoping review provided a comprehensive picture on SACT and supportive care medicines used in paediatric haematological malignancies based on observational research but further exploration on the use of medicines from the perspective of clinical trials may be required. The clinical trial settings are potentially considered as usual care in the treatment of paediatric patient especially in many industrialised, high-income countries. Conducting a systematic review of interventional studies to investigate the anticancer medicines and supportive care medicines prescribed for the management of haematological malignancies would be useful. The systematic review might provide evidence on the role of novel SACT and supplementary medicines. The aims of this recommended review may further expand to estimate the effectiveness of medicines investigated in the retrieved interventional studies systematically. Incorporation of novel medicines into treatment plans in clinical practice might suggest novel regimens to adopt in the area of paediatric cancer. Further, this future review may support the use of novel medicines in the practice especially with the limited evidence on the use of medicines in children.

Conducting another large-scale documentary study aimed to compare the documents that support the prescribing in the areas of interest between European countries might be valuable. This potential study may enhance the understanding of the content of

available clinical guidelines, formularies, and SOPs in Europe. Additionally, it may suggest some recommendations to harmonise clinical guidelines and SOPs that are relevant to children across Europe.

The provision of health care for children incorporates other stakeholders such as children and their guardians. A future document analysis-based study may identify which information sources patients and their guardians seek to get information about supportive care medicines. With the overload of information at the present time and the availability of misleading information, patients and their guardians might not be accessible to appropriate documents for obtaining information on medicines.

Another knowledge gap is the quality of the identified evidence-based documents. The document analysis aimed to explore the available documents and their content. Conducting a critical review to formally evaluate the quality of the identified evidence-based documents (clinical guidelines, etc.) systematically in line with validated tools (e.g. AGREE II) would attest the validity, quality, and applicability of clinical guidelines in the areas of supportive care of interest. Further, such assessment may further increase the confidence while using these guidelines in evidence-endorsing practice.

It is unknown whether prescribers in the other two paediatric cancer centres in Scotland are using the information sources to prescribe the three group of supplementary medicines of interest in similar way. Therefore, Scotland-wide and UK-wide e-Delphi studies may be applied to reach consensus from prescribers on the information sources for prescribing in the thesis's topics of interest and on challenges throughout the process. This may further inform the prescribing practice Scotland-wide and UK-wide. This study may give rise to other concerns or challenges while prescribing for children in the UK.

8.5 Strengths and limitations

The strengths and limitations of each individual study were highlighted in the respective chapter (Chapters 3 (scoping review), 5 (document analysis), 6 (interview study)). This section describes the overall strengths and limitations of this PhD project.

The main strength of this PhD is the novelty of the conducted studies. The conducted studies add evidence to the existing evidence base (2013-2023) regarding the prescribed medicines for populations of interest and prescribing-informing information

sources for emesis, PCP prophylaxis, and TLS. In view of the implemented methodology (part 2), the data were collected through two different methods; data triangulation was used to consolidate the final findings. The conducting of a qualitative study mirrored different experiences in a Scottish paediatric oncology ward. Sharing these lived experiences contributed to the reflection of accurate situation of the usual practice of using information sources.

The main limitation was the discontinuity between part 1 and part 2 due to the challenges mentioned in Chapter 7. Another limitation was the inherent subjectivity of the qualitative research which was the foundation of this thesis. The limitations also included the absence of the theories and theoretical frameworks in this thesis which would have further strengthened the findings. Furthermore, the non-generalisability of the findings of the single-centre study (Chapter 6) to other related institutions represents a limitation. The practice of using information sources was not observed through conducting an observational study because of ethical challenges, which could be considered as a limitation. This limitation should be acknowledged because the observational study would have been an ideal method to understand the use of information sources in routine practice. Additionally, the project did not provide insights into the silent cognitive process in the context of interest.

8.6 Final conclusion

This project adds new qualitative-driven evidence relative to prescribing-informed information sources to the evidence base, with particular relevance to Scotland due to the exploration of these information sources in the context of Scotland. It furthered understanding of existing information sources and their actual use where evidence-based information sources were at the forefront of prescribing for the three clinical indications of interest: emesis, TLS, and PCP prophylaxis. Evidence-based documents (clinical guidelines, SOPs, formularies, etc.) and other information sources such as human information sources were at hand to guide patient-centred prescribing. Specific challenges (i.e. information source-related challenges, personal challenges, and infrastructure-related challenges) were identified. Moreover, the use of a wide range of medicines (SACT $\pm$ corticosteroids and add-on supportive care medicines) for the management of paediatric haematological malignancies internationally indicated the complexity of this management in clinical care. Theoretically, this complexity, therefore, may imply the complexity of prescribing cascades especially if

prescribers refer to all information sources for prescribing all needed medicines for the management of cancer and the diagnosed complications.

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Appendices

Supplementary information for Chapter 3 (Appendix1)

Table S3.1 Full search strategies**Database:** PubMed**Conducted on February 16, 2023**

Number	Search terms	Retrieved articles
1	(((((((((pediatrics [MeSH]) OR (pediatric* [tiab])) OR (paediatric* [tiab])) OR (child [MeSH]) OR (child* [tiab])) OR (adolescen* [tiab])) OR (infant* [tiab])) OR (newborn* [tiab])) OR (neonate* [tiab]))	3341382
2	((((((((((((((((((((((((((((((((((Neoplasms [MeSH]) OR (neoplasm* [tiab])) OR (tumour* [tiab])) OR (tumor* [tiab])) OR (cancer* [tiab])) OR (carcinoma* [tiab])) OR (oncolog* [tiab])) OR (leukemia [MeSH]) OR (leukemia* [tiab])) OR (leukaemia* [tiab])) OR (lymphoma [MeSH]) OR (lymphoma [tiab])) OR (metastas* [tiab])) OR (malignanc* [tiab])) OR (sarcoma* [tiab])) OR (melanoma* [tiab])) OR (myeloma [tiab])) OR (Hodgkin [tiab])) OR (ependymoma [tiab])) OR (medulloblastoma* [tiab])) OR (non-hodgkin [tiab])) OR (neuroblastoma* [tiab])) OR (astrocytoma [tiab])) OR (craniopharyngioma [tiab])) OR (glioma* [tiab])) OR (meningioma* [tiab])) OR (ganglioglioma* [tiab])) OR (osteosarcoma* [tiab])) OR ("pleuropulmonary blastoma" [tiab])) OR (retinoblastoma [tiab])) OR (rhabdomyosarcoma [tiab])) OR (mesothelioma* [tiab])) OR (Pheochromocytoma* [tiab])) OR (paraganglioma* [tiab]))	5061825
3	((((((((((((((((((((((((((((((((((drug prescriptions [MeSH]) OR (drug ADJ prescri* [tiab])) OR (pharmacotherap* [tiab])) OR (drug utilization [MeSH]) OR (drug ADJ utili* [tiab])) OR (drug ADJ usage [tiab])) OR (drug ADJ use [tiab])) OR (drug therapy [MeSH]) OR (drug ADJ therap* [tiab])) OR (defined daily ADJ dose* [tiab])) OR (prescribed daily ADJ dose* [tiab])) OR (drug ADJ dispens* [tiab])) OR (prescription ADJ pattern* [tiab])) OR (drug ADJ administration [tiab])) OR (pharmacoepidemiology [MeSH]) OR (pharmacoepidemiolog* [tiab]))	1554198
4	(((((((((case report* [ti]) OR (RCT [ti] OR randomised controlled study [ti])) OR (RCT [ti] OR randomized controlled study [ti])) OR (expert opinion* [ti])) OR (conference abstract* [ti])) OR (review* [ti])) OR (systematic review* [ti])) OR (clinical trial* [ti]))	1023370
5	1 AND 2	384589
6	1 AND 2 AND 3	29998
7	6 NOT 4	28343
8	Limit 7 to date range of 2013- present, English language and Human species	7924

Database: Embase**Conducted on February 16, 2023**

Number	Search terms	Retrieved articles
1	pediatrics.mp. or exp pediatrics/	190159
2	"pediatric*".ab,ti.	567646
3	"paediatric*".ab,ti.	137200

4	child.mp. or exp child/	3691633
5	"child*".ab,ti.	2214442
6	"adolescen*".ab,ti.	453494
7	"infant*".ab,ti.	597605
8	"newborn*".ab,ti.	249451
9	"neonate*".ab,ti.	145081
10	Neoplasms.mp. or exp neoplasm/	5886747
11	"neoplasm*".ab,ti.	228022
12	"tumour*".ab,ti.	487761
13	"tumor*".ab,ti.	2391780
14	cancer.mp. or exp malignant neoplasm/	5586929
15	"cancer*".ab,ti.	3135462
16	"oncolog*".ab,ti.	356134
17	drug prescriptions.mp. or exp prescription/	248915
18	(drug adj prescri*).ab,ti.	8825
19	"pharmacotherap*".ab,ti.	65102
20	drug utilization.mp. or exp drug utilization/	26523
21	(drug adj use*).ab,ti.	98324
22	drug therapy.mp. or exp drug therapy/	6605264
23	(drug adj therap*).ab,ti.	64893
24	(defined daily adj dose*).ab,ti.	4830
25	(prescribed daily adj dose*).ab,ti.	463
26	(drug adj dispens*).ab,ti.	1854
27	(prescription adj pattern*).ab,ti.	3918
28	(drug adj administration).ab,ti.	87474
29	pharmacoepidemiology.mp. or exp pharmacoepidemiology/	14795
30	"pharmacoepidemiolog*".ab,ti.	4627
31	"case report*".ti.	411221
32	(RCT or randomised controlled trial).ti.	26729
33	(RCT or randomized controlled trial).ti.	75543
34	"expert opinion*".ti.	2464
35	"conference abstract*".ti.	238
36	"review*".ti.	809699
37	"systematic review*".ti.	251139
38	"clinical trial*".ti.	127894
39	31 or 32 or 33 or 34 or 35 or 36 or 37 or 38	1364594
40	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9	4529384
41	10 or 11 or 12 or 13 or 14 or 15 or 16	7100181
42	17 or 18 or 19 or 20 or 21 or 24 or 25 or 26 or 27 or 28 or 29 or 30	513523
43	40 and 41 and 42	5052
44	43 not 39	4692
45	limit 44 to (human and english language and yr="2013 - Current")	3027

Database : Scopus
Conducted on February 16, 2023

The final number of retrieved articles was 863.

((TITLE-ABS ((pediatric*) OR (paediatric*) OR (child*) OR (adolescen*) OR (infant*) OR (newborn) OR (neonate*))) AND (TITLE-ABS ((neoplasm*) OR (tumour*) OR (tumor*) OR (cancer*) OR (carcinoma*) OR (oncolog*) OR (leukemia*) OR (leukaemia*) OR (lymphoma) OR (metastas*) OR (malignanc*) OR (sarcoma*) OR (melanoma*) OR (myeloma) OR (hodgkin) OR (non-hodgkin) OR (ependymoma) OR (medulloblastoma*) OR (neuroblastoma*) OR (astrocytoma) OR (craniopharyngioma) OR (glioma*) OR (meningioma*) OR (ganglioglioma*) OR (osteosarcoma*) OR (pleuropulmonary blastoma) OR (retinoblastoma) OR (rhabdomyosarcoma) OR (mesothelioma*) OR (pheochromocytoma*) OR (paraganglioma*))) AND (TITLE-ABS ((drug PRE/0 prescri*) OR (pharmacotherap*) OR (drug PRE/0 utili*) OR (drug PRE/0 usage) OR (drug PRE/0 use*) OR (drug PRE/0 therap*) OR (defined AND daily PRE/0 dose*) OR (prescribed AND daily PRE/0 dose*) OR (drug PRE/0 dispens*) OR (prescription PRE/0 pattern*) OR (drug PRE/0 administration) OR (pharmacoepidemiology) OR (pharmacoepidemiolog*)))) AND NOT (TITLE ((case AND report*) OR ((RCT) OR randomised AND controlled AND trial*) OR ((RCT) OR randomized AND controlled AND trial*) OR (expert AND opinion*) OR (conference AND abstract*) OR (review*) OR (systematic AND review*) OR (clinical AND trial*))) AND (LIMIT-TO (PUBYEAR , 2023) OR LIMIT-TO (PUBYEAR , 2022) OR LIMIT-TO (PUBYEAR , 2021) OR LIMIT-TO (PUBYEAR , 2020) OR LIMIT-TO (PUBYEAR , 2019) OR LIMIT-TO (PUBYEAR , 2018) OR LIMIT-TO (PUBYEAR , 2017) OR LIMIT-TO (PUBYEAR , 2016) OR LIMIT-TO (PUBYEAR , 2015) OR LIMIT-TO (PUBYEAR , 2014) OR LIMIT-TO (PUBYEAR , 2013)) AND (LIMIT-TO (LANGUAGE , "English"))

Table S3.2 The data extraction tool for eligible studies

The extracted data	
First Author	
Year of publication	
Country of study	
Title	
Aim	
Data Source	
Study design	
Sample size	
Demographics (Age at diagnosis, Gender (Male/Female), Ethnicity)	
Targeted area (rural or urban), clinical settings (hospital, out-patient facility...)	
Cancer type, immunophenotype (n/N), risk stratification(n/N)	
Treatment Protocol (s), (original or modified)	
Any deviation from the applied protocol and the reason	
Treatment phase(s)	
Systemic anti-cancer therapy (SACT)	Drug
	Indication
Supplementary/supportive	Drug
	Indication
Drug approval	
Ethical statements (Ethical approval and consent)	
Main limitation(s)	
Additional notes	

Table S3.3 Characteristics of the individual included studies

Author	Year of publication	Country of study	Study design	Sample size of included patients (P)	Demographics age at diagnosis (years), gender (male/female), ethnicity	Haematological malignancy categories and subcategories p/P^b, risk stratification p/P^b
Leukaemia						
Michalowski et al (228)	2021	Brazil	Retrospective cohort study ^a	419	>1 – < 18, 257/162, N/A	ALL, T-cell ALL 46/419, B-cell ALL 370/419, Bi-phenotype ALL 2/419, missing data 1/419, LR 85/419, IR 117/419, HR 205/419, 12/419 missing data
Lins et al (211)	2019	Brazil	Retrospective cohort study	220	< 19, 130/90, N/A	AML, acute promyelocytic leukaemia (APL) (M3) 50/220, AML with Down syndrome 16/220, other AML subcategories 154/220, N/A
Avila et al (181)	2014	Canada	Retrospective longitudinal study	22	< 18, 16/6, White Caucasian, African American, Indian subcontinental, Mixed background, Hispanic	ALL, early pre-B cell ALL, pre-B cell ALL, T-cell ALL, N/A
Flank et al (198)	2017	Canada	Prospective cohort study ^a	70	4.1–17.6, 51/19, N/A	ALL, N/A, N/A
Zhang et al (222)	2020	China	Retrospective cohort study ^a	115	1–15, 58/57, N/A	AML, N/A, LR 97 /115, IR 18/115
Hu et al (226)	2021	China	Cohort study ^a	183	0.3 –14.2, 106/77, N/A	AML, ("M1/M2" 81/183,"M4/M5" 80/183,

Author	Year of publication	Country of study	Study design	Sample size of included patients (P)	Demographics age at diagnosis (years), gender (male/female), ethnicity	Haematological malignancy categories and subcategories p/P ^b , risk stratification p/P ^b
						M6 1/183, M7 8/183, Unclassified 13/183), LR 25/183, IR 105/183, HR 53/183
Wei et al (192)	2015	China	Retrospective cohort study ^a	74	1–15, 57/17, N/A	ALL, T-cell ALL, IR 29/74, HR 43/74, unknown 2/74
Sun et al (235)	2020	China	Retrospective cohort study ^a	163	0.2 –14, 90/73, N/A	ALL, B-cell 139/163, T-cell 24/ 163, LR 61/163, IR 102/163
Hu et al (236)	2016	China	Prospective cohort study	379	0.25 – 16, 224/155, N/A	ALL, B-cell ALL, SR 149/349, IR 110/349, HR 90/349
Hanna et al (170)	2020	Egypt	Cross-sectional study	54	2.02 – 6.10, 34/20, N/A	ALL, N/A, LR 23/54, SR 31/54
Makkeyah et al (227)	2021	Egypt	Retrospective cohort study ^a	220	0.5 –16, 120/100, N/A	ALL, pre-B cell ALL 185/220, T-cell ALL 34/220, mixed phenotype acute leukaemia (MPAL) 1/220, SR 110/220, HR 110/220
Hafez et al (237)	2019	Egypt	Retrospective cohort study	370	0.67 – 17, 224/146, N/A	ALL, AML, infantile leukaemia, and MPAL, B-cell ALL 206/370, T-cell ALL 47/370, AML

Author	Year of publication	Country of study	Study design	Sample size of included patients (P)	Demographics age at diagnosis (years), gender (male/female), ethnicity	Haematological malignancy categories and subcategories p/P ^b , risk stratification p/P ^b
						100/370, MPAL 17/370, LR 131/370, SR 190/370, HR 49/370
Loimijoki et al (220)	2020	Finland	Retrospective cohort study ^a	270	1.1 –16.2, 139/131, N/A	ALL, pre-B cell ALL 228/270, T-cell 21/270, MPAL 21/270, SR 164/270, HR 85/270
Berranger et al (187)	2013	France	Retrospective cohort study ^a	226	< 18, 106/119, N/A	AML, N/A, N/A
Boztug et al (238)	2014	Germany, Italy, UK, Poland, Russia, Netherlands, Switzerland, Finland, Lithuania, Israel	Retrospective cohort study ^a	71	0.81–7.9, 41/30, N/A	ALL N/A, N/A
Vyas et al (206)	2018	India	Prospective cohort study ^a	106	1–18,73/33, N/A	ALL, B-cell ALL 86/106, T-cell ALL 20/106, SD 45/106, HR 61/106
Seetharam et al (214)	2019	India	Prospective cohort study ^a	166	2–13, 90/76, N/A	ALL, B-cell ALL 138/166, T-cell ALL 25/166, mixed phenotype 3/166, N/A
Trehan et al (201)	2017	India	Retrospective cohort study ^a	374	1–13, 268/106, N/A	ALL, B-cell ALL 297/374, T- cell ALL 20/374,

Author	Year of publication	Country of study	Study design	Sample size of included patients (P)	Demographics age at diagnosis (years), gender (male/female), ethnicity	Haematological malignancy categories and subcategories p/P ^b , risk stratification p/P ^b
						unclassified, 57/374, SR 246/374, HR 128/374
Malhotra et al (203)	2018	India	Retrospective cohort study ^a	208	0.5 –18, 159/49, N/A	ALL, B-cell ALL 166/208, T-cell ALL 41/208, Bi-phenotype 2/208, SR 42/208, IR 117/208, HR 49/208
Lashkari et al (219)	2020	India	Retrospective cohort study ^a	107	1–18, 68/39, N/A	ALL, B-cell ALL 99/107, T-cell ALL 8/107, SR 59/107, HR 48/107
Hamidieh et al (209)	2019	Iran	Retrospective cohort study ^a	127	≤ 15, 90/37, N/A	ALL, pre-B ALL 104/127, T-cell ALL 21 /127, mature B-cell ALL 2/127, N/A
Al-Hadad et al (174)	2021	Iraq	Retrospective cohort study ^a	1415	1 – < 15, 780/635, N/A	ALL, N/A, SR 719/1415, HR 696/1415
Giona et al (176)	2018	Italy	Cohort study ^a	57	2.8 – 17.9, N/A, N/A	CML, 57/57 chronic phase, N/A
Sakaguchi et al (213)	2018	Japan	Retrospective cohort study ^a	220	0.8 –15, 109/111, N/A	AML, M0 7/220, M1 22/220, M2 79 /220, M3 18/220, M4 27/220, M5 38/220, M6 2/220, M7 12/220, Unclassified 15/220, N/A
Kato et al (185)	2013	Japan	Retrospective cohort study ^a	460	0 – 15, 237/223, N/A	ALL (241/460), B-cell ALL 198/241, T-cell ALL

Author	Year of publication	Country of study	Study design	Sample size of included patients (P)	Demographics age at diagnosis (years), gender (male/female), ethnicity	Haematological malignancy categories and subcategories p/P ^b , risk stratification p/P ^b
						22/241, unclassified 21/241, AML (219/460), M0 7/219, M1 31/219, M2 37/219, M3 3/219, M4 31/219, M5 46/219, M6 6/219, M7 48/219, unclassified 7/219, N/A
Ishida et al (188)	2015	Japan	Retrospective cohort study ^a	220	< 18, 107/113, N/A	AML, M0 19/220, M1 36/220, M2 68/220, M4 26/220, M5 28/220, M6 10/220, M7 24/220, missing data 9/220
Salami et al (239)	2013	Jordan	Retrospective cohort study ^a	23	1.67–17, 16/7, N/A	Philadelphia chromosome-positive acute lymphoblastic leukaemia (Ph+ ALL), pre-B cell ALL 21/23, T-cell ALL 2/23
Weelderen et al (232)	2021	Kenya	Retrospective cohort study ^a	73	0 –16, 41/32, N/A	AML, M1 12/73, M2 20/73, M4 5/73, M5 4/73, M6 2/73, missing data 30/73
Jaime-Perez et al (233)	2016	Mexico	Comparative, longitudinal, and retrospective study	246	0 –16, 115/131, N/A	ALL, B-cell 234/246, T-cell 12/246, SR 109/246, HR 137/246

Author	Year of publication	Country of study	Study design	Sample size of included patients (P)	Demographics age at diagnosis (years), gender (male/female), ethnicity	Haematological malignancy categories and subcategories p/P ^b , risk stratification p/P ^b
Pacheco et al (240)	2014	Nicaragua	Prospective cohort study ^a	540	< 18, 285/255, N/A	ALL, B-cell ALL 422/540, T-cell ALL 25/540, unknown 84/540, AUL 9/540, SR 278/540, HR 262/540
Nazir et al (202)	2017	Oman	(Retrospective/prospective) cohort study ^a	62	0.85 –11.4, 32/26, N/A	ALL, N/A, N/A
Amjad et al (207)	2019	Pakistan	Retrospective cohort study ^a	150	1–15, 102/48, N/A	ALL, pre-B cell ALL 139/150, pre-T cell ALL 11/150, SR 120/150, HR 30/150
Jabeen et al (241)	2016	Pakistan	Retrospective cohort study ^a	255	1–17, 157/98, N/A	ALL, B-cell ALL 188/255, T-cell ALL 47/ 255, MPAL 3/255, uncharacterized leukaemia 17/255, N/A
Ghafoor et al (217)	2020	Pakistan	Retrospective cohort study ^a	219	0.75 –15, 140/79, N/A	AML, M0 17/219, M1 24/219, M2 103/219, M4 27/219, M5 13/219, M6 5/219, M7 5/219, N/A
Mushtaq et al (242)	2013	Pakistan	Retrospective cohort study ^a	121	<15, 79/42, N/A	ALL, pre-B cell ALL 87/121, T-cell ALL, 13/121, missing data 22/121, SR 75/121, HR 46 /121

Author	Year of publication	Country of study	Study design	Sample size of included patients (P)	Demographics age at diagnosis (years), gender (male/female), ethnicity	Haematological malignancy categories and subcategories p/P ^b , risk stratification p/P ^b
Dujua et al (197)	2017	Philippines	Retrospective cohort study	78	0 –18, 48/30, N/A	ALL, pre-B cell ALL 76/78, T-cell ALL 2/78, SR 72/78, HR 6/78
Smeding et al (172)	2019	Poland	Retrospective cohort study ^a	14	1.3-16.9, 12/2, N/A	CML, 13/14 chronic phase, 1/14, accelerated phase, N/A
Jastaniah et al (180)	2017	Saudi Arabia	Retrospective multicentre cohort study ^a	30	2.3–14.7, 13/7 (10 missing data), N/A	AML, APL, (M3) 30/30, N/A
Mustafa et al (212)	2019	Saudi Arabia	Retrospective single-centre cohort study ^a	50	1 –15, 33/17, N/A	r/r ALL, 25/50, r/r AML 25/50
Sutiman et al (183)	2021	Singapore	Retrospective cohort study	62	0 –18, 29/33, Chinese 36/62, Malay 13/62, Indian 4/62, Another 10/62	AML, M0 5/62, M1 11/62, M2 18/62, M3 0/62, M4 5/62, M5 12/62, M6 3/62, M7 6/62, unknown 2/62, ((Good risk ° 5 /36, SR/HR 23/36, Down syndrome 7/36, Unclassified 1/36), (SR 13/26, HR 8/26, Down syndrome 4 /26, unknown 1/26))
Yeh et al (243)	2014	Taiwan	Cohort study	149	0.2-18, 65/48, N/A	ALL 113/149, AML 36/149, N/A
Kersten et al (179)	2013	Tanzania	Cohort study	111	1–18, ALL 43/38, AML 13/12, N/A	ALL 81 /111, AML 25/111, CML 3/111, juvenile myelomonocytic

Author	Year of publication	Country of study	Study design	Sample size of included patients (P)	Demographics age at diagnosis (years), gender (male/female), ethnicity	Haematological malignancy categories and subcategories p/P ^b , risk stratification p/P ^b
						leukaemia 1/111, mature B-cell ALL 1/111, N/A, N/A
Yalcin et al (244)	2021	Turkey	Retrospective cohort study ^a	72	0.8 –17.4, 47/25, N/A	ALL, N/A, N/A
Güneş et al (245)	2014	Turkey	Retrospective cohort study ^a	343	1–17.5, 200/143, N/A	ALL, pre-B cell ALL 265/343, T-cell ALL 60/343, Unclassified 18/343, SR 44/343, IR 226/343, HR 71/343
Özdemir et al (246)	2016	Turkey	Retrospective cohort study ^a	48	1.5-16.5, 27/21, N/A	ALL 40/48, AML 8/48, N/A
Koka et al (247)	2014	Turkey	Retrospective cohort study	242	< 18 ,144/98, N/A	ALL, B-cell 199/242, (pre-B cell ALL 13/242, pro- B-cell ALL 8/242), T-cell ALL 43/242, SR 65/242, IR 137/242, HR 40/242
Smitherman et al (175)	2017	United states	Retrospective cohort study	197	0–18, N/A, N/A	ALL, N/A, N/A
Moskop et al (173)	2022	United states	Retrospective cohort study ^a	14	0-9, N/A, N/A	ALL, B-cell ALL, N/A
Reinecke et al (215)	2019	United states	Retrospective cohort study ^a	67	0.25-18, 35/32, N/A	ALL 44/67, AML 23/67, N/A, N/A
Lymphomas						
Oliveira et al (189)	2015	Brazil	Retrospective cohort study	27	≤ 16, 18/9, N/A	NHL, lymphoblastic lymphoma (LL), T-cell

Author	Year of publication	Country of study	Study design	Sample size of included patients (P)	Demographics age at diagnosis (years), gender (male/female), ethnicity	Haematological malignancy categories and subcategories p/P ^b , risk stratification p/P ^b
						lymphoblastic lymphoma (T-LL) 16/27, pre-B cell LL 11/27, early stages (Stage I-II) 8/27, advanced (Stage III – IV) 18/27, Unclassified 1/27
Marr et al (204)	2017	Canada	Retrospective cohort study ^a	55	6–17. 30/25, N/A	HL, nodular sclerosing 47/55, mixed cellularity 5/55, not otherwise specified 3/55, early 20 /55, Advanced 35/55, I 2/55, II 26/55, III 18/55, IV 9 /55
Gao et al (186)	2013	China	Retrospective cohort study	108	1.3–15.9, 79/29, N/A	NHL, LL, I 2/180, II 5/180, III 55 /180, IV 46/180
Huang et al (225)	2021	China	Retrospective cohort study ^a	78	1 – 14, 65/13, N/A	NHL, Burkitt lymphoma (BL), Stage IV
Sayed et al (195)	2016	Egypt	Retrospective cohort study ^a	77	1–17, 54/23, N/A	NHL, LL, I 2/77, II 11/77, III 51/77, IV 13/77
Sherief et al (190)	2015	Egypt	Retrospective cohort study ^a	59	3 – 14, 37/22, N/A	HL, mixed cellularity 30/59, nodular sclerosis 17/59, lymphocyte-rich 11/59, lymphocyte-depletion 1/59, Stage I 7/59, Stage II 19/59,

Author	Year of publication	Country of study	Study design	Sample size of included patients (P)	Demographics age at diagnosis (years), gender (male/female), ethnicity	Haematological malignancy categories and subcategories p/P ^b , risk stratification p/P ^b
						Stage III 25/59, Stage IV 8/59
Ceppi et al (193)	2016	El Salvador, Nicaragua, Dominican R., Guatemala, Honduras, Costa Ric	Retrospective cohort study	31	0 –18, 17/14, N/A	NHL, Anaplastic large-cell lymphoma (ALCL), Stage II 6/31, Stage III 19/31, Stage IV 6/31, N/A
Seror et al (196)	2016	France	Retrospective cohort study ^a	417	3 –18, 222/195,	HL, nodular sclerosing 345/417, mixed cellularity 50/417, lymphocyte predominant 8/417, lymphocyte depleted 1/417, Unclassified 10/417), (IA, IB) 29/417, (IIA, IIB) 193/417, (IIIA, IIIB) 87/417, (IVA, IVB) 108/417
Jain et al (251)	2016	India	Retrospective cohort study ^a	167	2–18, 151/16, N/A	HL, Nodular lymphocyte predominant Hodgkin lymphoma (NLPHL) 6/167, mixed cellularity 83/167, nodular sclerosis

Author	Year of publication	Country of study	Study design	Sample size of included patients (P)	Demographics age at diagnosis (years), gender (male/female), ethnicity	Haematological malignancy categories and subcategories p/P ^b , risk stratification p/P ^b
						43/167, lymphocyte rich 18/167, lymphocyte depleted 02/167, unclassified 15/167, I 32/167 II 82/167 III 40/167 IV 13/167, early (Stages I and II) 114/167 advanced (Stages III and IV) 53/167
Parambil et al (248)	2020	India	Retrospective cohort study ^a	126	≤ 15, 104/22, N/A	HL, mixed cellularity 31/126, nodular sclerosis 22/126, lymphocyte rich 8/126, unclassified 53/126, LR 12/126, IR 18/126, HR 96/126
Jan et al (218)	2020	Pakistan	Retrospective cohort study	41	4–15, 5/1, N/A	HL, mixed cellularity 26/41, nodular sclerosis 14/41, unclassified 1/41, Stage I 5/41, Stage II 11/41, Stage III 7/41, Stage IV 18/41
Vijayasekharan et al (230)	2022	India	Retrospective cohort study ^a	21	1-14, 15/6, N/A	NHL, B-cell lymphoblastic lymphoma (B-LL), Stage I 6/21, Stage II 3/21, Stage III 9/21, Stage IV 3/21, N/A

Author	Year of publication	Country of study	Study design	Sample size of included patients (P)	Demographics age at diagnosis (years), gender (male/female), ethnicity	Haematological malignancy categories and subcategories p/P ^b , risk stratification p/P ^b
Patel et al (205)	2018	India	Retrospective cohort study ^a	42	3-18, 35/7, N/A	NHL, BL 19/42, diffuse large B-cell lymphoma (DLBCL) 15/42, peripheral T-cell lymphoma PTCL 5/42, follicular lymphoma grade III 1/42, NKT cell lymphoma 1/42, ALCL 1/42, Stage I 23/42, Stage II 19/42
Bhethanabhotla et al (199)	2016	India	Retrospective cohort study ^a	186	3–18, 153/33, N/A	HL, nodular sclerosis 60/186, mixed cellularity 82/186, lymphocyte rich 5/186, lymphocyte depleted 2/186, NLPHL 2/186, unspecified 35/186, Stage II 46/186, Stage III 106/186, Stage IV 34/186
Palayullakandi et al (231)	2022	India	Retrospective cohort study ^a	143	1.9 – 13.2, 122/21, N/A	HL, N/A, N/A
Vijayasekharan et al (221)	2020	India	Retrospective cohort study ^a	72	0.083 –15, 57/15, N/A	NHL, ALCL, SR 27/72, HR 45/72
Opanga et al (171)	2019	Kenya	Cross-sectional study	85	≤15 ,67/18, N/A	NHL, BL 39/85, non-Burkitt's Lymphoma 44/85, BL relapse 1/85

Author	Year of publication	Country of study	Study design	Sample size of included patients (P)	Demographics age at diagnosis (years), gender (male/female), ethnicity	Haematological malignancy categories and subcategories p/P ^b , risk stratification p/P ^b
						Non Burkitt's Relapse 1/85, N/A
Buckle et al (191)	2016	Kenya	Prospective cohort study ^a	569	0.8–14.4, 348/221, N/A	NHL, BL, Stage I 249/ 569, Stage II 17/ 569, Stage III 289/ 569, Stage IV 14/ 569, N/A
Choi et al (216)	2020	Korea	Retrospective cohort study ^a	56	1.9 –16.9, 32/24, N/A	HL 12/56, BL 12/56, ALCL 10/56, LL 9/56, DLBCL 8/56, NK/T-cell lymphoma 4/56 Subcutaneous panniculitis T-cell lymphoma 1/56, Stage I 2/56, Stage II 6/56, Stage III 21/56, Stage IV 27 /56, N/A
Resham et al (234)	2019	Pakistan	Retrospective cohort study ^a	32	< 16, 24/8, N/A	NHL, ALCL, HR 22/32, SR 9/32, unclassified 1/32
Wali et al (177)	2019	Pakistan	Retrospective cohort study ^a	25	<18, N/A, N/A	HL, r/r HL
Alkhatat et al (224)	2021	Saudi Arabia	Retrospective cohort study ^a	80	3–16 ,45/35, N/A	HL, lymphocyte rich 9/80, mixed cellularity 18/80, nodular sclerosis 44/80, lymphocyte depleted 0/80, NLP HL

Author	Year of publication	Country of study	Study design	Sample size of included patients (P)	Demographics age at diagnosis (years), gender (male/female), ethnicity	Haematological malignancy categories and subcategories p/P ^b , risk stratification p/P ^b
						9/80), Stage I 5/80, Stage II 25/80, Stage III 42/80, Stage IV 8/80, LR 12/80, IR 44/80, HR 24/80
Davidson et al (184)	2013	South Africa	Retrospective cohort study ^a	114	1.16 – 15.25, 81/33, N/A	NHL, human immunodeficiency virus HIV-negative B-cell lymphoma (92/114), (85/92, DLBCL 6/92, NHL with features intermediate between Hodgkin lymphoma, DLBCL 1/92) HIV-positive B-cell lymphoma (22/114) (BL 13/22, DLBCL 8/22, plasmablastic lymphoma 1/22)
Geel et al (182)	2017	South Africa	Retrospective cohort study	294	2.9–18.8 ,225/69, African ancestry 217/294, mixed ancestry 43/294, Caucasian 22/294 and Indian descent 12/294	HL, nodular sclerosing 125/294, mixed cellularity 120/294, lymphocyte depleted 12/294, lymphocyte rich 0/294, NLPHL 9/294, interfollicular 2/294, unclassified 26/294,

Author	Year of publication	Country of study	Study design	Sample size of included patients (P)	Demographics age at diagnosis (years), gender (male/female), ethnicity	Haematological malignancy categories and subcategories p/P ^b , risk stratification p/P ^b
						Stage I 22/ 294, Stage II 108/294, Stage III 83/294, Stage IV 80/294, missing data 1/294, N/A
Choeprasert et al (208)	2019	Thailand	Retrospective cohort study ^a	114	1.8–15.0, 75/39, N/A	NHL, BL 26 /114, DLBCL 23/114, LL 24/114, unspecified 11/114, large cell lymphoma 23/114, peripheral T-cell lymphoma 18/114, LL 13/114, T-LL 7/114, B-LL 6/114, Stage I 17/114, Stage II 15/114, Stage III 49/114, Stage IV 33/114
Karhan et al (210)	2019	Turkey	Retrospective cohort study ^a	102	2 – 4.9, 81/21, N/A	HL, mixed cellularity 63/102, lymphocyte rich 11/102, nodular sclerosis 12/102, lymphocyte depleted 3/102, NLPHL 2/102, Unclassified 1/102, Stage I 45/102, Stage II 32/102, Stage III 16/102, Stage IV 9/102
Vural et al (229)	2021	Turkey	Retrospective cohort study ^a	42	3 – 14, 34/8, N/A	NHL, BL, Stage III 36/42, Stage IV 6/42

Author	Year of publication	Country of study	Study design	Sample size of included patients (P)	Demographics age at diagnosis (years), gender (male/female), ethnicity	Haematological malignancy categories and subcategories p/P ^b , risk stratification p/P ^b
Büyükkapu-Bay et al (249)	2015	Turkey	Retrospective cohort study ^a	41	< 18, 32/9, N/A	HL, mixed cellular 21/41, nodular sclerosis 15/41, lymphocyte-rich 1/41, NLPHL 4/41, Stage I-II 26/41 Stage III-IV 15/41
Afify et al (223)	2022	United States	Retrospective cohort study	35	< 18, 26/9, N/A	NHL, post-solid-organ transplant BL, Stage I 1/35, Stage II 4/35, Stage III 19/35, Stage IV 11/35
Leukaemia and Lymphoma						
Dhingra et al (178)	2020	India	Retrospective cohort study ^a	184	1–18, N/A, N/A	ALL 168/ 184, B-cell ALL 146/184, T-cell ALL 22/184, T-cell NHL 16/184, N/A, N/A
Kishimoto et al (200)	2017	Japan	Retrospective cohort study	45	5-15, 27/18, N/A	ALL 28/45, AML 11/45, Lymphoma 6/45, N/A, N/A
Sugiyama et al (250)	2019	Japan	Retrospective cohort study	15	4 – 15, 7/8, N/A	ALL 9/15, pre-B cell ALL 7/15, 2/9 pre-B cell Ph+ ALL, NHL 3/15, HL 2/15, AML relapse 1/15, N/A, N/A
Olmos-Jime'nez et al (194)	2017	Spain	Prospective cohort study ^a	41	1 – 14, 24/17, N/A	ALL 35/41, AML 4/41, NHL 2/41, N/A, N/A

^a The study design is not explicitly stated in the identified paper ^b P: Total number of patients, p: number of patients in the subcategory ^c Patients with favourable characteristic. ALL= acute lymphoblastic leukaemia; AML= acute myeloid leukaemia; APL=acute promyelocytic leukaemia; CML= chronic myelogenous; HL= Hodgkin's lymphoma; NHL =non-Hodgkin lymphoma; r/r= refractory /relapsed; LR= low risk; IR= intermediate risk; SR= standard risk; HR= high risk; BL= Burkitt lymphoma; ALCL= anaplastic large-cell lymphoma; LL= lymphoblastic lymphoma; B-LL= B-cell lymphoblastic lymphoma; T-LL=T-cell lymphoblastic lymphoma DLBCL= diffuse large B-cell lymphoma; NLPHL= nodular lymphocyte predominant Hodgkin lymphoma; PTCL= peripheral T-cell lymphoma

Table S3.4 Treatment protocol for the management of haematological malignancies

Treatment protocol	Number of studies / Total number of studies
Acute lymphoblastic leukaemia	
Modified versions Berlin-Frankfurt-Muenster (BFM)	(12/82) (174, 203, 206, 214, 228, 233, 240-242, 245, 247)
Modified versions UK-ALL	(5/82) (174, 179, 201, 207, 219)
Chinese Children's Leukaemia Group- ALL-08 (CCLG-2008)	(2/82) (192, 236)
St. Jude	(2/82) (170, 239)
Beijing Children's Hospital (BCH-2003)	(1/82) (192)
Children's Cancer Group (CCG)	(1/82) (227)
Nordic society of paediatric haematology and oncology (NOPHO)	(1/82) (220)
Grupo Brasileiro de tratamento da leucemia infantil (GBTLI)	(1/82) (228)
Reduced-dose intensity therapy for paediatric lymphoblastic leukaemia (RELLA)	(1/82) (228)
International treatment protocol for infants under one year with acute lymphoblastic or biphenotypic leukaemia (INTERFANT)	(1/82) (228)
Modified Berlin-Frankfurt-Muenster/Hong Kong Acute Lymphoblastic Leukemia (BFM95/HKALL97)	(1/82) (197)
China Childhood Cancer Group CCCG-ALL-2015	(1/82) (235)
St. Jude total therapy XV	(1/82) (170)
King Hussein Cancer Centre (KHCC) ALL-1102	(1/82) (239)
Acute myeloid leukaemia	
Programa Español de Tratamientos en Hematología (PETHEMA)	(1/82) (180)
Medical Research Council (MRC) AML12	(1/82) (183)
Malaysia Singapore AML (MASPORE) 2006	(1/82) (183)
Non-Hodgkin lymphomas	
Modified Multicentric Protocol-842 (MCP-842)	(2/82) (221, 234)
Adriamycin-Prednisolone-Oncovin (APO)	(2/82) (193, 234)
CCCG-99	(1/82) (186)
SCMC-T-NHL-2002	(1/82) (186)
ALCL99	(1/82) (234)
Ramathibodi Hospital large cell lymphoma (RAMA-LCL) protocol	(1/82) (208)
American Association of Paediatric Haematology Oncology (AHOPCA)	(1/82) (193)
Guatemala-ALCL (Guat-ALCL)	(1/82) (193)
LBL-CHOF-2006 *	(1/82) (186)
BFM-90	(1/82) (230)
BFM-83	(1/82) (189)
LSA2L2 *	(1/82) (189)

Modified Beijing Children's Hospital (BCH)-B-NHL	(1/82) (225)
St. Jude Children Research Hospital ALL Total Therapy XV	(1/82) (195)
Modified Multicentric Protocol (MCP)	(1/82) (221)
Jaramogi Oginga Odinga Teaching and Referral Hospital (JOOTRH) Burkitt lymphoma	(1/82) (191)
French Pediatric Oncology Society protocol Lymphomes Malins B LMB-89 and LMB-96	(1/82) (184)
European Intergroup's ALCL-99	(1/82) (184)

**The abbreviation of the protocol was not mentioned.*

Table S3.5 Routes of administration of systemic anti-cancer therapy for the treatment of haematological malignancies

Malignancy subtype	Route of administration	Systemic anti-cancer therapy	Studies*
Acute lymphoblastic leukaemia	Intramuscular	L-Asparaginase	(206, 214, 219, 227, 228, 233, 239-241, 247)
		Methotrexate	(233, 239, 240)
	Intrathecal	Hydrocortisone	(197, 239, 240)
		Cytarabine	(197, 233, 239, 247)
		Methotrexate	(197, 206, 214, 227, 233, 239, 247)
		Prednisone	(247)
	Intravenous	Cyclophosphamide	(197, 227, 233, 239, 240, 247)
		Cytarabine	(197, 212, 227, 233, 239, 240, 247)
		Daunorubicin	(206, 214, 219, 239, 240, 247)
		Doxorubicin	(197, 227, 233, 240, 247)
		Etoposide	(239)
		Fludarabine	(212)
		Idarubicin	(212)
		L-Asparaginase	(197, 206, 214, 219)
		Methotrexate	(197, 227, 233, 239, 240, 247)
		Vincristine	(197, 206, 214, 219, 227, 233, 239, 240, 247)
	Oral	Mercaptopurine	(197, 227, 233, 239, 240, 247)
		Dexamethasone	(197, 206, 219, 227, 233, 239, 240, 247)
		Methotrexate	(197, 227, 233, 240, 247)
		Prednisolone	(197, 206, 214, 239, 247)
		Prednisone	(233, 240)
		Thioguanine	(227, 240)
	Subcutaneous	Cytarabine	(227, 233, 239, 240)
Acute myeloid leukaemia	Intramuscular	L-Asparaginase	(226)
		Methotrexate	(180)
	Intravenous	Amsacrine	(183)
		Arsenic trioxide	(180)

Malignancy subtype	Route of administration	Systemic anti-cancer therapy	Studies*
		Cytarabine	(180, 183, 212, 217, 226)
		Daunorubicin	(180, 183, 217)
		Etoposide	(183, 217, 226)
		Idarubicin	(180, 212, 217)
		Fludarabine	(183, 212, 217, 226)
		Mitoxantrone	(183, 217, 226)
		Omacetaxine mepesuccinate	(12) (226)
	Oral	Mercaptopurine	(180)
		ATRA	(180)
		Methotrexate	(180)
Hodgkin's lymphoma	Intravenous	Subcutaneous Cytarabine	(226)
		L-Asparaginase	(183)
		Cyclophosphamide	(210)
		Bleomycin	(210)
		Dacarbazine	(210)
		Doxorubicin	(210)
		Vincristine	(210)
		Vinblastine	(210)
	Oral	Procarbazine	(210)
		Prednisolone	(210)
Non-Hodgkin lymphomas	Intramuscular	Cyclophosphamide	(193)
		L-Asparaginase	(193, 208)
	Intrathecal	Hydrocortisone	(184, 193, 208, 234)
		Cytarabine	(184, 193, 208, 229, 234)
		Methotrexate	(184, 191, 193, 208, 229, 234)
		Prednisolone	(229)
	Intravenous	Bleomycin	(171)
		Carboplatin	(208)
		Cyclophosphamide	(16-23)
		Cytarabine	(184, 193, 208, 229, 234)
		Daunorubicin	(193)
		Dexamethasone	(193, 208, 234)
		Doxorubicin	(171, 184, 191, 193, 205, 208, 229, 234)
		Etoposide	(184, 193, 208, 229, 234)
		Ifosfamide	(184, 193, 208, 229, 234)
		Methotrexate	(184, 193, 208, 229, 234)
		Prednisone	(208, 229)

Malignancy subtype	Route of administration	Systemic anti-cancer therapy	Studies*
		Vincristine	(171, 184, 191, 193, 205, 208, 229, 234)
		Vinblastine	(193, 234)
	Oral	Mercaptopurine	(171, 193, 208, 234)
		Dexamethasone	(184, 193, 208, 229, 234)
		Methotrexate	(171, 184, 193, 234)
		Prednisolone	(205, 208, 234)
		Prednisone	(171, 184, 191, 193, 229)
		Thioguanine	(193)
	Subcutaneous	Cytarabine	(171, 208)

** Not all studies highlighted the route of administration of the used SACT.*

Table S3.6 The identified duration of infusions for some systemic anti-cancer therapy agents

Infusion Duration	Systemic anti-cancer therapy agent *
30 minutes	Cytarabine (183), Fludarabine (212)
1 hour	Amsacrine (183), Cyclophosphamide (247), Daunorubicin (217, 247) Doxorubicin (247), Etoposide (247), Idarubicin (212, 217), Ifosfamide (247), L-Asparaginase (247)
2-3 hours	Cytarabine (183, 233, 247)
4 hours	Cytarabine (183, 212), Etoposide (183, 217)
6 hours	Daunorubicin (183), Mitoxantrone (183)
24 hours	Cytarabine, Daunorubicin (247), Methotrexate (233, 247)
36 hours	Methotrexate (247)

** Not all studies highlighted the duration of the infused SACT agents.*

Table S3.7 Doses of medicines for the management of newly diagnosed cases with acute lymphoblastic leukaemia

Systemic anti-cancer therapy /Corticosteroids	Dose mg/m² or unit	Phase(s)	Studies*
Cyclophosphamide	200	Consolidation / Intensification	(192, 245)
	500	Consolidation / Intensification	(240)
	600	Consolidation / Intensification	(192)
	1000	Consolidation/ Intensification	(174, 192, 197, 201, 227, 233, 241, 242, 245, 247)
	1000	Induction	(174, 239, 245, 247)
Cytarabine	75	Induction	(174, 239, 245, 247)
	75	Consolidation / Intensification	(174, 192, 197, 201, 227, 233, 241, 242, 245, 247)
	200	Consolidation / Intensification	(245)
	300	Consolidation / Intensification	(192)
	1500	Consolidation / Intensification	(233)
	2000	Consolidation / Intensification	(192, 239, 245, 247)
Daunorubicin	25	Induction	(174, 239, 242)
	30	Induction	(192, 206, 214, 240, 241, 245, 247)
	30	Consolidation	(192, 240, 245)
	45	Induction	(174, 219)
	50	Consolidation	(247)
Dexamethasone	2.5	Consolidation / Intensification	(197)
	5	Consolidation / Intensification	(197)
	6	Induction	(201, 233, 240)
	6	Interim maintenance	(192, 201, 227, 233)
	6	Maintenance	(174, 192, 197, 201, 233, 240, 241)
	6	Consolidation / Intensification	(192, 241, 245)
	6.5	Consolidation / Intensification	(206)
	8	Consolidation / Intensification	(192)
	10	Consolidation / Intensification	(174, 197, 201, 227, 233, 242, 247)
	20	Consolidation / Intensification	(192, 239, 245, 247)

Systemic anti-cancer therapy /Corticosteroids	Dose mg/m² or unit	Phase(s)	Studies*
	60	Consolidation / Intensification	(245)
Doxorubicin	25	Induction	(174, 197)
	25	Consolidation / Intensification	(174, 197, 201, 227, 233, 241, 242)
	30	Consolidation / Intensification	(192, 240, 247)
	40	Consolidation / Intensification	(233)
	40	Induction	(220, 233)
Etoposide	100	Consolidation / Intensification	(192, 239, 245)
	150	Consolidation / Intensification	(13)
Ifosfamide	400	Consolidation / Intensification	(13)
	800	Consolidation / Intensification	(192, 245)
Imatinib	340	All phases	(239)
L-Asparaginase**	1000	Induction	(220)
	1500	Induction	(206)
	1500	Consolidation / Intensification	(206)
	2500	Induction	(242)
	5000	Induction	(192, 197, 206, 240, 245)
	5000	Interim maintenance	(174)
	6000	Induction	(174, 201, 233, 241)
	6000	Consolidation / Intensification	(174, 201, 227, 233, 241)
	6500	Induction	(220)
	10000	Induction	(174, 214, 239, 247)
	10000	Consolidation / Intensification	(174, 197, 206, 245, 247)
	15000	Interim maintenance	(227)
	25000	Consolidation / Intensification	(192, 239, 245, 247)
	30000	Induction	(220)
Methotrexate	15	Interim maintenance	(227, 241)
	15	Maintenance	(241)
	20	Interim maintenance	(174, 192, 201, 227, 233, 240)
	20	Maintenance	(174, 192, 197, 201, 233, 245)
	30	Consolidation / Intensification	(233)
	30	Maintenance	(233)
	40	Maintenance	(170)

Systemic anti-cancer therapy /Corticosteroids	Dose mg/m² or unit	Phase(s)	Studies*
	75	Interim maintenance	(242)
	100	Interim maintenance	(227)
	100	Consolidation / Intensification	(174)
	500	Consolidation / Intensification	(240)
	1000	Consolidation / Intensification	(247)
	1500	Consolidation / Intensification	(233)
	2000	Consolidation / Intensification	(197)
	4000	Consolidation / Intensification	(239)
	5000	Consolidation / Intensification	(174, 192, 197, 245)
	5000	Interim maintenance	(241)
Mercaptopurine	20	Maintenance	(241)
	25	Consolidation / Intensification	(192, 245)
	25	Interim maintenance	(241)
	50	Induction	(240)
	50	Consolidation / Intensification	(192, 233, 239, 240)
	50	Interim maintenance	(192, 240)
	50	Maintenance	(192, 197, 233, 245)
	60	Induction	(174, 239, 245, 247)
	60	Consolidation / Intensification	(174, 197, 201, 227, 233, 241, 247)
	60	Interim maintenance	(227)
	75	Induction	(174)
	75	Consolidation / Intensification	(174, 201, 227, 233)
	75	Interim maintenance	(174, 201, 227, 233)
	75	Maintenance	(174, 201, 233)
	100	Consolidation / Intensification	(247)
Prednisolone	40	Induction	(206, 239)
	60	Induction	(192, 197, 206, 214, 220, 241, 242)
Prednisone	40	Induction	(174)
	40	Interim maintenance	(174)
	40	Maintenance	(174)

Systemic anti-cancer therapy /Corticosteroids	Dose mg/m² or unit	Phase(s)	Studies*
	60	Induction	(233, 245, 247)
	60	Consolidation/ intensification	(233)
	60	Maintenance	
Thioguanine	60	Consolidation/ intensification	(192, 227, 240, 245)
	100	Consolidation/ intensification	(247)
Teniposide	-	Consolidation/ intensification	(192)
Vincristine	1.5	Induction	(174, 192, 197, 201, 206, 214, 233, 239-242, 245, 247)
	1.5	Consolidation/ intensification	(174, 192, 197, 201, 206, 227, 233, 240-242, 245, 247)
	1.5	Interim maintenance	(174, 192, 201, 227, 233)
	1.5	Maintenance	(174, 192, 201, 233, 245)
	2	Induction	(220)
	2	Maintenance	(170, 240)
Vindisine	3	Consolidation/ intensification	(192, 245, 247)

* Not all studies highlighted the doses of SACT agents.

Table S3.8 Doses of medicines for the management of newly diagnosed cases with acute myeloid leukaemia

Systemic anti-cancer therapy /Corticosteroids	Dose mg/m² or unit	Studies*
Mercaptopurine	60-70	(180)
All-trans retinoic acid	25	(180)
Amsacrine	100	(183)
Cytarabine	100	(232)
	200	(180)
	100-2000	(226)
	100-3000	(179, 183, 217, 222)
Daunorubicin	45	(179)
	50	(180, 183, 217)
Doxorubicin	50	(232)
Etoposide	50	(179, 180)
	100	(183, 217)
	100-150	(222, 226)
	200	(232)
Expanded activated autologous lymphocytes	3 × 10 ⁹ CD3+ CD8+	(222)
Fludarabine	30	(183, 217, 226)
Harringtonine	4-6	(222)
Idarubicin	8-10	(222)
	10	(217)
	12	(180)
L-asparaginase	6000	(183, 226)
Mitoxantrone	10	(183, 226)
Methotrexate	20-25	(180)
Omacetaxine mepesuccinate	1-50	(226)
Prednisolone	20	(179)

* Not all studies highlighted the doses of SACT agents.

Table S3.9 Doses of systemic anti-cancer therapy for the management of newly diagnosed cases with chronic myeloid leukaemia

Systemic anti-cancer therapy	Dose mg/m² or unit	Studies
Imatinib	150-350	(172)
	Dose mg/kg	
Hydroxyurea	100	(176)

Table S3.10 Other regimens to treat Hodgkin's lymphoma

Regimen	Systemic anti-cancer therapy ± Corticosteroids	Number of studies / Total number of studies
COPDAC	Cyclophosphamide, vincristine, prednisolone, dacarbazine	(3/82) (218, 231, 248)
COPP	Cyclophosphamide, vincristine, procarbazine, prednisone/ prednisolone	(4/82) (182, 196, 210, 251)
OPPA	Vincristine, procarbazine, prednisone, doxorubicin	(2/82) (182, 196)
OEPA	Vincristine, etoposide, prednisolone/ prednisone, doxorubicin	(3/82) (182, 231, 248)
MOPP	Mechlorethamine hydrochloride, vincristine, procarbazine, prednisolone	(1/82) (210)
ChIVbPP	Chlorambucil, vinblastine, prednisone, procarbazine	(1/82) (182)
VBVP	Vinblastine, bleomycin, VP16 (etoposide), prednisone	(1/82) (196)
MINE	Mitoguazone, Ifosfamide, vinorelbine, Etoposide,	(1/82) (196)
IVA70	Ifosfamide, VP16 (etoposide), doxorubicin	(1/82) (196)

Table S3.11 Doses of medicines for the management of newly diagnosed cases with Hodgkin's lymphoma

Systemic anti-cancer therapy / Corticosteroids	Dose mg/m² or unit	Studies*
Cyclophosphamide	600	(210)
	650	(196)
Doxorubicin	25	(199, 210)
	35	(196)
	40	(196)
	40-70	(196)
	70	(196)
Bleomycin	10	(196, 199, 210)
Dacarbazine	375	(199, 210)
Etoposide	100	(196)
	150	(196, 210)
Ifosfamide	1500	(196)
Procarbazine	100	(196, 210)
Prednisolone	40	(210)
Prednisone	40	(196)
	60	(196)
Mitoguazone	500	(196)
Vinblastine	6	(196, 199, 210)
Vincristine	1.4-1.5	(196, 210)
	1.5	(196)
Vinorelbine	15	(196)

* Not all studies highlighted the doses of SACT agents.

Table S3.12 Doses of medicines for the management of newly diagnosed cases with Non-Hodgkin lymphoma

NHL subtype(s)	Systemic anti-cancer therapy / Corticosteroids	Dose	Studies*
All except lymphoblastic subtypes	Cyclophosphamide	750	(205)
	Doxorubicin	40	(205)
	Prednisolone	40	(205)
	Vincristine	1.5	(205)
Non-Hodgkin lymphoma	Bleomycin	15	(171)
	Cyclophosphamide	300,500, 1000,1200	(171)
	Cytarabine	75	(171)
	Doxorubicin	50,60	(171)
	Mercaptopurine	75	(171)
	Methotrexate	25	(171)
	Prednisone	40	(171)
	Vincristine	1.4,1.5,2	(171)
Anaplastic large-cell lymphoma	Cyclophosphamide	200	(193, 221, 234)
		300	(221)
		800	(221, 234)
		1000	(208)
		1200	(193)
	Carboplatin	560	(208)
		150	(193, 234)
		1000	(221, 234)
		2000	(193)
		3000	(208)
	Dexamethasone	10	(193, 234)
		25	(208)
	Daunorubicin	60	(193)
	Doxorubicin	20	(221, 234)
		25	(193, 234)
		30	(193, 230)
		40	(208)
		60	(208)
		75	(193, 234)
		303	(234)
		330	(186)
	Etoposide	60	(221)
		100	(184, 208, 234)
		150	(216, 225)
		200	(193)
	Ifosfamide	400	(193)
		800	(234)
		1200	(221, 234)
	L-Asparaginase	6000	(193)
	Mercaptopurine	50	(221)
		225	(234)

NHL subtype(s)	Systemic anti-cancer therapy / Corticosteroids	Dose	Studies*
	Methotrexate	15	(221, 234)
		60	(193) (234)
		1000	(193)
		1500	(208)
		3000	(193) (234)
	Prednisolone	40	(205, 221, 234)
		120	(234)
	Prednisone	30	(193)
		40	(193)
		60	(193)
		120	(193)
		180	(193)
	6-Thioguanne	300	(193)
	Vinblastine	6	(221, 234)
	Vincristine	1.5	(193, 208, 234)
Burkitt's lymphoma	Cyclophosphamide	200	(184, 229)
		250	(184)
		300	(171, 184, 208)
		500	(184, 208, 225)
		800	(184)
		1000	(171, 184, 208)
		1200	(171, 184, 191)
	Cytarabine	30	(208)
		50	(184, 208)
		75	(171)
		100	(184, 208)
		150	(184)
		2000	(184)
		3000	(208, 225)
	Doxorubicin	25	(171, 184)
		30	(225)
		50	(171)
		60	(191, 208, 225)
	Etoposide	100	(184)
		150	(208)
		200	(208)
	Ifosfamide	800	(184, 229)
	Methotrexate	300	(184)
		3000	(184, 208)
		5000	(229)
		8000	(208, 225)
	Prednisolone	5	(229)
		10	(229)

NHL subtype(s)	Systemic anti-cancer therapy / Corticosteroids	Dose	Studies*
		60	(208)
		30	(229)
	Prednisone	60	(184, 225)
		1	(184)
		1.4	(171)
		1.5	(171, 184, 191, 229)
		2	(171, 184, 225)
		1000	(184)
Lymphoblastic lymphoma	Cyclophosphamide	1000	(195, 230)
		2000, 3000, 3250, 4750, 10500	(186)
	Cytarabine	75	(186, 195, 230)
		300	(186)
		400	(195)
		1500	(186)
		2000	(186)
	Daunorubicin	30	(195, 230)
	Doxorubicin	30	(195)
		75, 90, 120, 180, 240, 300, 330	(186)
	Dexamethasone	8	(230)
		12	(195)
	Etoposide	1800	(186)
	L-Asparaginase	6000	(186)
		10000	(230)
		25000	(195)
	Methotrexate	20	(230)
		40	(195)
		400	(186)
		3000	(230)
		4000	(186, 195)
	Prednisolone	60	(230)
	Prednisone	40	(195)
	6-Thioguanine	40	(230)
	Vincristine	1.5	(195, 230)
		2	(195)
	Systemic anti-cancer therapy	mg/kg	
	Doxorubicin	2.5**	(234)

* Not all studies highlighted the doses of SACT agents; ** patients < 10 kg use.

Table S3.13 Salvage regimens for refractory / relapsed Hodgkin's lymphoma

Salvage regimen	Systemic anti-cancer therapy ± Corticosteroids	Number of studies / Total number of studies
Platinum-containing regimens	(Etoposide-Methylprednisolone sodium succinate (solu-medrol) ®-Cytarabine- Cisplatin)	(224)
	(Etoposide-Ifosfamide-Carboplatin)	(190, 224)
	(Etoposide- Prednisolone - Ifosfamide - Cisplatin)	(177, 218)
	(Dexamethasone - Carboplatin - Cytarabine)	(177)
Gemcitabine-containing regimen	(Gemcitabine -Vinorelbine)	(177, 218)

Table S3.14 Doses of medicines for the management of refractory /relapsed cases

Systemic anti-cancer therapy / Corticosteroids	Dose mg/m ² or unit	Studies*
Cisplatin	60	(177)
Dexamethasone	40	(177)
Carboplatin	600	(177)
Carmustine	300	(218)
Cytarabine	200	(218)
	2000	(177, 212)
Etoposide	100	(177)
	200	(218)
Fludarabine	30	(212)
Gemcitabine	1000	(177, 218)
Idarubicin	8	(212)
Ifosfamide	1000	(177)
Melphalan	140	(218)
Prednisolone	60	(177)
Vinorelbine	25	(218)
Systemic anti-cancer therapy	Dose cells, m ² /kg	Studies*
Arsenic trioxide	0.15	(180)
Tisagenlecleucel	1.3-4.6 10 ⁶ cells	(173)

* Not all studies highlighted the doses of SACT agents.

Table S3.15 Doses of medicines to prepare for Hematopoietic Stem Cell Transplantation

Systemic anti-cancer therapy	Dose mg/m² or unit	Studies*
ACNU 1-(4-amino-2-methyl-5-pyrimidinyl)-methyl-3-(2-chloroethyl)-3-nitrosourea hydrochloride	150	(216)
BCNU 1,3-Bis (2-chloroethyl)-1-nitrosourea	150	(216)
Cyclophosphamide	1500	(216)
Cytarabine	2000	(212)
Etoposide	800	(216)
Fludarabine	30	(212)
	120-180	(238)
Idarubicin	8	(212)
Melphalan	140	(238)
Treosulfan	3×9– <3×11	
Systemic anti-cancer therapy	Dose mg/kg	
Cyclophosphamide	60	(209)
	120	(187, 238)
Busulfan	4	(209)
	6.4	(188)
	16	(187)
Thiotepa	8-10	(238)

* Not all studies highlighted the doses of SACT agents.

Table S3.16 The scores of critical appraisal assessment

Author	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Score
Davidson et al (184)	Y	U	U	U	N	U	U	U	U	U	N	1
Jan et al (218)	N/A	N/A	U	N	N	U	Y	N	U	U	U	1
Oliveira et al (189)	N/A	N/A	N/A	U	U	U	Y	N	U	U	U	1
Resham et al (234)	U	U	U	N	N	U	Y	N	U	U	U	1
Nazir et al (202)	U	U	U	U	N	U	Y	N	U	U	U	1
Özdemir et al (246)	U	U	U	U	U	U	Y	U	U	U	U	1
Wali et al (177)	N/A	N/A	U	N	N	U	Y	U	U	U	U	1
Sugiyama et al (250)	U	U	U	U	N	U	Y	U	U	U	U	1
Smeding et al (172)	N/A	N/A	N/A	U	N	U	Y	N	Y	U	U	2
Salami et al (239)	N/A	N/A	U	U	N	N/A	Y	N	Y	U	U	2
Lashkari et al (219)	N/A	N/A	U	U	N	Y	Y	N	U	U	U	2
Gao et al (186)	U	U	U	U	N	U	Y	N	Y	U	U	2
Reinecke et al (215)	U	U	U	U	N	Y	Y	U	U	U	N	2
Moskop et al (173)	N/A	N/A	N/A	Y	U	U	Y	N	U	U	U	2
Giona et al (176)	N/A	N/A	U	N	N	U	Y	Y	U	U	U	2
Jaime-Perez et al (233)	U	U	U	Y	N	U	Y	N	U	U	U	2
Ceppi et al (193)	U	U	U	U	Y	Y	U	N	U	U	U	2
Dhingra et al (178)	N/A	N/A	Y	U	N	U	Y	U	U	U	U	2
Amjad et al (207)	U	U	N	Y	Y	U	Y	U	U	U	U	3
Seetharam et al (214)	N/A	N/A	U	Y	N	Y	Y	U	U	U	N	3
Michalowski et al (228)	Y	U	U	Y	U	U	U	N	U	U	Y	3
Güneş et al (245)	N/A	N/A	U	Y	U	U	Y	Y	U	U	U	3
Makkeyah et al (227)	U	U	U	Y	U	Y	Y	U	U	U	U	3
Hafez et al (237)	N/A	N/A	U	Y	U	Y	Y	U	U	U	U	3

Alkhatay et al (224)	U	N/A	N/A	Y	U	U	Y	Y	U	U	U	3
Patel et al (205)	N/A	N/A	U	Y	Y	U	U	U	U	U	N	3
Choeprasert et al (208)	U	N/A	N/A	U	N	U	Y	Y	Y	U	U	3
Vural et al (229)	N/A	N/A	U	U	N	U	Y	Y	Y	U	U	3
Flank et al (198)	U	U	U	U	U	Y	Y	U	Y	U	U	3
Yeh et al (243)	Y	U	U	U	N	Y	Y	U	U	U	U	3
Sherief et al (190)	N/A	N/A	U	Y	U	U	Y	U	Y	U	U	3
Jastaniah et al (180)	U	U	U	Y	Y	U	U	Y	U	U	Y	4
Weelderen et al (232)	N/A	N/A	N	Y	U	Y	Y	U	Y	U	U	4
Dujua et al (197)	N/A	N/A	U	Y	U	Y	Y	N	Y	N	U	4
Boztug et al (238)	U	U	U	Y	Y	U	Y	U	U	U	Y	4
Parambil et al (248)	N/A	U	U	Y	Y	U	Y	N	U	U	Y	4
Marr et al (204)	N/A	U	U	Y	U	Y	Y	Y	U	U	U	4
Karhan et al (210)	U	U	U	Y	Y	U	U	Y	U	U	Y	4
Sayed et al (195)	N/A	U	U	Y	U	Y	Y	Y	U	U	U	4
Palayullakandi et al (231)	U	U	U	Y	Y	U	Y	N	U	U	Y	4
Buckle et al (191)	N/A	N/A	N/A	Y	Y	Y	U	N	N/A	U	Y	4
Choi et al (216)	U	N/A	N/A	Y	Y	U	Y	N	U	U	Y	4
Büyükcapu-Bay et al (249)	U	U	U	Y	Y	U	U	N	Y	U	Y	4
Afify et al (223)	N/A	N/A	U	Y	N/A	Y	Y	Y	U	U	U	4
Koka et al (247)	N/A	N/A	N/A	Y	Y	Y	Y	U	N/A	N/A	Y	5
Hu et al (236)	N/A	N/A	N/A	Y	Y	Y	Y	U	U	U	Y	5
Hamidieh et al (209)	N/A	N/A	N/A	Y	Y	U	Y	Y	U	U	Y	5
Loimijoki et al (220)	U	U	Y	Y	Y	U	Y	U	U	U	Y	5
Mushtaq et al (242)	N/A	N/A	U	Y	Y	Y	Y	N	U	U	Y	5

Pacheco et al (240)	Y	U	U	U	U	Y	Y	Y	Y	U	Y	5
Kato et al (185)	Y	U	U	Y	Y	U	U	Y	U	N/A	Y	5
Ishida et al (188)	Y	N/A	N/A	Y	Y	Y	U	N	U	U	Y	5
Yalcin et al (244)	Y	N/A	N/A	Y	Y	U	Y	N	U	U	Y	5
Vyas et al (206)	Y	Y	Y	U	N	Y	Y	N	U	U	U	5
Mustafa et al (212)	U	N/A	N/A	Y	Y	Y	Y	U	U	U	Y	5
Ghafoor et al (217)	N/A	N/A	U	Y	Y	Y	Y	U	U	U	Y	5
Trehan et al (201)	Y	U	U	Y	Y	U	Y	N	U	U	Y	5
Lin et al (211)	N/A	N/A	U	Y	Y	Y	Y	U	U	U	Y	5
Sun et al (235)	N/A	N/A	Y	Y	U	Y	Y	U	U	U	Y	5
Vijayasekharan et al (230)	N/A	U	U	Y	Y	U	Y	U	U	Y	Y	5
Seror et al (196)	N/A	N/A	N/A	Y	Y	U	Y	Y	N/A	N/A	Y	5
Vijayasekharan et al (221)	N/A	N/A	N/A	Y	Y	U	Y	Y	U	U	Y	5
Avila et al (181)	N/A	U	U	Y	Y	Y	Y	U	U	U	Y	5
Malhotra et al (203)	N/A	N/A	U	Y	Y	Y	Y	U	U	U	Y	5
Olmos-Jime'nez et al (194)	N/A	N/A	Y	Y	Y	U	Y	U	U	U	Y	5
Sakaguchi et al (213)	Y	N/A	N/S	Y	Y	Y	U	Y	U	U	Y	6
Wei et al (192)	Y	U	U	Y	Y	Y	Y	N	U	U	Y	6
Jabeen et al (241)	N/A	N/A	N/A	Y	Y	U	Y	Y	Y	U	Y	6
Al-hadad (174)	N	U	U	Y	Y	Y	Y	Y	U	U	Y	6
Smitherman et al (175)	Y	U	U	Y	Y	Y	Y	U	U	U	Y	6
Jain et al (251)	N/A	N/A	U	Y	Y	Y	Y	Y	U	U	Y	6
Opanga et al (171)	Y	Y	Y	Y	U	U	U	Y	Y	–	–	6
Kersten et al (179)	U	U	U	Y	Y	Y	Y	U	Y	U	Y	6
Kishimoto et al (200)	Y	U	U	Y	Y	Y	Y	U	U	U	Y	6

Sutiman et al (183)	Y	U	U	Y	Y	Y	Y	Y	U	N	Y	7
Zhang et al (222)	Y	U	U	Y	Y	Y	Y	Y	U	N	Y	7
Berranger et al (187)	Y	U	U	Y	Y	Y	Y	Y	U	U	Y	7
Hanna et al (170)	Y	Y	U	Y	Y	Y	Y	Y				7
Hu et al (226)	Y	U	U	Y	Y	Y	Y	Y	U	U	Y	7
Bhethanabhotla et al (199)	N/A	N/A	N/A	Y	Y	Y	Y	Y	Y	U	Y	7
Huang et al (225)	N/A	N/A	U	Y	Y	Y	Y	N	Y	Y	Y	7
Geel et al (182)	U	U	U	Y	Y	Y	Y	Y	Y	U	Y	7

Table S3.17 Systematic Reviews and Meta-analysis Extension for Scoping Reviews checklist

No.	Guide questions/description	Location in the thesis / comments	Notes
1. Title	Identify the report as a scoping review.	Page 20	
2. Structured summary	Provide a structured summary that includes (as applicable): background, objectives, eligibility criteria, sources of evidence, charting methods, results, and conclusions that relate to the review questions and objectives.	XIV	It was not considered to be in consistent with other chapters. However, the thesis abstract highlighted the main highlights of scoping review
3. Rationale	Describe the rationale for the review in the context of what is already known. Explain why the review questions/objectives lend themselves to a scoping review approach.	Page 21-22	3.1 Introduction section 3.4.1 Scoping review as a method section
4. Objectives	Provide an explicit statement of the questions and objectives being addressed with reference to their key elements (e.g., population or participants, concepts, and context) or other relevant key elements used to conceptualize the review questions and/or objectives.	Page 21-22	3.2 Aim section 3.3 Research question section
5. Protocol and registration	Indicate whether a review protocol exists; state if and where it can be accessed (e.g., a Web address); and if available, provide registration information, including the registration number.	Page 22	3.4 Methods section
6. Eligibility criteria	Specify characteristics of the sources of evidence used as eligibility criteria (e.g., years considered, language, and publication status), and provide a rationale.	Page 23	3.4.2 Eligibility criteria section

7. Information sources	Describe all information sources in the search (e.g., databases with dates of coverage and contact with authors to identify additional sources), as well as the date the most recent search was executed.	Page 24	3.4.3 Search strategy section Appendix
8. Search	Present the full electronic search strategy for at least 1 database, including any limits used, such that it could be repeated.	Page 24	3.4.3 Search strategy section Appendix 1
9. Selection of sources of evidence	State the process for selecting sources of evidence (i.e., screening and eligibility) included in the scoping review.	Page 24	3.4.4 Study selection section
10. Data charting process	Describe the methods of charting data from the included sources of evidence (e.g., calibrated forms or forms that have been tested by the team before their use, and whether data charting was done independently or in duplicate) and any processes for obtaining and confirming data from investigators.	Page 25	3.4.5 Data extraction section
11. Data items	List and define all variables for which data were sought and any assumptions and simplifications made	Page 25	3.4.5 Data extraction section Appendix 1
12. Critical appraisal of individual sources of evidence	If done, provide a rationale for conducting a critical appraisal of included sources of evidence; describe the methods used and how this information was used in any data synthesis (if appropriate).	Page 26	3.4.7 Critical appraisal of the included articles
13. Synthesis of results	Describe the methods of handling and summarizing the data that were charted.	Page 25	3.4.6 Data synthesis and presentation section
14. Selection of sources of evidence	Give numbers of sources of evidence screened, assessed for eligibility, and	Page 27	Figure 3.1

	included in the review, with reasons for exclusions at each stage, ideally using a flow diagram		
15. Characteristics of sources of evidence	For each source of evidence, present characteristics for which data were charted and provide the citations.	Page 26	3.5 Results section Appendix 1
16. Critical appraisal within sources of evidence	If done, present data on critical appraisal of included sources of evidence	Page 51	3.5.6 Results of critical appraisal assessment section Table S3.16, Appendix
17. Results of individual sources of evidence	For each included source of evidence, present the relevant data that were charted that relate to the review questions and objectives.	Page 26	3.5 Results section Appendix 1
18. Synthesis of results	Summarize and/or present the charting results as they relate to the review questions and objectives.	Page 26	3.5 Results section
19. Summary of evidence	Summarize the main results (including an overview of concepts, themes, and types of evidence available), link to the review questions and objectives, and consider the relevance to key groups.	Page 49	3.6 Discussion section
20. Limitations	Discuss the limitations of the scoping review process.	Page 55	3.6.4 Limitations and strengths of the scoping review section
21. Conclusions	Provide a general interpretation of the results with respect to the review questions and objectives, as well as potential implications and/or next step	Page 56	3.7 Conclusion section

22. Funding	Describe sources of funding for the included sources of evidence, as well as sources of funding for the scoping review. Describe the role of the funders of the scoping review.	Page 22	3.4 Methods section
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NB: the criteria were in line with Systematic Reviews and Meta-analysis Extension for Scoping Reviews (PRISMA-ScR) checklist (161).

Supplementary information for Chapter 5 (Appendix 2)

Table S5.1 Addressing of criteria of Checklist for Assessment and Reporting of Document Analysis

No.	Guide questions/description	Location in the thesis / comments	Notes
1. Title	Identify the study involved in document analysis.	Page 68	
2. Abstract	Identify the methods as mixed (listing the methods) or solely document analysis.	XIV	The abstract was not included searching for consistency with other chapters. However, it has been mentioned in Chapter 8 that multimethod was used. The thesis abstract was included
3. Rationale	Describe the rationale for the use of documents in the study.	Page 70	5.4.1 Document analysis as a chosen method section
4.Objectives	Provide an explicit statement of the research objective(s) or question(s) of the study.	Page 69	5.2 Aim and Objectives section
5. Eligibility criteria	Specify the eligibility criteria for including documents as data in this specific study.	Page 71	5.4.2 Inclusion and exclusion criteria section
6. Document corpus	How many documents there were. What kinds of documents were involved (e.g., local curriculum guides and national policy papers).	Page 75	5.9.1 Characteristics and description of identified document section Appendix 2
	The documents' media (print, electronic etc.).	Page 75	5.9.1 Characteristics and description of identified document section Appendix 2
	The original purposes of the document where existing documents	Page 75	5.9.1 Characteristics and description of

	were used (e.g., Target audience. Who produced them, when and why?)		identified document section Appendix 2
	Include a table or equivalent documentation of all the documents used (either in the paper or as a supplementary table).	Page 75	5.9.1 Characteristics and description of identified document section Appendix 2
7. Document provenance	How they were elicited and from whom. Whether they were researcher- or participant-created. For example, where diary entries or reflective writing are used and explain why the rationale behind the target group of participants and the guidance given to participants in respect of producing texts.	Page 71	5.4.2 Inclusion and exclusion criteria section
	When the documents were created and when they were collected as part of the study (e.g., January 2020 to the end of December 2020).	Page 72	5.4.3 Data collection section Appendix 2
	How the documents were identified (e.g., archives or websites searched). If appropriate, present the full search strategies for document identification, including any filters and limits used (e.g., English language only and particular websites only).	Page 72	5.4.3 Data collection section Appendix 2
	The data limits of any searches and the rationale for these data limits.		
8. Document collection and management	How documents were obtained, managed etc. Report if any of the documents used are	Page 72 Page 72	5.4.3 Data collection section 5.4.4 Data management section

	publicly available and where they can be found.		
9. Document quality	Consider the “quality” of the documents and the relation of document quality to the study objectives. For existing documents:	Page 73	5.4.6 Data analysis section
	Were they complete?	Page 72	5.4.3 Data collection section Face validity was done to check if it complete
	Were there gaps in the documents?	Page 76	5.9.2 The content of identified documents section
	Were they redacted?	Page 72	5.4.4 Data management section
	Did you need to do more searching or rely on additional documents than planned?	N/A	No
	Were some documents not available or accessible?	N/A	No
	Did participants engage in the process as intended?	N/A	No
	Were the data comprehensive or sparse?	Page 78	5.9.2 The content of identified documents section
	How much researcher effort was required to elicit the data, and what might be the implications of researcher interventions (e.g., frequent reminders)?	Page 74	5.5 Rigour and trustworthiness section
10. Reflexivity/positionality (may be placed in the methods or discussion section of your paper)	Role and experience of researchers, experience in DA and positionality.	Page 74	5.6 Research team and reflexivity RA, TM, and NW did not experience any of the clinical

	Consider the potential presence of positionalities, both in a document (links back to #8) and of the researcher(s).		indications before and didn't use any of these documents for the study of interest.
11. Preliminary data analysis	Specify the approach to preliminary or organising data analysis, the methods used to collect data from the documents (e.g., Bowen's "first-pass document review" [p. 32] ¹¹ ; often using variations on thematic or content analyses). Specify if any automation tools were used in the process (e.g., AntConc and Wordsmith).	Page 73	5.4.6 Data analysis section No automation tools were used in the process
12. Document analysis	Outline the analytical steps taken—what methodology or methods were involved? Explain whether the analysis focused on content, latent content, linguistics or some other document content or characteristics.	Page 73	5.4.6 Data analysis section
	To what extent and in what ways did analysts immerse or attune themselves to the content, style, subtexts and other dimensions of the documents they analysed?	Page 73	5.4.6 Data analysis section
	Was a theoretical lens used to ensure transferability?	N/A	
	How were findings synthesised to arrive at findings?	Page 73	5.4.6 Data analysis section
13. Results directly relate to research questions or goals	General: ensure what is presented is set out in a logical order and aligns with the research question.	Page 75	5.9 Results section

14. Findings directly relate to DA	Clarify how the document data informed the results/findings—including whether contextual, triangulation or as the primary data source or the object of the research approach.³¹ If using quotes, link back to the document as you would when referencing a publication (e.g., document name and page number).	Page 75	5.9 Results section
15. Findings are balanced	Results and balanced and proportional to the form of DA used and the nature of the corpus In MMR, DA component should be represented in results according to its weighting within the study as a whole	Page 75	5.9 Results section
16. Consequences for DA methods	Be clear about what the document analysis added to the study.	Page 139	Chapter 8
	What did the study add to DA?	Page 139	Chapter 8
	Consider the strengths and limitations of the use of DA.	Page 95	5.10.5 Strengths and limitations section
17. DA in context	Provide a general interpretation of the results in the context of other DA studies.	N/A	No document analysis studies were found
18. Overall	Are the details provided sufficient to reproduce the study?	Page 70	5.4 Methods section Appendix 2

NB: the criteria were in line with Checklist for Assessment and Reporting of Document Analysis (CARDA) (337).

Table S5.2 The used terms in searching on Google and Bing

Indication terms and synonyms	
“Tumour lysis” OR cell Lysis” “PCP Prophylaxis” OR “Pneumocystis pneumonia” “Emesis” OR “vomiting” OR “nausea”	
Source of information terms and synonyms	
Guideline	Guide OR guidance OR recommendation OR protocol OR standard OR framework OR flowchart OR checklist OR principles
Formulary	Handbook OR manual OR code OR model
Policy	Procedure OR practice
Population terms and synonyms	
Children OR adolescent OR paediatric	
Disease terms and synonyms	
Cancer OR malignancy OR oncology OR tumour	
Intervention terms and synonyms	
Treatment OR prescribing OR management OR “supportive care” OR “palliative care”.	
Region terms and synonyms	
Scotland OR Scottish OR England OR Britain OR British OR “UK” OR “United Kingdom” OR Grampian OR Lothian OR Greater Glasgow and Clyde OR Glasgow OR Edinburgh OR Aberdeen	

Table S5.3 Websites of included NHS health boards

NHS health board	The website
Greater Glasgow and Clyde NHS	https://www.nhsggc.scot/
Lothian NHS	https://www.nhsllothian.scot/
Grampian NHS	https://www.nhsgrampian.org/

Table S5.4 Results of data analysis of antiemetics

The content	Document																							
	Natl.	Natl.	Natl.	Natl.	Natl.	Natl.	Reg.	Reg.	Reg.	Intl.	Natl.	Reg.	Reg.	Natl.	Natl.	Reg.	Reg.	Reg.	Natl.	Reg.	Reg.			
	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	Q	R	S	T			
Aprepitant																								
Dose, interval, route																								
Population of treatment																								
Formulation																								
Drug dispensing																								
Drug administration																								
Monitoring measures																								
Duration of treatment																								
Precaution																								
Drug allergy /Hypersensitivity																								
Response to toxicities																								
Drug storage																								
Drug disposal																								

The content	Document																							
	Natl.	Natl.	Natl.	Natl.	Natl.	Natl.	Reg.	Reg.	Reg.	Intl.	Natl.	Reg.	Reg.	Natl.	Natl.	Reg.	Reg.	Reg.	Natl.	Reg.	Reg.			
	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	Q	R	S	T			
Chlorpromazine																								
Dose, interval, route																								
Population of treatment																								
Formulation																								
Drug dispensing																								
Drug administration																								
Monitoring measures																								
Duration of treatment																								
Precaution																								
Drug allergy /Hypersensitivity																								
Response to toxicities																								
Drug storage																								
Drug disposal																								

The content	Document																							
	Natl.	Natl.	Natl.	Natl.	Natl.	Natl.	Reg.	Reg.	Reg.	Intl.	Natl.	Reg.	Reg.	Natl.	Natl.	Reg.	Reg.	Reg.	Natl.	Reg.	Reg.			
	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	Q	R	S	T			
Cyclizine																								
Dose, interval, route																								
Population of treatment																								
Formulation																								
Drug dispensing																								
Drug administration																								
Monitoring measures																								
Duration of treatment																								
Precaution																								
Drug allergy /Hypersensitivity																								
Response to toxicities																								
Drug storage																								
Drug disposal																								

The content	Document																							
	Natl.	Natl.	Natl.	Natl.	Natl.	Natl.	Reg.	Reg.	Reg.	Intl.	Natl.	Reg.	Reg.	Natl.	Natl.	Reg.	Reg.	Reg.	Natl.	Reg.	Reg.			
	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	Q	R	S	T			
Dexamethasone																								
Dose, interval, route																								
Population of treatment																								
Formulation																								
Drug dispensing																								
Drug administration																								
Monitoring measures																								
Duration of treatment																								
Precaution																								
Drug allergy /Hypersensitivity																								
Response to toxicities																								
Drug storage																								
Drug disposal																								

The content	Document																							
	Natl.	Natl.	Natl.	Natl.	Natl.	Natl.	Reg.	Reg.	Reg.	Intl.	Natl.	Reg.	Reg.	Natl.	Natl.	Reg.	Reg.	Reg.	Natl.	Reg.	Reg.			
	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	Q	R	S	T			
Fosaprepitant																								
Dose, interval, route																								
Population of treatment																								
Formulation																								
Drug dispensing																								
Drug administration																								
Monitoring measures																								
Duration of treatment																								
Precaution																								
Drug allergy /Hypersensitivity																								
Response to toxicities																								
Drug storage																								
Drug disposal																								

The content	Document																							
	Natl.	Natl.	Natl.	Natl.	Natl.	Natl.	Reg.	Reg.	Reg.	Intl.	Natl.	Reg.	Reg.	Natl.	Natl.	Reg.	Reg.	Reg.	Natl.	Reg.	Reg.			
	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	Q	R	S	T			
Granisetron																								
Dose, interval, route																								
Population of treatment																								
Formulation																								
Drug dispensing																								
Drug administration																								
Monitoring measures																								
Duration of treatment																								
Precaution																								
Drug allergy /Hypersensitivity																								
Response to toxicities																								
Drug storage																								
Drug disposal																								

The content	Document																						
	Natl.	Natl.	Natl.	Natl.	Natl.	Natl.	Reg.	Reg.	Reg.	Intl.	Natl.	Reg.	Reg.	Natl.	Natl.	Reg.	Reg.	Reg.	Natl.	Reg.	Reg.		
	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	Q	R	S	T		
Hyoscine Hydrobromide																							
Dose, interval, route																							
Population of treatment																							
Formulation																							
Drug dispensing																							
Drug administration																							
Monitoring measures																							
Duration of treatment																							
Precaution																							
Drug allergy /Hypersensitivity																							
Response to toxicities																							
Drug storage																							
Drug disposal																							

The content	Document																						
	Natl.	Natl.	Natl.	Natl.	Natl.	Natl.	Reg.	Reg.	Reg.	Intl.	Natl.	Reg.	Reg.	Natl.	Natl.	Reg.	Reg.	Reg.	Natl.	Reg.	Reg.		
	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	Q	R	S	T		
Haloperidol																							
Dose, interval, route																							
Population of treatment																							
Formulation																							
Drug dispensing																							
Drug administration																							
Monitoring measures																							
Duration of treatment																							
Precaution																							
Drug allergy /Hypersensitivity																							
Response to toxicities																							
Drug storage																							
Drug disposal																							

The content	Document																							
	Natl.	Natl.	Natl.	Natl.	Natl.	Natl.	Reg.	Reg.	Reg.	Intl.	Natl.	Reg.	Reg.	Natl.	Natl.	Reg.	Reg.	Reg.	Natl.	Reg.	Reg.			
	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	Q	R	S	T			
Levomepromazine																								
Dose, interval, route																								
Population of treatment																								
Formulation																								
Drug dispensing																								
Drug administration																								
Monitoring measures																								
Duration of treatment																								
Precaution																								
Drug allergy /Hypersensitivity																								
Response to toxicities																								
Drug storage																								
Drug disposal																								

The content	Document																							
	Natl.	Natl.	Natl.	Natl.	Natl.	Natl.	Reg.	Reg.	Reg.	Intl.	Natl.	Reg.	Reg.	Natl.	Natl.	Reg.	Reg.	Reg.	Natl.	Reg.	Reg.			
	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	Q	R	S	T			
Lorazepam																								
Dose, interval, route																								
Population of treatment																								
Formulation																								
Drug dispensing																								
Drug administration																								
Monitoring measures																								
Duration of treatment																								
Precaution																								
Drug allergy /Hypersensitivity																								
Response to toxicities																								
Drug storage																								
Drug disposal																								

The content	Document																						
	Natl.	Natl.	Natl.	Natl.	Natl.	Natl.	Reg.	Reg.	Reg.	Intl.	Natl.	Reg.	Reg.	Natl.	Natl.	Reg.	Reg.	Reg.	Natl.	Reg.	Reg.		
	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	Q	R	S	T		
Metoclopramide																							
Dose, interval, route																							
Population of treatment																							
Formulation																							
Drug dispensing																							
Drug administration																							
Monitoring measures																							
Duration of treatment																							
Precaution																							
Drug allergy /Hypersensitivity																							
Response to toxicities																							
Drug storage																							
Drug disposal																							

The content	Document																							
	Natl.	Natl.	Natl.	Natl.	Natl.	Natl.	Reg.	Reg.	Reg.	Intl.	Natl.	Reg.	Reg.	Natl.	Natl.	Reg.	Reg.	Reg.	Natl.	Reg.	Reg.			
	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	Q	R	S	T			
Nabilone																								
Dose, interval, route																								
Population of treatment																								
Formulation																								
Drug dispensing																								
Drug administration																								
Monitoring measures																								
Duration of treatment																								
Precaution																								
Drug allergy /Hypersensitivity																								
Response to toxicities																								
Drug storage																								
Drug disposal																								

The content	Document																						
	Natl.	Natl.	Natl.	Natl.	Natl.	Natl.	Reg.	Reg.	Reg.	Intl.	Natl.	Reg.	Reg.	Natl.	Natl.	Reg.	Reg.	Reg.	Natl.	Reg.	Reg.		
	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	Q	R	S	T		
Olanzapine																							
Dose, interval, route																							
Population of treatment																							
Formulation																							
Drug dispensing																							
Drug administration																							
Monitoring measures																							
Duration of treatment																							
Precaution																							
Drug allergy /Hypersensitivity																							
Response to toxicities																							
Drug storage																							
Drug disposal																							

The content	Document																							
	Natl.	Natl.	Natl.	Natl.	Natl.	Natl.	Reg.	Reg.	Reg.	Intl.	Natl.	Reg.	Reg.	Natl.	Natl.	Reg.	Reg.	Reg.	Natl.	Reg.	Reg.			
	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	Q	R	S	T			
Ondansetron																								
Dose, interval, route																								
Population of treatment																								
Formulation																								
Drug dispensing																								
Drug administration																								
Monitoring measures																								
Duration of treatment																								
Precaution																								
Drug allergy /Hypersensitivity																								
Response to toxicities																								
Drug storage																								
Drug disposal																								

The content	Document																							
	Natl.	Natl.	Natl.	Natl.	Natl.	Natl.	Reg.	Reg.	Reg.	Intl.	Natl.	Reg.	Reg.	Natl.	Natl.	Reg.	Reg.	Reg.	Natl.	Reg.	Reg.			
	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	Q	R	S	T			
Palonosetron																								
Dose, interval, route																								
Population of treatment																								
Formulation																								
Drug dispensing																								
Drug administration																								
Monitoring measures																								
Duration of treatment																								
Precaution																								
Drug allergy /Hypersensitivity																								
Response to toxicities																								
Drug storage																								
Drug disposal																								

The content	Document																						
	Natl.	Natl.	Natl.	Natl.	Natl.	Natl.	Reg.	Reg.	Reg.	Intl.	Natl.	Reg.	Reg.	Natl.	Natl.	Reg.	Reg.	Reg.	Natl.	Reg.	Reg.		
	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	Q	R	S	T		

Dark blue indicates fully addressed information. Light blue indicates partially addressed information. White indicates the absence of information. Intl.= international; Natl.= national; Reg.= regional

Table S5.5 Results of data analysis of medicines for PCP

The content	Document																						
	Natl.	Natl.	Natl.	Natl.	Natl.	Natl.	Reg.	Reg.	Reg.	Intl.	Natl.	Reg.	Reg.	Natl.	Natl.	Reg.	Reg.	Reg.	Natl.	Reg.			
	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	T			
Atovaquone																							
Dose, interval, route																							
Population of treatment																							
Formulation																							
Drug dispensing																							
Drug administration																							

The content	Document																			
	Natl.	Natl.	Natl.	Natl.	Natl.	Natl.	Reg.	Reg.	Reg.	Intl.	Natl.	Reg.	Reg.	Natl.	Natl.	Reg.	Reg.	Reg.	Natl.	Reg.
	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	T
Monitoring measures																				
Duration of treatment																				
Precaution																				
Drug allergy /Hypersensitivity																				
Response to toxicities																				
Drug storage																				
Drug disposal																				
Co-Trimoxazole																				
Dose, interval, route																				
Population of treatment																				
Formulation																				
Drug dispensing																				

The content	Document																			
	Natl.	Natl.	Natl.	Natl.	Natl.	Natl.	Reg.	Reg.	Reg.	Intl.	Natl.	Reg.	Reg.	Natl.	Natl.	Reg.	Reg.	Reg.	Natl.	Reg.
	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	T
Drug administration																				
Monitoring measures																				
Duration of treatment																				
Precaution																				
Drug allergy /Hypersensitivity																				
Response to toxicities																				
Drug storage																				
Drug disposal																				
Dapsone																				
Dose, interval, route																				
Population of treatment																				
Formulation																				

The content	Document																			
	Natl.	Natl.	Natl.	Natl.	Natl.	Natl.	Reg.	Reg.	Reg.	Intl.	Natl.	Reg.	Reg.	Natl.	Natl.	Reg.	Reg.	Reg.	Natl.	Reg.
	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	T
Drug dispensing																				
Drug administration																				
Monitoring measures																				
Duration of treatment																				
Precaution																				
Drug allergy /Hypersensitivity																				
Response to toxicities																				
Drug storage																				
Drug disposal																				
Pentamidine																				
Dose, interval, route																				
Population of treatment																				

The content	Document																			
	Natl.	Natl.	Natl.	Natl.	Natl.	Natl.	Reg.	Reg.	Reg.	Intl.	Natl.	Reg.	Reg.	Natl.	Natl.	Reg.	Reg.	Reg.	Natl.	Reg.
	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	T
Formulation																				
Drug dispensing																				
Drug administration																				
Monitoring measures																				
Duration of treatment																				
Precaution																				
Drug allergy /Hypersensitivity																				
Response to toxicities																				
Drug storage																				
Drug disposal																				

Dark blue indicates fully addressed information. Light blue indicates partially addressed information. White indicates the absence of information. Intl.= international; Natl.= national; Reg.= regional

Table S5.6 Results of data analysis of medicines for tumour lysis syndrome (TLS)

The content	Document																					
	Natl.	Natl.	Natl.	Natl.	Natl.	Natl.	Reg.	Reg.	Reg.	Intl.	Natl.	Reg.	Reg.	Natl.	Natl.	Reg.	Reg.	Reg.	Natl.	Reg.		
	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	T		
Allopurinol																						
Dose, interval, route																						
Population of treatment																						
Formulation																						
Drug dispensing																						
Drug administration																						
Monitoring measures																						
Duration of treatment																						
Precaution																						
Drug allergy /Hypersensitivity																						
Response to toxicities																						

The content	Document																						
	Natl.	Natl.	Natl.	Natl.	Natl.	Natl.	Reg.	Reg.	Reg.	Intl.	Natl.	Reg.	Reg.	Natl.	Natl.	Reg.	Reg.	Reg.	Natl.	Reg.			
	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	T			
Drug storage																							
Drug disposal																							
Rasburicase																							
Dose, interval, route																							
Population of treatment																							
Formulation																							
Drug dispensing																							
Drug administration																							
Monitoring measures																							
Duration of treatment																							
Precaution																							
Drug allergy /Hypersensitivity																							

The content	Document																						
	Natl.	Natl.	Natl.	Natl.	Natl.	Natl.	Reg.	Reg.	Reg.	Intl.	Natl.	Reg.	Reg.	Natl.	Natl.	Reg.	Reg.	Reg.	Natl.	Reg.			
	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	T			
Response to toxicities																							
Drug storage																							
Drug disposal																							

Dark blue indicates fully addressed information. Light blue indicates partially addressed information. White indicates the absence of information. Intl.= international; Natl.= national; Reg.= regional.

Table S5.7 The characteristics of documents to prescribe medicines for three indications in the three Scottish centres.

Number of document	Type of document	Length of the source (Pages)	Document title	Version (Edition) , Year of publication / revision	Author /Publisher	Public availability (open access)	Target Population	Purpose of publishing	Target healthcare professionals audience	URL
All indications										
National documents										
A	Drug formulary	1984 (Print version)	British National Formulary (BNF)	Edition 89 (Print version) / February -2025 (Online version)	Joint Formulary Committee / - BMJ - Royal Pharmaceutical Society	Yes	Adults and children	Provide prescribers , pharmacists, and other healthcare professionals with sound up-to-date information about the use of medicines.	Pharmacists , and other healthcare professionals	http://www.bnf.org
B	Drug formulary	1352 (print version)	BNF for Children (BNFC)	Edition 2024-2025 (Print version) / February -2025	Joint Formulary Committee / - BMJ - Royal Pharmaceutical Society	Yes	Children	Is for rapid reference by UK health professionals engaged in prescribing	Health professionals engaged in prescribing, dispensing, and administering	https://bnfc.nice.org.uk/

Number of document	Type of document	Length of the source (Pages)	Document title	Version (Edition) , Year of publication / revision	Author /Publisher	Public availability (open access)	Target Population	Purpose of publishing	Target healthcare professionals audience	URL
				(Online version)				dispensing , and administering medicines to children	g medicines to children	
C	Summaries	N/A	Clinical Knowledge Summaries (CKS)	N/A	National Institute for Health and Care Excellence (NICE) / Clarity Informatics Ltd (trading as Agilio Software Primary Care)	Yes	Adults and children	Providing primary care practitioners with a readily accessible summary of the current evidence base and practical advice on best practice.	Primary care professionals including GPs, GP registrars, nurses, pharmacists,	https://cks.nice.org.uk/
	Summaries	N/A	Summary of product characteristics (SmPC)	N/A	- Pharmaceutical companies - Medicines regulator	Yes	Adults and children	Explains how to use and prescribe a medicine.	Healthcare professionals - such as doctors, nurses, and pharmacists	https://www.medicines.org.uk/emc#gref

Number of document	Type of document	Length of the source (Pages)	Document title	Version (Edition) , Year of publication / revision	Author /Publisher	Public availability (open access)	Target Population	Purpose of publishing	Target healthcare professionals audience	URL
					(MHRA or EMA) / Datapharm					
E	Textbook	4800 (print version) available digitally via Medicines Complete.	Martindale : The Complete Drug Reference	41st Edition	Alison Brayfield and Catherine Cadart / Pharmaceutical Press Royal Pharmaceutical Society's knowledge business.	No	Adults and children	The Complete Drug Reference for concise and specific detail to identify and understand drugs, herbals, and other pharmaceutical substances.	N/A	http://www.medicinescomplete.com
F	Formulary	273	Association for Paediatric Palliative Medicine (APPM)	6th edition 2024	Lynda Brook Anita Aindow/Association for	Yes	Children with palliative care	Support prescribers working in paediatric palliative care	Paediatric palliative care prescribers	https://www.appm.org.uk/

Number of document	Type of document	Length of the source (Pages)	Document title	Version (Edition) , Year of publication / revision	Author /Publisher	Public availability (open access)	Target Population	Purpose of publishing	Target healthcare professionals audience	URL
					Paediatric Palliative Medicine					
Regional										
G	Formulary	53	Greater Glasgow and Clyde (GGC) Paediatric Formulary	October 2019	N/A / NHS GGC	Yes	Paediatric patients	Aimed primarily at acute paediatric services, though much of it is relevant to prescribers in Primary Care	Prescribers within NHS GGC	https://gcm medicines.org.uk/other-formularies/paediatric-formulary/
H	Formulary	-	East Region Formulary	-	East Region Formulary Committee / NHS Borders, NHS Fife and NHS Lothian	Yes	Adults and children	Provides guidance on appropriate and cost-effective prescribing for general practice and hospitals in	Healthcare professionals in NHS Borders, Fife, and/or Lothian	https://www.nhs.uk/patients-and-visitors/our-services/general

Number of document	Type of document	Length of the source (Pages)	Document title	Version (Edition) , Year of publication / revision	Author /Publisher	Public availability (open access)	Target Population	Purpose of publishing	Target healthcare professionals audience	URL
								NHS Borders, NHS Fife and NHS Lothian.		- services /medicines- and-prescribing/nhs-borders - formulary/
I	Formulary	-	Grampian Area Formulary	Version 8.3	N/A /NHS Grampian	Yes	Adults and children	The main aim of this formulary is to promote safe, evidence-based, cost-effective prescribing.	All staff involved in the prescribing, dispensing and administration of medicines within NHS Grampian	https://www.grampianformulary.scot.nhs.uk/default.asp?siteType=Full
Emesis										
International										

Number of document	Type of document	Length of the source (Pages)	Document title	Version (Edition) , Year of publication / revision	Author /Publisher	Public availability (open access)	Target Population	Purpose of publishing	Target healthcare professionals audience	URL
J	Guideline	85 pages	Guideline for Classification of the Acute Emetogenic Potential of Antineoplastic Medication in Pediatric Cancer Patients	(August 2010)	L. Lee Dupuis, Sabrina Boodhan, Lillian Sung, Carol Portwine, Richard Hain, Patricia McCarthy, Mark Holdsworth /Paediatric Oncology Group of Ontario (POGO)	Yes	Children and youth with cancer who are receiving antineoplastic medication and who are at risk of experiencing anti-cancer therapy induced nausea and vomiting (AINV)	Provide physicians, nurses, pharmacists and other health care providers who care for children aged 1 month to 18 years who are receiving antineoplastic medication with an approach to assess the emetogenic potential of antineoplastic regimens.	Physicians, nurse practitioners, nurses, and pharmacists in Ontario clinicians in other jurisdictions, administrators, educators and researchers	https://www.pogo.ca/wp-content/uploads/2014/10/POGO-Emetogenicity-Classification-Guideline-Summary-Final-rev-250111.pdf

Number of document	Type of document	Length of the source (Pages)	Document title	Version (Edition) , Year of publication / revision	Author /Publisher	Public availability (open access)	Target Population	Purpose of publishing	Target healthcare professionals audience	URL
National										
K	Guideline	24 pages	Children and Young People's Cancer Association(CCLG) Guideline for the Management of Chemotherapy-Induced Nausea and Vomiting (CINV)	Version 2.1 (November 2023)	Children's Cancer and Leukaemia Group (CCLG)/ CCLG Supportive Care Group	No	Children with cancer	The aim of providing a comprehensive overview which may be taken to standardise therapy across CCLG Centres for the management of chemotherapy induced nausea and vomiting.	Treating clinicians	-
Regional 1										
L	standard operating procedure (SOP)	13 pages	Anti-emetics in haematology	Version 4, (June 2023)	<u>Anonymous</u>	No	Children with cancer	N/A	The management of patients with nausea	N/A

Number of document	Type of document	Length of the source (Pages)	Document title	Version (Edition) , Year of publication / revision	Author /Publisher	Public availability (open access)	Target Population	Purpose of publishing	Target healthcare professionals audience	URL
			patients for chemotherapy-induced nausea and vomiting (CINV)						and vomiting will be directed by the Consultant/ Associate Specialist or a senior member of the medical team. The Medical/Nursing team will be responsible for administration and monitoring.	
Regional 2										
M	Guideline	15	Paediatric Haematology/Oncology Anti-emetic Guideline	Version 2.0	<u>Anonymous</u>	No	Children and young people with cancer	This document provides guidance for prescribing and	All nursing, medical and pharmacy staff involved in managing, planning,	-

Number of document	Type of document	Length of the source (Pages)	Document title	Version (Edition) , Year of publication / revision	Author /Publisher	Public availability (open access)	Target Population	Purpose of publishing	Target healthcare professionals audience	URL
								administration of anti-emetics for children and young people with cancer attending the Haematology/Oncology service at	prescribing, and administering SACT within <u>Anonymous</u>	
Tumour lysis syndrome										
National										
N	Clinical trial protocol	231	United Kingdom National Randomised Trial For Children and Young Adults with	Version 7.0 (February 2018)	Professor Ajay Vora/ - Cancer research UK clinical trial units - University of Birmingham	No	Children and young adults suffering from ALL or LBL (T-cell non-Hodgkin's Lymphoma	Define whether further refinement of minimal residual disease (MRD) based risk	Those providing care to patients enrolled in UKALL Consultant, HSCT associate specialist or	-

Number of document	Type of document	Length of the source (Pages)	Document title	Version (Edition) , Year of publication / revision	Author /Publisher	Public availability (open access)	Target Population	Purpose of publishing	Target healthcare professionals audience	URL
			Acute Lymphoblastic Leukaemia and Lymphoma 2011 (UKALL trial 2011)		m - Bloodwise		(NHL) or Smlg-ve precursor B-NHL	stratification and treatment regimen improves survival whilst reducing overall burden of therapy in children and young adults suffering from acute lymphoblastic leukaemia or lymphoblastic lymphoma (T-cell non-Hodgkin's Lymphoma (NHL) or	a senior member of the medical team, medical/nursing team	

Number of document	Type of document	Length of the source (Pages)	Document title	Version (Edition) , Year of publication / revision	Author /Publisher	Public availability (open access)	Target Population	Purpose of publishing	Target healthcare professionals audience	URL
								Smlg-ve precursor B-NHL).		
O	Guideline	11	Guidelines for the management of tumour lysis syndrome in adults and children with haematological malignancies on behalf of the British Committee for Standards in Haematology	2015	Gail L Jones, Andrew Will, Graham H Jackson, Nicholas J A Webb, Simon Rule/ the British Committee for Standards in Haematology	Yes	Adults and children	To provide healthcare professionals with clear guidance on the management of patients with tumour lysis syndrome	Those providing care to patients at risk of tumour lysis syndrome or Patients with tumour lysis syndrome- Haematologists, nephrologists and intensive care physicians, ...	https://doi.org/10.1111/bjh.13403
Regional 1										

Number of document	Type of document	Length of the source (Pages)	Document title	Version (Edition) , Year of publication / revision	Author /Publisher	Public availability (open access)	Target Population	Purpose of publishing	Target healthcare professionals audience	URL
P	SOP	5 pages	Tumour Lysis Syndrome	Version 4.0, June 2023	<u>Anonymous</u>	No	Children with cancer	N/A	Consultant, HSCT associate specialist or a senior member of the medical team, the Medical/Nursing team	N/A
Regional 2										
Q	Guideline	10 pages	Paediatric Guideline: Prevention and Management of Tumour Lysis Syndrome	Version 3	<u>Anonymous</u>	No	Children and young people at risk of tumour lysis syndrome	To provide guidance on the prevention and management of tumour lysis syndrome.	All medical, nursing and pharmacy staff involved in the care of patients at risk of tumour lysis syndrome	N/A
Regional 3										

Number of document	Type of document	Length of the source (Pages)	Document title	Version (Edition), Year of publication / revision	Author /Publisher	Public availability (open access)	Target Population	Purpose of publishing	Target healthcare professionals audience	URL
R	Local guideline	4 pages	Prevention and management of tumour lysis syndrome policy	Version: 2.0 (September 2024)	<u>Anonymous</u>	No	Children and young people with cancer	N/A	Healthcare professionals within NHS Grampian	N/A
PCP prophylaxis										
National										
S	Guideline	23	Guidelines for the prophylaxis of Pneumocystis Jirovecii Pneumonia (PJP) in children with solid tumour	(November 2016)	CCLG	Yes	Children ≤19 years who are immunocompromised for reasons other than treatment for a solid malignancy	Guidelines on the indications and methods for prophylaxis against Pneumocystis Jirovecii Pneumonia (PJP) in Paediatric	Healthcare providers	https://www.cclg.org.uk/write/MediaUploads/Member%20are%20Treatment%20guidelines/PJP_Propylaxis_Guidelin

Number of document	Type of document	Length of the source (Pages)	Document title	Version (Edition) , Year of publication / revision	Author /Publisher	Public availability (open access)	Target Population	Purpose of publishing	Target healthcare professionals audience	URL
								Oncology Patients.		e_Final.pdf
Regional										
T	SOP	5 pages	Pneumocystis Jirovecii Pneumonia (PJP) prophylaxis	Version: 1 (September 2023)	<u>Anonymous</u>	No	Children with cancer	N/A	All registered nursing staff can administer oral medications.	-

Table S5.8 The background of publishers of documents

Publisher	Documents	Notes
Professional bodies (n=6)	A, B, E, F, K, T	Documents A, B were jointly published by two bodies
NHS board (n=5)	G, H, I, M, Q	-
Clinical trial unit (n=3)	J, N, S	Document N was jointly published by three bodies
Health institution (n=3)		-
Medical journal (n=3)	A, B, O	Documents A, B were jointly published by two bodies
IT service company (n=2)	C, D	-
Health regulatory (n=1)	D	Document D was jointly published by two bodies
Academic institution (n=1)	N	Document N was jointly published by three bodies
Third sector organisation (n=1)	N	Document N was jointly published by three bodies
National organisation (n=1)	R	-
Pharmaceutical companies (n=1)	D	Document D was jointly published by two bodies

Table S5.9 Dose-banding across documents

Treating population	Medicine name	Documents
Paediatric Population defined by age	Change from mg/kg to fixed doses	
	Alloprinol	D, E, F
	Aprepitant	L
	Chlorpromazine	A, B, D, F, L
	Cyclizine	A, B, F, K, L, M
	Fosaprepitant	B, D, E, K, M
	Granisetron	B, E, K, L, M
	Haloperidol	B, L
	Levomepromazine	B, E, F, K, L, M
	Lorazepam	F, M
	Change from mg/m2 to fixed doses	
	Ondansetron	K
	Change from mg/kg to mg/m2	
	Ondansetron	L
	Formula (mg or µg/kg) for all children	
	Allopurinol	D, E, N
	Rasburicase	D, E, N, O, P, Q, R
	Granisetron	D
	Metoclopramide	F, K
	Olanzapine	K
	Palonosetron	D, E, J, K, L
	Dapsone	E, S
	Pentamidine	T
	Formula mg/m2 for all children	
	Ondansetron	6
	Fixed dose mg for each age band	
	Aprepitant	B
	Cyclizine	E
	Dexamethasone	F, L
	Hyoscine Hydrobromide	K, M
	Metoclopramide	D, E
	Ondansetron	B
	Co-trimoxazole	D
	Dapsone	D
	Pentamidine	B
	Fixed dose ml for each age band	
	Cotrimoxazole	D

Treating population	Medicine name	Documents
Paediatric Population defined by weight	Change from mg/kg to fixed doses	
	Allopurinol	O
	Change from mg/m2 to fixed doses	
	Allopurinol	P
	Change from mg/kg formula to fixed doses	
	Ondansetron	D
	Fixed dose mg for each weight band	
	Aprepitant	K, L, M
	Metoclopramide	E, K, L
	Nabilone	F, K, L, M
	Ondansetron	L, M
Paediatric Population defined by surface area	Formula of mg/m2 for each surface area band	
	Ondansetron	D,
	Fixed dose (mg) for each surface area band	
	Dexamethasone	K, M
	Cotrimoxazole	T
	Change from mg/kg formula to fixed doses	
	Cotrimoxazole	S
Un-defined Paediatric Population	Formula (mg or µg/kg)	
	Lorazepam	K, L
	Metoclopramide	B
	Atovaquone	S, T
	Dapsone	B, T
	Pentamidine	S
	Formula (mg/m2)	
	Allopurinol	Q, R
	Cotrimoxazole	A, B, E
	Fixed doses (mg)	
	Pentamidine	D

Table S5.10 Notes on variations of doses.

Medicine	Notes
Aprepitant	Variation in the recommended doses of certain bands among regional and national documents.
Chlorpromazine	One variation in the recommended dose for 6-11 years among regional and national documents.
Dexamethasone	Variation in the recommended doses of certain bands among all documents.
Granisetron	Unlike other documents, IV doses for patients >16 ranged between 1 to 3 mg among regional and national documents.
Haloperidol	The variation was present in the upper limit of the recommended intravenous and subcutaneous dose for patients (1 month -11 years) among regional and national documents.
Levomepromazine	Variation in the recommended doses of certain bands among all documents.
Lorazepam	Variation in the recommended doses of certain bands among all documents.
Ondansetron	Variation in the recommended doses of certain bands among all documents.
Cotrimoxazole	Variation in the recommended doses of certain bands among regional and national documents.
Allopurinol	Slightly higher upper dosing limit for allopurinol among regional and national documents.

Table S5 .11 Texts of unlicensed use in the collected documents

Medicine	Indication	Notes on un-licencing status	Document
Atovaquone	PCP prophylaxis	Not licensed for prophylaxis against pneumocystis pneumonia.	A
		Not licensed for use in children.	B
Co-trimoxazole	PCP prophylaxis	Not licensed for use in children under 6 weeks.	A, B
Dapsone	PCP prophylaxis	Monotherapy not licensed for children for prophylaxis of P. jirovecii pneumonia.	B
Pentamidine	PCP prophylaxis	Not licensed for primary prevention of Pneumocystis jirovecii (Pneumocystis carinii) pneumonia by inhalation of nebulised solution.	A
		Not licensed for prevention of pneumocystis pneumonia in children.	B
Cyclizine	Emesis	Tablets not licensed for use in children under 6 years.	A
		Injection not licensed for use in children.	B
		Cyclizine lactate injection is not licensed for use in children in the UK.	E
		Tablets are not licensed for use in children under 6 years old. Injection is not licensed for use in children	F
Haloperidol	Emesis	Not licensed for use in children with nausea and vomiting	F
Granisetron	Emesis (treat and prevent acute and delayed CINV)	Oral and topical formulations not licensed in children	K, M
		Tablets not licensed in children (age range not specified by manufacturer).	B
Olanzapine	-	Not licensed for use in children.	A, B
		Although unlicensed in the UK for use in children and adolescents aged under 18 years,	E
		Not licensed for use in children and adolescents less than 18 years of age	F
Ondansetron	Emesis	Not licensed for radiotherapy-induced nausea and vomiting in children.	B
		Injection is not licensed for subcutaneous administration.	F
Levomepromazine	Emesis	Available as an unlicensed or special preparation	G
Nabilone		Not licensed for use in children	B

Medicine	Indication	Notes on un-licencing status	Document
	Emesis (treat and prevent CINV)	Not licensed for use in children	F
Metoclopramide	Emesis (prevent delayed CINV)	Maxolon ® tablets not licensed for use in children.	B
		Not licensed for use in infants less than 1 year of age. Tablets not licensed for use in under 15 years (body weight less than 61 kg). Not licensed for continuous infusion.	F
Rasburicase	Prophylaxis and treatment of tumour lysis	Not licensed for use in children.	B

Supplementary information for Chapter 6 (Appendix 3)

Table S6.1 Addressing of consolidated criteria for reporting qualitative research (376)

No.	Guide questions/description	Location in the thesis / comments	Notes
Domain 1: Research team and reflexivity			
Personal Characteristics			
1. Interviewer/facilitator	Which author/s conducted the interview or focus group?	Page 106	6.4.5 Data collection section RA conducted the interviews.
2. Credentials	What were the researcher's credentials? <i>E.g. PhD, MD</i>	Page 109	6.6 Research team and reflexivity section RA had MSc in Clinical Pharmacy. TM and NW had a PhD. HA had MSc in clinical Pharmacy.
3. Occupation	What was their occupation at the time of the study?	Page 109	6.6 Research team and reflexivity section RA was a student at Strathclyde Institute of Pharmacy & Biomedical Sciences (SIPBS), University of Strathclyde TM and NW were RA's supervisors, full-academics, and senior researchers. HA was a student at Strathclyde Institute of Pharmacy & Biomedical Sciences (SIPBS), University of Strathclyde
4. Gender	Was the researcher male or female?	Page 106	6.4.5 Data collection section RA was a female. HA was a male.
5. Experience and training	What experience or training did the researcher have?	Page 109	6.6 Research team and reflexivity section RA had taken several courses on qualitative methods and interviewing before conducting the study. TM and NW had extensive training and experience in the qualitative research field.
6. Relationship established	Was a relationship established prior to study commencement?	Page 109	6.6 Research team and reflexivity section

			TM, NW, and RA met one of the participants to discuss some issues related to paediatric cancer in Scotland one year before conducting the study.
7. Participant knowledge of the interviewer	What did the participants know about the researcher? e.g. <i>personal goals, reasons for doing the research</i>	Page 104 Page 106	6.4.3.1 Participant information sheet (PIS) and consent form 6.4.5 Data collection section As part of recruitment, the PIS was disseminated, and it contained some information about the projects' aim and research team. RA introduced herself and reminded the participants of the study's aims before proceeding to the interview questions.
8. Interviewer characteristics	What characteristics were reported about the interviewer/facilitator? e.g. <i>Bias, assumptions, reasons and interests in the research topic</i>	Page 109	6.6 Research team and reflexivity section RA is a pharmacist and has interest in the provided care for paediatric patients with cancer. TM is a pharmacist and has interest in rational use of medicines and health policy. NW is a pharmacist and has interest in healthcare services and community pharmacy. HA is a pharmacist and has interest in healthcare services.
Domain 2: study design			
Theoretical framework			
9. Methodological orientation and Theory	What methodological orientation was stated to underpin the study? e.g. <i>grounded theory, discourse analysis, ethnography, phenomenology, content analysis</i>	Page 99 Page 107	6.4 Methods section 6.4.6 Data analysis section
Participant selection			

10. Sampling	How were participants selected? <i>e.g. purposive, convenience, consecutive, snowball</i>	Page 105	6.4.2.2 Sample strategy section
11. Method of approach	How were participants approached? <i>e.g. face-to-face, telephone, mail, email</i>	Page 105	6.4.4 Recruitment methods section
12. Sample size	How many participants were in the study?	Page 110	6.9.1 Participants demographics (Baseline characteristics) section
13. Non-participation	How many people refused to participate or dropped out? Reasons?	Page 110	6.9.1 Participants demographics (Baseline characteristics) section
Setting			
14. Setting of data collection	Where was the data collected? <i>e.g. home, clinic, workplace</i>	Page 110	6.9.1 Participants demographics (Baseline characteristics) section
15. Presence of non-participants	Was anyone else present besides the participants and researchers?	N/A	
16. Description of sample	What are the important characteristics of the sample? <i>e.g. demographic data, date</i>	Page 110	It was not provided due to the sample size of participants
Data collection			
17. Interview guide	Were questions, prompts, guides provided by the authors? Was it pilot tested?	Page 101 Page 104 Page 104	6.4.3.3 Interview guide (Interview schedule) section 6.3.3.1 Usability test (A pre-piloting test) section 6.3.3.2 Piloting section
18. Repeat interviews	Were repeat interviews carried out? If yes, how many?	N/A	No interviews were repeated
19. Audio/visual recording	Did the research use audio or visual recording to collect the data?	Page 106	6.4.5.1 Data management section
20. Field notes	Were field notes made during and/or after the interview or focus group?	Page 106	6.4.5 Data collection section
21. Duration	What was the duration of the interviews or focus group?	Page 110	6.9.1 Participants demographics (Baseline characteristics) section
22. Data saturation	Was data saturation discussed?	Page 105	6.4.2.1 Sample strategy section
23. Transcripts returned	Were transcripts returned to participants for comment and/or correction?	N/A	No, no need to return it to participants.
Domain 3: analysis and findings			
Data analysis			

24. Number of data coders	How many data coders coded the data?	Page 107	6.4.6 Data analysis section
25. Description of the coding tree	Did authors provide a description of the coding tree?	Page 107	6.4.6 Data analysis section
26. Derivation of themes	Were themes identified in advance or derived from the data?	Page 107	6.4.6 Data analysis section
27. Software	What software, if applicable, was used to manage the data?	Page 107	6.4.6 Data analysis section
28. Participant checking	Did participants provide feedback on the findings?	N/A	No, however, participants have the right to ask for providing the final findings.
Reporting			
29. Quotations presented	Were participant quotations presented to illustrate the themes / findings? Was each quotation identified? e.g. <i>participant number</i>	Page 111	6.7.2 Emerged themes and subthemes section
30. Data and findings consistent	Was there consistency between the data presented and the findings?	Page 111	6.7.2 Emerged themes and subthemes section
31. Clarity of major themes	Were major themes clearly presented in the findings?	Page 111	6.7.2 Emerged themes and subthemes section
32. Clarity of minor themes	Is there a description of diverse cases or discussion of minor themes?	Page 111	6.7.2 Emerged themes and subthemes section

NB: the criteria were in line with consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups (376). *N/A; not applicable.*

Figure S6.1 Participant Information Sheet



Participant Information Sheet (PIS) for Healthcare Provider

I am a PhD student at the University of Strathclyde with a background in pharmacy, currently working on a project focusing on children with cancer. I am supported by two supervisors who are full-time lecturers (supervisors) in Pharmacoepidemiology, which is the science of studying the use of medicines on large populations, and Health Services Research at the University of Strathclyde's Institute of Pharmacy and Biomedical Sciences.

We would like to invite you to take part in my research study about medical and nonmedical prescribers' experiences on the use of information sources for prescribing supportive care. Please take your time to read the following information carefully and discuss it with others whenever you want. The contact details of the research team are provided below if you have questions.

What is the purpose of this research?

The aim of this research is to discuss the sources of information prescribers use to prescribe medicines for emesis (nausea and vomiting), tumour lysis, and Pneumocystis pneumonia (PCP) prophylaxis for paediatric patients with cancer (aged < 19 years). We would like to understand how you access and use these sources to prescribe medicines for the above symptoms and conditions. We are also seeking to learn about the challenges you face while using these sources to prescribe medicines for emesis, tumour lysis and PCP prophylaxis in paediatric cancer area.

Do you have to take part?

No, taking part in this study is entirely voluntary. You have the right not to accept the invitation. If you accept it and the researcher interview you, you may take a break or choose not to answer any question or end the interview at any time.

What will you do in the project?

You will be asked questions by a single researcher (PhD student) to describe your experience using sources of information to prescribe medicines for emesis, tumour lysis, and PCP prophylaxis. There will be questions on challenges of using

information sources for prescribing these medicines for paediatric patients with cancer. The interview will be carried out over Microsoft Teams © at a mutually convenient time and will last about 50 minutes. The option of an in-person interview in the place you are working is also available if preferred. The interviews will be recorded for transcribing (only voice & transcript). Video recording is optional in this study.

Why have you been invited to take part?

You have been invited because of your role in treating paediatric patients with cancer. This study will be open to both medical prescribers (physicians) and nonmedical prescribers (pharmacists and nurses) who have obtained prescribing qualifications, and who prescribe supportive care medicines for paediatric patients with cancer (< 19 years) in routine clinical care in Scotland.

What information is being collected in the project?

The interviews aim to collect information related to your experiences on prescribing medicines for above clinical areas in paediatric cancer hospitals. You will be asked to provide your name, your email address, basic demographic information, and information sources you use to prescribe medicines for emesis, tumour lysis, and PCP prophylaxis by filling a short questionnaire separately before arranging the interview. Data will be anonymised after collection, before analysis and dissemination. All names and other potentially identifiable information will be removed from the transcript during the anonymisation process. Your interview responses can be withdrawn until the date of anonymisation. Some anonymised quotes of your own words might be displayed when sharing the results. Results and de-identified transcript will be sent upon request.

Who will have access to the information?

The access to the information will be limited to the research team. All personal data will be processed in line with the provisions of the Data Protection Act 2018 and GDPR regulations.

Where will the information be stored and how long will it be kept for?

All data will be stored safely on secure University of Strathclyde cloud-based systems, including OneDrive © and Microsoft Teams ©. Paper-based data will be kept in a locked cabinet. Data will be stored until publishing of peer-reviewed

paper and defencing of dissertation then it will be destroyed securely and appropriately. Digital data will be deleted from all university systems irreversibly.

All personal data will be processed in accordance with data protection legislation. Please read our Privacy Notice for Research Participants for more information about your rights under the legislation.

What if something goes wrong?

If you have a concern about any aspect of this study, you should ask to speak to the lead pharmacist who will do their best to answer your questions. If you remain unhappy and wish to complain formally, you can do this by contacting the

Chief Investigator and lead supervisor:

Dr Tanja Mueller

Strathclyde Institute of Pharmacy and Biomedical Sciences

University of Strathclyde

161 Cathedral Street

Glasgow G4 0RE

tanja.muller@strath.ac.uk

This research was granted ethical approval by the Strathclyde Institute of Pharmacy and Biomedical Science Ethics Committee.

If you have any questions/concerns, during or after the research, or wish to contact an independent person to whom any questions may be directed or further information may be sought from, please contact:

Secretary to the University Ethics Committee Research & Knowledge Exchange Services

University of Strathclyde

Graham Hills Building

50 George Street Glasgow

G1 1QE

Telephone: 0141 548 3707

Email: ethics@strath.ac.uk

What happens next?

We would like to thank you for your time to read this information sheet. If you are interested in participating in this study, confirm you have read this information sheet by ticking the box below, and completing the demographic and contact questions on the following pages of this form (click the arrow to proceed). I (Rahaf Alkhlaifat, PhD student) will contact you to agree on a date and time for the interview suitable for you.

To ask any question or to obtain a summary of the final results of the study **Please contact me (Rahaf, PhD student) using the contact details below, at any time:**
Rahaf Alkhlaifat

Strathclyde Institute of Pharmacy and Biomedical Sciences

University of Strathclyde

161 Cathedral Street Glasgow G4 0RE

Email: rahaf.alkhlaifat@strath.ac.uk

you can also contact any member of the research team at any point.

Chief Investigator and lead supervisor details:

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Glasgow G4 0RE

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Figure S6.2 Invitation email template

Dear.....

I hope this email finds you well.

I am Rahaf Alkhlaifat, a PhD student at the University of Strathclyde, who will conduct the interviews with paediatric medical and non-medical prescribers in NHS GGC as part of the following research study:

Study title (Full): Prescribers' experiences on the use of information sources for prescribing supportive care medicines in Scottish paediatric oncology wards: A qualitative interview study.

Study title (Short): Prescribers' experiences on the use of information sources

IRAS reference:

Chief investigator: Dr Tanja Mueller

As the aforementioned project has officially been approved, I am now asking for your help with distributing the study invitation to eligible prospective participants. I have attached a template of the invitation email, along with the Participant Information Sheet (PIS) and a consent form. The PIS comprises all relevant information but please do get in touch with either myself or Dr Tanja should any questions arise.

Thank you for your time and consideration.

Respectfully,

Rahaf

Table S6.2 The collected information from certain healthcare providers or teams

Profession	Nature of information	Illustrative quotes
Emesis		
Speciality teams	Practical information on the management (n=4)	<i>"...if we were going into a kind of difficult to control symptoms and territory, I probably would be actually physically speaking to the palliative care team" (P7, pharmacist, talking about emesis)</i>
Medical doctor (MD)	Practical information about patient (n=1)	<i>"...sometimes I use a consultant for because they'll know the patient quite well or the senior doctor who's really been involved in their care because they'll know the patient quite well or they'll know the history of like they've not reacted very well to this antiemetic in the past" (P4, pharmacist, talking about emesis)</i>
Pharmacist	Information about medicines (n=4)	<i>"So, then I sought support and advice from pharmacy colleagues to ensure that we consulted with them drugs, the formularies to make sure there were no drug interactions." (P5, Medical doctor, talking about emesis)</i>
Pharmacy technician	Practical information about medicines (n=1)	<i>"If it's something that they've not really seen that much, then they they won't know the answer, but they'll know what we've done routinely before or I've done quite a lot in the past. So, they're quite good for telling me, oh, this disperses really, really well. So, for example, with like levomepromazine tablets, they've told me that the three milligram disperses a lot better than the six does" (P4, pharmacist, talking about emesis)</i>
Nurse	Practical information about patient (n=2)	<i>"...sometimes the nurses know the patients much better than I do because they see them more regularly." (P6, Medical doctor, talking about PCP prophylaxis)</i>
Pneumocystis pneumonia prophylaxis		
Infectious disease MD	Objective information (n=1)	<i>"So, if I had somebody that I thought had an allergy. It's because infectious disease also has the immunology. So, if I needed somebody allergy tested to be certain that I could use the prophylaxis that I wanted to."</i>
Pharmacist	Information about medicines (n=4)	<i>"I tend to decide on which drugs to use and then I often ask the pharmacy team as to guide me as to which is the correct dose" P6, Medical doctor, talking about PCP prophylaxis)</i>
Nurses	Practical information to start administering medicines (n=1)	<i>"There can be times that nurses are feeding in, times that we have a I can think of a clinical nurse specialist who had pointed out that when the child was getting their methotrexate and we're trying</i>

		<i>not to do Septrin on the days that they were trying to clear it" (P8, Medical doctor, talking about PCP prophylaxis)</i>
	Practical information about the most suitable route of administering medicines" (n=1)	<i>"Maybe speak with nursing staff about their opinion on the best alternatives to use and route of administration. What's been tolerated best by other patients." (P5, Medical doctor, talking about PCP prophylaxis)</i>
	Practical information about patient (n=1)	<i>"We've got our ENPs [note: Emergency Nurse Practitioner], they're quite good. Um, we've got our outreach nurses that sometimes go and visit people's homes"</i>
Tumour lysis syndrome		
Pharmacy technician	Practical information about medicines (n=1)	<i>"They are good to let me know what formulations of stuff are available. So, they're very, very experienced." (P4, pharmacist, talking about TLS)</i>