The Provision of Pharmaceutical Care in a System for the Use of Methotrexate in the Treatment of Patients with Rheumatoid Arthritis

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Author's Declaration

Abstract

Background: Rheumatoid arthritis (RA) is a chronic, long-term disease, which requires close monitoring by primary and secondary health care providers. However, the involvement of community pharmacist in the disease management process has not been previously identified in literature.

Aim: The research aimed to provide a system for a provision of pharmaceutical care for the patients with rheumatoid arthritis with respect to methotrexate (MTX) therapy.

Methods: The exploration of the issues around the management of RA was undertaken by using qualitative interviews. The patterns of methotrexate and other disease-modifying anti-rheumatic drugs (DMARDs) use were identified by retrospective reviews of databases and clinical documents. The Delphi technique was used in order to achieve a consensus among specialists on the prescribing and monitoring of methotrexate and patient self-management strategies.

Results: The qualitative interviews highlighted the shortcomings in the communication pathway between healthcare professionals and emphasised the lack of pharmacists' involvement in the disease management process for the patient with RA. The effectiveness of methotrexate therapy was confirmed by the higher continuation rate compared to the other DMARDs, where socio-economic environment of patients did not show any effect on the treatment discontinuation. The results of the Delphi survey revealed there are variations in the practice of rheumatology specialists in the use of methotrexate therapy. Recommendations for patient self-management activities during methotrexate therapy were suggested through the Delphi. In the practice of methotrexate prescribing and dispensing process, criteria for quality assessment of the methotrexate prescriptions were suggested. Finally, a new model of care to integrate the community pharmacist's contribution to the management of RA with MTX was designed and tested.

Conclusion: The findings from this thesis contribute to the understanding of pharmaceutical care provision in patients with RA. The implications of the research on further development of pharmaceutical care services in this arena are discussed.

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ALT	Alanine Aminotransferase
AST	Ankylosing Spondylitis
ASMP	Arthritis Self-Management Programme
AST	Aspartate Transaminase
ATTRACT	Anti-TNF Trial in RA with Concomitant Therapy
AZA	Azathioprine
BMQ	Beliefs about Medicines Questionnaire
BNF	British National Formulary
CDTM	Comprehensive Drug Therapy Management
CI	Confidence Interval (95%)
CLASS	Celecoxib Long-term Arthritis Safety Study
COX	Cyclooxygenase
CPD	Continuing Professional Development
Cr	Creatinine
CRP	C-Reactive Protein
CSM	Committee on Safety of Medicines
DAS	Disease Activity Score
DHFR	Dihydrofolate reductase
DMARDs	Disease-Modifying Anti-Rheumatic Drugs
DoE	Department of Environment
DoH	Department of Health
DTP	Drug Therapy Problem
EID	Extent of Information Desired
ENT	Ear, Nose and Throat
ERAS	Early Rheumatoid Arthritis Study
ESR	Erythrocyte Sedimentation Rate
FBC	Full Blood Count
FDA	Food and Drug Administration
GGHB	Greater Glasgow Health Board
GI	Gastro-intestinal

GP	General Practitioner
HAQ	Health Assessment Questionnaire
Hb	Haemoglobin
HCPs	Health Care Professionals
HLA	Human Lymphocyte Locus-A
HYCQ	Hydroxychloroquine
i.m	Intramuscular
i.v	Intravenous
IDI	Intrinsic Desire for Information
IL	Interleukin
IQR	Interquartile Range
ISD	Information Statistics Division
LFTs	Liver Function Tests
LHCC	Local Health Care Co-operative
MCP	Metacarpophalangeal
MORI	Market and Opinion Research International
MTP	Metatarsophalangeal
MTX	Methotrexate
NGT	Nominal Group Technique
NHS	National Health Service
NHSiS	National Health Service in Scotland
NICE	National Institute of Clinical Excellence
NPSA	National Patient Safety Agency
NSAIDs	Non-steroidal Anti-Inflammatory Drugs
OTC	Over-The-Counter
PCG	Primary Care Group
PCT	Primary Care Trust
PEN	Penicillamine
PHCTs	Primary Health Care Teams
PIP	Proximal Interphalangeal
PMR	Patient Medication Record
PPIs	Proton Pump Inhibitors

PRED	Prednisolone
PsA	Psoriatic Arthritis
QoL	Quality of Life
RA	Rheumatoid Arthritis
RF	Rheumatoid Factor
RPSGB	Royal Pharmaceutical Society of Great Britain
s.c	Subcutaneous
SCPPE	Scottish Centre for Post Qualification Pharmaceutical Education
SD	Standard Deviation
SHO	Senior House Officer
SHOW	Scottish Health On the Web
SIGN	Scottish Intercollegiate Guidelines Network
SMR	Standardised Mortality Ratio
SPSS	Statistical Package for Social Sciences
SSZ	Sulphasalazine
TNF	Tumour Necrosis Factor
TNFR	Tumour Necrosis Factor Receptor
U&E's	Urea and Electrolytes
UK	United Kingdom
VEGF	Vascular Endothelial Growth Factor
WCC	White Cell Count
WHO	World Health Organisation
WTE	Whole Time Equivalent

Publications and Presentations

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Preface

The management of chronic diseases has been a key priority of the National Health Service (NHS) agenda. An evidence-based practice in disease management has encouraged a shift towards a patient-centred approach in the patient care process. The introduction of the concept of 'pharmaceutical care' initiated the necessary changes in the philosophy of practice for health care professionals. Although the definition of pharmaceutical care has varied across the continents, implications of the philosophy have provided invaluable evidence to support the new structure of care provision which has been the focus of health care researchers.

An increased emphasises on the concepts of 'patient empowerment' and 'patient self-management' has led researchers to explore patients' opinions on their beliefs, knowledge about their disease and its treatment to support a patient-centred care approach.

The management of rheumatoid arthritis demands close relationships between health care providers and patients. Complex drug therapy, the need for continuous patient monitoring, and implementation of guidelines about new drug treatment alternatives has led health care professionals to be more vigilant and to work collaboratively with patients during treatment process. Drug therapy management in rheumatoid arthritis involves patient education and counselling, prescribing and dispensing of medicines, monitoring the effectiveness of drug treatment and outcome assessments, therefore opportunity to improve the patient care process requires consideration of all these processes. Individual studies undertaken in this thesis contribute towards a holistic approach to the patient care process, focusing in particular on methotrexate therapy, in order to provide a system to assess the quality of care.

Chapter One reviews the previous work within the field that relates to the overall concept of this thesis. The health care system in the United Kingdom is examined in order to give insights into the provision of health care. The impact of social inequalities in health has been explored, in particular in relation to patients with rheumatoid arthritis. The concept of pharmaceutical care and its provision are reviewed from the perspective of chronic disease management and the potential role of the community pharmacist in the disease management processes is described. Patients' behaviour and their attitudes towards their treatment processes are reviewed in the light of psychological theories, which provide a better understanding for patient's intentions towards self-management. Issues around rheumatoid

arthritis are reviewed in terms of its clinical features, management approaches and its impact on public health. The drug treatment alternatives are summarised, focussing in particular on methotrexate therapy. Lastly, medication errors are reviewed in a broad sense followed by a description of specific medication errors that have occurred with methotrexate therapy. The chapter ends with an in-depth analysis of the inquiry of the Oxfordshire Health Authority into the death of a Cambridgeshire patient.

Chapter Two specifically focuses on the management of rheumatoid arthritis and provides information from the perspective of health care providers. Qualitative interviews with various health care professionals have been undertaken and the potential barriers to the effective management of rheumatoid arthritis are explored. The exploratory feature of this study provided a conceptual framework for further studies within the thesis. The identification of health care providers' perceptions on the responsibilities of other members of the care team and shortcomings in communications between health care providers conveys their understanding of the provision of care for patients with rheumatoid arthritis.

In ***Chapter Three,*** the use of methotrexate and other disease-modifying anti-rheumatic drugs (DMARDs) in the treatment of patients with rheumatoid arthritis is examined through the perspective of socio-economic deprivation. The duration of methotrexate treatment and other DMARD therapies is compared between 'deprived' and 'non-deprived' patient populations. The toxicity profiles of these treatments are summarised and the importance, value and benefits of methotrexate treatment compared with other DMARDs are highlighted in order to provide the basis for further studies in this thesis.

Chapter Four reports on the consensus building process for good practice in methotrexate prescribing and dispensing and patient self-management in patients with rheumatoid arthritis. Differences in preferences among rheumatology specialists in Scotland on the criteria for monitoring patients receiving methotrexate treatment and the variability in local guidelines has led to different practices in the provision of care for the patient population. Therefore, consensus has been sought on the criteria for good practice of methotrexate prescribing, monitoring and patient self-management processes in the management of patients with rheumatoid arthritis Recommendations have been made by the experts in the field on the issues for other health care providers who may lack specialist knowledge of the management of this patient group.

In ***Chapter Five,*** methotrexate prescribing and dispensing pattern in Scotland have been investigated. The prescribing and dispensing pattern of the two tablet strengths of methotrexate (2.5mg and 10mg) have been examined between 1991-2001. Since medication errors with methotrexate therapy previously occurred in hospital and community settings, some criteria for the assessment of quality of the prescribing and dispensing of methotrexate are suggested. A sample of prescriptions with 2.5mg and 10mg tablet strengths of methotrexate have been assessed according to the proposed criteria. Conclusions are drawn on requirements for the improved quality of written prescriptions for methotrexate.

Chapter Six describes the evaluation of a new model of care which is based on the community pharmacist's involvement in the management of rheumatoid arthritis with methotrexate therapy. The previous work in the thesis highlighted a need for community pharmacists to be closely involved in the patient care process with methotrexate therapy in order to ensure safe and effective use of this drug. The contribution of community pharmacist in the management of rheumatoid arthritis has not been explored previously in the literature. The new care model designed and tested in this study creates an opportunity for health care professionals to work in collaboration towards disease management and drug treatment processes and provides a standard communication pathway between the health care providers.

And lastly, ***Chapter Seven*** summarises the key findings of the studies undertaken within this thesis and highlights the contribution of the thesis to the knowledge of pharmaceutical care provision and health service research in this area. The investigation of the patient care process through different perspectives and the value of having a system or tool to measure outcomes of the care provided are discussed as a means of providing a quality assurance system for drug therapy use.

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Chapter 1: Background to the Research Field

1.1 Introduction

This chapter aims to build a theoretical framework for the research by reviewing relevant literature. An established framework would then help to identify the research questions which have not been answered explicitly by previous studies.

The concepts discussed in this chapter are reviewed from different perspectives and disciplines including medicine, health care, pharmacy profession and provision of pharmaceutical care and auxiliary disciplines such as sociology and psychology.

This chapter consists of ten sections, including this preface. The second section provides an overview for the definition of health and delivery of health care within the National Health Service (NHS) in the United Kingdom.

The third section explores inequalities in health and its impact on the population, particularly patients with rheumatoid arthritis.

Sections four, five and six examine relevant pharmacy-related literature and provide information regarding the pharmaceutical care concept, chronic disease management and the role of pharmacists within these processes.

Section seven provides insights into self-care and patient self-management concepts in the context of psychological and sociological theories.

Section eight mainly reviews common clinical features of rheumatoid arthritis and its treatment strategies.

Finally, Section nine incorporates the facts about patient safety and medication errors in the process of delivery of health care, including an analysis of a fatal incident in Oxfordshire.

1.2 Definition of health and delivery of health care in the United Kingdom

Health is defined according to different perspectives and is interpreted through various medical models. The bio-medical model defines health in the light of scientific rationality as an absence of a disease or the maintenance of physiological indicators within proposed limits. The World Health Organisation's (WHO) definition in 1948 expressed that health is 'a state of complete physical, psychological and social well-being, not only the absence of disease or illness'. Thereafter in 1984, the definition has moved towards interpretations of the social model on the social and personal resources and has emphasised a person's ability to change or cope with the environment in everyday life.[1, 2] The sociological perspectives conceptualise health in accordance with the psychological perspective as 'a status of maximised capacity of an individual or a society in order to perform social roles and, therefore being able to produce benefits'.

Advanced technological achievements have revealed greater need and expectations for continuous provision of health care and its uniform distribution across the population. In United Kingdom, the National Health Service (NHS) was introduced in 1948 and re-organised in 1974 in order to meet the population's health-related needs in order to provide and deliver optimum health care with a closer link between primary and secondary care settings. Observed changes in the population's demographics, particularly an increase in the proportion of the elderly people has had implications for the distribution of health services and delivery of health care in the UK. An emphasis on secondary care has shifted towards primary care along with distribution and utilisation of funding in the NHS structure.[3]

A report which was published in 1991, known as the Community Care Act, initiated a number of changes within the organisation of the National Health Service in England, Scotland and Wales. Consequently, autonomous Health Trusts began to facilitate hospital and the community services, and the Local Health Authorities became responsible for planning community care in their areas. Following the Health Authorities Act (1995) and the Government White Paper (1997), the health care system is hierarchically re-structured which allowed the Local Health Authorities to perform on a local basis in order to reduce management costs and able to allocate a greater proportion of the NHS budget towards direct patient care. Currently, Health Authorities are responsible for the purchase of hospital and community health services and payment for family health services, including the community

pharmacies.[3] In April 1999, 481 Primary Care Groups (PCGs) were established throughout England and two years after their establishments, 164 independent Primary Care Trusts (PCTs) were delivering a health care to 24.3 million people.[4] These authorities were represented within Health Boards in Scotland.

Fifteen Health Boards are institutionalised in Scotland, focusing on the health protection, health improvement and health promotion; needs assessment; service development; resource allocation and utilisation; and performance management of the Trusts' in the implementation of Health Improvement Programmes. These Health Boards retain the local identity in service development and are involved in the implementation of changes. Therefore, they are the responsible/accountable body to ensure effective delivery of health care and implementation of the strategies that have been developed previously through active co-operation of other agencies. The Trust Health Boards have responsibilities in identifying expected levels of services to be delivered; changes that are required within the service and the pathways to achieve proposed changes and available resources for local environments.[5]

The Department of Health (DoH) recently published a document that sets out the programme, arrangements and targets for implementation of the NHS plan.[6] It has been stated that the new NHS plan should provide services which allow provision of preventative services, support self-care, social care, primary care, intermediate care and hospital care which are based around patient or health service users. The comparison of the old and the new NHS models are summarised below in Table 1.1.

Table 1.1 Comparison of 1948 and the new NHS model

	1948 model	The new model
Values	Free at all at the point of need/delivery	Free at point of need
Spending	Annual lottery	Planned for 3/5 years
National standards	None	NICE, NSFs and single independent healthcare inspectorate/regulator
Providers	Monopoly	Plurality – state/private/voluntary
Staff	Rigid professional demarcations	Modernised flexible professions benefiting patients
Patients	Handed down treatment **(disempowered)**	Choice of where and when get treatment **(empowered)**
System	Top down	Led by frontline – devolved to primary care
Appointments	Long waits	Short waits, booked appointments

Reference: http://www.doh.gov.uk/deliveringthenhsplan/index.htm

1.3 Inequalities in health and its impact on delivery of health care

The factors that have influences on an individual's health can be categorised as external factors (physical or socio-economic environment and issues related to the health service) and internal factors (genetic, biological or ethnic factors, lifestyles and health behaviours) which create the core feature of delivery of health care. The distribution of these factors within the population is scattered and has therefore resulted in inequalities in health, differences in health outcomes and access to the health services.

Health inequalities have been interpreted in terms of inequalities in health ('equal outcomes for equal needs') and inequalities in health care ('equal access for equal need'). The phenomenon is explained by cultural and behavioural aspects, which are affected by an individual's socio-economic and educational status or his/her understanding of the impacts upon lifestyle (at the micro level). It is also explained at the macro level through social (or natural) or structural aspects in regards to the structure of society and material living that affect the process of employment and its impact upon health.[7]

The likelihood of association between health and socio-economic factors has generated wide interest amongst researchers who are involved in the process of the provision of health care. The studies have emphasised that relative deprivation, social life disruption, under-investment in public resources and income inequalities may have an effect on an individual's health. In a study of a cohort of the middle aged Scottish population, Chalmers and Capewell[8] indicated that 44% of men (30% for women) in the least deprived fifth had died compared to 72% of men (50% for women) in the most deprived fifth during 23 years of follow-up. They concluded that the risk of premature death in middle age was much greater in the most deprived fifth which occurred 6-7 years earlier than the least deprived.[8] Although the effect of income inequality on mortality, life expectancy and self-rated health has been acknowledged[9, 10], a recent study suggested that association between income inequality and life expectancy has disappeared.[9, 11]

Material interpretation of inequalities suggested that absolute deprivation of an individual and community is explained by income inequality. The theory argues that the impact of income inequalities on health embodies a combination of negative exposures and lack of resources held by individuals and systematic under-investment across health services and social infrastructures.[12] Wilkinson argued that income inequality produces psychological stress for people within the lower socio-economic hierarchy, thus continuous stress leads to

deterioration of health and higher mortality over time. On the other hand, other researchers emphasised variations in individuals. Lynch et al debated that reciprocal interaction between distribution of health related resources in deprived communities and an individual's social and physical infrastructure may results in higher mortality within communities.[11] Kaplan et al suggested that income inequality is significantly correlated with unemployment rate, social resources and measure of an individual's educational accomplishment.[10]

Watt indicated that economic policy in the UK caused a widening gap among individuals in terms of inequalities in health, therefore there was conspicuous need for a population strategy for understanding of relationships between health, education and economic policy and its consequences. He continued his argument indicating that inequalities in health cannot be addressed satisfactorily by focusing only on disadvantaged groups, it is rather important to get involved with all parts of the society and share the community resources in order to increase the awareness of the association between health and education.[13]

The Black Report (1980/1982) was published in the UK and highlighted inequalities in health and access to health care resources in respect to social classes. The main finding was that despite the fact that overall mortality rates have declined during the last century, there are wide differences between higher and lower social classes in terms of mortality and morbidity, where disadvantage exists for the lower social class.[14] The report also considered explanations for health inequalities according to a person's occupation, gender, geography, ethnicity and housing tenure and categorised these explanations under four headings. The explanation claims that health and social class are artificial variables and the relationship between them is not very significant. The natural/social selection explanation suggests that health determines social class and therefore can contribute to its gradients in health. The cultural/behavioural explanation argues that an individuals' health behaviour and lifestyles damage the health. And lastly, the materialist/structural explanation promotes the idea that the physical condition of life (health) is determined by an occupational class which produces class gradients in disease and death.[7, 12]

Thereafter in 1997, the Acheson Report highlighted problems with maintaining balance between provision of services required ('equal access for equal need') and available resources (number of staff or procedures) in order to encourage the best health outcomes.[7] It also emphasised the importance of 'equitable allocation of the NHS resources' which drawn into attentions of government and the NHS policy. The government acknowledged the effect of poverty and deprivation on health and distribution of resources across the population. Two

years after the Acheson Report, the Department of Health issued a White paper called 'Saving Lives: Our Healthier Nation'.[15]

The National Health Service in Scotland (NHSiS) issued Guidance on Priorities and Planning (1998-1999) in health service focusing on inequalities in order to ensure equity of provision and access to services for different groups in society according to their needs, particularly groups vulnerable to deprivation. Inequalities in health may occur as a result of differences in access, provision and quality of services provided by the NHSiS.[14] This report suggested five main strategic priorities for the NHS;

1. Improving health
2. Developing primary health care
3. Promoting care in the community
4. Reshaping hospital services
5. Tackling inequalities in health

Deprivation is considered as a reflection of poverty, where absolute poverty is defined as 'the absence of the minimum resources for physical survival and relative poverty is a reflection of the standards of living of a particular society at a specific time'. Within the concept, deprivation is independent of income or resources in general and is categorised as material, social and multiple deprivation.[14] Material deprivation indicates individuals being access to material goods in order to continue their membership roles in the society. Social deprivation is related to people's roles, their relationships and social contacts in society. Multiple deprivation expresses the occurrence of several forms of deprivation concurrently.

It is acknowledged that there is a lack of general agreement on the definition of deprivation which makes it difficult to measure, however this would be helpful in order to explore differences, assess needs, plan and ensure resource allocation at different levels or by adjusting the effect of deprivation to examine other factors. In 1971, the Department of Environment (DoE) used census variables to identify localities exposed to adverse social and economic conditions. Since then, there have been indices developed to measure deprivation using the original DoE measure and census data; the Jarman underprivileged area (UPA) index, Townsend and colleagues' index in North of England and Carstairs and Morris's index in Scotland. These indexes combine variables to generate a summary score which is assumed to reflect the relative socio-economic status of a locality.

The Carstairs and Morris index of deprivation was first developed in the 1980s using 1981 census data. It consisted of four criteria that composite a score range from 1 (less deprived) to 7 (highly deprived). These criteria are: overcrowding (persons living at a density of more than one person per room as a proportion of all persons in private households); male unemployment (proportion of economically active males who are seeking work); social class IV or V (proportion of all persons in private households with head of household in social class 4 or 5); and proportion of all persons in private households with no car. This score has been revised by McLoone using 1991 census data and the new postal code configuration. The main disadvantages of using area-based measures including the Carstairs and Morris index are;

- assumes that suggested variables best represent material deprivation
- areas are not internally homogeneous
- includes only areas with population over 2,000
- presence of ecological inconsistency
- uses census data which are only updated every ten years

1.3.1 Social deprivation and its impact on the patient population diagnosed with rheumatoid arthritis

Many recent studies have focused on the effects of environmental factors and lifestyle variations on occurrence of rheumatoid arthritis (RA), its progression and disease outcomes. Socio-economic environment has an impact on health status as well as health care utilisation in the population. However its effect on these variables is still not precise.

Bankhead et al examined the likelihood of the relation between the disease incidence and indicators of socio-economic deprivation.[16] Although there has been debate about whether risk of developing rheumatoid arthritis is related to socio-economic deprivation, they concluded that there is no evidence to support this argument. The highest incidence occurred in those employed as skilled manual workers with an estimated incidence of 14/100,000 person-years for men and 45/100,000 person-years for women compared to those employed as professional, managerial and technical workers (9/100,000 person-years in men and 38/100,000 person-years in women). They suggested that socially deprived areas do not particularly have an increased risk of developing RA, however there are possibilities that those who have the lowest socio-economic status may seek more medical attention during their treatment.

Vlieland and her colleagues investigated the effects of socio-demographic factors including level of formal education, marital and employment status on the disease outcomes in a cohort of young women diagnosed with rheumatoid arthritis.[17] Although the study sample was not large enough to show any statistical significance, they concluded that patients in low and medium education groups had more severe disease outcomes but this effect disappeared after correction of confounding variables.

McEntegart and her colleagues surveyed the effect of deprivation on disease severity, functional disability and disease outcomes in a rheumatoid arthritis population in the Glasgow area.[18] They found that functional status was significantly worse in patients from the most deprived areas which had relative contributions from co-morbid conditions, smoking, formal education level and dietary habits. The reasons suggested for having worse functional status in the most deprived group were that they tended to consult to their general practitioner (GP) only when they had severe disease and that there were differences in perception of onset of disease due to different educational levels. There was also a trend towards worse disease activity in patients living in more deprived areas. They emphasised that patients domiciled in more deprived areas may require provision and allocation of resources in their health care.

Urwin et al surveyed the adult UK population in order to estimate the frequency of musculoskeletal pain and physical disability in different geographical sites and its association with social deprivation.[19] In this self-report survey, the authors found that musculoskeletal pain was associated with social deprivation score, whereas a relationship between disability and social deprivation was less apparent.

Brekke et al investigated the effect of social deprivation on disease activity and self-efficacy in patients diagnosed with rheumatoid arthritis.[20] The patients domiciled in affluent areas showed better health status and perceived self-efficacy for pain management and dealing with other arthritic symptoms. The authors confirmed the findings suggested by McEntegart and her colleagues, that indicators of disease activity in patients with rheumatoid arthritis did not vary according to social deprivation whereas patients domiciled in more deprived areas had poorer functional status. The authors also suggested that the explanation for why patients in more deprived areas showed poorer perceived health status might be attributable to social circumstances, behavioural and physiological risk factors and adherence to health recommendations.

Another group of researchers from Glasgow explored influences of lifestyle on outcomes in rheumatoid arthritis.[21] They found an association between social deprivation and increased likelihood of smoking, obesity and reduced red cell folate in patients with RA. They concluded that reasons for why patients domiciled in deprived areas have poorer functional outcome could not be solely explained by lifestyle factors; however, exploration of the influence of co-morbid conditions on functional outcome warranted further study. Therefore it was recommended that the holistic care for these patients should include modification of cardiovascular risk factors such as smoking, obesity and hypertension.

The Early Rheumatoid Arthritis Study (ERAS) group examined influences of socioeconomic deprivation on markers of the disease progression and outcomes.[22] They followed up 869 patients over a three year period. The authors pointed out that the patients in more deprived areas were more likely to be put on complex second line drug treatments and also require more inpatient medical care. These trends lost significance after adjustment of age, sex and treatment centre variables. They identified that the patients domiciled in more deprived areas presented more severe diseases and disease progression over the first three years which was worse compared to the patients in less deprived areas. They suggested that age, sex, health assessment questionnaire (HAQ) and Carstairs deprivation score are useful for risk stratification in order to identify the patients diagnosed with RA who may need more intensive drug treatment.

Maiden et al explored the relation between social deprivation and mortality in RA patients.[23] After a 12 year follow-up period, they found a higher proportion of deaths had occurred in the most deprived area compared to most affluent areas (61% vs 36%); the relative rate of mortality was 1.66 times higher than in the affluent group. The main reasons for deaths were cardio-respiratory causes and malignancy. There was only one death attributed to methotrexate therapy (sudden pancytopenia). They concluded that having social disadvantages contributes to premature mortality in patients with RA.

1.4 A background to pharmaceutical care and role of community pharmacist

1.4.1 Definition of pharmaceutical care

The definitions of the mission of the pharmacy profession and its way of practising have changed over time with the emergence of new evidence in the practice of patient care delivery.

The new philosophy for pharmacy practice underpinning pharmaceutical care can be traced back to Brodie in 1966 in the USA. Initially, he described control of drug use as 'the system of knowledge, understanding, judgements, procedures, skills, controls and ethics that assures optimal safety in the distribution and use of medication which gives a direction, recognises need and fulfilment in the patient-pharmacist relationship'. He further proposed that 'pharmaceutical care includes the determination of drug needs for a given individual and provision not only of drugs required and also necessary services (before, during, or after treatment) to assure optimally safe and effective therapy'.[24, 25] Therefore, this new definition allowed the pharmacy profession to be recognised as not only a drug supplier but also a health care provider in these processes.

The report from the Millis Commission (Study Commission on Pharmacy in USA) in 1975 concluded that 'pharmacy is a health service. The only justification for inventing, manufacturing, distributing, prescribing or dispensing drugs is that they can and do have a beneficial effect upon people who are ill and that drugs can cure disease, control disease, prevent disease or ameliorate the suffering of the victims of disease'.[26]

The new viewpoints have emerged along with changing perceptions of the profession which acknowledged that pharmacy is a provision of health care in collaboration with other health care professionals, not only a provision of drug knowledge and dispensing medicines, but also ensuring safe and effective use of drug therapies. Mikeal et al (1976) defined pharmaceutical care as 'the care that a given patient requires and receives which assures safe and rational drug usage and is not provided by one health practitioner exclusively'. It has been further acknowledged that pharmaceutical care is a changing force in the field of pharmacy and demands contributions from pharmacy practitioners, educators, health system organisations and remunerative groups.[25, 27]

In 1987, Hepler initially proposed a definition for pharmaceutical care from a process-oriented perspective as 'a covenantal relationship between a patient and a pharmacist in which the pharmacist performs drug-use control functions (with appropriate knowledge and skill) governed by awareness of, and commitment to, the patient's interests'.[25, 28]

Thereafter in 1990, this new philosophy of practice is defined by Hepler and Strand as 'the responsible provision of drug therapy for the purpose of achieving definite outcomes that improve a patient's quality of life'.[29] The implementation of this philosophy expects practitioners to ensure that a patient's drug therapy is appropriate, most effective, safest and convenient for the individual to take as indicated and therefore able to identify, resolve and prevent any drug therapy problems that might interfere with pre-defined goals. It is a continuous process which requires continuous risk assessment, knowledge and skills in order to achieve desired outcomes for individual patients.[30] Strand (1992) further proposed that 'pharmaceutical care is the component of pharmacy practice which entails the direct interaction of the pharmacists with the patient for the purpose of caring for that patient's drug related needs'.

> *Pharmaceutical care is a practice in which the practitioner takes responsibility for a patient's drug-related needs and is held accountable for this commitment.*
>
> *Cipole RJ, Strand LM, Morley PC, 1998*[31]

Various definitions have been suggested as language and health care structure changes from one country to another.[25] In the Dutch perspective, pharmaceutical care is defined as 'structured, intensive care by a pharmacist for an optimal pharmacotherapy in which patient and his/her condition are the primary concern. The aim is to obtain optimal health related quality of life'.

The philosophy of pharmaceutical care practice is specific to the pathway of the delivery of care rather than the individual actions of a practitioner. It allows practitioners to meet a patient's unique needs in order to achieve successful delivery of care within a 'patient-centred' approach which emphasises the fact that identifying patients' concerns, expectations, understanding and preferences in disease management is an essential part of the practitioner's responsibility. The recognition of patients' social needs, implementation of a patient-centred approach and taking responsibility for identifying, resolving and preventing drug-related problems are crucial issues in the practice of pharmaceutical care. The patient is

recognised as an active member of a health care team, therefore establishment of full involvement during the treatment process, by defined responsibilities, allows the achievement of agreed outcomes in therapy. Pharmaceutical care is an explicit understanding of patient care processes. In contrast to the 'biomedical paradigm', the pharmaceutical care model also emphasises the importance of patients' active involvement in their disease management.

The conceptualisation of levels of pharmaceutical care is proposed by Smith and Benderev as primary, secondary and tertiary levels in order to provide a framework for the provision of pharmaceutical services. It is suggested that categorisation of levels of pharmaceutical care are valuable in the design of pharmacy education programmes and leads to new dimensions for practice-related research. The categorisation also facilitates a process of implementation of the philosophy, a selection of type of practice for pharmacists, and establishing a structure as a reference for health care assessment.[24] The determination of level of pharmaceutical care needed by a patient is accomplished through identifying risk factors associated with the patient's clinical characteristics, the patient's diseases and the patient's pharmacotherapy.[30]

There are common tasks established by Smith & Benderev and Strand, which are driven by the philosophy that pharmacists are able to practice regardless of level of pharmaceutical care.[24, 30] These are;

- identify the potential or actual drug-related problems and any possible risk to the patient
- establish and list the desired therapeutic outcomes for each drug-related problem identified
- consider all the therapeutic interventions to produce the desired therapeutic outcomes for each problem (interpret, question, clarify, verify and validate)
- select and record the therapeutic alternatives and dosage regimen for each medication
- formulate and document a pharmacotherapeutic monitoring plan to verify the achieved desired outcomes
- provide a safe and efficient drug-dispensing system
- monitor drug therapy for safety, efficacy and desired clinical outcome
- screen, detect and report for drug allergies, drug-drug interactions, drug-food interactions, and concomitant drug use
- teach health care providers and patients about drug use and assist in the selection of the drugs of choice and dosage forms
- systematic data collection and documentation of relevant information

It has been known that provision of pharmaceutical care services requires prioritisation and documentation of pharmaceutical care activities.[32] Patients may present miscellaneous pharmaceutical needs, varying from prescription-related issues to counselling or advice requests, which should be addressed by health care professionals. Adoption of a systematic approach in prioritisation of pharmaceutical care ensures that patients' pharmaceutical care needs are prioritised to be addressed and met at a particular time within the overall care processes. Continuous assessment of patients' pharmaceutical needs is a key step in the systematic approach which requires confirmation of patient's needs through identifying actual and potential care issues and documentation of a patient medication profile. The pharmaceutical care needs can be identified by the patient or by any health care providers. Patients' characteristics and circumstances and risk factors associated with medication should be sought when actual and potential care issues are identified. Documentation of pharmaceutical care issues within the patient medication profile provides updated information about a patient and their care processes for other health care professionals to implement and forms the basics shared responsibilities within a system of care.[33]

In Scotland, a framework for pharmacists to practise in a patient-orientated way defines the systematic process and is driven by 'desired outcomes' with 'care issues'. Desired outcomes are the 'statements of what the health care provider intends to achieve for a patient in relation to their pharmaceutical care issues'. These outcomes should be agreed and ideally expressed as measurable endpoints by the multi-disciplinary health care providers and the patient in order to achieve resolution within a defined time scale. Therefore, progress towards an achievement of desired outcomes at specified intervals could be measured.

1.4.2 Pharmaceutical care or medicines management

Recently, there has been a growing interest in defining the process of improved medicines use as 'medicines management'. Medicines management is defined as the process of optimising beneficial outcomes and minimising harm from medicines, through provision of medication review (appropriateness), monitoring and advice to patients and prescribers.[34]

Another definition is suggested by the Department of Medicines Management in Keele University, indicating that the practice 'seeks to maximize health through the optimal use of medicines. It encompasses all aspects of medicine use, from the prescribing of medicines through the ways in which medicines are taken or not taken by patients'.

Medicines management is a system of processes which aims to improve use of medicines by the patient and by the health care system. The activities indicated in the philosophy of medicine management are assessment, monitoring and review of prescribing for individuals, improving repeat prescribing through implementing policies and audits, risk management and disease prevention and provision of health education about medicines.[35] It has been proposed that provision of medicines management services, including use of formularies, guidelines and discharge planning, would overcome communication problems/failures between primary and secondary care.

Simpson commented in the Pharmaceutical Journal that 'in reality, pharmaceutical care is a type of medicines management. It falls within its ambit, but the two terms are not synonymous'. He proposed that pharmaceutical care is medicines management but medicines management is not necessarily pharmaceutical care.[36]

The comparison of the concepts of pharmaceutical care and medicines management has been indicated in Table 1.2.

Table 1.2 Key features of Pharmaceutical Care and Medicines Management

	Pharmaceutical Care	Medicines Management
Focuses on...	patient *(holistic approach)*	medicines *(rationalistic approach)*
Process is...	teamwork, involves all health care providers	pharmacist's responsibility acting through teamwork
Outcome is...	improved patient care and quality of life	minimising harm from medicines optimising effectiveness of medicines
Requires...	explicit knowledge on medicines collaborative inter- and intra-disciplinary relationships continuous standardised follow-up/monitoring	

1.4.3 Implications of pharmaceutical care in practice

There have been problems observed in the process of provision of pharmaceutical care since the concept has faced with reimbursement of the services provided. Twenty years after its original definition, objectives of the pharmaceutical care activities were revised in order to complete its philosophy and its practicality in the current health system.[37] These revisions envisaged establishment of a new standard for medication use by an individual patient, creation of a patient care practice that interfaces with standards of medical and nursing professions, achieving recognition and reimbursement for patient care services and therefore becoming part of the health care system.

The implications of the pharmaceutical care concept have been extensively studied in recent years both in hospital and community settings. The studies have mainly focused on the process of review of drug therapies or patient counselling, health promotion and advice-giving by pharmacists.

Lobas et al investigated the impact of pharmaceutical care activities in 184 patients attending outpatient clinics in the University hospital over a period of 14 months.[38] There were 360 recommendations made by pharmacists regarding drug therapy changes and of those 82.5% were accepted by doctors, of which 80% resulted in resolution/improvement in patients' conditions.

Phillips and Carr-Lopez studied the impact of pharmacist's contribution to geriatric outpatient clinics where a pharmacist reviewed patients' medication profiles and recommended changes for drug therapy.[39] They concluded that there is a 32% reduction in total number of prescriptions during the study period and the number of medications associated with adverse drug reactions in the elderly is reduced by 42%.

Zimmerman et al conducted a quality improvement study which aimed to identify hospital pharmacist's interventions in the light of pharmaceutical care practice.[40] In the first year of the study, 409 interventions were evaluated and of those 96% were found clinically appropriate, 62% were documented in medical records by pharmacists and 92% were implemented when accepted by the doctor.

Tully and Seston reviewed 55 published journal articles, particularly those conducted outside the United States, on the impact of pharmacists providing a prescription review and

monitoring service in primary and in secondary care settings.[41] The reviewed studies indicated that involvement of community pharmacist consistently is accompanied by improvements in some or all of the patients' clinical outcomes, quality of life, knowledge of their conditions and its treatment and satisfaction with pharmacy services. The authors concluded that amongst the majority of the studies included, community pharmacists had no access to information about the patients, compared to their colleagues in other settings. They obtain any information regarding the patients through interviewing or examining the patient, which multiplies their efforts and the time spent with the patient on each visit.

Carter and his colleagues studied structure and process of pharmaceutical care and its effects on desired global health outcomes in nine veterans affairs medical centres.[42] In the intervention group, pharmacists used a standard form for patients to document pharmaceutical care activities (types of problems addressed, whether problems are resolved, type of contact and times required) over a 12 months period. There were 3048 drug-related recommendations made by pharmacists (for 523 participating patients), of which 69% were resolved. The most common problems were patient education requirements regarding medications (94%), drug overdose (68%) and being experienced with adverse effects (58%). Although the study aimed to reduce cost and increase patient satisfaction and quality of life, there were not significant improvements observed during the study period. The authors suggested that in order to overcome disadvantages in patient follow-up in a current multiple-clinic system, a new structure should be established where the pharmacist participates in interdisciplinary primary care clinics and sees patients at a similar time to other primary care providers.

Krska and her colleagues investigated the feasibility of provision of pharmaceutical care in the primary care settings for patients aged over 65 years.[43] A total of 332 patients were assessed for pharmaceutical care issues from six general practices, of those 168 patients received pharmaceutical care plans. Among the issued care plans, the pharmacists identified 1,206 pharmaceutical care issues; of those 265 were identified from the prescription records and resolved by accessing the medical notes, 98 were identified from the records and resolved by patient interview. The GPs agreed with 95.8% of the identified pharmaceutical care issues and made recommendations to resolve the 87.3% of care issues. The authors concluded that there is a significant reduction in the frequency of pharmaceutical care issues following the formulation and implementation of care plans, where a substantial number of care issues were resolved without any contact with GPs. Therefore it has been suggested that delegation of authority to the pharmacists for monitoring activities and implementations of

such suggestions and changing the computer records would reduce the workload created by the delivery of pharmaceutical care.

There are limitations reported which constrain pharmacists to engage themselves in patient care activities and also in providing pharmaceutical care. It is documented that provision of pharmaceutical care is affected by perception of the pharmacist's role as mainly drug-orientated; and also by patient expectations, lack of services, trained staff and computer support, inappropriate pharmacy practice environment, lack of co-operation from other health care providers, limited access to patient medical information, lack of incentives/competency, and lack of remuneration.[29, 44]

A study undertaken in the United States indicated that implementation of pharmaceutical care is enhanced by factors related to pharmacists and the pharmacy environment itself.[27] Telephone interviews with pharmacists explored potential barriers for non-providers and facilitating factors for providers in the provision of pharmaceutical care. Half of the pharmacists who did not provide pharmaceutical care believed that their patients have low expectations for services provided by pharmacists. The patients perceived pharmacists as drug-oriented service suppliers with very limited time who did not present themselves as a profession being able to reduce drug-related morbidity in community settings. The authors suggested that delegation of treatment of some minor illnesses to a pharmacist and creating opportunities for advice-giving regarding prescribing strategies and prescribed drug therapies would enhance the professional status of pharmacists.[45]

A study reported that approximately 60-70% of pharmacists acknowledged that access to patient medical information was a primary barrier for provision of pharmaceutical care, particularly for patients who are not willing to volunteer information to a pharmacist about their condition. As a result, it appeared that establishment of a better communication system between other health care providers, creating a structure that enables patients to provide information regularly and supporting this structure with a computer-assisted patient medical record (PMR) system, which helps to observe drug-related problems for specific patients, would resolve many barriers faced by pharmacists in the provision of pharmaceutical care.[27]

Krska and Veitch interviewed 16 pharmacists from various backgrounds in order to indicate factors influencing the development of pharmaceutical care practice in primary care settings.[46] Although Scotland has had a guideline since 1999 which outlines Clinical Pharmacy Practice in Primary Care[33], there are problems which were also indicated by many

authors in the literature that restrain community pharmacists in the practice of pharmaceutical care. The interviews showed that pharmaceutical care is defined by participants as not only a practice of medication review but overall the long-term process of ensuring patients benefit from their medicines. Within this process a key role for community pharmacists is acknowledged and their continuous education and training requirements are emphasised. The interviews highlighted the problems regarding provision of pharmaceutical care in community pharmacies requiring solutions at institutional level; lack of staff time, private space within the pharmacy, documentation systems, literature access and also cognitive level due to; unmet training needs, relationships with prescribers and patients, legislative factors and remuneration. Delegation of a part of their dispensing role to another member of staff in the pharmacy, documentation of their activities through a dedicated computer programme which enables information to be shared with other health care professionals would embrace community pharmacists to provide pharmaceutical care and create the opportunity for reimbursement. One of the main findings of the interviews was that pharmacists are seeking robust evidence for the benefit of providing pharmaceutical care services, which is not available at the moment. There is a need for pharmacist's role to be emphasised by other health care professionals, therefore patients are able to acknowledge the patient medical information requests by pharmacists for provision of care.

1.5 Chronic diseases management and community pharmacist involvement in patient care processes

It is estimated that about 17.5 million adults, approximately 66-75% of all people aged over 75 years, living in Great Britain suffer from a long-term condition and approximately one third of the population are experiencing a chronic disease. Unfortunately, this has risen over the last 5 years; in 1996, forty-three percent of the adult population reported themselves having a long-standing illness and this proportion rose by 1% in 1998.[47] This figure also increases with social class in both the male and female populations. People with chronic diseases may experience disability, intense pain and embarrassment in the social environment. Moreover, they suffer various aspects of their illness in different intensity while they also have common requirements in health care.

The Scottish Health Statistics-2000 has indicated that about 5% of hospital discharges were due to musculoskeletal system and connective tissue diseases. Inflammatory polyarthropathies and arthrosis accounted for 1.3% of total hospital discharges in Scotland

and were more commonly seen in patients aged over 65 years old. It is also estimated that approximately 12.5% of the male population and 17.5% of the female population is aged over 65 years old which emphasises the importance of care of elderly in the NHS system.[48]

The management of chronic disease demands multi-dimensional approaches and involves psychosocial and biomedical challenges. The principles of the 'biomedical model' suggest that patients mostly rely on health care professionals' decisions and their pre-defined actions in the management of their diseases. It is indicated that patients have few responsibilities or influences on their own health care processes and therefore become a passive and receptive member of health care processes with limited contributions. The implication of the biomedical model for chronic diseases exposed some shortcomings in the patient care process. First, most chronic diseases, such as rheumatoid arthritis, are more likely to occur because of the combination of multiple factors whose aetiology still remains unknown, hence the 'cure' for the disease is not available yet. Second, the model recognises health as a mind-body dualism rather than their mutual interactions. And lastly, patient monitoring has emphasised high technology laboratory and imaging data which has not focused on patient's self- evaluation and preferences.[49]

Chronic diseases have enormous effects on the health care system and they are becoming the main causes of mortality and disability worldwide. The World Health Organisation (WHO) has recently introduced a project called 'Innovative Care for Chronic Conditions' which aims to analyse and deliver appropriate health care for chronic conditions.[50] It is suggested that strategies to improve clinical care should be integrated into national health care systems and comprehensive health care should be supported by local and/or national health policies and evidence-based guidelines. Governments and health care organisations should be encouraged to initiate and implement potential benefits and outcomes of published studies.

Re-organisation of the pathways for delivery of care across various health care settings will maintain the information flow between patients and the health care providers where the quality of proposed care is sustained. Provision of education and support for patients through encouraging them to engage themselves in disease management activities, appropriate use of their medications and effective utilisation of health care resources should also be considered.

The scenario is similar for chronic disease management. Responsive and accessible patient information systems, resource management techniques and community based opportunistic health screening as well as patient education and counselling are crucial for effective disease

management programmes. There are also patient-related factors that contribute to delivery of effective care for patients with chronic diseases, including accomplished self efficacy, increased outcome expectancy, increased knowledge, awareness and agreement on appropriate care for particular chronic condition.

In the new NHS plan, the government laid out a programme for pharmacy's new vision in delivery of care.[51] It is expected in the near future that patients would be able to get repeat prescriptions from a pharmacy without having to contact their doctor's surgery each time and they would get extra help in medicines use and in reducing unwanted affects of medicines caused by inappropriate use. Therefore, it has been suggested that implementation of the new programme would benefit patients in terms of reducing adverse reactions and ineffective treatments caused by inadequate self-management, increase opportunities in gaining information about health, with better use of OTC medications and reduced unnecessary visits to GP surgeries.

Moreover, the plan also indicated that by ensuring effective use of pharmacies, pharmacists would be able to work more in confidence with their health care colleagues and focus on individual patients' clinical needs in order to improve use of medicines. Expanding pharmacy's new vision would create an opportunity for pharmacists to be more accessible and provide expertise in promoting good health and medicine management.

The Scottish Office published a document regarding provision of community-based NHS pharmaceutical services and indicated that continuity in patient care is maintained by shared responsibilities amongst health care providers while a patient transfers to another environment during their care processes. The quality of care relies on health care providers' expertise and their collaboration with each other in order to achieve definite outcomes.[33]

In this framework, it is highlighted that pharmacists in community settings are in a position to provide pharmaceutical care services to their patients via providing their expertise to maximise drug efficacy and minimise toxicity. Extending pharmacists' roles beyond the dispensing process itself contributes to patient care and disease management. They also have responsibilities in the provision of drug information to other health care providers, particularly to GPs, interpretation of prescribing data, facilitating rational and cost effective prescribing, medication review for patients at risk of medication-related problems and in the management of individual patients with chronic diseases.[33]

A study undertaken amongst Scottish pharmacists indicated that almost 90% agreed that community pharmacists should devolve their duties within the dispensary to allow them to practise pharmaceutical care. The study also indicated that the majority of community pharmacists would change their attitudes towards pharmaceutical care practice if the current remuneration system is changed.[52]

It has been documented that provision of pharmaceutical care in community pharmacies has faced potential barriers. This might be influenced by factors such as working in an independent pharmacy, a chain or a surgery pharmacy, the number of prescriptions dispensed per day, the number of pharmacists able to work at the same time, number of technicians, and the ability to have easy access to patients' medical records and the internet.[46, 53]

Besides those potential problems, pharmacists reported several services that they have provided in their practice settings. A study conducted in Scotland demonstrated that community pharmacists are more likely to assess patients' needs regarding lifestyle or screening requirements and provide advice on medicines and lifestyle arrangements.[52] Whereas practice pharmacists are more likely to provide services including screening, recommendations for changes in therapy or referral for drug monitoring. Approximately 80% of both community and practice pharmacists reported that they provide services in respect to monitoring compliance with medicines or side effects in particular groups of patients. They are inclined to provide these aspects of care for the elderly population, frequent prescription requests, multiple therapy situations and circumstances for any side effects reported. Only just under half of the community pharmacists accommodated care issues about recommendations for changes after review or monitoring of therapy, although 74% of the same group of pharmacists provided recommendations for changes in therapy during dispensing or while responding to a condition.[52]

The pharmacist's involvement in the patient medication review process has also been examined by Krska and her colleagues in primary care settings.[54] In one study pharmacists contributed to assessment of regularly prescribed medicines and identified potential and actual pharmaceutical care issues for patients aged over 65 years who were taking at least four medicines at a time. The results showed that pharmacists identified 2586 pharmaceutical care issues (of those 52% from prescriptions, 18% from medical notes review and 30% from patient interviews) of 332 patients. In a group of 168 patients where pharmacists contributed to the patient's care, there were 1206 identified care issues; of those 96% were agreed by GP

and 87% required further action to be resolved. There were statistically significant differences between intervention and control groups in terms of resolution of care issues after implementation of a care plan by pharmacist (70% in intervention vs 14% in control group). Significantly more care issues were resolved by involvement of the pharmacist in the intervention group compared to the control group regarding potential/suspected adverse drug reactions (84% vs 58%), monitoring (95% vs 78%), potential/actual compliance (69% vs 30%) and discrepancies between dose prescribed and dose used (96% vs 3%). Although the authors did not find any evidence that pharmacists' involvement in the medication review process could reduce medicine cost and contacts with health and social services they suggested that this contribution reduced hospital admissions which warranted further study.[54]

Grymonpre et al identified the impact of pharmaceutical care services provided for elderly patients in the community.[55] Pharmacists involved in a group of 135 patients' care identified a total of 578 drug-related (specific pharmacotherapeutic) issues which 28% of those were resolved by follow-up. There were no statistically significant differences found between active (n=69) and control group (n=66) patients at baseline and follow-up in terms of number of prescribed drugs taken, drug costs, symptoms reported and medication adherence. However the physicians' perceptions were sought in relation to service provided and 94% of physicians (involved for 33 out of 35 clients) agreed with 75% of recommendations made by pharmacists and 83% thought that services were somewhat/very useful. They concluded that lack of verbal communication between physicians and pharmacists might have led to a low rate for issues resolved at follow-up. Thus, the establishment of successful working relationships involving direct contact between community pharmacists and physicians and understanding of pharmacist's extended role was suggested to be a necessity to enhance patient care.

Teh and her co-workers examined the impact of pharmacist-delivered health information/promotion and screening services on consumers' attitudes using two comparisons of cohort groups.[56] The results showed that there is no change in consumers' acceptance (perception) over the role of pharmacists in health information/promotion activities during a 6 years period, whereas positive changes occurred towards pharmacists' activities in screening. This was particularly evident for retired customers who had less positive attitudes towards the pharmacist's role in health information/promotion and screening. The study indicated that pharmacists were already perceived as a resource for health advice/information, and moreover, they have potential for the provision of

screening/monitoring services for their patients in their practice which could be appreciated by customers.

Harris et al surveyed participation of community care liaison pharmacists in patient needs assessment processes and referral activities.[57] Participating community pharmacists were initially trained for patient assessment and referral processes and then were asked to record their activities during a ten week period. The study showed that out of a total of 858 enquiries only 7% were initiated by other health care professionals, 6% by pharmacists and mainly (57%) by the patients. The majority of all enquiries (57%) were related to physical symptoms and prescribed medication (27%) which resulted in pharmaceutical advice or referral initiated by pharmacists. The interesting finding in the study was that the number of assessments was positively correlated with average number of monthly prescriptions dispensed and number of whole time equivalents of additional staff. They indicated that community pharmacists routinely assess the needs of individuals and decide whether to offer advice, recommend purchase of a medicine or make a referral according to patients' demands and that this process establishes a safety-net within health and social care.

Oborne and Dodds surveyed seamless pharmaceutical care at the primary secondary care interface and aimed to develop the communication process between hospital and community pharmacists at discharge.[58] The study showed that over half of community pharmacists were not satisfied with overall liaison between hospital and community. Two possible methods were suggested for improving communication; a provision of a medicine record card which would be held by a patient and shown to all health care professionals and a letter from the hospital pharmacist which details potential medication-related problems for patients to take their community pharmacists. The study concluded that the most practical option for transferring medicine-related information is through the patient, particularly by a record card which is favoured by patients and community pharmacists.

Binyon conducted a study over a five month period which aimed to assess the effects of pharmaceutical care services on elderly population through provision of communication between hospital and community settings.[59] The hospital pharmacists were involved in activities for undertaking a drug history, patient counselling and thereafter in initiation of a pharmaceutical care plan at the time of discharge. The care plan included information on drug therapies started and stopped during hospital stays, details of discharge medications, intended medication changes to be made in the community and a patient's drug reminder sheet. The pharmacists also visited patients at their home within a month of discharge to

monitor medication changes in accordance with the care plan. The author concluded that home visits created an opportunity for pharmacists to solve patient's medication problems and use of the care plan would improve the communication between hospital and community settings.

Dvorak and her colleagues examined the impact of a pharmacy to pharmacy referral form in a process of continuity of care.[60] The referral form included information regarding discharge medications and past medical history. The pharmacists were interviewed about usefulness of the form and its content in order to make modifications, according to community pharmacists' requirements, on the discharge planning process. Approximately 80% of pharmacists agreed that information provided is beneficial for specific patient counselling and has a positive impact on patient-pharmacist interactions. The pharmacists also stated the value of additional requested information about patients including a copy of discharge orders, the patient's prognosis, intended duration of use of medications, third-party payer, name and contact number of attending doctor, doctor's follow-up plan and extent of counselling provided at discharge. The study indicated that provision of a referral form to the community pharmacist is valuable and well appreciated. However the proposed way for information exchange was labour intensive and the timing for pharmacists to receive this form before patient attends the pharmacy was problematic. Therefore it is concluded that alternative methods of transferring and storing referrals are needed in order to improve the efficiency of the referral process.

1.6 A new role for the pharmacy profession

A profession is known by its features of specialised knowledge and lengthy training, service orientation, self-regulation and monopoly of practice.[61, 62] It is believed that pharmacist professional development has been hindered, largely because of medicine's control over its clinical autonomy which also initiates an economic autonomy too. Professional self-government is defined as the profession having control over its remuneration (economical), being able to influence policy decisions (political), and being able to make its own clinical judgements (clinical).[62, 63]

The remuneration of pharmacy services within the NHS system is based on the numbers of dispensed prescriptions. Therefore pharmacists have had to spend a majority of their time in the dispensary which has affected the public's opinion and the pharmacist's credibility as a frontline health care professional. The recent survey is undertaken by Market and Opinion

Research International (MORI) indicated that the public considers pharmacists not as professionals and includes them in the category of non-manual workers.[62] Moreover, the public's willingness to challenge professional knowledge and authority (consumerism), entry of automation and routinisation by new technology, market forces and service orientation (mercantilism), bureaucracy and incomplete control over medicines have undermined pharmacy's professional status.[64]

At the beginning of the 21st century, the world has undergone remarkable changes along with new technological developments in order to meet people's needs. Progress in computer technology and basic sciences yields new arenas for entrepreneurs to apply their imaginations on our daily lives. Since pharmacy is a well-established profession, it could not resist those developments and changes, therefore it started its re-professionalisation at social and political levels.

The increased quality in pharmacy education and ability of pharmacists to take new responsibilities has expanded the status of pharmacy in the health care system. This new role for the pharmacist is formed by appropriate utilisation and implementation of learned skills, self-assurance for responsibilities in health care and recognition and approval accorded by other health care professionals. Therefore pharmacists have begun to enhance the status of their profession through self-improvement based on ethical behaviour and have gained power by being committed to assuming meaningful responsibilities.[63]

In UK, the Royal Pharmaceutical Society of Great Britain (RPSGB) identified that pharmacists are underused resources in health care although they have the potential to be more closely involved in the care process. The Society emphasised the critical role of the community pharmacist in prescribed-medicine management, chronic disease management, management of common ailments and healthy life style promotion. The Nuffield Report in 1986, the White Papers 'Choice and Opportunity: Primary Care in the Future' in 1996 and 'The New NHS, Modern and Dependable' in 1997 explored opportunities for community pharmacists to be integrated into primary care health services more efficiently.[65]

The Nuffield Report endeavoured to identify current structure of practice in pharmacy and its potential contribution to health care. The report concluded that the pharmacy profession has a distinctive and indispensable contribution to make to health care that is capable of still further development.[64] The concept of exploring community pharmacist's role has arisen and therefore the report published by the Royal Pharmaceutical Society of Great Britain and the

Department of Health in 1992, called 'Pharmaceutical Care: the future for community pharmacy', identified contributions of the practice of community pharmacy services.[66] On the other hand, professionalisation of hospital pharmacy services has experienced changes since the 1980s and hospital pharmacists have established new activities, including development of hospital formularies and specialisation in particular areas of clinical pharmacy.[64]

Re-organisation of the NHS and establishment of the Primary Care Trusts have created new opportunities for pharmacists to be effectively integrated into the patient care processes. Re-definition of the community pharmacist's role is being attempted by the establishment of Primary Health Care Teams (PHCTs). Pharmacists are employed directly to work in GP practices and to be involved in repeat prescribing, composition of formularies and guidelines, disease management, provision of medication review and compliance services. Moreover, they are also employed by the Health Authorities to review overall prescribing patterns and budgets of practices in order to optimise medicine use in primary health care services.[3]

Consequently, the pharmacy profession has established and implemented strategies in order to seek to provide optimum health care for the public. They have promoted open access to the public and other health care professionals to get benefit from their knowledge and this has emphasised re-channelling of their dispensing duties, provision of advisory services to create opportunities for professional judgement in the provision of pharmaceutical care and enhanced service delivery.[64]

Edmund and Calnan undertook a qualitative research study which aimed to identify the perceptions of community pharmacists and other health care professionals in the re-professionalisation of community pharmacists.[65] They interviewed a purposive sample of community pharmacists (n=37) and GPs (n=26) by telephone. As a result of the study, they found that pharmacists believe that they could provide more help with medicines management, healthy life style promotion and advice to other health care professionals via fuller use of their skills and qualifications. It has been suggested that most of the patients attend regularly the same pharmacy which ensures continuity of care. Therefore, the continuity of care is more important issue than patient choice, particularly in chronic conditions in which pharmacists are able to identify drug interactions, side effects and establish a continuous relationship with patient. The concerns raised by community pharmacists and GPs regarding continuity of care were similar to some extent. The

community pharmacists mentioned difficulties in registration of patients to a particular pharmacy, the feelings of intrusion in the clinical decisions of GPs, insufficient use of PMR systems and a current system of remuneration which does not encourage/motivate them to get involved in medicines management. The benefit of the pharmacist's new role would be in reducing workload of GPs, especially in repeat prescribing and chronic disease management. On the other hand, GPs were less enthusiastic about involvement of community pharmacists in patient care since they perceived this as a threat to their autonomy.

Sheppard et al surveyed views of pharmacists who practise in community settings or in health authorities in the UK, in order to identify acceptability of the extended role of pharmacy services.[45] Approximately 67% of respondents reported that pharmacist's skills are not fully utilised in drug knowledge, the diagnostic and screening process, in counselling and in health education. The authors also compared views of pharmacists and GPs on proposed roles for pharmacists. There were agreements on pharmacy's/pharmacist's new vision amongst two professions in terms of reporting adverse drug reactions directly to the CSM (Committee on Safety of Medicines), providing health advice, issuing repeat prescriptions by prior arrangement with GPs, issuing formal GP referral documents to patients and providing therapeutic drug monitoring. However GPs were less likely to consider pharmacists taking initiatives in treating minor illness, supplying diagnostic/screening services and selecting medicine and dosage within agreed protocols to treat a condition diagnosed by the GP. The GPs believed that provision of screening services should remain within the primary health care team where continuity of care can be guaranteed because extension of the care team in disease management would create communication problems that would affect provision of good care. It has been claimed that collaboration between GPs and pharmacists might be hindered in the future mainly because of perceptions of and attitudes towards each other, inter-professional opposition and suspicion, problems with role definitions and lack of trust.[45]

Although the new assembly of the NHS organisations has aimed to provide effective delivery of care for the population, potential barriers have been identified for delivery of care across the primary and secondary care interface. These boundaries might occur in any care settings at any time while progressively obscuring the gateway for the provision of care. Lack of opportunities to establish an iterative network amongst health care providers, non-existent or incompatible electronic information systems for transferring information from one to another care settings, poor understanding of other's professionals roles and the

multiplicity of health care providers involved in the process may interrupt continuity of care and result in errors in effective delivery of care.[3] .

Bond suggested that effective team working amongst health care providers can be achieved by sharing a common purpose and recognising common interests, having a clear understanding of roles and responsibilities of others, blending knowledge, skills and resources and sharing a responsibility for outcomes.[61]

1.7 Self-efficacy, self-care, self-motivation and understanding of patient self-management processes

A notion of self-care is highly captivated by the health care providers along with the implementation of the NHS new agenda. The report called 'Patient Focus and Public Involvement', published by the Scottish Executive, indicated that there should be ways to improve health care services in order to do things *with* the people rather than *to* the people.[67] An introduction of new policies has highlighted the importance of patient self-management strategies and application of theoretical frameworks for explaining patients' behaviour in their disease management. Therefore, the following sections have focused on some of the theoretical models which are considered to be helpful to understand the self-care and self-management activities in patients with chronic illnesses.

The patient's involvement in disease management begins with an understanding of the concept of adherence and concordance. Non-adherence is one of the main concerns of health care professionals requiring observation and assessment in chronic disease management. Non-adherence is a complex and dynamic issue which is affected by social, medical, economical and behavioural factors and consequently yields increased morbidity and mortality in the population.[3] It has been shown that 40% of patients with hypertension and 55-70% of patients with arthritis are reported as non-adherent.[68] Although adherence is recognised as the patient's ability to take their medications as directed, there are other issues beyond patient competence.

The term 'concordance' defines outcomes of agreement between the patient and the health care professionals on drug treatment processes, which does not necessarily guarantee adherence. It has been suggested that recognition of major risk factors for non-adherence, such as asymptomatic and/or chronic conditions, cognitive impairments, complex regimens,

multiple daily doses, patient's fears and concerns related to medication effects and poor communication between patients and practitioners, would help health care professionals to facilitate adherence to proposed treatment. Non-adherence may occur in relation to lack of beliefs and motivation in drug therapy (intentionally) or lack of skills and inability of patient (unintentionally). Therefore, it becomes crucial for health care professionals to understand reasons for being non-adherent and how to overcome these situations.[3]

The factors which affect adherence to drug treatment can be categorised into three headings; (i) disease related factors, (ii) treatment related factors and (iii) patient related factors and these are summarised in Table 1.3.

Patient-related factors have a predominant effect on improving adherence to drug treatment in chronic diseases. Therefore, it is assumed that promotion of self-efficacy, patient empowerment and application of self-management strategies would lead to successful management of chronic diseases. Patient empowerment is seen as a continuous process which emphasises education of patients and their families about disease and its treatment, patients being able to take control over their illnesses and its consequences on daily activities which to a certain extent can be enhanced by health care professionals. These strategies become more problematic and less manageable in the elderly population considering they have physical disabilities, cognitive limitations, limited access to health services and may be subject to polypharmacy.

Table 1.3 Factors affecting adherence to drug treatment

Adherence	Disease related	Treatment related	Patient related
Increased by	Perceived or actual severity of disease ***(health threat)***	Perceived benefits of therapy ***(beliefs about medication)***	Good communication and satisfactory relationship with health care professionals (HCPs) ***(confidence in HCPs)***
	Perceived susceptibility to the disease or developing complications ***(illness representation)***	Convenience of treatment ***(practicalities)***	Participation in establishing the treatment plan ***(active participation in action plan-intention)***
		Medication provides symptomatic relief ***(appraisal)***	External support (e.g. family members and friends)
		Written and verbal instruction ***(information provision)***	Knowledge about illness ***(education)***
Reduced by	Lack of symptoms	Significant behavioural change requirements	Physical disability or cognitive impairments
	Chronic diseases	Actual and perceived side effects ***(concerns)***	Lack of social support
			Low educational status
		Regimen complexity and duration	Failure to recognise the need for medication ***(necessity beliefs)***
		Medication takes time to show its effect	Risk/benefit ratio
			Negative expectations or attitudes towards treatment ***(lack of self-efficacy)***

1.7.1 Understanding of patients' attitudes and behaviours in health care process

There has been a growing understanding of social and behavioural aspects of health care. Since sociology consists of contrasting and contested sets of theoretical perspectives and deals with real-world issues, which are exposed to change over time, the pharmacy profession finds a close link with these issues in practice. Sociology creates an opportunity for people to conceptualise the social world and think through different perspectives in order to identify the nature of social structure and relationships between the individual and society.[69] A nature of the relationships of people within and/or with the society can be conceived by a firm understanding of an individual's behaviour.

According to Bandura, behaviour is determined by 'personal, behavioural and environmental influences and based upon expectancies, utility of specific outcomes or consequences. Expectancies are derived from a person's beliefs in their capabilities and opportunities to execute behaviour and their assessment of the chance that certain behaviour would have a beneficial effect (desired outcome)'.[70, 71]

Health-related behaviours are summarised as; (i) health behaviour (ii) illness behaviour and (iii) sick-role behaviour.[72]

The health behaviour is defined by Kasl and Cobb in 1966 as 'any activity undertaken by a person believing him/herself to be healthy for the purpose of preventing disease or detecting it at an asymptomatic stage'. It is believed that health behaviour has an impact on patient's quality of life, therefore modifications in health behaviour might yield positive outcomes in disease management in order to achieve delayed onset of chronic disease or extended active lifetime.[70] The factors that affect health behaviour and might lead to desirable outcomes once targeted are summarised by Cummings et al as follows;[70]

1. Accessibility of health care services
2. Attitudes to health care (beliefs about quality and benefits of treatment)
3. Perceptions of disease threat
4. Knowledge about disease
5. Social network characteristics
6. Demographic factors

As it can be seen from these factors, health behaviour is affected by individual, social and environmental variables, which further develops specific models in order to explain different aspects of health behaviour.

Health behaviour has been explained by means of various frameworks. They enable health care professionals to understand patient's attitudes and their effects on the patient's behaviours with the goal of the patient remaining healthy or having an asymptomatic status of health. It is basically a behavioural extension of health beliefs and motives of the patient.[72]

The following section outlines the main components of the theories suggested which are believed to illuminate the overall picture of health care processes and visualise/create opportunities for health care professionals to be involved.

The *Conditioning Theory*, which was originated by Pavlov and further modified as 'operant conditioning' by Skinner, suggests that behaviour is determined by environmental factors and not affected by cognitive processes. The theory focuses on the relationships between reinforcement, stimuli (facilitative or suppressive) and responses. Therefore, reinforced or rewarded behaviour would continue or increase in frequency, as in smoking cessation programmes. Once a person is encouraged to quit smoking, any success would result in rewards for that person. Besides, an individual also faces a social negative reinforcement from their peer to continue smoking or receives a positive reinforcement from family/friends or health care professionals to quit smoking. The reinforcement process within the theory has implications on undertaking/maintenance of lifestyle advice in health promotion activities.[3]

The *Social Cognition Model* is suggested by Bandura and explains potential cognition and their interrelationships -by which they regulate a person's behaviour- in order to predict an individual's compromised behaviours and outcomes. This approach provides an understanding of determinants of an individual's behaviour and changes in his/her attitude which is caused by environmental and cognitive factors. It is suggested that expectancies in intended outcomes and in self-efficacy direct individuals to change their behaviour in the longer term and these behaviours and new skills can be learnt. The individuals put a value on the long-term benefits of behaviour change in their health and judge this new behaviour against the short-term rewards of not engaging themselves.[3, 70] The contents of the theory find its place in promotion of self-care and self-management activities in order to encourage patients to participate in to these programmes.

The *Protection Motivation Theory* explains adaptive (behavioural intention) and maladaptive coping with health threats, which are originated by a threat appraisal and a coping appraisal. The threat appraisal is based on the perceptions of vulnerability to illness and perceived severity of health threat/illness. The coping appraisal involves a process of assessing the behavioural alternatives (self-efficacy expectancies) which might diminish the threat (outcome expectancies). These coping strategies arise from an individual's expectancy of behaviour that would overcome the threat (action-outcome efficacy) and belief in their capability to achieve recommended actions (self-efficacy). Adaptive (protection motivation) or maladaptive (avoidance) responses are likely to occur as a result of these cognitive processes. Individuals, who perceive themselves as susceptible to threat or believe that threat is severe, are more likely to respond in adaptive ways. The theory is used to explain behavioural intentions in the prediction of regular exercise, in smoking cessation programme and in cancer-related preventive behaviours.[70, 73]

The *Health Belief Model* consolidates two aspects of representation of health behaviour; perception of illness threat (vulnerability) and evaluation of behaviours to overcome/compensate for this threat, which determines the likelihood of an individual taking health-related actions. Individuals are more likely to respond when they perceive an action is beneficial to overcome the threat that they face. This response is affected by individual demographics, social pressure, personality and motivation but not by individual's emotional response.[70, 73] The model has been successfully used to explain patient compliance with drug treatment, potential barriers for patients to be compliant[72], breast self-examination, exercise programmes[3, 74], relationships between health and treatment perception and the use of prescribed medication/ home remedies.[75]

The *Health Locus of Control Model* is based on Social Learning Theory, but is differentiated by the definition of internal and external locus of control aspects. In a concept of internal locus of control, individuals believe that events are the consequence of their own actions whereas in external locus of control theory, it is believed that events are unrelated to individuals' actions and determined by other powerful people (doctors) or factors beyond their control.[3, 70] The model is used to explain control over specific health processes, such as participating/maintaining in self-management programmes in chronic diseases, but it does not give insights in prediction of care-seeking behaviour of individuals. Gustafsson et al used the model in order to explain differences in reported pain intensity between RA and fibromyalgia patients and found that external locus of control was the mediator for the patients with fibromyalgia in their pain coping strategies.[76]

The *Theory of Reasoned Action* suggested by Fishbein and Ajzen, identifies relationships between beliefs, attitudes and behaviour and expresses the importance of a person's intent to perform that behaviour and rational decision making process. It is suggested that an intention for behaviour to be undertaken is also influenced by subjective norms (social pressure) and normative beliefs (approval by reference person).[3, 73] The theory has been used to identify the reasons for missed medication doses in patients with rheumatoid arthritis.[77]

The *Theory of Planned Behaviour* extends the explanation of the Theory of Reasoned Action and explains the measure of control that a person has over a behaviour, which depends on their knowledge, specialised skills and other resources and opportunities. It has been suggested that there is the possibility of perceived behavioural control (might be referred as self-efficacy in the Social Cognition Model) predicting an action, without influencing the intention, where there is no actual control over the behaviour.[3, 73] However, this theory does not explain avoidance behaviour, which is caused by emotional responses such as fear, anxiety or denial and does not include the issue of health threat. The theory has been used to investigate cognitive predictors of adherence; to explain levels of physical exercise, use of oral contraceptives in patients and also been used in order to examine the factors influencing pharmacists' behaviour regarding implementation of pharmaceutical care.[75]

The *Stage Theories* have identified different levels of behaviour changes. Prochaska and DiClemente suggested that three dimensions, which includes five stages, five levels of change and ten processes, exist in decision making and adopting/changing behaviour (Transtheoretical Model). According to this model, individuals may be at different stages of being prepared for behaviour change. The stages are outlined as pre-contemplation (not intending to change), contemplation (decisional-intending to change but being undecided on when to begin), preparation (post-decisional; actively planning change within near future), action (actional-making changes) and maintenance (evaluative- taking steps to sustain change and resist temptation to relapse) stage.[78, 79] In this cyclical model, a person may move from one stage to another reciprocally which also describes the stages for personal susceptibility towards a particular health risk.[3, 73] The theory has been applied in various health promotion activities in order explain patient's behaviour; where exercise programme for weight reduction is intended or in provision of advice/information for smoking cessation programme. It has been also used to measure pharmacists' readiness to adopt a new standard for assessing the appropriateness of client's request for non-prescribed medicines and their training in order to help people in giving up smoking.[75, 80]

Keefe et al explored adaptation of the Transtheoretical Model on arthritis patients in order to understand their self-management activities.[81] Therefore it has been suggested that it is helpful to know that certain activities may be undertaken at certain stages which can be directed during the self-management process for particular group of patients.

The *Health Action Process Model* incorporates aspects of the Health Belief Model, Theory of Reasoned Action, Health Locus of Control and Stage Theories and emphasises relationships between behaviour, outcome expectancies, risk perception and self-efficacy. The model assumes that new health behaviours are maintained when behavioural change is supported by structural and social environment, which creates opportunities for health care professionals to make contributions into the processes. The model also provides explanatory information on health promotion, particularly in patient counselling at different stages in the decision making processes.[3, 73]

The *Self-Regulatory Model* is suggested by Leventhal and proposes that the patient is an 'active problem solver' and their health-related behaviours and coping ability are affected by the patient's own beliefs and illness representations. It is suggested that illness beliefs are framed by features of diseases and identity of symptoms; also by the duration, cause, consequences and possibility of cure/control. It offers an explanation for adherence to treatment being influenced by dynamic interaction between patient's disease representation, appraisal and coping abilities.[82] Several studies have investigated the self-regulatory model in order to explain patients' behaviour in chronic diseases, including rheumatic diseases.[83] It has been suggested that the impact of rheumatic conditions are mediated by patient's perceptions of pain, disability and dependence which also influences their emotional response, coping skills and appraisals.[84]

The self-regulation process consists of mental and behavioural activities of people who accomplish their self-conceptions, revise their behaviour, or alter their environment in order to achieve outcomes in their self-perceptions and personal goals. It is indicated that setting of goals, cognitive preparations, ongoing monitoring and evaluation of goal-directed activities would sustain this process. Gollwitzer (1990) distinguished two phases in this behavioural model; a motivational phase and a volitional phase. It is suggested that people are inclined in their motives and expectations to choose between goals and implied actions in a motivational phase; whereas in a latter phase, people prepare their plans and actions to achieve pre-defined goals. It is assumed that this approach could be applied in health psychology to explain health-related behaviours and a patient's response to treatment.[72]

The *Attribution Theory* is used to explain how certain factors induce people to change their behaviour, re-train themselves and improve self-efficacy. In this theory, three dimensions have been suggested; locus of causality, stability and controllability. Its implication on the health care concept indicated that patient's previous experiences have affects on his/her future behaviour, which is determined by perceptions and perceived controllability of the factors.[73] It is believed that different attributions lead to different behavioural consequences, therefore it is possible to change the behaviour of person by changing the attributions that he/she makes. The implications of this theory have been undertaken in circumstances in loneliness, alcoholism, smoking, losing weight and also in changing individual's behaviour, such as in attempts to improve reading skills of children.

A theory suggested by Marlatt and Gordon and combined attribution theory and self-efficacy, is called *Relapse Prevention Theory.*[73] This theory explains failures in changing behaviours when high-risk situations exist. Patients with chronic diseases develop coping responses in order to overcome high-risk situations such as complications or consequences of diseases, as a result it increases self-efficacy and decreases probability of relapse. It has been suggested that absence of a coping response does not necessarily lead to a lapse, it only increases perception of one's own self-efficacy in coping with a situation.[73] Therefore, self-efficacy of a person might be enhanced through influencing the frame of reference of a person; searching for high risk situations and learning of coping skills; practising of these coping skills and learning how to handle relapses.

Self-efficacy is an estimation of skills and ability to overcome barriers, and prediction of future behaviour and behavioural changes, which depends on a situation and the perceived task difficulty. Improved self-efficacy in health is achieved by patient's motivation to behave in a healthier way, education of the patient in required skills, setting realistic and achievable goals, assessing high-risk situations by self-monitoring and continuous input from health care providers.

As is indicated in this summary of theoretical models and their applications in different populations of patients with various illnesses, health behaviour is a dynamic and interactive concept, which overlaps with individual, social and environmental factors. Therefore, it is likely to be affected by circumstances that patients face with. In the following section, self-care and self-management strategies are explored in a concept of patient's participation in health service provision.

1.7.2 Self-care/ self-management/ self-treatment

Disease management begins with symptoms management at baseline of a theoretical therapeutic pyramid and escalates up towards to self-care, primary care, specialised secondary care and tertiary care at the top end.[85] Patients' willingness to seek help for disease management originates from a need for better understanding of their symptoms, and builds on patient's self-enablement, their relationships with health care professionals and availability of resources in the community.[3] As a disease progresses, management strategies change according to patients' needs, their understanding of their therapy, their ability to engage in the partnership and availability of financial resources. Effective chronic disease management can be achieved by establishment of a partnership process based on shared understandings and taken actions, which requires inquiry, interpretation, learning and negotiation. Provision of information in regard to self-care, disease management and drug therapy is crucial to ensure patient's involvement, which is pre-requisite for participation.

Patient participation is defined as 'the process whereby a person can function on his/her own behalf in the maintenance and promotion of health, the prevention of disease, the detection, treatment and care of illness and adaptation to continuing disability'.[86] The patient's role in this process is to engage him/herself with maximum feasible amount of self-management through provision of knowledge and facilitation by health care professionals.[87]

Sims explored potential factors that influence the patients' desire to participate in the management of their hypertension.[86] She indicated that the patients viewed the management as something that doctors do and they further mentioned that the limited availability of time and finances, having arthritis and ageing are barriers to make changes in their own lives. Although over half of the patients expressed a desire to be involved in their disease management, many patients were willing to follow the doctor's instructions rather than be pro-active. Age, socio-economic status, gender, level of knowledge or having severe disease status appeared to have no influence on patient's willingness to participate in disease management. Despite the fact that the detrimental effect of excess information was being highlighted, the patients indicated that they require more individualised information and advice about management of hypertension in order to contribute to their care in a way which would help to encourage further self-management activities.

Self-care has been interpreted as a holistic approach to individuals taking more control over their own health independently through their experience of health and illness.[88]

According to Dean there are three forms of self-care activities; routine daily habits that affect health, conscious health maintenance behaviour, and self-treatment or responses to the symptoms of illness. She further defined self-treatment as 'the decision by lay persons to diagnose and treat perceived symptoms themselves rather than seek professional treatment services'.[71]

Another definition comes from Orem which indicates self-care as 'a behaviour that exists in concrete life situations directed by persons to self or to the environment to regulate factors that affects their own development and functioning in the interests of life, health or well-being'.[89]

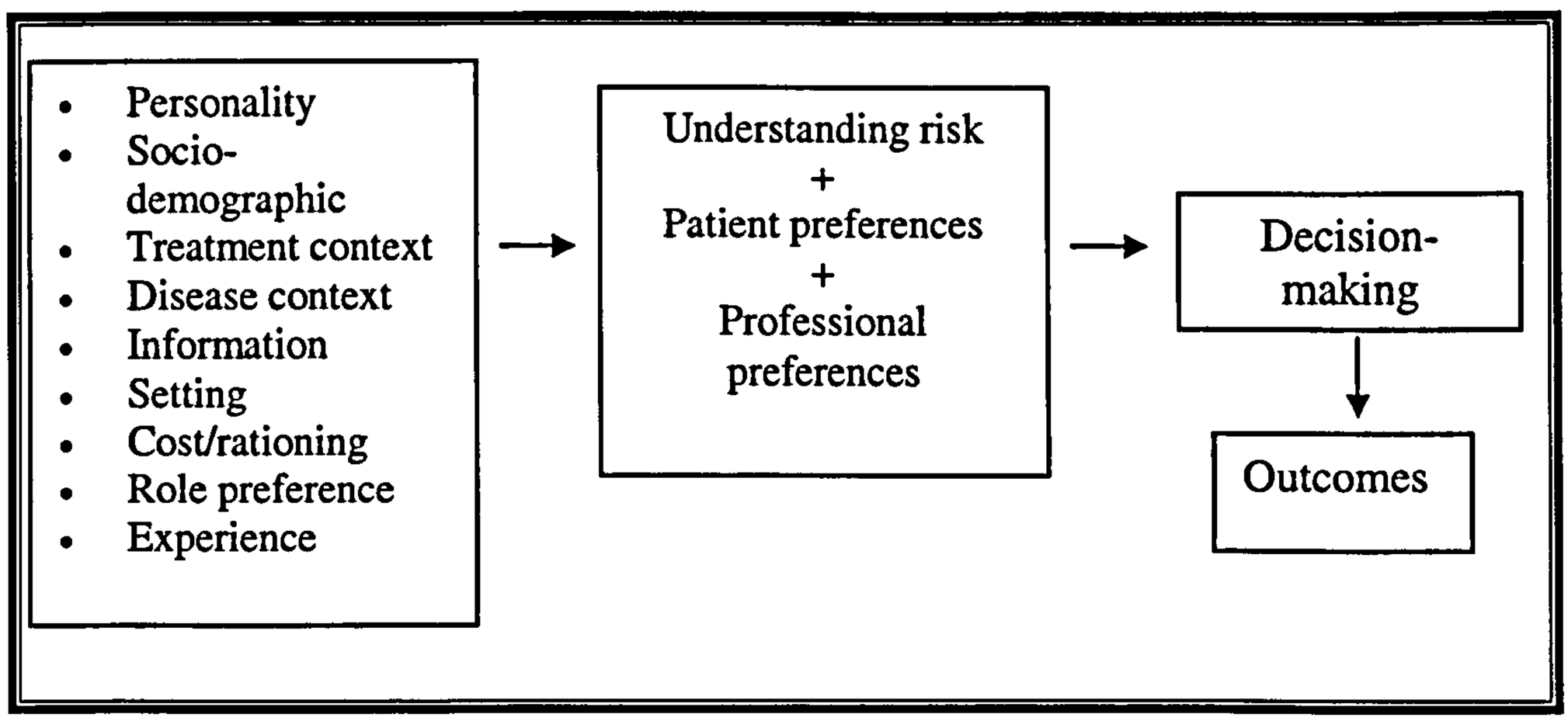
> *Self-care involves individual medicines users determining their most important priorities and goals, deciding which advice and treatment to accept and actively making the best of their situation in order to decide on their personal health outcomes.....Patient empowerment is something that people ultimately take for themselves and can be best seen as acquiring a positive mindset and becoming a critical information seeker. Supporting self-care is about improving health outcomes and service quality, not merely about trying to make savings in the drugs bill by encouraging people to pay for over-the-counter medicines out of their own pockets.'*
>
> *Christine Glover (Pharmaceutical Journal, October 2001)* [90]

The concept of self-care is mostly acknowledged by the nursing perspective.[91] It has been assumed that patients know why and how they should make effective self-care decisions in order to achieve management goals in chronic illnesses. The decision making processes are often complex, overlapping, multi-factorial and inconsistent. These processes are affected by duration of disease, disease severity, past and present life experiences of patients, values that they put on their self-care and their culture. Therefore, the main question to ask is how to encourage patients with chronic illnesses to participate in decision making and self-care processes. Their willingness and ability to engage in the self-care process is mostly determined by behavioural, physiological and socio-cultural factors. The patient's perception of risk also affects this process.

Risk assessment is another aspect of the self-management concept. Patients who consider themselves more vulnerable to certain effects may become more involved in their disease management. On the other hand, Weinstein has shown that people commonly consider the

hazard as more risky for other people than for themselves. They also may underestimate the risk associated with certain behaviour. Patients' understanding and interpretation of risk might be affected by various factors including immediacy of effect, its controllability, and its novelty (see Figure 1.1). During communication with patients in health care settings, overconfidence among health care providers could also lead patients to underestimate the risk in their appraisal. The format information about the risk presented by health care professionals also affects the interpretation of patients and their ability to recall this information in future. The data indicated that many patients have poor comprehension and recall of risk information.[92] There is a need for an appropriate tool, which helps patients to understand the risk and benefit of information presented, how to weight or prioritise this information and how to make a decision for action in their self-care processes.

Figure 1.1 Risk assessment and decision-making pathways in health care processes[93]



It is indicated that the self-care process is rational, consistent and generic to all chronic diseases. Long term experiences with diseases ground an expertise in self-care and requires commitments to be actively involved in disease management. Therefore, engaging patients with self-care activities would achieve successful outcomes (such as sustaining symptoms or positive physiological indicators) in disease management in chronic illness.

Chapple and Rogers reviewed qualitative studies that have examined the self-care concept in chronic disease management.[88] They found that there is diversity in the extent of patients'

willingness to participate in self-care practices which varies according to whether they have a minor condition or a chronic, long-standing illness. Particularly in the elderly population, self-care activities were affected by social interaction with the medical consultant or family and friends and by perception of health as ageing process. They emphasised that relevance of timing and stages of illnesses have an impact on a person's receptiveness to undertaking self-care activities.

The US study undertaken amongst patients diagnosed with diabetes indicated variability in the provision of recommendations and patterns of self-care activities in this group of patients.[94] Unlike findings of the study by Sims, this self-reported study indicated differences on self-management levels according to age, working status and knowledge of patients. The authors verified the importance of developing an integrated self-care plan with the support of the health care team in order to improve communication of self-management goals between individuals and the diabetes team.

It has been indicated by Sowell (1997) and Dowd (1991) that use of self-care practices is determined by patients' perceptions of their particular experience at different times, their trust in their health care providers, satisfaction with their medical treatments and their levels of physical functioning. Therefore, it becomes important to advise self-care activities at an appropriate stage of illness and target different levels of functioning.[88]

The management of self-care activities requires patients' dedication to health promotion through preserving their physiological status, maintenance of obligations in communication with health care providers, adherence to agreed treatment protocols, understanding and recognition of physical and psychological symptoms in order to make appropriate decisions for self-monitoring, sufficient ability and self-esteem in managing consequences of their illnesses.[95]

It is believed that the health care system should create opportunities in order to facilitate effective self-care activities and manage the gap between demand for health care and its provision via applying modifications on an individual or service level. It is acknowledged that these practices should be well established within the existing socio-environments of patients.[88] The shift towards involving pharmacists in provision of public health care creates an opportunity to prevent illness where possible and treat effectively where necessary. Therefore, pharmacists both in the community and in the hospitals would be able to use their scientific knowledge on medicines and their extended ability to contribute to diagnosis and

treatment in partnership with other health care professionals. Improving community pharmacists' access to patient's medical records and their authority to amend them would ensure continuity of care while processing self-care.

Self-management is defined by Alderson et al as 'inter-disciplinary group education, based on the principles of adult learning, individualised treatment and case management theory'. On the other hand, Nakagawa-Kogan et al emphasised an individualised approach in self-management and described it as 'a treatment that combines biological, psychological and social intervention techniques, with a goal of maximal functioning of regulatory processes'. Furthermore, Clarke et al interpreted self-management as not only preventive self-care strategies but also 'day-to-day tasks that individuals must undertake to control or reduce the impact of disease on physical health status' which requires a collaboration and guidance of the individual's physician and other health care providers. In the light of a literature review of self-management concept in chronic diseases, Barlow et al defined self-management as 'individual's ability to manage the symptoms, treatment, physical and psychosocial consequences and life style changes inherent in living with a chronic condition. Efficacious self-management encompasses the ability to monitor one's condition and to effect the cognitive, behavioural and emotional responses necessary to maintain a satisfactory quality of life'.[96]

Self-management is also defined as 'having or being able to obtain, the skills and resources necessary to best accommodate the chronic disease and its consequences'.[73] Therefore, acquired knowledge of chronic disease, appropriate self-management practices and the established relationship between self-management and medical management would produce effective chronic disease management. In this partnership, patients are able to identify impact of disease and treatment and its consequences, while health care professionals provide knowledge about nature of disease and the treatment alternatives.

Self-management processes can be supported by provision of clinical information and system decision support through arranging community resources, policies and organisation of care.[87] The problems arise from issues regarding lack of supportive policies, reliance of patient referrals and gaps in information system. On the other hand, from the patient's perspective, problems may occur due to limitations in accessibility of care, severity of disease and dealing with uncertainty, self-knowledge and therapeutic relationships.

Jones et al surveyed views of health care professionals and patients on guided self-management plans for asthma and found that there is not much enthusiasm amongst health care professionals for guided self-management plans for these patients.[97] The importance of continuous patient education and an ongoing monitoring and individualised patient care plan was contrasted with the danger of patients relying on a guided self-management plan and not attending the clinics regularly were the issues raised by health care professionals.

Self-management is seen as a process in which patients accept responsibility for changing their health behaviours, obtain knowledge of their disease and its treatment, and establish meaningful relationships with their health-care providers while emphasising their self-determination.[98] Therefore it is a continuous reciprocal process which aims to achieve defined goals. Extending the patient's role in management of their diseases through appropriate utilisation of community resources, changing health behaviour and provision of knowledge would lead to successful outcomes in their therapy. Patients develop explicit understanding about their disease and treatment alternatives, as well as consequences of their behaviours and attitudes and therefore acquire self-management abilities to overcome any problems that they experience.

An understanding of patients' preferences has considerable importance in shared care processes. Patients are likely to use information given in order to assess the impact of their diseases on their quality of life.

The shared care concept is developed upon a basis of social learning and self-regulation theories. These philosophies presume that disease management depends on patients' behaviour, their motivation and self-efficacy which are influenced by a learned self-directed process, their social environment and the contribution of health care providers. These theories can be implemented by setting pre-defined goals, identifying patient's willingness for self-care, splitting self-care tasks into manageable parts, feeding back to patients individually, acquiring self-monitoring, providing and ensuring social support and regular re-assessment of patient commitment to essential tasks. It is important that patient's and health care provider's perspectives should be considered mutually when problems are defined and solutions to overcome these problems are set. It has been suggested that establishing continuous self-management training and supportive educational and emotional services would facilitate patients' abilities in self-care processes and so would allow successful shared disease management.[95]

Development of the self-management concept has led to the hope that achieving safe and cost-effective disease management, particularly in chronic diseases, does not solely depend on clinical improvements or effective drug treatment in long-term therapy but also depends on patients' physical and psychosocial well-being.[96]

Being engaged with the basic skills of self-management are important for the management of chronic diseases.[73] Therefore, patients should be able to;

a) minimise and overcome physical discomfort of the disease
b) establish realistic expectations and emotional responses to the disease consequences
c) interpret and manage symptoms
d) learn how to judge effects of medications and manage their use
e) become accomplished in problem solving as they arise
f) communicate with health care professionals and
g) use community resources appropriately

A particular example of patient self-management programmes for arthritic conditions is developed by Lorig and her colleagues, which aims to improve patient's disability, pain, fatigue and depression (Arthritis Self-Management Programme-ASMP). It has been shown that a patient's knowledge, skills and disease symptoms are improved after attending the course and sustained up to 12 months and patients are able to improve their psychological well-being and communication with health providers.[99-101] The self-management programmes attempted to train and educate patients in order to facilitate their ability to manage the principles of self-management practices in chronic disease management. These key principles are defined as follows;[102]

- Recognise and respond to symptoms
- Use medications prescribed
- Manage acute episodes
- Maintain good nutrition and appropriate diet
- Maintain adequate exercise and use relaxation and stress-reducing technique
- Interact with health care providers and communicate with others
- Seek information and use community resources
- Adapt work and other role functions
- Manage negative emotions and psychological response to illness

In chronic diseases, patients generally become competent in these skills, particularly at interpreting symptoms and solving problems. It is essential to differentiate whether symptoms are disease-related or have occurred due to particular behaviour, emotional distress, medication errors or adverse effects of a drug.

As a part of disease management, drug treatment is intended to alleviate symptoms rather than cure disease in chronic conditions. It is therefore an important issue for patients to use their medication as prescribed. Patients sometimes require self-management skills in the use of medicines which enable them to comply with a regimen, interpret effects of medication, recognise side effects, seek medical advice and prompt a change in treatment programme when necessary. Patient's ability in problem solving can be enhanced through teaching general skills and providing access to appropriate counselling or supervision. Therefore, patients become responsible in seeking advice at the right time, describing their symptoms and expressing their concerns properly, differentiating different stages of disease-while acquiring an understanding and interpreting disease patterns, using specific self-management practices and applying preventative approaches in their disease management.

Self-management begins with recognition of the pattern of chronic diseases and importance of the patient's role in disease management; thereafter it continues with developing appropriate skills, confidence and co-ordination of health care services. It has been suggested that there is also a need for training of health care professionals in order to maintain and foster patients' self-management abilities in clinical settings.[96]

There is a new challenge for the NHS which initiates a shift in chronic disease management towards encouragement of patients to enable them to take an increasingly more active role in their own care. Therefore it is assumed that definition of roles and responsibilities would achieve improved disease management where patients are expected to manage specific aspects of their disease effectively; become less severely incapacitated by fatigue, sleep disturbances, low energy level and emotional consequences; able to access health and social care services, well-informed about their condition and medications and have higher self-esteem in order to improve their condition or prevent their condition becoming worse.

The new NHS Plan aims to achieve maintenance of health and improved quality of care with a safer environment for patients through comprehensive Expert Patient Programmes.[103] These programmes are developed to improve patient confidence and motivation to use their ability and knowledge in order to manage their own chronic diseases more effectively

(patient empowerment). Patients' experiences with symptoms of their disease and their attempts to overcome difficulties by themselves over the course of their treatment are recognised. Patients have their own expertise in experiencing illness, social circumstances and how to adapt themselves to a particular situation, their perception of risk, preferences and their outcome assessment. As a result, patients' own expertise in control of their disease is acknowledged with the introduction of these programmes.

> *When acute disease was the primary cause of illness, patients were generally inexperienced and passive recipients of medical care. Now that chronic disease has become the principal medical problem, the patient must become a co-partner in the process."*
>
> *Holman and Lorig, BMJ, 2000*[104]

1.8 Rheumatic diseases and treatment strategies in rheumatoid arthritis

1.8.1 Arthritic conditions and its impact on the public health

Arthritis and its associated conditions are the commonest cause of physical disability and long-standing illness in the United Kingdom among the group of musculoskeletal conditions. Approximately one in eight of the adult UK population report themselves to be disabled and almost 50% of these individuals report a musculoskeletal complaint, of which arthritis is the most common. Arthritis affects approximately 8.5 million people in the UK (approximately 10% of the adult UK population), of those about half of them are aged under 55 years including 14,500 children. The greatest burden comes from rheumatoid arthritis and osteoarthritis, although diagnostic uncertainty makes estimation of exact prevalence difficult. In 1990, more than 8 million people consulted GPs about some form of arthritis. In a population of 10,000; 60 cases would be expected to consult GPs for RA and the consultation rate increases with age in both men and women.[105]

The World Health Organisation classifies arthropathies into five groups; 'cyrstal arthropathies', 'infectious arthropathies', 'inflammatory polyarthropathies', 'osteoarthrosis' and 'other joint disorders'.[106] Table 1.4 summarises the clinical definitions and prevalences of different forms of arthritis.

The disease has a potential impact on a patient's quality of life by leading to physical disability, social isolation and chronic pain. A large survey in one NHS area used questionnaire and interview assessments to report that 5-8% of the adult population suffered disability associated with an arthritic condition.[107, 108] In a recent Scottish survey, half of the sampled adult population reported chronic pain and 16% of the general population gave 'arthritis' as the cause.[109]

Table 1.4 Forms of arthritis

Diagnosis	Clinical definition	Prevalence
Osteoarthritis	Degenerative damage and loss of articular cartilage, especially in the weight bearing joints and hypertrophy in the subchondral bone.	**3-6%**
Rheumatoid arthritis	Chronic systemic inflammatory disease characterised by potentially deforming symmetrical polyarthritis and extra-articular features	**0.5 – 1%**
Juvenile chronic arthritis	Inflammatory joint disease with chronic synovitis in children in whom the onset of disease occurred before the age of 16	**0.1%**
Psoriatic arthritis	Peripheral inflammatory polyarthritis with presence of psoriasis without rheumatoid nodules	**0.1%**
Ankylosing spondylitis	Progressive, chronic, systemic inflammatory rheumatic disease with involvement of sacroiliac joints and spine, absence of microbial infection with various extra-articular manifestations	**0.1 - 0.3%**
Gout	Abnormality of urate metabolism resulting in deposition of monosodium urate monohydrate crystals in the synovial fluid, soft tissue and urinary tract causing an inflammatory response	**0.2 - 0.6**

In the UK, the medical cost of treating musculoskeletal disorders is estimated at about 8% of the total NHS budget. The total UK cost of arthritis was estimated in 1990 to be £1,200 million (excluding lost earnings) and was equivalent to approximately 4% of the total NHS budget. In the UK in 1997 more than 26 million prescriptions were issued for musculoskeletal and joint diseases, costing a total of £205 million. In 1998, 3 million (approximately 5% by volume and by cost) out of a total of 57 million prescriptions dispensed in Scotland were for musculoskeletal and joint disorders.[110] The treatment of musculoskeletal disorders in the UK was responsible for approximately 6% of hospital and

15% of community health and personal social service expenditure in 1996. The provision of new therapeutic approaches and pharmaceutical services should therefore be considered in terms of economic value as well as clinical outcomes.

The survey indicated that distribution of rheumatology specialists does not adequately match distribution of health care needs of patients in the UK and this has been a particular disadvantage for the socially deprived population. The figures showed that there are 37 consultants in Scotland who provide care in two ambulatory clinics per week for a 100,000 population which only meets 41% of optimal provision in year 2001 (calculated by the need for one whole-time equivalent -WTE- consultant rheumatologist per 85,000 population). Throughout the UK, the number of hours that rheumatologists are working has increased since 1997, at present consultants spend 46% of their time in clinics and 14% in ward rounds. The number of consultants that have an established multi-disciplinary teams in their current practices increased from 75% to 81%, between 1999-2001.[111]

Roberts and his colleagues surveyed GP's perceptions and opinions on management of musculoskeletal disease in primary care settings.[112] It has been shown that GPs are less confident to manage early rheumatoid arthritis with their own skill and knowledge or with advice from a consultant. Thirty-four percent of GPs, whom they felt able to make the diagnosis, would prefer to refer to a specialist for management. The interviews with GPs revealed demands for multidisciplinary-interactive education for GPs and concerns over lack of resources in supporting services which emphasised a need for a multidisciplinary approach.

1.8.2 Rheumatoid arthritis, its prognosis and impacts on health care

Rheumatoid arthritis (RA) is a type of inflammatory arthritic condition which is an autoimmune, chronic debilitating disease affecting 0.5-1% of the population. It is approximately three times more likely to occur in women than in men and can occur at any age; its peak incidence is in those aged 50-70. The occurrence of rheumatoid arthritis varies little between countries but the disease is less commonly seen in Chinese and African populations whereas it has a higher prevalence in some Native American groups, particularly in Chippewa and Pima Indians.[113, 114] The disease has potential effects on both individuals and society in terms of physical, psychosocial and economical impact.

The prognosis and outcomes of rheumatoid arthritis are unpredictable. About 25% of patients first admitted to hospital remain fit for most activities, 40% will present moderate functional limitations, 25% will be severely disabled and 10% will be wheelchair-bound in ten years time.[115] It has been estimated that approximately half of the RA patients will be unable to work within 10 years and about 30% of out-patients will also develop severe disability in 20 years.[116] Young et al examined the impact of RA 5 years after the onset of the disease and indicated that approximately 40% of people had minimal or no impairment, 16% were severely disabled, 17% had undergone surgery and 10% had home adaptations or were wheelchair users.[117]

The studies confirmed reduced life expectancy in patients with rheumatoid arthritis with a Standardised Mortality Ratio (SMR) of 1.5-3.0; in severe RA mortality becomes worse as bad as in Hodgkin's disease and triple vessel coronary artery disease.[118, 119] It has been reported that predictors of mortality in RA were increased age, presence of nodules and high titres of RA latex. Deaths were not related to arthritis itself, rather they are associated mainly with cardiovascular events or occur due to infection, respiratory, renal or gastrointestinal diseases.[119] Recently, it has been shown that heart disease is twice as common in people with RA as in the general population and RA becomes an independent risk factor for coronary heart disease.[120]

Rheumatoid arthritis affects approximately 600,000 people in the UK population. It has been indicated that although consultation rates in primary care for RA in the UK are declining, RA still constitutes just over half of the rheumatology workload in secondary care and is responsible for about 54 GP consultation per year in the average general practice.[120]

Recent results showed that in the year 1999-2000 there were 66,931 rheumatology outpatient attendances at the 34 clinic sites in Scotland and 20% of those were new referrals and 2,760 discharges from the 13 in-patient units. It is estimated that RA accounted for approximately 33,500 outpatient attendances with total cost of £1.5 million and approximately £3.5 million for inpatient treatments.[120]

The overall estimated annual inclusive cost of RA in the UK is between £0.8 and £1.3 billion, which is made up of direct medical costs, work disability costs and residential and nursing home care costs. It has been estimated that direct and indirect costs per person with RA were approximately £3500 per year and the secondary care costs for the first five years of disease was £22million.[121] The recent studies indicated in England, the cost of rheumatoid

arthritis is estimated about £1.26 billion and 15% of the direct medical costs was accounted for by drug cost, including monitoring and management of toxicity.[120, 122]

1.8.3 Clinical features and complications of rheumatoid arthritis

Rheumatoid arthritis is the most common systemic inflammatory disease which mainly affects diarthroidal joints and is characterized by deforming polyarthritis and extra-articular features such as rheumatoid nodules, vasculitis, eye inflammation, neurological complications, cardiopulmonary disease, lymphadenopathy and splenomegaly. The majority of patients present at least some extra-articular features and these are more likely to occur in patients with high titres of rheumatoid factor. These features could be fairly insignificant (such as episcleritis) but could also be potentially life threatening such as systemic vasculitis or pleuropericarditis. The main reason for appearance of those features remains unsolved but is considered as a result of inflammation of potentially involved membranes, nodule formation and vasculitis.

The aetiology and explicit pathogenesis of rheumatoid arthritis are still unknown; however, genetic endowment and environmental agents seem to be involved. The inflammatory response might be triggered by various causes such as immunological, genetic or environmental factors. Initial inflammatory reaction begins in both the joints and their surrounding structures, particularly in the synovial membrane which leads to thickening of the surface (hypertrophy of the synovium) by infiltration of lymphocytes and plasma cells resulting in production of rheumatoid factors. This can diffuse to cause erosive destruction of the cartilage and bone. Biochemical, inflammatory and immunological effects play a role in cartilage destruction and loss of joint space. The damage is further complicated by tendon involvement and ligament damage leading to chronic deformity particularly in the cervical spine.

The diagnostic criteria for rheumatoid arthritis are defined by the American Rheumatism Association and were last revised in 1987 (see Table 1.5).[123] Rheumatoid arthritis is diagnosed when the patient meets at least 4 of the 7 criteria and criteria 1, 2, 3 and 4 must be present for at least 6 weeks.

Table 1.5 The American Rheumatism Association: Criteria and definitions for RA (1987)[123]

	Criterion	Definition
1	Morning stiffness	Morning stiffness lasting at least 1 hour before maximal improvement
2	Arthritis of 3 or more joint areas	At least 3 joint areas are swollen including PIP*, MCP*, wrist, elbow, knee, ankle and MTP* joints
3	Arthritis of hand joints	At least one area swollen in a wrist, MCP or PIP joint
4	Symmetrical arthritis	Bilateral joint involvement of PIPs, MCPs or MTPs is acceptable without absolute symmetry
5	Rheumatoid nodules	Subcutaneous nodules, over bony prominences, or extensor surfaces, or in juxta-articular regions
6	Serum rheumatoid factor	Demonstration of abnormal amounts of serum rheumatoid factor
7	Radiographic changes of RA	Radiographic changes typical of RA on hand and wrist radiographs

**Proximal interphalangeal (PIP) joints; Metacarpophalangeal (MCP) joints; Metatarsophalangeal (MTP) joints*

The radiological investigation is limited by lack of sensitivity to identify early changes in joints. Laboratory tests are also not specific enough to discriminate between different types of arthritis. Inflammatory arthritis, including rheumatoid arthritis and other spondylarthropathies, tends to cluster in families. Certain types of human lymphocyte locus-A (HLA) antigens such as HLA-R1, HLA-DR4 and HLA-B27 subtypes are found more frequently in patients with inflammatory arthritis. Most patients with rheumatoid arthritis have HLA antigen serotypes HLA-DR1 or HLA-DR4. HLA-DR4 serotype is associated with more severe cases of rheumatoid arthritis (70% of severe cases) and especially Felty's syndrome (splenomegaly and leucopenia associated with rheumatoid arthritis) (90%). In general, acute phase reactants such as C-reactive protein (CRP) and the erythrocyte sedimentation rate (ESR) or serum viscosity are increased in inflammatory arthritis and can be used to evaluate disease activity. Rheumatoid factor (RF) is an autoantibody (usually of the IgM class) found in the serum and directed against human IgG. RF is a non-specific indicator present in 60-70 per cent of patients with RA. In other forms of inflammatory arthritis, including ankylosing spondylitis, are usually sero-negative for RF.[115, 124]

Poor prognosis of rheumatoid arthritis is associated with the presence of rheumatoid factor, HLA DR4 alleles, early development of joint erosions, increasing number of affected joints, early disability, older age at onset, fewer years in formal education and presence of extra-articular features.[114]

Rheumatoid arthritis presents general features of arthritic conditions such as pain, stiffness, swelling, limitation of movement, inflammation, tenderness and joint instability. Different forms of arthropathies produce particular patterns of pain, swelling, tenderness and stiffness around affected joints, and the symptoms vary in terms of their intensity, localisation and duration (see Table 1.6 for the comparison of the features of RA with other arthropathies). Constitutional symptoms such as malaise, fatigue, loss of appetite, anxiety and depression are also associated with RA.[125]

The affected joints localisation often shows symmetrical and usually polyarticular pattern, more commonly in distal areas rather than proximal joints. It commonly affects small joints (hands and wrist) particularly peripheral joints of the fingers and also affects elbow, shoulder, knee, hip, ankles, toes and jaw.

Pain is the most common symptom and can be differentiated as articular pain (mechanical or inflammatory involvement of the joint) or periarticular pain (emanating for instance from the bursa, tendon or ligament). Patients with rheumatoid arthritis suffer from a pain which moves from joint to joint, and it remains at rest and even increases with immobility.

In rheumatoid arthritis, prolonged morning stiffness often exceeds 30 minutes and may remain throughout the day, but may be relieved by modest activity. Swelling of joints is caused by fluid accumulation, proliferation of soft tissues or enlargement of bone. Localised inflammatory involvement may cause joint and soft tissues to be red and warm. Joint movement is generally painful. Chronic inflammation, biomechanical changes and failure to maintain exercise result in limitation of motion compounded by muscle atrophy, weakness and deformity.

RA progression is characterised by progressive X-ray changes and then irreversible joint deformities such as ulnar deviation of the fingers, boutonniere deformities (hyperextension of the DIP joint and flexion of the PIP joint) or swan neck deformities (hyperextension of the PIP joint and flexion of the DIP joint). Joint destruction can be seen by radiographic evidence which is present in more than 70% of patients within the first 2 years.[114] Rheumatoid arthritis is a systemic disease which affects various systems in the body. Extra-articular symptoms are associated with disease progression and include skin and mucous membrane changes, eye complications, gastro-intestinal, cardiopulmonary, genito-urinary, neurological and haematological disorders. Subcutaneous nodules are hallmarks of rheumatoid arthritis.

Table 1.6 Comparison of features of arthritic conditions

	Osteoarthritis	Rheumatoid arthritis	Other forms of arthritis
Joint pattern	Asymmetrical Often monoarticular Commonly affects large joints (knee, hip, hand and spine)	Often bilateral Usually polyarticular Commonly affects small joints (hands and wrist) particularly peripheral joints of the fingers. Also affects elbow, shoulder, knee, ankles, toes and jaw	Asymmetrical and affects fewer joints than rheumatoid arthritis. *Characteristic* distribution, for example the spine and the sacroiliac joints (AS*), distal interphalangeal joints (PsA*, *gout*)
Pain	Localised Worsens with activity (especially in knees and hips)	Moves from joint to joint Increases with immobility and remains when at rest	*AS has gradual onset* Often poorly localised and rather diffuse in location Worsens with immobility Improves with activity and tends to recur after rest
Stiffness	(In mornings) is less than 30 minutes Transient joint stiffness occurs after rest	(In mornings) often exceeds 30 minutes Relieved by modest activity	*In AS;* (In morning) affects low back, buttocks and back of the upper thighs Relieved by modest activity Recurs following inactivity
Extra-articular features	Constitutional symptoms (such as malaise, loss of appetite and depression)	Fatigue, weight loss, dry eye (Sjogren's syndrome), episcleritis, cardiopulmonary diseases, haematological complications, rheumatoid nodules, vasculitis Premature death	*AS:* Anterior uveitis, aortic valve disease (aortitis and valvulitis), cardiopulmonary disease *PsA*: Ocular inflammation

Ankylosing spondylitis (AS); Psoriatic arthritis (PsA)

Rheumatoid nodules occur in 20-30 per cent of patients with RA. The nodules are asymptomatic and mostly occur on the extensor surfaces of the elbows, forearms, hands and on the sacral areas but can also be found in other tissues including eye, pleura, pericardium, lung and heart.

Vasculitis occurs in about 25 per cent of patients with long-standing RA. It is due to inflammatory cell infiltration and necrosis of blood vessel walls and it may be complicated by skin ulceration. Vasculitis most commonly involves the ends of the fingers or toes, especially around the nail beds, and presents small areas of black dead tissues around the nail margins.[126] The involvement of larger vessels may result in ulceration in the lower extremities or peripheral neuropathies. Extensive arterial involvement of larger-vessels may produce life-threatening complications such as ischaemia and may provide a portal of entry for infection.

Eye involvement is common in RA and other forms of inflammatory arthritis. Episcleritis, inflammation of the episclera resulting in red, painful and light sensitive eye, is self-limiting, often transient lesion associated with vasculitis. In contrast scleritis, which involves the deeper layer of the sclera, is a painful, less common but more serious condition which may lead to perforation of the eyeball. Dry, itchy eyes are found in 20 per cent of patients with rheumatoid arthritis and result from reduced tear formation (keratoconjunctivitis sicca or Sjögren's syndrome). Uveitis is a common condition in the other spondylarthropathies, especially in ankylosing spondylitis.

Pulmonary fibrosis causes progressive dyspnoea, inspiratory crepitations and clubbing of the fingers. Pulmonary fibrosis is seen in 2 per cent of patients with rheumatoid arthritis, particularly in men. The risk is increased by smoking. Cardiopulmonary involvement when present may reduce life expectancy.

Cardiac involvement is more common in men and is usually subclinical; valvulitis occurs in 20 per cent of cases in rheumatoid arthritis but is rarely symptomatic.

Lymphadenopathy affects 2 per cent of cases and is more common in patients with Felty's syndrome. Anaemia, thrombocytopenia, persistent vasculitic leg ulceration, weight loss and recurrent infection are other frequently presented features in rheumatoid arthritis.

Other manifestations of arthritis include peripheral neuropathy and carpal tunnel syndrome, which is caused by local pressure on the median nerve at the wrist. Dysphagia may occur in Sjogren's Syndrome secondary to dry mouth. Later in the disease cervical myelopathy is a significant neurological complication in rheumatoid disease caused by damage to the upper cervical spine.

Septic arthritis is a serious complication with a mortality rate of 25% in some cases in patients with rheumatoid arthritis. It generally presents as mono-articular along with blurred/ hidden clinical features (such as fever, rigors, neutrophil leucocytosis and local inflammation of the joints).

1.8.4 Treatment strategies in rheumatoid arthritis

1.8.4.1 Traditional pyramidal approach and use of non-steroidal anti-inflammatory drugs

The treatment of rheumatoid arthritis has traditionally introduced a pyramidal approach which indicates commencing patients on conservative management with analgesics or non-steroidal anti-inflammatory drugs (NSAIDs) in the early stage of the disease for several years until erosion has clearly been seen by radiography. The disease modifying anti-rheumatic drugs (DMARDs) are added individually as the disease progresses.

Simple analgesics (mainly paracetamol alone or in combination) are the first choice for pain relief in osteoarthritis; nonsteroidal anti-inflammatory drugs are considered as alternatives or adjuncts for pain relief in those who do not respond adequately to simple analgesics. The analgesic effect of NSAIDs can be achieved within a week whereas three to four weeks are required for anti-inflammatory effect. It has been shown that NSAIDs are more effective than simple analgesics in inflammatory arthritis. Although topical anti-inflammatory agents are suggested to be used for pain localised to specific joints, it seems their effectiveness is limited and they are overprescribed.

Differences in efficacy between most NSAIDs are small but response in individuals shows high variation. It has been indicated that gastrointestinal toxicity (GI) of NSAIDs is dose-related and amongst them ibuprofen has the lowest risk of GI complications.[127-133] The risk factors for GI symptoms are being aged >65years, history of peptic ulcer disease, GI bleeding or perforation, concomitant use of oral corticosteroids or anticoagulants, presence

of serious co-morbidity (cardiovascular disease, renal or hepatic impairment, diabetes and hypertension) and prolonged use of maximal doses of NSAIDs. It has been suggested that misoprostol and proton pump inhibitors, and to a lesser extent H_2 antagonists, reduce the risk of peptic ulcers and they may be co-prescribed with NSAIDs.[134] Renal adverse effects are the next most common side effects of NSAIDs and these drugs may also provoke bronchoconstriction. Therefore researchers suggested avoiding chronic use of NSAIDs where possible.

NSAIDs are widely prescribed and constitute 5 per cent of the NHS prescriptions in the UK with ibuprofen, naproxen and diclofenac being the most commonly prescribed in general practice.[127, 135] In 1999, approximately 18.5million NSAIDs treatments were prescribed in England at a cost of £170million.[136]

The consequences of overconsumption and risks of toxicity of NSAIDs, especially when they are prescribed on an 'as required' basis, were brought to attention of clinicians.[127] Annually 12,000 hospitalisations and about 2,000 deaths have been attributed to NSAID use in the UK.[134] Patients who are taking NSAIDs have a three to five fold increased risk of GI complications compared to non-users and the risk increases with age. Studies indicated that people aged 60-69 years have 2.4 fold, those aged 70-80 years have 4.5 fold and those over 80 years have 9.2 fold increase in the risk of serious GI complications compared to people aged 25-49 years.[136]

Misoprostol and proton pump inhibitors may be prescribed to reduce NSAID-associated GI complications but prophylaxis with those agents is not cost-effective except in targeted high risk groups. The MUCOSA study showed that serious upper GI complications (perforation, gastric obstruction or bleeding) were reduced from an incidence of 0.95% to 0.57% in the patients with RA who receives misoprostol 800micrograms/day (OR=0.65, 95% CI 0.36-0.98, NNT of 263).[137] However, 27% of the patients in the misoprostol group withdrew because of side effects in this study. Side effects, such as diarrhoea and abdominal pain which is approximately two times more frequent than with omeprazole, sometimes limit use of misoprostol.

The meta-analysis of five randomised controlled trials' results showed that addition of proton pump inhibitors (PPIs) reduced NSAID-related endoscopic gastric and duodenal ulcers from 35.6% to 14.5% (OR=0.23, 95% CI 0.18-0.31).[136] Studies have indicated that

omeprazole 20mg once daily dose is effective and well tolerated in the prevention of both gastric and duodenal ulcer in patients receiving NSAIDs.

Misoprostol and PPIs are effective in prevention of gastric and duodenal ulceration, whereas use of H_2 antagonists is limited by their ability to prevent only duodenal ulceration.[138] Therefore it has been suggested to use H_2 antagonists in order to reduce NSAIDs-associated symptoms in patients at low risk of GI complications (http://www.prodigy.nhs.uk).[136]

Following establishment of the second isoform of the cyclo-oxygenase (COX) enzyme in 1990s, use of selective COX inhibitors is suggested in order to minimise NSAID-induced complications (mainly GI side effects). The prostaglandin synthase H1 (COX-1) is the constitutive isoform of cyclo-oxygenase and it is responsible for production of physiological prostaglandins which protect gastric, small and large-bowel mucosa, control endothelial cell functions, promote platelet aggregation and maintain renal blood flow; whereas the prostaglandin synthase H2 (COX-2) is an inducible form and is localised mainly to inflammatory sites (macrophages, synoviocytes, fibroblasts, endothelial cells) and is induced by cytokines. As a result of these discoveries, available NSAIDs are categorised according to their selectivity to these two isoforms; preferential COX-1 inhibitors (most of the available NSAIDs), preferential or selective COX-2 inhibitors (etodolac, meloxicam and nimesulide) and specific COX-2 inhibitors (rofecoxib and celecoxib).[139-142] Their clinical value in long-term treatment is still being assessed. Currently meloxicam and rofecoxib are licensed in the UK although only in the case of rofecoxib does that presently include osteoarthritis.

The use of COX-2 inhibitors in patients with osteoarthritis or rheumatoid arthritis, who are at high risk of developing GI complications, is estimated at an annual incremental cost of £25million to the NHS. Therefore, the National Institute for Clinical Excellence (NICE) issued guidance for the use of COX-2 inhibitors in patients with osteoarthritis and rheumatoid arthritis. It has been suggested that these drugs should only be used instead of standard NSAIDs in patients who are at high risk of developing GI complications and should not be used regularly in patients with rheumatoid arthritis or osteoarthritis.[143]

Recent meta-analysis shows that rofecoxib has a lower incidence of upper GI effects including perforation, ulcer and bleeding than traditional NSAIDs.[141] The VIGOR study compared the GI complications over a nine months period in patients with RA who received either naproxen or rofecoxib, and found that rofecoxib is associated with fewer GI

complications (perforation, obstruction or bleeding; RR=0.43, 95%CI 0.24-0.77) compared to naproxen.[144]

The CLASS study assessed the GI safety of celecoxib in comparison with ibuprofen and diclofenac over a 6 months period in patients with osteoarthritis or RA.[145] Although the annual incidence of upper GI complications and symptomatic ulcers were lower in patients group who received celecoxib (2% vs 3.5%, in celecoxib and ibuprofen/diclofenac respectively. RR=0.59, 95% CI 0.38-0.94), this benefit is lost by 12 months (RR=1.1, 95% CI 0.47-2.58).[136]

Long term, large randomised controlled studies for the assessment of GI safety of selective COX-2 inhibitors are still needed in order to draw a robust conclusion concerning their value in the treatment of rheumatoid and osteoarthritis.

1.8.4.2 New strategies in the use of disease modifying anti-rheumatic drugs and combination therapies

Although it has been shown that NSAIDs are effective in ameliorating the symptoms of rheumatoid arthritis, no effects on the disease progression have been demonstrated. Remission or control of inflammatory joint diseases as expressed by improved symptoms, decreased ESR level and number of swollen joint counts, requires use of disease modifying anti-rheumatic drugs (DMARDs). In UK practice, sulphasalazine is the most popular drug (80% of patients with rheumatoid arthritis receive it in the first year of their treatment) and is followed by methotrexate, gold and penicillamine, which are commonly the preferred disease modifying anti-rheumatic drugs. Approximately 90 per cent of patients with RA take a DMARD at some stage of their disease. DMARDs have conventionally been used in patients with radiological evidence of erosive disease, or in rapid functional decline[146] but recent studies showed that they are increasingly being used earlier and more intensively in RA.[147-149]

Assessments by meta-analysis have suggested that methotrexate and hydroxychloroquine have the highest efficacy/toxicity ratio.[150] It has been indicated that median duration for patients remaining on mono-therapy with DMARDs (excluding methotrexate) in clinical practice was less than 2 years.[114]

Guidelines are published by the Royal College of Physicians and the British Society for Rheumatology in the UK and the American College of Rheumatology in US on rheumatoid arthritis (1992) and on osteoarthritis of the hip and knee (1993).[151-157] However those guidelines do not reflect the findings of recent studies that have prompted new strategies for the treatment of rheumatoid arthritis, in particular trends in the earlier use of disease modifying drugs. Moreover, a guideline for management of early rheumatoid arthritis was issued in December 2000 by the Scottish Intercollegiate Guidelines Network (SIGN).[158]

A wider range of agents is now used in the treatment of RA. Although the relative effectiveness of different strategic approaches to DMARD treatments are unclear at present, the increase in treatment options for RA requires general medical practitioners to refer patients to specialists early in the disease process.

DMARDs are also being used in combination in order to make the best use of an individual component. The research has studied effectiveness of the combination therapy but results are inconclusive. There has been a debate amongst rheumatology specialists regarding the use of combination therapies in early stage of the disease or where there is no optimal response achieved with methotrexate therapy.[159]

Emphasis is placed on systematic monitoring of disease progression to signal the need to make changes in DMARD regimen.[160] A 'Sawtooth' strategy indicates continuous use of one or more DMARDs in the early stage of the treatment process, monitoring disability and other outcomes; setting ceilings in acceptable disability in order to define decision points for the need to change treatment; modifying treatment systematically by changing DMARD treatment at each decision point; and use of analgesic/NSAIDs as adjunctive (symptomatic) treatment only. The strategy of using changes in treatment regimens to achieve greater individualisation of the treatment course challenges the notion of comparing individual regimens in clinical trials and makes comparative evaluation of treatments difficult.

The 'step-up' approach indicates administration of one DMARD initially and addition of another if the first agent is insufficient. A 'step down' approach has also been advocated where DMARD combinations are first used intensively to achieve 'remission' of disease activity and the more toxic components(s) are gradually withdrawn with the aim of limiting toxicity while maintaining disease control. Corticosteroids and NSAIDs are used as adjunctive agents to provide what has been termed 'bridge therapy' while DMARDs take effect.[159, 161]

It is not clear whether a 'step-up' or a 'step-down' approach is more effective; however, studies have showed that combination therapies (double or triple) are more effective than the mono-therapies and these therapies do not necessarily result in increased toxicity.[159, 162, 163]

In a view of published studies, O'Dell has recommended that rapid acceleration of methotrexate dose along with low dose prednisolone would be effective in the early stage of RA therapy and aggressive step-up DMARD combinations, such as addition of hydroxychloroquine and sulphasalazine, would be considered for patients who do not respond to this initial therapy. If an optimal response is not achieved with these therapies, patients should be commenced on specific the Tumor Necrosis Factor Alpha (TNFα) blockers with/without methotrexate therapy.[159]

1.8.4.3 An overview of the disease modifying anti-rheumatic drugs

Sulphasalazine

Sulphasalazine is now more commonly used in early stage of the treatment of arthritis. It has been shown that it is as effective as injectable gold, penicillamine and methotrexate and significantly better than antimalarials, oral gold and azathioprine. It has a better effect on disease progression compared with hydroxychloroquine. The studies suggested that triple combinations with steroid plus methotrexate are more effective than sulphasalazine alone.[150, 162, 164-167] The adverse effects with sulphasalazine treatment include gastrointestinal or central nervous system complications, neutropenia, skin rashes and hepatotoxicity. Continuous monitoring is required during the therapy, in order for patients to remain on the drug in the longer term without any complications. It is recommended that a full blood count (FBC) should be performed every two to four weeks for three months and every three months thereafter; liver function tests (LFTs) should be checked monthly for the first three months and every three to six months thereafter.[156, 168, 169] The treatment should be withheld if the white cell counts are $<4x10^9/L$ or platelets counts are $<150x10^9/L$ or if liver function tests exceed two times the upper limit of the reference range.[168]

Antimalarials (Hydroxychloroquine, Chloroquine)

Antimalarials tend to be reserved for patients with mild, slowly progressive arthritis or in those where disease overlaps with connective tissue disorders. They are relatively well tolerated, meta-analysis demonstrated a relatively high efficacy:toxicity ratio compared with other DMARDs. Hydroxychloroquine (rather than chloroquine) is being used in current

practice. It has been shown that a combination of chloroquine and methotrexate is more effective than methotrexate alone. Another study showed that triple therapy with hydroxychloroquine, sulphasalazine and methotrexate is more effective than using either hydroxychloroquine plus sulphasalazine or using methotrexate alone.[150, 165, 167, 170] Gastrointestinal symptoms can be avoided by starting with low doses and increasing gradually. The major side effect of these drugs is ocular toxicity which is dose-related and may produce corneal or retinal deposits. Although visual field problems are rare with hydroxychloroquine, early detection of retinopathy is necessary. Therefore ophthalmic examination every six to 12 months is recommended.[156, 169]

Methotrexate

Methotrexate inhibits dihydrofolate reductase (DHFR) and neutrophil chemotaxis. Mechanism of action in the treatment process of rheumatoid arthritis includes reducing rheumatoid factor (RF) production, decreasing IL-1 production, secretion and binding, stimulation of IL-2 production and also decreasing IL-6 activity. Anti-inflammatory effect may be the result of decreased secretion of pro-inflammatory cytokines (TNFα) and increased secretion of the inhibitory cytokine IL-10. Although methotrexate does not cure rheumatoid arthritis, studies suggest that it has an effect on slowing progression of erosions more effectively than azathioprine and can improve outcomes.

Methotrexate is increasingly being used in an individualised weekly dose regimen (7.5-25mg/week), although careful use is crucial to avoid toxicity. Methotrexate is usually given in an oral low dose (7.5-10mg) regimen weekly in the beginning of the treatment and slowly increased to a maximum 25mg/week. Rapid onset of action and alternative administration routes are advantages of the therapy. If the patient cannot tolerate the oral form of methotrexate, subcutaneous (s.c) or intramuscular (i.m) administration should be considered.

Adverse effects previously limited its use in long-term treatment. It has been shown that NSAIDs may increase GI toxicity and reduce renal elimination of methotrexate, therefore caution is required in co-prescribing NSAIDs with methotrexate. Concomitant prescribing with folic acid (5-10mg/week) reduces its side effects, such as alopecia, stomatitis, GI intolerance and haematological toxicity.[171-173] However recent studies indicate that the discontinuation rate of therapy due to side effects is less than with other DMARDs and therefore more patients have remained on methotrexate after five years (46-64%) and ten years of treatment (34-38%).[174-176]

The toxicity profile of methotrexate and its severity are widely defined.[177] Gastrointestinal complications and bone marrow suppression are more common adverse efffects. Mouth ulceration, abdominal distress and nausea as well as megaloblastic anaemia are early signs of toxicity. When stomatitis and diarrhoea are reported treatment should be withdrawn, otherwise haemorrhage, intestinal perforation and death as a consequence may occur. Megaloblastic anaemia is mainly seen in elderly patients receiving long-term methotrexate therapy. Folate supplementation allows continuation of methotrexate therapy without need for dose reduction.

Acute hepatotoxic reactions may occur after high dose of methotrexate or chronically after the long-term administration. Concomitant alcohol intake and repeated daily doses rather than weekly administration are contributing factors towards liver damage. Increased serum aminotransferases transiently in the beginning of the methotrexate treatment are not a risk for developing hepatotoxicity (hepatic fibrosis or cirrhosis). The incidence of cirrhosis is controversial and liver biopsies are recommended only after 5 years or if liver function tests are frequently elevated. Baseline liver function tests and full blood count repeating 2-4 weeks initially then every 4-8 weeks are also recommended during therapy.[156, 168, 169]

Pulmonary hypersensitivity is rare (1-7%) but can be life threatening.[177] It is unpredictable and also may recur after re-treatment. The drug should be withdrawn in patients with first signs of respiratory intolerance such as dyspnoea or cough. Risk factors include age over 60, history of pulmonary disease, previous DMARDs therapy, low serum albumin and also smoking and diabetes mellitus.

Although the incidence of infection with methotrexate therapy remains controversial, opportunistic infections have been reported repeatedly. Central nervous system effects are common (13-35%) and mild symptoms occur such as headache, fatigue, malaise.[177]

Methotrexate is probably the most effective and most rapidly acting drug amongst DMARDs (onset of action takes about 4-8 weeks). However single agent therapy may fail to induce remission.[163, 178] Scattered toxicity profiles and unpredictable effects of disease modifying agents on the disease outcomes in the long-term treatment lead to use of these drugs in combination therapies. Combinations of methotrexate with cyclosporin and with sulphasalazine and hydroxychloroquine showed better clinical outcomes than methotrexate alone.[150, 165, 167, 177, 179, 180]

It is recommended that tests for a full blood count, urea and electrolytes, creatinine, and LFTs, along with chest X-ray should be performed before initiating therapy. The tests for FBC should be performed fortnightly until 6 weeks after the last dose increment of methotrexate is achieved and monthly thereafter providing the dose is stable. Liver function tests should be checked monthly or every 2-4 months. The tests for U&E's should be undertaken every 6-12 months if there is no reason to suspect deterioration of renal function.[156, 168, 169] The treatment should be withheld if the white cell count is $<4x10^9/L$ or platelets count is $<150x10^9/L$; liver function tests increase above two times the upper limit of reference range; an unexplained fall in albumin levels exists; or rash or oral ulceration, new or increasing dyspnoea or cough are observed.[168]

Gold (intramuscular/oral)

Intramuscular gold is given weekly initially, followed by a fortnightly or monthly maintenance dose regimen. Oral gold (auranofin) is significantly less effective than methotrexate, sulphasalazine, penicillamine and injectable gold.[165, 167] The studies showed that combination with corticosteroids increases effectiveness of oral or i.m gold. Haematological, renal (proteinuria) and pulmonary side effects have been reported with gold treatments. Full blood count and urinalysis at the time of each injection[168], full blood count and urine dipstick for protein every one to two weeks for the first 20 weeks, then before every injection are recommended for monitoring.[156] The oral route is associated with reduced effectiveness and greater delay in onset of gold treatment. Diarrhoea also limits the use of oral gold.

D-Penicillamine

Penicillamine is as effective as i.m gold, methotrexate and sulphasalazine. The treatment with penicillamine and oral gold combination showed improved outcomes compared to penicillamine treatment alone. However there is lack of evidence for long-term efficacy and poor long-term tolerance for this drug.[165, 167, 181] Side effects are generally dose-dependent but do limit its usefulness. It is recommended that haemoglobin, full blood count and urine dipstick for protein should be done every two weeks until dosage is stable, then every one to three months.[156, 168] Oral iron and antacid impair its absorption and should be given two hours before or after penicillamine. A common reason for discontinuation is drug toxicity which includes mucocutaneous reactions (rash), haematological, GI (nausea and loss of taste) and renal complications (proteinuria). The treatment should be withheld if >1+ proteinuria or >1+ haematuria on >1 occasions is observed.

Azathioprine

Azathioprine is used mainly in patients with progressive disease who have failed to respond to either methotrexate or gold therapy. Methotrexate plus azathioprine combination therapy is not better than either methotrexate or azathioprine alone. In aggressive therapy, the triple combination of methotrexate, hydroxychloroquine and azathioprine showed good clinical response. Common side effects are nausea, vomiting, diarrhoea, mouth ulcers, rash, bone marrow suppression and liver toxicity. Full blood counts are required every one to two weeks with changes in dosage and every one to three months thereafter. Liver function tests should be checked at least every three months.[156] In the UK, it has been suggested that the tests for full blood count should be performed weekly for 6 weeks, 2 and 4 weeks after each dose increments and monthly thereafter; and liver function tests for every month until the dose is stable.[168] It is advised that concomitant use with allopurinol should be avoided.

Corticosteroids

Steroids are not considered to be traditional DMARDs; however, meta-analysis of studies of oral prednisolone 2.5-12.5mg/day confirmed their effectiveness in symptomatic control in RA. Addition of prednisolone 7.5mg to other DMARD regimen showed short-term rather than long-term effects in the disease control.[182-185] It is recommended that glucose and blood pressure should be checked every three to six months. Sudden withdrawal may cause resurgence of RA. It is shown that corticosteroids in combination with other treatments reduce disease progression in early active RA. Long-term adverse effects such as osteoporosis limit their routine use. I.V administration is used as pulse treatment to avoid long-term toxicity and intra-articular injections are used in acute episodes of RA where patients have effusion in the joint (although it provides temporary benefits only). It is suggested that pulse i.v methylprednisolone 400-1000mg repeated on three consecutive days, or on three alternative days, or once a month for 6 months might be safer than long term oral corticosteroid therapy. Local injection into the same joint is preferably limited to no more than once every three months in order to avoid joint erosion and risk of infection.

Cyclosporin

Cyclosporin has been introduced as a DMARD for patients with severe, progressive disease in whom most other DMARDs have failed. It is less well tolerated because of hypertension and nephrotoxicity, which are common and dose-related. The study showed that combination with methotrexate increases effectiveness of therapy.[179] It has been reported that long term therapy with cyclosporin is associated with a high rate of withdrawal, mainly because of elevated creatinine levels, hypertension and lack of efficacy and approximately 20% of

patients are remained on the therapy after 3 years.[159] It is suggested to use cautiously in patients aged >65 years, and those with hypertension, active infection, on anti-epileptic treatment and or undergoing surgery. If a good clinical response is achieved within three months, the dose can be reduced by 0.5mg/kg/day every month to achieve the lowest effective dose. It is recommended that the dose should be reduced for one month or the treatment should be withheld if plasma creatinine rises >30 per cent of baseline, and the drug plasma concentration should be measured every two weeks until stable, and monthly thereafter. Serum creatinine and blood pressure should be checked every two weeks; full blood counts and LFTs every month until the dose has been stable for three months and thereafter every month and every three months, respectively.[168]

Leflunomide

Leflunomide is a newly licensed disease-modifying antirheumatic drug which affects pyrimidine synthesis through an effect on dihydro-orotate dehydrogenase. It has a relatively rapid onset of action (within 4 weeks). However leflunomide exerts its effect through an active metabolite with a long half-life (15-18 days) which undergoes enterohepatic circulation. The therapy is initiated with a loading dose of 100mg/day and maintained with a dose of 10-20mg orally per day. The reported side effects are a variety of skin disorders (24%), diarrhoea (33%), abdominal pain, alopecia (8-10%), dizziness and hypertension. Monitoring of liver function during therapy is also recommended. There is potential additive toxicity in combination with other DMARDs. It has been reported that it is as effective as methotrexate for the first year of the therapy.[186] The studies indicated that combination of methotrexate may be useful in RA patients who do not respond adequately to methotrexate alone but increased hepatotoxic effects can be seen.[187-190]

It has been recommended that FBC should be performed fortnightly, liver function tests and blood pressure monitoring monthly for the first 6 months and every 8 weeks thereafter.[168]

Minocycline

Minocycline is found to be effective in the treatment of RA even though it is not fall into categorisation of DMARDs.[191] The drug has antibacterial, antimetalloproteinase and immunomodulating effects and evidence suggested that it is effective for controlling disease activity in seropositive RA within the first year of disease, although the evidence comes from limited controlled trials. The main problem reported with minocycline therapy is local hyperpigmentation.[192]

1.8.4.4 New biological agents in the treatment of RA

The new era in the treatment of rheumatoid arthritis begins with the use of biological agents to suppress disease progression which is modulated by imbalance in the cytokines. Cytokines are local messenger and signalling molecules involved in development of the immune system, cell growth and differentiation, repair mechanisms and the inflammatory cascade. They may be 'pro-inflammatory', such as tumour necrosis factor alpha (TNFα), interleukin 1 (IL-1), interleukin 6 (IL-6), leukotrien-alpha (LTα) and chemokines, or 'anti-inflammatory', such as soluble TNF receptor (sTNFR), interleukin 1 receptor (IL-1Ra), soluble interleukin 1 receptor (sIL-1R), interleukin 4 (IL-4), interleukin 10 (IL-10) and TGFβ. TNFα is an important pro-inflammatory cytokine produced by activated macrophages. Its levels are elevated in joints of people with rheumatoid arthritis. It acts by increasing production of cytokines that promote inflammation, increasing adhesion molecules which lead to cell migration into joints and increasing production of matrix degrading enzymes resulting in cartilage destruction. Alteration of cytokine function can be achieved by use of local or systemic monoclonal antibodies (such as infliximab), soluble cytokine receptors (such as etanercept), cytokine receptor antagonists and administration of cytokines which have opposing effects on the targeted cytokines.[193-195]

Etanercept is licensed for adult patients with RA and also for patients with juvenile chronic arthritis in the UK. The drug is a recombinant human TNF dimeric receptor fusion-protein which binds specifically to two molecules of TNFα or lymphotoxin (TNFβ). It reduces inflammation by blocking TNFα interaction with cell surface receptor and therefore the production of pro-inflammatory cytokines (IL-1). It also affects expression of adhesion molecules that regulate serum levels of some cytokines (such as IL-6).[116] It is administered at a dose of 25mg twice a week subcutaneously therefore patients are able to administer the drug at home. The main problems with etanercept therapy are increased risk of infection (particularly upper respiratory tract infections) and injection site reactions such as erythema, itching, pain or swelling (approximately 40% of patients experienced). It has been reported that blood dyscrasias such as pancytopenia and aplastic anaemia and central nervous system demyelinating disorders have been seen in RA patients treated with etanercept. However absence of tachyphylaxis with prolonged use, apparent lack of anti-etanercept antibodies and a better tolerability profile suggested that it has advantages over infliximab in the treatment of RA.[196] Weinblatt et al showed efficacy of etanercept in a combination therapy with methotrexate.[197]

Infliximab is a chimeric monoclonal antibody which reduces inflammation by binding to and neutralising TNF on the cell membrane and in the blood. It reduces serum levels of inflammatory mediators and the expression of chemokines in the synovial tissue, reduces leukocyte migration and reduces serum levels of vascular endothelial growth factor (VEGF). It is approved for treatment of Crohn's disease and is licensed for RA treatment in combination with methotrexate. The ATTRACT (Anti-TNFα Trial in Rheumatoid Arthritis with Concomitant Therapy) study demonstrated that combination therapy with methotrexate also prevents radiographic progression of the disease.[198] It has a rapid and long duration of action but multiple infusions of infliximab may cause development of anti-infliximab antibodies in long term therapy which is considered to be reduced by combination therapy with methotrexate. Combination with oral methotrexate has significantly reduced the proportion of patients with anti-infliximab antibodies and prevented tachyphylaxis. The most common adverse effects with infliximab are upper respiratory tract infections, headache, nausea, sinusitis, rash and cough. Therefore, it has been suggested that all patients should be evaluated for both active and latent tuberculosis before the treatment starts.

The British Society of Rheumatology and the British Paediatric Rheumatology Group issued guidelines for prescribing new agents in patients with rheumatoid arthritis and juvenile rheumatoid arthritis, respectively.[116, 199] It is recommended that patients who have active disease, have failed at least two standard DMARDs (including methotrexate) and who have a DAS28 score of >5.1, are eligible for these treatments.

The recent studies indicated that the main effect of these new biological products is only to suppress disease activity during treatment and relapse is unavoidable once treatment is discontinued. Overall, cost of the therapy is the main concern to initiate these treatments for patients with RA. Therefore their place in current treatment strategies for RA is likely to be in combination with methotrexate or alone in the early stage of the disease once further evidence has emerged from long-term trials. The estimation of drug cost and total monitoring cost for 3 months of etanercept treatment was £1,950 and £60 compared to £7.63 and £172 for methotrexate treatment. It is estimated that the treatment cost of etanercept and infliximab would be approximately £8500/patient/year in the UK.[116]

Anakinra is the first interleukin-1 receptor antagonist (IL-1Ra) which is licensed in Europe and in the United States for the treatment of rheumatoid arthritis in combination with methotrexate for the patients who have failed to respond to methotrexate therapy alone. The use of anakinra in conjunction with TNF inhibitors would be safe in regards to increased

susceptibility of infections, US Food and Drug Administration (FDA) did approve this combination therapy. Although it is difficult to judge from the findings of different studies, it has been suggested that anakinra is likely to be less effective than etanercept and infliximab in order to reduce clinical symptoms and signs of RA. Anakinra is administered by subcutaneous injection, is usually well-tolerated but it has been reported that the commonest side effects of therapy are injection site reactions, headache, neutropenia and serious infections, particularly in patients with a history of asthma.[200]

Adalimumab is another human anti-TNF monoclonal antibody which is suggested to have an effect on the treatment of rheumatoid arthritis, however late-phase clinical trials have been continuing for this drug to be licensed in the treatment of RA. It has already been reported that patients with RA sustained good response and reduced radiological disease progression within the first year of the treatment. The only toxicity that has led to withdrawal of the treatment has been peri-infusional allergic reactions and skin rash.[201]

1.9 Patient safety and medication errors in health care system

Chronic diseases usually demand long-term drug treatment. Drug therapies aim to improve the patient's disease status and prevent further hazard from its complications. Since drug treatment becomes an essential component of chronic disease management, it is necessary that current health systems and health care providers ensure safety of patients by safeguarding the process of drug treatments.

Drug prescribing and dispensing issues have not been given a high priority in the treatment process in chronic diseases and generally have been undervalued by practitioners. People are vulnerable to making errors, whether intentionally or unintentionally. It is a basic requirement of safe systems to detect errors before they result in severe consequences. Therefore effective systems are developed to reduce or prevent those errors and make the process as safe as possible through making these errors visible.

Error is defined as 'the failure of a planned action to be completed as intended or the use of a wrong plan to achieve an aim'.[202] Medication errors occur in the process of prescribing, dispensing and administration as summarised in Table 1.7.

Table 1.7 Pathways of medication errors

Process perspective	Structure perspective
Prescribing	***Institutional level***
Unfamiliarity with particular drug regimens	No recording/reporting scheme available
Issuing prescription (computer originated/ hand written)	
Dispensing	***Organisational level***
Non-alerted pharmacist	Staff workload
New staff arrivals	No education/training programme
Out-of-hours requests	Poor communication
No record for the intervention being made to prevent errors	Information overload
Administration	***Individual level***
Faulty equipment	Misinterpretation
Poor physical environment	Staff inexperience/inadequate training

In the UK, the Department of Health (DoH) has started to take actions against errors occurring within the health care system and has proposed to reduce serious medical errors for prescribed drugs by 40% by 2005 through working with an established National Patient Safety Agency (NPSA). By doing so, the same errors repeatedly occurring in time become predictable and therefore preventable. The NPSA suggested that medicines-related incidents are accounted for 12-20% of all NHS incidents. The DoH indicated in their report of 'Building a Safer NHS for Patients' that adverse events occurred in approximately 10% of admissions which is approximately 850,000/year and cost £2 billion/year in hospital stay alone. The data from United States showed a pattern of medication errors occurred which are mainly in regard to problems in orientation/training (60%), communication (40%), information availability (28%), competency (25%) and labelling (25%).[203]

It has been argued that there are repetitive patterns occurring in regard to medication errors due to misreading (such as Losec for Lasix), 'sound-a-like' or 'look-a-like' drug names and use of abbreviations including use of 'U' for unit, 'μg' for microgram, 'D/C' for discontinue/discharge which are reported to be dangerous.[204]

A report from Cardiff and Wales NHS Trust indicated that approximately 7,000 medication errors were reported in years between 1995-2000 and a preliminary analysis of 2,000 errors showed that two thirds of dispensing errors occurred due to dispensing of wrong drug or wrong strengths of the correct drug and one third of them were due to labelling.[204]

It is suggested that errors occur at institutional level, organisational/management level and individual level. The NHS encourages health professionals to use the Yellow Card Scheme in order to report any adverse events or incidence that occurred in the health care system regarding drug treatment. In addition to the self report medication error scheme (Yellow Card Scheme), there are also inquiries that have been reported by organisations/health authorities (an inquiry by the Cambridgeshire Health Authority) which helped to identify potential problems and failures in health care delivery.

The questionnaire study of an assessment of anonymous errors reporting scheme conducted in England showed that community pharmacists are willing to report errors in prescribing (100%), dispensing (95%), administration (84%) and near misses (84%). Furthermore the respondents believed that audit, feedback, group discussion, implementation of peer's suggestions, highlighting specific problems to individuals and flagging common problems on computer systems are important factors to change the practice.[205] Although the study was conducted amongst a small number of pharmacists, the results highlighted the lack of emphasis on the importance of reporting medication errors in the community settings given the fact that the pharmacists saw a median of 97 prescribing, dispensing and administration errors or near misses annually which averages <2 per community pharmacy over a nine month period.

The procedures to eliminate drug-related errors could be achieved by reducing complexity of the system, optimising information processes, understanding current barriers and identifying candidates at increased risk. Patients who are educated about their drug therapy are an available resource for pathways for identifying errors. It is believed that optimisation of the information process increases an understanding of current treatment, reduces negative effects of the memory-based approach and increases interaction between patient and health care providers.[206] It is also demonstrated that use of information technologies are successful in preventing medication errors such as computerised physician order entry (decrease by 55-83%), bar coding (decrease by 80%), automated dispensing devices or medication administration record and computerised adverse drug event detection systems.[207]

Prescribing is an additional pathway for errors occurring within the process. Errors are derived from incomplete details about legal requirements, dosage form or strength, dose or dosage regimen, quantity or duration of treatment on the prescription or incorrect details, such as incorrect drug or indication for use, duplicate therapy, drug interactions and contraindicated or inappropriate therapy. Those errors are associated directly with the

prescription itself but also compound errors during the dispensing process, which is likely to result in improper counselling, advice or information provided by the pharmacist (intellectual errors).[64]

Medication errors have been reported as a common problem in secondary care settings. The estimation of their exact prevalence is somehow difficult due to variations in definitions used by different authors.

A pilot study by Neale et al indicated that the main causes of adverse events in hospital admissions are poor clinical assessment at the time of discharge or insufficient education of patients and/or their caregivers about available community-based care givers and resources.[208] Potential contributing factors for these incidents were reported as inadequate liaison between members of the care team in preparation of the patient for discharge and variable patterns of communication among general practitioners and community support services regarding patient status. A study from Australia previously indicated that cognitive errors play an important role in the overall system which were categorised as failure in technical performance (35%), failure to act appropriately on available information (16%), failure to arrange for an investigation (12%) and lack of care and attention to the patient (11%). In the light of this Australian study, the authors suggested that concordance in implementation of policies or protocols, improved formal quality monitoring, improved education and training are all essential strategies in order to prevent adverse events.[208]

Shah et al conducted a study over 2 month periods in order to identify frequency and types of errors occurring in general practices. They identified 2,816 errors with a rate of 7.5% (95% CI 7.2-7.8). The highest error rate (37.5% of all errors) is found in circumstances where direction for use of a medicine is absent. They indicated that 9% of all errors occurred due to missing strength of a product where various strengths are available and no guidance is available in the BNF. The errors even occurred in computer-generated items (7.9%), not only hand written items (10.2%). About 8% of errors were accounted for by missing/misleading or indication for a large prescribed quantity and less than 1% of errors occurred because name of medicine was not clearly indicated or the strength was not clear. They argued that although most errors relating to directions were not serious, the prescription for using methotrexate 'as required' could have had disastrous consequences if the patient had misunderstood any verbal directions that have been given. Therefore, they indicated the potential role for community pharmacists in detecting errors and checking prescriptions, alerting general practices particularly with respect to repeat prescribing.[202]

Hence, a report by the Department of Health indicated that there is a need for an integrated approach in order to learn from medication errors and near misses which will standardise the system and make the errors visible.[203] Panel 1.1 outlines the key elements of the risk management strategy.

Panel 1.1 Features of the Risk Management Strategy

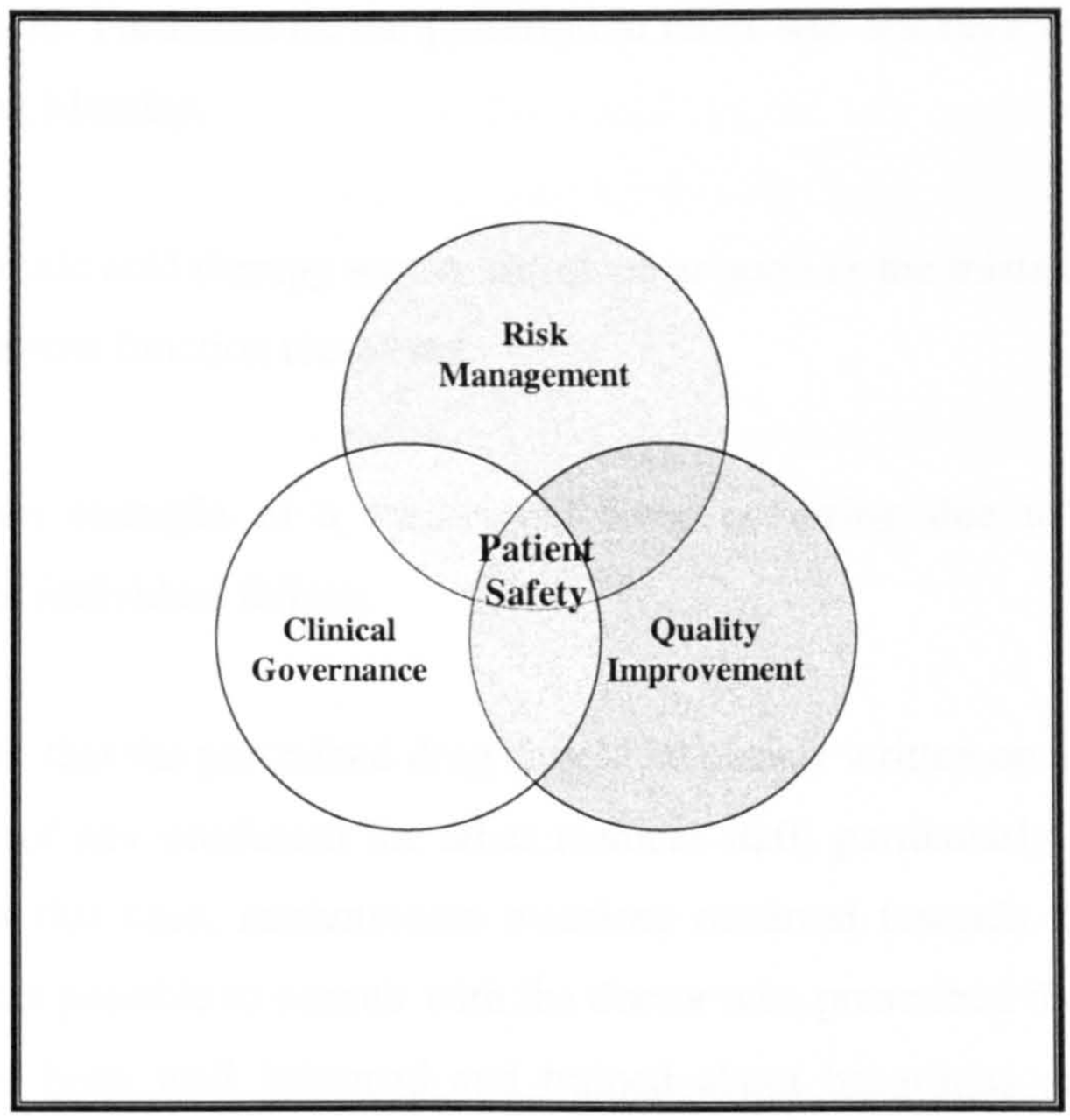
- Recording details of any dispensing incidents
- Use of records to identify patterns of errors
- Being comfortable with communication tools
- Review of care environment to identify environmental and care practice changes
- Building safety into purchasing policies
- Explore potentials for computers to reduce errors
- Creating a clear role for patients (involving patients)
- Changing individual/organisational behaviour
- Defining clinical controls and management

Since the term "clinical governance" has been introduced in the UK health care system in order to explain the quality in care, its main components incorporate the safety agenda of the NHS through;

- defining responsibility and accountability for the overall quality of clinical care
- designing a comprehensive programme of quality improvement activities (clinical audit, continuing professional development, clinical guidelines/evidence based practice, research and development, effective monitoring of clinical care)
- initiating policies which aim to assess and manage risks
- determining procedures for all professions to identify and improve poor performance

It is a way for organisations and individuals to ensure the delivery of high quality health care and continuously to monitor and improve standards of care. The relationships between the clinical governance and the patient care system is summarised in Figure 1.2.

Figure 1.2 Patient Safety System



Therefore, it can be seen that risk management is a dynamic system which is maintained by interactions between the processes for establishment of the context in the first instance and identifying, analysing, evaluating and treating the risk within the concept of monitoring and communication.

1.9.1 Medication errors related to methotrexate treatment

There are seven cases reported regarding medication errors in methotrexate treatment. These errors occurred in both primary and secondary care environments. Although detailed information regarding the cases is not available, the following sections focus on these errors in depth, in order to identify reasons for their occurrences in each case individually and seek clarifications/actions in order to prevent similar errors in future.

1.9.1.1 Case 1: The absence of pharmacist[209]

The patient was prescribed folinic acid 15mg three times daily as a rescue therapy for overdose of oral methotrexate which occurred on late Friday night.

Error: Nursing staff administered folic acid instead of folinic acid as a mistake.

Reason: Extremely poor handwriting had made it difficult to differentiate prescribed folinic acid from folic acid. Furthermore, the prescription chart was not reviewed by a pharmacist until the following Monday.

Action taken: Folinic acid therapy was commenced as soon as the mistake is recognised and patient's bone marrow function recovered.

This case was an example of a medication error occurring due to a combination of organisational and individual failure.

It is recommended that the prescribed drug should be clearly written on a patient's chart and not be the cause of any confusion for other medical staff, particularly during out of hour circumstances. In this case, methotrexate overdose occurred towards the end of the day, therefore it was not possible to consult with the doctor who prescribed the drug. The nursing staff should have been well informed and trained about hazardous drugs and treatment options for the complications. They should have sought further clarifications for prescribed medication. Moreover, it is acknowledged that the primary role of the pharmacist is to ensure accuracy of the prescription during ward visits, therefore all prescriptions should have been checked by a pharmacist before the drug was administered. It has been suggested that a resident pharmacy scheme or on-call pharmacist service enables patients to receive the correct drug and dose in out of hours without the prescription being seen. In the UK, pharmacists are paid for emergency duty commitment but only a few hospitals have a pharmacist residency scheme.

1.9.1.2 Case 2: Multiple errors[210]

A 69 year old male patient was re-admitted and died in hospital after being discharged with a supply of methotrexate tablets instead of the required thyroxine tablets.

Error: Pharmacist misread hand written discharge prescription and provided a two weeks supply of incorrect drug which patient took as directed and the consequence was fatal.

Reason: There are several factors identified which contributed to this event. There was an increased workload in the pharmacy department where the current level of required staff was not enough to overcome barriers. A badly written prescription caused confusion; 'Th' of

thyroxine was mistaken for an 'M' by both dispensing technician and pharmacist. Use of abbreviation for doses also induced the error. The 25 microgram dose of thyroxine was not written out in full according to hospital policy and abbreviated as 25µg (mcg) which was misread as 25mg. It was clearly stated on the inpatient drug chart that the patient was taking maintenance thyroxine therapy and had not been started on a course of methotrexate treatment. There was also a doubt whether the patient's discharge therapy had been checked by the named nurse before supplies were handed to the patient.

Action taken: The pharmacy department had undergone a review of staffing levels. The patient died after administration of wrong medication and this event was published in national newspapers bringing the error to public attention.

It has been argued that introduction of computerised prescribing systems might overcome potential problems with handwriting by indicating prescribed medication for discharge if mismatching the inpatient profile. Computer prescribing also provides printing of prescriptions more clearly and alerting the prescriber to high risk drugs which require more attention, such as methotrexate. It has been a common practice to use abbreviations for dose and timing for prescribed medicines although it has caused confusion with milligram (mg) doses instead of microgram (mcg). Therefore, it is suggested that the practice policy should encourage health care providers to use clear instructions for the prescribed doses and time intervals in order to achieve accurate and safe practice, particularly with these potentially hazardous drugs. It is also recommended to check discharge prescriptions against inpatient medication profiles before medicines are dispensed to patients on discharge. Pharmacists are qualified professionals who are required to implement these procedures to prevent potential medication errors and safeguard in the discharge process. Since the pharmacy department in this case did not have a policy of checking discharge prescriptions, final dispensing to the patient or his/her caregiver might have been checked by nursing staff instead of leaving this process to the patient or his/her caregiver.

1.9.1.3 Case 3: Problems with medicine packs[211]

An 80 year old woman received seven times the safe limit of methotrexate, which was prescribed for her arthritis, after admission to hospital. Patient subsequently died due to toxic effect of the drug which caused kidney and heart failure.

Error: There were two discharge letters in the patient's medical record. One of the letters was a hand-written prescription, indicating the dose 10mg weekly and the other one was a

typed letter, addressed to the doctor and indicating the dose for methotrexate at 10mg daily. The patient followed her GPs' instruction and took the methotrexate 10mg daily instead of once a week.

Reason: A junior doctor had failed to check the typed letter correctly before it had been sent to the GP. The reason was given by the doctor as increased workload and time limitation. Furthermore, the GP assumed that the dose on the received letter was correct and he/she consequently had issued the prescription.

Action taken: The GP subsequently disinclined to amend the prescription when the high dose was queried by the community pharmacist on receipt of the prescription.

This is an example of communication failure between health care professionals, particularly at the primary and secondary care interface. These types of errors have been previously reported in hospital rheumatology and dermatology outpatient clinics and severe consequences can be prevented by involvement of hospital pharmacists in checking prescriptions prior to discharge. Although it is not the routine duty of hospital pharmacists to check discharge letters to ensure appropriateness and accuracy of medication, it has potential benefit for the health care system.

In current practice, there are few other medicines that are administered in weekly dosage regimens with which health care providers need to be familiar. Methotrexate is also administered on a once daily regimen but only for a short period of time for chemotherapy and not in the treatment of arthritis. It is available in 2.5mg and 10mg tablet strengths which are very similar in appearance and 10mg tablets are only available in bottles of 100. It is recommended that a 28 day calendar pack containing four doses should be developed for a once a week dosage regimen which usually reinforces the weekly dose. There is a need for change of packaging for methotrexate tablets in order to prevent recurrence of this incident which has been brought to the attention of the manufacturers.

1.9.1.4 Case 4: Safeguard role[212]

A female patient was receiving methotrexate 12.5mg once a week for treatment of her rheumatoid arthritis. She was admitted to hospital for an unrelated condition.

Error: Methotrexate was prescribed on the regular drug section of the prescription chart which is usually used for regular daily medication although the frequency of methotrexate

was stated as 'once/52'. The chart was sent to pharmacy on Saturday with a request for supply. Tablets for one dose of 12.5mg were issued and methotrexate entry was endorsed '*once a week*' in red ink by a member of pharmacy staff. The prescription was sent to pharmacy again on Monday, with a request for a further supply. Three daily doses (Saturday, Sunday and Monday mornings) had been signed for by the nursing staff. Despite being signed for, the Sunday dose had not been given. However the patient had received a second dose of methotrexate on Monday using her own tablets brought in from home.

Reason: Nursing staff were not familiar with methotrexate and its dose regimen in the treatment of rheumatoid arthritis and intended to give it as a daily regimen. The prescriber used an abbreviation to indicate methotrexate weekly dose regimen (as in 'once/52') which was not properly understood by the nursing staff, particularly when it was written in the daily medication section of the drug chart. The patient used her own supply of tablets which should have been checked by health care providers previously in order to prevent further risk.

Action taken: The medical staff were informed and the patient was given a short course of oral folinic acid as a precaution. The patient did not experience any side effects.

It has been indicated that there is an obvious ignorance of health care practitioners towards pharmacist's input and prescription endorsement in this event. Particularly, nurses should have been reminded that they do not have an authority to write on the prescription section of the drug chart. Intentionally designed packaging for supplies of once weekly methotrexate tablets might have alerted nursing staff administering the patient's own supply and could have prevented the error.

The Committee on Safety of Medicines has raised issue of safe prescribing and dispensing of methotrexate. It is advised that tablet strength and the dose (daily or weekly) should be stated, pharmacists should carefully check tablet strength, the dose, the indication and should consult the prescribing doctor if there are any doubts. The dosage regimen and tablet strengths should also be clearly explained to the patient. The Committee also advised patients to report any signs of infection immediately.[213]

1.9.1.5 Case 5: Unfamiliarity with the treatment[214]

A 74 year old female patient was prescribed 15mg once a week oral methotrexate for chronic psoriasis.

Error: Methotrexate was prescribed 15mg daily and administered for 8 days during the patient's hospital admission.

Reason: The patient's notes were misunderstood by the admitting doctor during the patient's hospital admission.

Action taken: The patient had complained of a sore throat and had difficulties in swallowing during her hospital stay. The doctor was concerned about methotrexate side effects and requested a full blood count test which subsequently confirmed severe bone marrow suppression. The methotrexate treatment was stopped and the patient transferred to another hospital for more intensive care. The patient died 4 days later.

1.9.1.6 Case 6: Errors continue to occur despite recommendations[214]

A 78 year old male patient was prescribed oral 2.5mg methotrexate once weekly for chronic psoriasis.

Error: The patient's GP prescribed methotrexate 2.5mg daily. Furthermore, the prescription was dispensed by a community pharmacist.

Reason: The GP misread the instruction given by the hospital and the community pharmacist dispensed the prescription without query.

Action taken: The patient followed a 2.5mg daily methotrexate regimen for 10 days but became unwell with diarrhoea and vomiting as a result. He was prescribed gentamicin following his admission to a medical ward where he became septic. He further developed renal failure and transferred to another hospital for renal dialysis.

1.9.1.7 Case 7: Confusion with packaging of tablets[215]

A patient had been treated with methotrexate 5mg once weekly and folic acid 5mg on the other 6 days of the week for 12 months.

Error: The patient took one 2.5mg methotrexate tablets daily for six days.

Reason: Folic acid tablets were dispensed in a plastic bottle instead of in a blister pack as it had been dispensed before.

Action taken: The error was recognised when the methotrexate tablets ran out and the patient self-referred to the hospital emergency department. The patient was unaffected by this overdose of methotrexatere.

Various computer software programmes have been used in the practices and some of those do not contain a warning about methotrexate dosing. The programme containing these warnings might also have been ignored by practitioners who have not been involved in their CPD programme and received updated information about methotrexate dosing and shared care guidelines.

1.9.2 In depth analysis of an inquiry into the death of a Cambridgeshire patient[216]

In July 2000, the Cambridgeshire Health Authority reported an inquiry into the incident which resulted in a fatality in the patient with rheumatoid arthritis treated with methotrexate therapy. This tragic event mainly occurred due to failures in the care pathway involving health care providers in shared care practice. The report outlined errors that occurred in the process and explored potential barriers as well as solutions. The panel members also made recommendations to guide health care professionals and organisations in order to establish safe and effective systems for the patient care process. The purpose of the report was;

- to investigate prescribing, dispensing and administration of methotrexate in community and hospital settings
- to make recommendations to the Health Authority and others on how to minimise the risk in the future to avoid similar occurrences.

The panel analysed three steps in the drug treatment processes. The first step is prescribing of a drug for a specific condition, which is the responsibility of doctors. The second step is dispensing of a prescription which has to be checked by a pharmacist in order to assure safety, quality and efficacy of the drug treatment. And the last one is indicated as administering a drug to a patient which is managed by the patient, carer or nurse as directed. In the perspective of these three stages, the panel attempted to review the whole process for this case. The following sections have reviewed the processes of care that led to errors in this patient's drug treatment.

Incident:

A 80 years old female patient had been taking a weekly dose of methotrexate for her rheumatoid arthritis. The strength (dose) of methotrexate had inadvertently been altered by her GP to a 10mg daily dose from the patient's usual single weekly dose of 17.5mg. The patient had been overdosed prior to admission and her immune system had become severely compromised. The hospital continued treatment with a daily dose of methotrexate and the mistake was realised only after four days. The patient died after 12 days following her admission to hospital.

Patient History:

The patient was diagnosed with RA in 1982. She was commenced on Penicillamine treatment by a hospital consultant in 1984 and was given a drug monitoring card for her treatment monitoring. The patient's doctor was also informed about the commenced therapy and monitoring procedures. Penicillamine treatment had stopped on January 1997.

Errors occurred within the process:

The patient was prescribed methotrexate by a hospital consultant on January 1997. The GP had been informed about shared care arrangement for monitoring methotrexate therapy. There was an agreement indicating that the hospital consultant is responsible for any dose changes but subsequent repeat prescriptions should be provided by the GP. Moreover, it was indicated that performing blood tests and reporting results to hospital are part of the GP's responsibility. The patient started on methotrexate treatment and the dose of methotrexate was increased gradually over the next six months up to 17.5mg per week (prescribed as 7x2.5mg tablets taken once weekly).

Over a period of three years, there had been effective control of the patient's condition with methotrexate therapy. Both parties in the health care provider system were clear about their responsibilities and continued to perform monitoring as required.

- ***Errors likely to lead to consequences:*** There was no clear confirmation on the issue of information given neither to the patient nor to her carer about methotrexate therapy and its monitoring.

- ***Preventative/corrective actions (actions that should have been considered):*** The patient should have been informed and counselled about methotrexate therapy, the side effect profile, dose increments and monitoring requirements as a part of shared care arrangements.

She should have been provided with a patient information sheet along with a drug monitoring card and this should have been reported in her medical records.

The patient was admitted to the hospital on January 2000 for elective right total knee replacement. Her methotrexate dose regimen had changed from 17.5mg/week to one 2.5mg tablet during her 8 days stay in the hospital.

- ***Errors likely to lead to consequences:*** It was stated in the medical notes as 'one 2.5mg tablet of methotrexate' which showed that this had not been the full dose of 17.5mg/week but the patient had not understood it. The patient had been discharged from the hospital with her former methotrexate regime of 17.5mg/week (7x2.5mg tablets once a week).

- ***Preventative/corrective actions (actions that should have been considered):*** The patient was admitted to the hospital and had received only one tablet of methotrexate which caused fewer side effects for her and proved much simpler to take. In these circumstances, health care professionals should have been more careful about shared arrangements in chronic disease management. The changes in the drug therapy should have been explicitly discussed with specialist colleagues and should have been clearly documented in medical records. Furthermore, the patient should have been counselled and informed about changes in the treatment with an explanation for the reason, which should have been documented too.

Three months after discharge, the patient accompanied by her daughter had visited her GP for phelebitis in her left leg and pain in her right knee. At the end of the consultation, the patient's daughter asked GP to prescribe methotrexate in a way that involves taking few tablets while referring to the situation that had happened during her hospital admission on January 2000.

- ***Errors likely to lead to consequences:*** The GP was a locum, who agreed and issued a prescription for methotrexate 10mg daily although the intention had been 10mg 'as directed'. The new methotrexate prescription was signed for '10mg daily' and recorded on the computer. The patient's husband visited the local community pharmacy on the same day to obtain a revised methotrexate prescription. The locum community pharmacist was alone on duty in the pharmacy. He/she dispensed 30 tablets of methotrexate 10 mg to be taken daily.

The GP intended to simplify the dose regimen by reducing the number of tablets to be taken. The 17.5mg once weekly methotrexate treatment should have been prescribed as 1x10mg and 3x2.5mg with withdrawals of previously prescribed 2.5mg tablets which the patient already had at home. The GP had made a second mistake by entering the dose of treatment to the computer system using the abbreviation of 'od (once daily)' instead of 'asd (as directed)'. This caused a computer generated prescription being issued as methotrexate 10mg daily without any warning from the system indicating that methotrexate is a weekly dosage regimen.

- ***Preventative/corrective actions (actions that should have been considered):*** Written prescriptions must be clear and explicit and should not have led to confusion with abbreviations. According to an agreed shared care protocol, GPs were not legitimate in making dose changes of methotrexate without consulting the hospital doctor. The health care providers should have been more cautious when modifying dosages of potentially toxic drugs in elderly patients. Computer assisted prescribing could have been used more efficiently if there were any supported warning alert programme available, therefore a system of vigilance could have prevented the errors before the prescription reached the patient.

Dispensing of a wrongly written prescription has led to a third error with an unintentional contribution from the locum community pharmacist. This was not a repeat of a previous prescription, therefore the pharmacist should have checked the dose and frequency, changed the computer record which the patient had been already registered in the pharmacy and contacted the prescriber if he/she had any concern about the issued prescription. Lack of dispensing staff and technicians in the pharmacy potentiated the likelihood of occurrence of the incident.

Lack of awareness about potentially hazardous drugs among health care professionals in primary care settings increased the risk of occurrence of errors. Education and training on prescribed weekly dosage regimen drugs, increased communication and keeping up-to-date both with the patient's medical records and computer based records could have prevented the error while it was still in the community setting.

The next day after receiving the prescription, the patient started to take one 10mg tablet daily which added up to a total dose of 70mg/week.

- ***Errors likely to lead to consequences:*** The patient had been taking methotrexate tablets in a weekly dosage regimen since 1997. She obviously had not been counselled about her new treatment regimen and had not had explained to her the reason why it had changed to a once daily regimen.

- ***Preventative/corrective actions (actions that should have been considered):*** In chronic disease management, patients should have been enabled to perceive unintentional changes as a part of the shared care arrangements which puts responsibility on the patient and her carer in order to ensure correct administration of the drug prescribed.

The patient had requested a repeat prescription six days after receiving the daily methotrexate prescription.

- ***Errors likely to lead to consequences:*** Different GP was on duty at the time and he/she recognised the excessive dose of methotrexate but never considered that this prescription had been prescribed and dispensed previously. He/she deleted the wrong dose of methotrexate on the prescription and indicated the correct dose on the prescription in order to be signed. However the GP had not inspected or changed the patient's computer record which included the wrong dose of methotrexate.

- ***Preventative/corrective actions (actions that should have been considered):*** The frequency of repeat prescription should have been assessed by health care professionals. In this case, the patient requested a new prescription just after 6 days which should have alerted the prescriber about frequency of dose being taken. Indeed, the error occurred due to system failure rather than individual's cognitive failure which could have been eliminated through a corrected computer file.

On the following day, the patient started to feel unwell and her daughter had contacted another GP in the surgery regarding the patient's sore mouth and vagina. Treatments were prescribed for sore mouth and vagina. The GP gave advice and issued treatments for the patient's complaints according to a written medical record.

- ***Errors likely to lead to consequences:*** The new methotrexate prescription was not recorded in hand-written notes by the first GP. Furthermore, the current GP was dealing with complaints by phone consultation and had not referred to a computer record which could have alerted the GP to the current methotrexate prescription dose.

The next day the GP, who had spoken with the patient's daughter over the phone, received a request for a home visit to the patient. Thereafter, he/she had offered to arrange the patient's admission to the hospital which was declined by the patient and her family.

- ***Errors likely to lead to consequences:*** Because the home visit was undertaken during out-of hours (on Saturday) by the GP, he/she had no patient record or notes to refer to. Therefore the GP had prepared handwritten notes after seeing the patient and stuck them into the patient's medical record on the following Monday.

- ***Preventative/corrective actions (actions that should have been considered):*** Patient-held information could be helpful during home visits for patients with chronic diseases, particularly in patients with complex drug treatments since medical records were not accessible out-of-hours. Therefore the patient's and her family's awareness about methotrexate treatment were an important element which could have highlighted potential problems that the GP could have identified in the first instance. On the other hand, the GP could have accessed the patient's medical details through the community pharmacist that the patient visits regularly. A community pharmacy's PMR system might have provided information that the GP needed at the time he/she visited the patient at home.

Two days after the home visit, the patient had complained about a sore throat and inflammation in her groin area. Following a request the GP made another home visit and observed that there were simultaneous perineal rash and a sore throat which was not a simple sore throat complaint. The next day, the patient's daughter phoned the GP in order to inform him/her about a worsening of the patient's condition and the GP arranged hospital admission to an ENT ward attended by a junior doctor.

- ***Errors likely to lead to consequences:*** The GP had faxed patient information to the doctor regarding the admission, which indicated that the patient would bring all medication with her but this fax had not been received by the ward doctor. Late in the afternoon, the patient was admitted to the hospital, she was interviewed and her medical history and own drugs were recorded by the doctor. Methotrexate 10mg was also noted in the drug history but its frequency was not indicated. The drug chart had been completed as 100mg of methotrexate daily by the doctor. Blood tests were ordered for the patient but two successive samples were not adequate for full blood count analysis.

Communication between GP and hospital doctor was not successfully achieved because patient information was not transferred in an appropriate way to secondary care. The fax machine was out of paper, therefore only one page of the referral letter had been received which did not reach the doctor. The junior doctor did not properly examine the patient on admission and immunosuppressant therapy was not highlighted. Subsequently entering methotrexate 100mg daily on the drug chart was an error which was only realised by the nurse afterwards.

There was no ward pharmacy service on the ENT ward and since methotrexate was not held in stock, the ward decided to use the patient's own drug according to hospital policy.

Two blood samples were not satisfactory for full blood tests to be conducted and investigations had not been followed through with subsequent blood samples which could have identified reasons for the patient's complaints.

- ***Preventative/corrective actions (actions that should have been considered):*** Continuity of care is essential when the patient transfers from one health care setting to another. Therefore the referral letter and its contents are critical for health care professionals in order to identify the patient's problems and take any action. Furthermore, emergency referral of elderly patients with undifferentiated medical problems to a specialist ward should be avoided; the patient had no previous ENT history. In secondary care settings, systems for acceptance of patients' own drugs should be revised in order to mobilise pharmacists and doctors to review potentially toxic and relatively uncommon therapies more closely.

On the following morning, the nurse recognised the mistake in the drug chart for the methotrexate prescription during the ward round and administered 10mg only after conferring with patient but the drug chart was not changed. She left a yellow paper note for the ENT SHO to amend the drug chart but unfortunately the SHO made no change on that day.

- ***Errors likely to lead to consequences:*** Although the nurse had realised a dosage error with methotrexate and confirmed the dose with the patient before administering the drug, using a yellow paper note for communication with other health care professionals was an inadequate action to be taken at that time.

The laboratory had reported that the blood sample was insufficient for testing and it should be repeated after the second blood sample had been received. That outstanding blood test was the single most important investigation which could have contributed to the diagnosis.

- ***Preventative/corrective actions (actions that should have been considered):*** Recognised prescription errors should be immediately reported by health care professionals to others through a formalised robust system which could easily reduce the risk of serious consequences. The reported actions should also be recorded in the patient's medical record.

The next day a 10mg daily methotrexate dose was administered by the nurse (because the drug bottle indicated 10mg) and the patient's drug chart was sent to hospital pharmacy. The pharmacist realised that methotrexate 100mg daily was wrong and crossed off methotrexate on the drug chart and then told the nurse to check intended correct methotrexate dose with doctor. The nurse informed the hospital junior doctor about the query from pharmacy and the doctor telephoned the GP surgery to ask about the prescribed methotrexate dose. A non-medical member of staff at the GP surgery checked the computer records and confirmed the methotrexate correct dose as 10mg daily. Subsequently the hospital doctor amended the dose of methotrexate prescription on the chart and re-prescribed it as 10mg per day.

- ***Errors likely to lead to consequences:*** When the hospital pharmacist identified the prescribing error with methotrexate she/he had taken initial action by crossing off the methotrexate 100mg daily prescription and identifying a need for checking the dose with the original prescriber by informing the hospital nurse. The error mainly occurred after the hospital doctor contacted the GP surgery. The doctor did not speak with the GP who prescribed methotrexate but confirmed the dose through non-medical staff. Methotrexate 10mg was administered.

- ***Preventative/corrective actions (actions that should have been considered):*** Queries regarding prescribing errors should have been communicated directly with the original prescriber. It is necessary to establish good practice on the wards and to have ward pharmacists who can develop relationships with other health care professionals regarding prescriptions and drug administration procedures, particularly during weekends and in the provision of out-of-hour services. Doctors who might have relatively less experience with some drugs and uncommon regimens should have been encouraged to use the BNF for drug-related problems or contact the pharmacist for further confirmation.

On the following day, after confirmation of the 10mg methotrexate dose with the GP surgery, the patient was seen by two specialist registrars and two senior house officers during her stay but there was no consultant review documented in the medical record. Ibuprofen was stopped but other drugs were not considered and 10mg daily methotrexate was administered. Indeed, the patient's condition started to deteriorate even though various doctors had seen the patient at different times and considered her condition as 'much improved'.

- ***Errors likely to lead to consequences:*** The patient's condition was considered as 'much improved' even though the patient was having gastro-intestinal side effects of the therapy which was potentiated by the use of ibuprofen. The patient's current status had not been assessed against the patient's status on admission.

- ***Preventative/corrective actions (actions that should have been considered):*** Training of junior doctors regarding drugs and their side effects and involvement of the consultant in early stage of the patient's condition could have identified obvious care issues and prevented further deterioration in the patient's condition.

The next day, the patient developed a rash over her trunk. The senior nurse asked the staff nurse to check the patient's medication in the BNF. Afterwards the staff nurse had contacted the doctor and suggested that methotrexate could be a reason for the patient's problems even it was thought unlikely by the doctor. The doctor agreed to review the patient and he realised that the blood count results were still outstanding at the time he examined the patient. The third blood sample was taken and showed low platelets and white cell counts which were caused by methotrexate overdose and the patient transferred to the care of haematology team.

- ***Errors likely to lead to consequences:*** Blood samples had not been chased during the patient's stay at hospital and those could have indicated the cause of the patient's problem earlier.

- ***Preventative/corrective action (actions that should have been considered):*** Nursing staff's attention to the patient's condition sought further information on the probable cause. Health care professionals' concerns about possible diagnosis or therapies should be shared explicitly within a clinical team.

After transferring the patient to the haematology team, the doctor informed the patient's relatives about the poor prognosis and the patient died 12 days after admission. Cause of death indicated a gastrointestinal haemorrhage, pancytopenia and methotrexate toxicity on the death certificate.

It is recommended that drug companies who have licensed methotrexate for use of psoriasis and rheumatoid arthritis should review their packaging for methotrexate which reinforces to pharmacists, doctors and patients in the community that it is a weekly dose. Also the appearance of methotrexate tablets should be reviewed in order to differentiate tablet strength. The similarity in 2.5mg and 10mg tablets carries a potential risk for methotrexate overdose incidents. It is considered that 10mg tablets may not need to be available in the community.

1.10 Summary

A review of relevant literature created a perspective for the research questions to be answered. Potential impacts of inequalities on health and delivery of health care have raised questions regarding the provision of health care, particularly in community settings. Currently available systems and models of care that have been used in order to meet the population's health-related needs have been subjected to changes along with new developments. Therefore it has become obvious that equal and safe provision of health care within the population depends on available resources, their appropriate utilisation and establishment of effective systems in community. It is rather important to recognise the potential roles and responsibilities of each health care professional in the process of equal and effective delivery of care and to initiate a system for improved collaboration among the health care professionals and with the patients. A developed system will therefore run itself effectively by active participations of the health care professionals and the patients in the support of the National Health Service.

Recognition of patients' attitudes towards being healthy or living healthily has invented new opportunities for individualised provision of health care. Suggested health belief models have experienced shortcomings in order to explain the whole process of patient's attitude and behaviour. Given the fact that this process is dynamic, complex and multilayered, it is difficult to describe every aspect of patient's attitude and behaviour by a unique model. Therefore, the patient role in the effective and safe delivery of care has been explained through the perspectives of individual, social and environmental factors. Introducing patient

self-care or self-management concepts to the management of chronic diseases has allowed patients alongside a wider range of health care professionals to be actively involved in the processes of health care.

Along with active participations of patients, the management of chronic diseases also requires safe pathways for the delivery of care, which can be ensured by increased awareness among the participants of the process of delivery of care. Ensuring systematic checks, immediate reporting and documentation of the errors that occurred in the process of delivery of care will create opportunities for health care providers to focus on safe and effective disease management. Therefore it is important to have a system, which secures the pathways of delivery of care at every point during the process of delivery.

Although treatment of rheumatoid arthritis is well documented, there are still issues that have not been addressed to some extent. Therefore this research endeavoured to investigate the prescribing of methotrexate further and to accomplish an efficient model in the provision of health care for patients diagnosed with rheumatoid arthritis.

Chapter 2: An exploratory study on the management of rheumatoid arthritis with methotrexate therapy

2.1 Introduction

The management of rheumatoid arthritis demands multi-professional contributions from health care providers in both primary and secondary care settings. Besides development of new drug treatments, there has been a growing interest in the effectiveness of physical exercise and patient educational programmes in disease management, which bring various professions into the care processes.

The aim of this chapter is to provide an understanding of the management of rheumatoid arthritis in practice and in particular, with methotrexate therapy. Therefore, the chapter explores perceptions of health care providers on methotrexate use in the treatment of rheumatoid arthritis and provides an overview for the disease management approaches from the perspectives of health care professionals.

In this chapter, a theoretical foundation for the research is established. A hypothesis for the research which underlines problems within the health care system that affect processes of disease management is examined. A review of different research approaches and data gathering is provided in conjunction with a discussion of the chosen research design and further data collection methods.

2.2 Aim of the study

The study aims to gather a firm understanding of the management of rheumatoid arthritis in a particular area and explore potential problems in maintenance of continuity of care between primary and secondary care settings.

2.3 Objectives

2.3.1 To identify potential health care providers who are involved in the management of rheumatoid arthritis with methotrexate therapy in four Local Health Care Co-operatives (LHCCs) environments chosen for further study (Anniesland/Bearsden/Milngavie LHCC, Eastwood LHCC, Drumchapel LHCC and South Glasgow LHCC).

2.3.2 To investigate health care providers' views, opinions and attitudes on the management of rheumatoid arthritis with methotrexate therapy.

2.3.3 To identify the potential gaps between the primary and secondary care settings in the management of rheumatoid arthritis and propose a model of care for the patients who receive methotrexate therapy in the treatment of rheumatoid arthritis.

2.4 Methodology

2.4.1 Justification for the qualitative research methods

Qualitative research can be considered as a general reflection of opinions and prejudices, which verifies, disproves, organises and generates theories and produces evidence. Conducting scientific research in the social arena in some ways can be more complex than other types of research, because it requires ethical and practical considerations, which are controlled by external conditions such as complexity and the nature of individual behaviour, social interactions or cultural beliefs. It has been widely accepted that studies in social science can be scientific because they adapt appropriate research methods to ensure rigid, critical and objective data collection, analysis and interpretation processes within the chosen methodology.

Qualitative and quantitative methods in combination can be used in health and social sciences in order to overcome the relative weaknesses of each. The decision to use a qualitative or a quantitative method largely depends on the intention of building the research on a breadth or depth perspective.

Qualitative methods provide flexibility in approaches, allow the researcher to work with complex issues in depth and are essential for exploring new topics or hidden dimensions.[75, 217] They are generally exploratory and/or descriptive and generate detailed information about small numbers of cases by emphasising meanings, experiences and views in order to expand an understanding of a particular situation that is intended to be investigated.[218, 219] Therefore, they enable researchers to address questions which cannot be answered easily by quantitative experimental methods.[218-221] The features of qualitative methods are summarised in Table 2.1. On the other hand, quantitative methods are appropriate when facts about an issue are relatively well known and are amenable to being assessed and measured in a standard way. Hence, such methods allow measuring reactions of vast number of people by a limited number of questions and they facilitate statistical aggregation of data in a general manner for comparison.

Use of a combination of qualitative and quantitative methods in a research ensures detailed and depth data collection which is capable of yielding generalisable findings across settings and populations. On the contrary, once a large population survey emphasises the significance of patterns of a particular situation, it is also useful to identify meanings and grounds of those patterns through in-depth analysis using qualitative methods.

Table 2.1 Features of qualitative methods

Qualitative Methods	
Help...	...to develop the concepts to answer questions regarding human interaction and its reasoning
But...	...they produce detailed and variable data in content the response data are not standardised or systematic which makes analysis more complicated they are limited by respondents' abilities (e.g. writing skills)
However, appropriate to use in...	...process evaluations for program improvement comparing programs to document diversity identifying theory of action clarifying a model or treatment legislative monitoring responsive and agreement evaluation approaches harmonising values between program philosophy and research methods confirming or elucidating the research through adding depth, detail and meaning to statistical data exploring anticipatory research and prospective studies

Adapted from Patton (1990 [217]

Qualitative methods can be applied in circumstances where they provide channels into complex issues or when the researcher intends to describe or understand a situation or behaviour and aims to supplement quantitative studies in order to explore complex phenomena and increase validity of results.[218] It has been argued that a researcher should explore phenomena in the surrounding complex settings. It is important to understand the meanings that people attribute to their actions in their social environment, which enables the researcher to explore their thoughts, feelings, beliefs and values with an in-depth perspective.[222] Therefore, research gains strength through its descriptive or exploratory features.

Qualitative research methods have been favourably used in health care research in regard to exploring and describing current practices from the professionals' points of views, describing changing prescribing patterns and policy, explaining relationships between dispensing

doctors and prescribing pharmacists and investigating a service development from patients' perspectives.[219]

Qualitative interviews are preferred where a researcher seeks more information about patient's experiences of living with various diagnoses[223-227] or aims to explore health care practitioners' views about policies, decision-making processes and practice.[228-231]

Use of qualitative methods in scientific research, particularly in the medical arena, has not been fully acknowledged because of existing beliefs about lack of validity and generalisability of findings.[219, 232] However, there are numbers of studies that acknowledge the strength and appropriateness of qualitative methods in pharmacy practice research. These earlier studies highlighted the importance of patients' views and their experiences in achieving an improved health status and service development which conveys policy makers.[219] It has been argued that qualitative research also has criteria to ensure scientific rigour which can correspondingly be summarised as credibility (refers to internal validity), dependability, confirmability (refers to objectivity) and transferability (refers to generalisability). The ways of improving validity of data can be through triangulation, respondent validation, clear description of methods of data collection and analysis and appropriate sampling techniques are the procedures that should be considered in the assessment of validity of a research plan.[232]

The term 'triangulation' indicates use of combined strategies in order to increase strength of a study design, assuming that any shortcomings in one method would be compensated by the strength in another.[217, 221] Exploration of the subject being studied in different perspectives broadens problems and their potential solutions. There are four types of triangulation that have been identified;

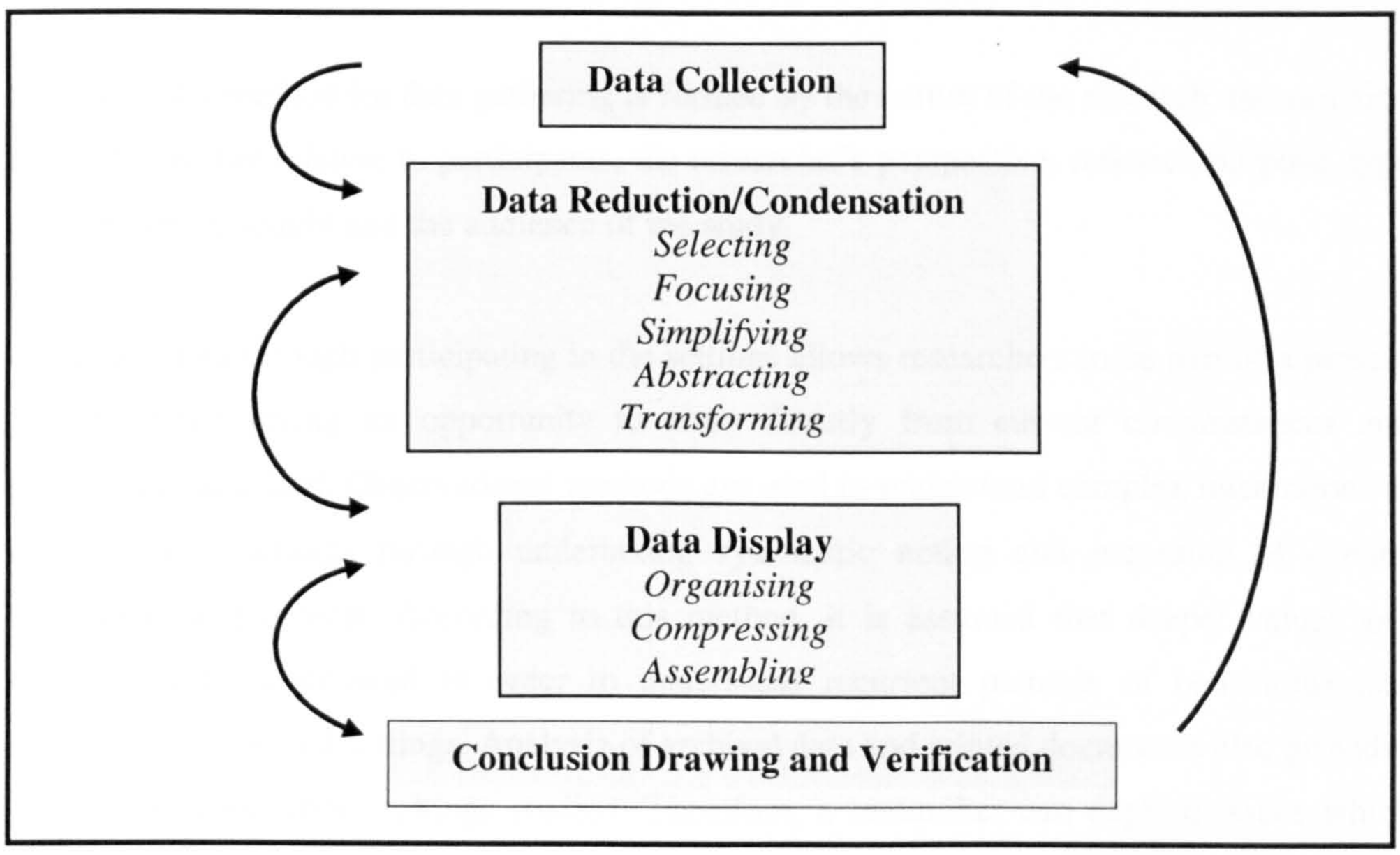
- *data triangulation* which uses different data sources in the study
- *investigator triangulation* that uses different researchers/ investigators in the study
- *theory triangulation* which uses different perspectives to explore and interpret a set of data in the study
- *methodological triangulation* that uses different methods to explore a single issue in the study

The feasibility of triangulation in studies also depends on time limitations and available staff and/or organisational resources. It has been suggested that the researcher should be specific about combining the data, methods or approaches in the same study.[221]

Data analysis in qualitative studies mainly involves 'de-contextualisation' and 're-contextualisation' processes of a vast amount of information collected (see also Figure 2.1).[233] Miles and Huberman identified a process of qualitative data analysis and summarised it as;[234]

- coding for collected data through observations or interviews
- noting observer/researcher reflections within the data
- arranging and refining data in order to identify similar or contrary themes
- identifying themes, patterns and processes including relationships between variables
- filtering a small set of generalisations that are consistent with overall data
- confronting these within known knowledge

Figure 2.1 Process of data analysis in qualitative studies



Adapted from Miles and Huberman (1994) [234]

According to Miles and Huberman, collected qualitative data are considered useful when they help to identify new leads of importance, extend the area of information, relate or bridge already existing elements, reinforce main trends, describe other information already gathered, exemplify or provide more evidence for an important theme and approve or disprove existing information.[234]

Three types of data analysis are indicated according to degree of pre-determined categories for interpretation; intuitive, data-based and theory-based analysis. Intuitive analysis enables

researchers to organise data through examining the text and then crystallising out the most important issues. Whereas in theory-based analysis, the researcher must organise the text according to pre-existing theoretical or logical categories in order to provide new aspects for a known phenomenon. The data-based analysis is somewhere between these two approaches which allows the researcher to identify units in the text and then re-organise it according to the basis of data-developed categories to resolve ambiguity.[232]

The data collection in qualitative studies can be categorised into five methods;[222]

1. participation in the settings
2. direct observation
3. analysing documents
4. questionnaires
5. in-depth interviewing

Selection of a method for data gathering is formed by the nature of the research, the situation of the researcher relative to participants, the researcher's perspective, research purpose, type of information sought and the audience of the study.

Gathering data through participating in the settings allows researchers to be part of a present process while giving an opportunity to learn directly from current circumstances and experiences acquired. Observational methods are used to understand complex interactions in natural social settings through undertaking systematic noting and recording of events, behaviours and objects. According to this method, it is assumed that deeper values and beliefs can be discovered in order to understand recurrent patterns of behaviours and relationships in social settings. Analysis of archival data and related documents also provides vital information about settings studied. Therefore, a researcher can explore issues which were discrete over a time period after data have been gathered. Questionnaire methods are a systematic way of collecting data about population characteristics, attitudes or beliefs on topic being explored. The researcher relies on honesty and accuracy of participants' responses to structured response categories or to open-ended questions. The interview methods can be considered as an overall strategy or one of the several methods that is used in a study and it is discussed in detail in the following section.

2.4.2 Interview techniques

Interview methods require a systematic and structured process that aims to access the perspective of a person being interviewed (interviewee) and explore feelings, beliefs, opinions, thoughts, concerns and expectations about represented incidents in detail which could not be observed directly. Its intent is to ascertain unknown social facts or beliefs in real world circumstances by using the most precise and objective methods (*positivists' perspective*). It also allows the researcher to discuss cultural changes in detail and prompt immediate follow-up questions for clarification when necessary. The interview technique is described in detail through the positivist and interactionist perspectives in Table 2.2 and the process is illusturated in Figure 2.1.

> *Qualitative interviewing begins with the assumption that the perspective of others is meaningful, knowable and able to be made explicit and its quality largely depends on the interviewer.*
>
> *M Q Patton*[217]

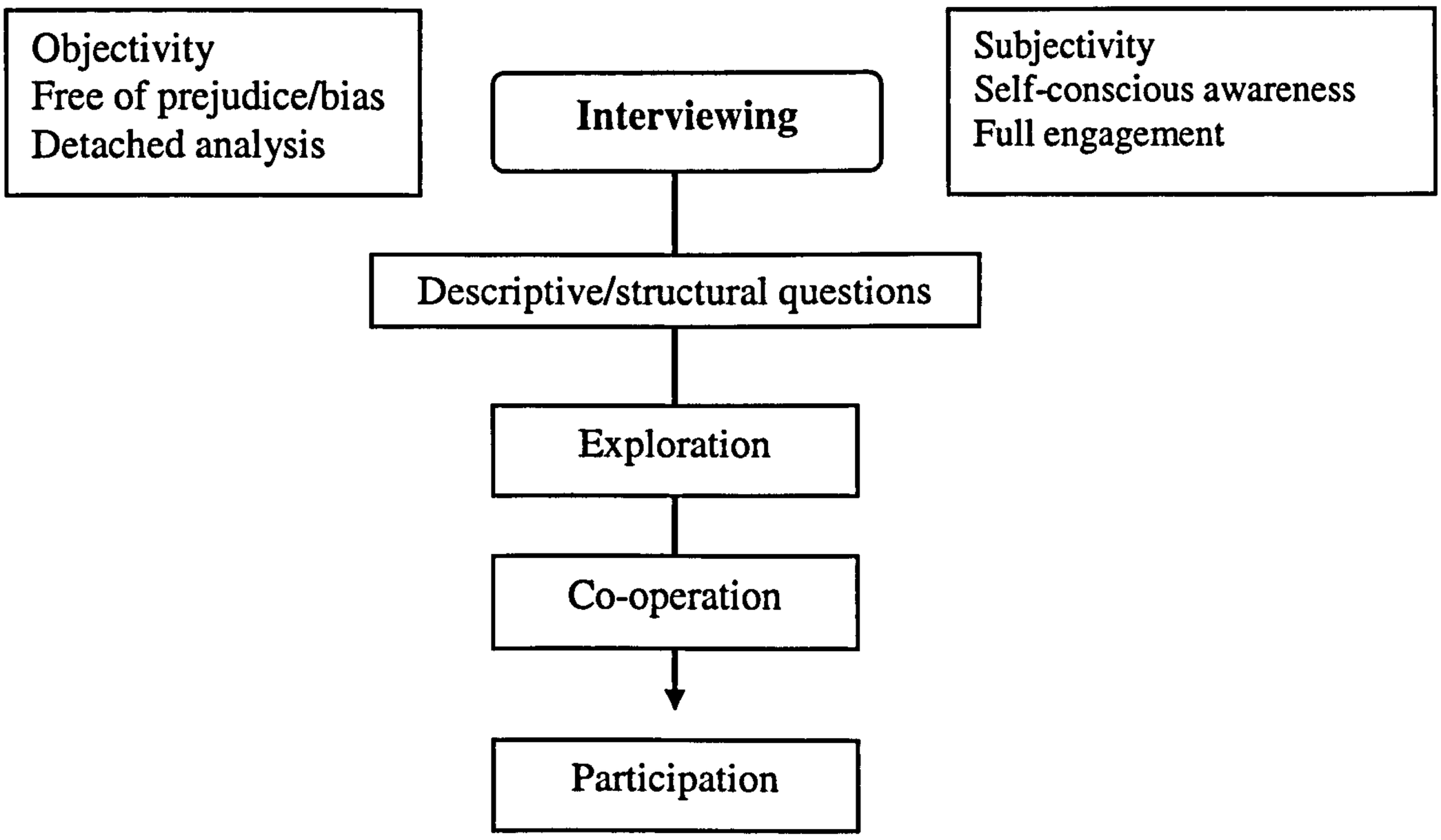
Table 2.2 Interview technique from different perspectives

	Positivist	Interactionist
Data are...	Facts about behaviour, attitudes and beliefs	Genuine experiences
Methodology...	Random samples, pre-tested standard questions, counting	Unstructured open-ended interviews
Interviewer	Object-following research protocol	Subject- creating interview context
Interviewee	Object-revealing items relevant to the research protocol	Subject- complying with or resisting definition of the situation
Interviews are treated as	Straightforward reports on external realities	Symbolic interaction or a report which express interpretative procedures and conversational practices underlies external realities

Interviews can be undertaken face to face or by telephone. The technique demands the most achievable interaction and co-operation between interviewer and interviewee in order to gather large amounts of information on a subject (*interactionists' perspective*). Readiness to

share ideas, thoughts or beliefs, and the nature of personal interactions increase the probability of obtaining valid and reliable information from an interviewee. Required data are obtained through interviewing and such data may be difficult to handle, therefore data must be interpreted against a background of the context in which they were produced.[222, 235]

Figure 2.2 The process of interviewing



The interview methods for data gathering can be categorised as; ethnographic interviewing, phenomenological interviewing, elite interviewing and focus group interviewing.[222] Ethnographic interviewing allows understanding of basic issues in cultural knowledge through the participant's perspective, and encourages the formulating of a hypothesis to work with. Phenomenological interviewing aims to describe the meaning of phenomena shared by different individuals and assumes that these meanings and experiences help to interpret action and interactions. The elite interviewing involves the selection of influential, prominent and well-informed people who have experiences in the subject being studied. The focus group interviewing creates opportunities for participants to expose their feelings, beliefs and values within a selected group of people. Therefore, participants are able to share their ideas with other members of the group while considering relevant questions and creating flexibility for the researcher to explore unanticipated issues as they arise during discussion.

Three approaches are acknowledged in the process of interviewing. The *informal conversational interviews* are preferable where the researcher can be in the settings for a period of time to observe and conduct interviews which can build on those that have already been done previously. Therefore, information gathered from interviews expands and moves towards new directions to be explored. The advantage of this technique is that the interviewer becomes highly responsive to individual differences and circumstantial changes. However it requires a great amount of time to collect systematic information, it has the possibility of a greater chance for interviewer bias and it is a prolonged/difficult process to combine and analyse the data gathered. The *general interview guide* approach endeavours to obtain same information from a number of people using same material (known as an interview guide) and allows the interviewer to follow a certain structure throughout the interview. The interview guide outlines topics and subjects to be discussed during the interview while allowing the interviewer to explore, probe and ask questions in the light of a pre-determined and focused subject in order to eliminate misinterpretation and ambiguous answers. It also gives confidence to the interviewer about how to use time efficiently and how to avoid deviation into issues as individuals' perspectives emerge.[219] The *standardised open-ended interview* is mainly used to minimise interviewer effects by the same questions being asked to all respondents through a similar systematic way in order to make data analysis easier.

The various approaches for undertaking interviews are summarised in Table 2.3 and Table 2.4. However, the decision to choose particular interview techniques largely depends on the purpose of the research being undertaken, the information required and the research objectives. The standardised approaches can be more appropriate to use in the evaluation of a specific situation by collecting the same information from different respondents in order to increase the credibility and accuracy of the processes that have been used.

Using open and non-leading questions allows respondents to express their views and opinions and raise potential issues which may not be considered by a researcher in the first place. In most studies, interviews are tape-recorded and transcribed verbatim which is fundamental for detailed and valid data analysis.

Researchers are likely to use established theoretical frameworks in the analysis of their data. 'Grounded Theory' methodology is one of the data analysis approaches that allows ideas, themes, hypotheses and theories to emerge from an analysis of data derived from natural settings. The researcher identifies common themes and groups them under certain categories

while refining data systematically. Therefore, the researcher is able to clarify the structures of the subject studied via this repeated process between inter- and intra- categories. However, it has been acknowledged that the researcher's awareness of the subtleties of the meanings of data and their own preconceptions are important features in the data analysis process which requires a systematic and rigorous approaches in order to maintain the validity of the methodology.[219]

Table 2.3 Comparison of interviewing approaches-I [217, 219, 222]

	Standardised or structured	In-depth, focused semi-structured
Advantages	Provides quantitative data for classifying, coding and analysis which is simpler Results comparable Higher reliability Greater opportunity for measurement Relatively economical Large samples of people can be included Reduce individual interviewer effect-less variation/less scope for bias	Appropriate for complex or unknown issues Questions can be deep, searching Data rich and full High degree of validity Can obtain clarification and elaboration of ambiguities through probing Allow respondents to answer more on their own terms Flexibility Allow discovery of 'meanings'
Disadvantages	Requires good pilot work and training of interviewer Pre-coded or closed questions must be simple and response choices may not be comprehensive Potential for choosing inappropriate answer by the interviewee Data lack depth Lower validity Does not allow interviewer to pursue unanticipated issues Cannot obtain clarification of ambiguities through probing	Interviewers need skill and training Passivity of the interviewer may create a powerful constraint and an interpretive problem Potential interviewer bias and greater interviewer variability Results often not comparable Reliability questionable Less scope for measurement

Table 2.4 Comparison of interviewing approaches-II

	Face-to-face	Over Telephone	Focus group
Advantages	Probe questions to clarify ambiguity, when necessary Complicated or detailed questions can be asked Inconsistencies and misinterpretations can be checked Friendly personal interactions with interviewee increase response rate No literacy requirements for respondents	Economic in terms of time and resources Computer assisted interviews provide speed and minimisation of interviewer bias	Explore group norms and dynamics Participants are allowed to comment and discuss their opinions Elaboration and/or clarification is achieved by encouragement of participants Interactive-interaction within group Provide insight into social relations
Disadvantages	Can be expensive and time consuming Potential interviewer bias	Bias for over or under-representation of population Only suitable for use with brief questionnaires and on non-sensitive topics Potential reluctance of interviewee in time	The researcher may have little or no control Caution is required in interpretation of the data (not reflecting one participant's view as a group view)

Various sampling strategies have been used in qualitative studies, such as maximum variation, homogenous, critical cases, theory based, conforming and disconforming cases, snowball or chain, extreme or deviant cases, typical cases, intensity, politically important cases, random purposeful, stratified purposeful, criterion, opportunistic, combination or mixed and convenience sampling.[222] Although the achievement of purposive and theoretical sampling is suitable in most settings, which makes them commonly used in qualitative studies, the decision on sampling strategies mainly depends on the purpose of the study, the availability of resources and the efficiency and adequacy of the suggested strategy.[219] The

purposive sampling involves intentional identification and selection of participants who have more experience in a relevant subject and are presumed to provide a larger amount of information regarding the subject being studied. Convenience sampling requires reaching the most accessible individuals or people who agree to participate in a study. In theoretical sampling procedures, participant selection is iterative and based on the concepts that have previously been proven relevant to the studied subject.[219]

2.5 Subjects and settings

The convenience sample of health care providers was initially contacted by the research pharmacist by telephone.

The health care providers were considered eligible if they:

- practise in one of the proposed LHCCs areas
- were nominated by any other health care providers
- were willing to participate in the study
- regularly see rheumatoid arthritis patients in their practice settings

Ten health care providers from various professions (two consultant rheumatologists, two community pharmacists, two nurse specialists and four general practitioners) were interviewed in their practice settings. Health care providers were chosen purposefully in order to gather more information about the subject being studied. They were also favoured according to their practice locations in order to explore any differences that might originate or occur owing to differences in patterns of socio-economic environments.

2.6 Data collection procedures and analysis

Identified health care providers were contacted by the research pharmacist via telephone and were asked for their participation in the study. Following the giving of brief information about the study, they were asked for an appropriate time for an interview to be undertaken. The research pharmacist arranged a visit to the practice settings of the health care providers' after agreement to participate was obtained.

The interviews were undertaken in different practice settings from June 2000 to December 2000. The semi-structured interview technique was used for all interviews. The research pharmacist prepared a list of pre-determined questions in order to maintain interviews within the intended scope of the subject, but allowed interviewees to explore their views and ideas

about issues discussed during the interviews (Appendix 2.1-Appendix 2.4). Interview questions were designed according to the profession of the interviewee and the practice settings of the health care providers. Initially, the researcher explained the purpose of the interview and asked permission for it to be tape recorded. The interviews were undertaken in a private room and recorded using a 'SONY' tape recorder and a desk microphone. The interviews were intended to last between thirty minutes to an hour approximately. All interviews but one were recorded and then transcribed verbatim for content analysis. Only one interview with a nurse specialist was not recorded due to non-availability of equipment at the time of an interview.

Content analysis was undertaken on verbatim transcripts of interviews using inductive coding procedures where data itself originates labels and codes for the themes in collaboration with an academic independent researcher who has previous experience on the analysis. Common themes were identified by the researcher following this coding and clustering process. Potential views, opinions and suggestions emerged from perspectives of different health care providers regarding the management of rheumatoid arthritis and methotrexate therapy were categorised and reported as described in the following sections.

2.7 Results and discussion

Interviews with various health care providers indicated a particular pattern for the management of rheumatoid arthritis in current practices. As a result, potential gaps in the management process of rheumatoid arthritis were revealed from the perspective of the different health care providers.

The information regarding the participants are summarised in Table 2.5. Common concerns and problems raised by respondents were categorised under general headings and summarised in the following section, illustrated by selected quotations.

Table 2.5 Characteristics of the interviewees

Interviewee No.	Profession	Gender	Postcode for practice setting	Carstairs Index for practice setting	Interview Date
1	Consultant rheumatologist	Female	G51 4TF	7	July 2000
2	Consultant rheumatologist	Male	G12 0YN	2	July 2000
3	Nurse specialist	Female	G51 4TF	7	June 2000
4	Nurse specialist	Female	G12 0YN	2	July 2000
5	Community pharmacist	Male	G52 3SX	4	June 2000
6	Community pharmacist	Female	G62 6BL	2	September 2000
7	General practitioner	Female	G51 1SL	6	November 2000
8	General practitioner	Male	G51 4BJ	7	November 2000
9	General practitioner	Male	G15 7TS	7	December 2000
10	General practitioner	Female	G13 2SW	6	December 2000

2.7.1 The management processes of rheumatoid arthritis with respect to methotrexate therapy

Second-line drug therapies in the treatment of rheumatoid arthritis, also known as disease modifying anti-rheumatic drugs (DMARDs), are mainly initiated by rheumatology specialists (consultant rheumatologist) in hospital settings. Therefore, the consultants have an initiating role in the treatment process.

Interviewed rheumatology specialists identified three critical stages during methotrexate therapy; (i) beginning of the therapy (initiation phase), (ii) a stage where the patient becomes stable on an achieved successful dose (dose escalation and maintenance phase) and (iii) a stage when the patient develops intercurrent illness. Therefore, this emphasises that the capacity for alerting the health care system by the patient is crucial during these three stages of therapy, where health care providers should become engaged in addressing particular problems identified by patients.

> *'...probably the biggest concern is earlier on in the therapy, when we first introduce, we have number of quite severe upsets, toxicity...so you never lower your guard with methotrexate...'*
>
> *(Consultant rheumatologist-2)*

The interviews with rheumatology specialists highlighted that there is enormous workload in rheumatology outpatient clinics. The rheumatologists consult approximately 50-60 patients diagnosed with rheumatological diseases (mainly with rheumatoid arthritis) every week. The frequency of clinic visits per patient varies according to preferences of the consultant, patient's disease severity, phase of methotrexate therapy and a patient's response to the therapy. Consequently, it has been revealed that an increased workload demands an effective and collaborative disease management protocol between rheumatology specialists and general practitioners (GPs) in order to maintain continuity of care between different care settings.

General practitioners also acknowledged a scale of workload and inadequacy in manpower in hospital outpatient clinics. Perceptions about their role in disease management appeared to be limited to drug monitoring because they believed that management of arthritis is the responsibility of specialists in secondary care settings. The amount of input from primary care is perceived as questionable by GPs themselves, because they believed that they are not involved in clinical decision making, they mainly follow recommendations from rheumatology specialists, which does not particularly reduce the workload of other health care providers. As a result, doubts about shared care requirements for primary care professionals have arisen. It has also been suggested by GPs that further education and training of GPs is necessary if there would be any further need for involvement in the disease management.

'...Where I find it a little bit difficult is the degree of side effects and this is really... I've only ever had it only once or twice,....the mouth ulcers. How much is the lot of mouth ulcers, I don't know... I wasn't a lot of help, I didn't cut down anyone's workload at the hospital.'

(General practitioner-1)

'...I wouldn't generally increase the, you know DMARD's dose myself, I just phone up for advice on that.'

(General practitioner-3)

'....Rheumatoid arthritis is not a brilliant disease for lending itself to primary care professionals to deal with ... We would only get involved if there is a

problem with side effects... there is no huge input from me, to be honest with you.'

(General practitioner-1)

'... .I don't know how much we can offer in primary care apart from very basic treatment... I just don't think that's a primary care disease, you know... a) don't see enough of it b) problems that both the illness and treatment are too complicated.'

(General practitioner-1)

In current practice, different rheumatology specialists are more likely to use different treatment strategies for methotrexate therapy, such as initiating methotrexate at different doses, using different dose escalations or monitoring intervals. These variations might also explain general practitioners' attitudes in the decision making process in order to treat individual patients.

'...the initial prescription will be a recommended dose from the clinic and dose escalations are outlined within the GP information sheet although we've offered escalation in different ways, so we actually specify on the GP letter any alteration that we've added, from the start, the dose is higher from the GP information sheet and escalated faster.'

(Consultant rheumatologist-2)

'...I would say that one of the difficulties we have, I am not sure if it is for monitoring with methotrexate or in general, is that even within Glasgow each unit has different criteria for monitoring and a different regime, which is crazy... the consultants have very rigid ideas and they don't want to change them, they have their own thoughts about monitoring.'

(Nurse specialist-2)

The local shared care treatment protocol is designed to guide general practitioners in order to monitor patients in collaboration with secondary care settings. However it is suggested by rheumatology specialists that the currently used local shared care treatment protocol seems insufficient to satisfy monitoring requirements of these treatments although GPs appreciated with the protocol provided by hospitals and indicated that it is clear enough for them to follow the advice.

'...I mean, we don't change the dose very often, we hardly change them at all. We probably would at the beginning if we're following the protocol we would just say 'ohh well that's what the protocol says' we would do that.... We do exactly what the main note says, just follow the instruction.'

(General practitioner-1)

The specialists also indicated that there is a lack of emphasis on particular issues on the protocol regarding methotrexate therapy, such as risk of pneumonitis and pregnancy during the treatment. It is believed that information about monitoring should be sufficiently weighted on the protocol in order to maintain continuous awareness and attention of general practitioners on methotrexate treatment.

Concerns about guidelines and/or local shared care protocols being used in current practice grounded a need for a standard protocol for monitoring across the city or even nationwide. Problems occur due to involvement of different Trusts, which may suggest different criteria for monitoring. Although there is an available local shared care protocol for almost all second line drugs, concerns and issues still exist around the disease management process and methotrexate use in this patient population. One of the main concerns expressed by the rheumatology specialists is that there is reluctance to increase methotrexate dose in the primary care settings. The GP's lack of awareness in methotrexate dose escalations and preferences for leaving decision making to the rheumatologist result in circumstances where patients may be kept on a lower methotrexate dose unnecessarily for a longer period of time.

'We find primary care very reluctant to increase methotrexate so we tend to do it in collaboration with our liaison sister'

(Consultant rheumatologist-1)

The interviews also revealed problems regarding use of drug monitoring card. Patients are provided a small card for their drug monitoring, which allows health care providers to record blood results during the treatment process. Patients are asked to carry this monitoring card for their visits to the GP surgery or outpatient clinics at the hospital.

Problems regarding the monitoring card occur intentionally or unintentionally in two directions; patient's and health care professionals' aspects. There is always the possibility that patients are likely to forget to bring the card to their appointments at clinic or at GP surgery,

which may affect its accuracy in the meantime. In addition, the use of currently available cards are not flexible enough for monitoring of all second line drugs and they do not include written values for the normal range of blood results which might have been helpful during treatment processes. The card is generally completed retrospectively by a practice nurse or by the GP in primary care settings and variation in time for recording blood results on a card is attributed to a lack of enthusiasm of health care providers.

> *'....there is no values written on the card or normal ranges and unless the patient asks....'*
>
> *(Consultant rheumatologist-1)*

> *'...the main problem with it is in fact it's very inflexible for some of the new ones, like leflunomide where blood pressure monitoring, it hasn't got blood pressure value on it....I think there is no space on it for liver function tests'*
>
> *(Consultant rheumatologist-1)*

> *'.....some patients are bad at bringing it, some practice nurses keep it even, although we say it's a liaison on the card and some practice nurses don't fill it in...we tend to fill in the preceding times monitoring space....if the patients attending the liaison sister because of a problem or because of a dosing regime increase, then it's probably much more regularly, and that's because she sees them much more often.'*
>
> *(Consultant rheumatologist-1)*

It is acknowledged by general practitioners that documentation of patient medical information at GP practice seems problematic. There is no standard routine documentation undertaken by GP and current computer system solely consists of minimum data sets and prescribing information, which does not necessarily help for monitoring purposes. The main information source for GPs is a letter from rheumatology specialists.

> *'...it would be purely blood counts, they'll ask them about specific side effects and that would be it. We don't go into things like, you know, how are you functioning, pain score and anything like that. It's going to be very basic.... very minimum data set...It's not terribly formalised, because they are so few people.'*
>
> *(General practitioner-1)*

Concerns regarding continuity of care amongst specialists also emerged during interviews and revealed that there is an assumption about patients being monitored regularly by general practitioners once they are prescribed second-line drugs. Information exchange regarding the treatment process is generally performed through personal communication by telephone or a letter. It is apparent that the drug monitoring card and shared care protocols are the only exchanged information between primary and secondary care settings. Consequently, the care system may become unmanageable because of variations in type and amount of information exchanged.

'...we rely on shared care with the GP...we just assume that the GP is assessing the results which they are.'

(Consultant rheumatologist-2)

'....one of the main problems for the system is that for all of us is actually quite difficult to fill in numbers....we want to transfer lots of information and on the other hand if you need them, the actual transfer system is too bulky and then nothing gets transferred.'

(Consultant rheumatologist-1)

'...because, if I was needing the information quickly I wouldn't be writing it down, ehm....and once I refer the patient, it would be unlikely that I would be writing to be honest with you. Because once they're in secondary care, they are in secondary care.... I don't have a huge amount to do. Ehhh.. We liaise closely with the community pharmacy, not necessarily through just because of methotrexate, but just in general we've got quite a reasonable relationship.'

(General practitioner-1)

'...There is never a problem contacting anybody to ask advice. Never... That's easy, so that's fine, I mean, there doesn't need to be a system for that because if you just pick up the phone somebody will always get back to you.'

(General practitioner-1)

The interviews suggested that community pharmacist involvement is not fully established within communication pathways and in the care process.

'...I can't think very much to do with community pharmacist unless there was confusion about the dosing or any other circumstances...I have some concerns about that. I am sure they are quite capable of following a protocol but it's rather outwith the ...I don't see the pharmacist have a much [referring to the contribution] overall.'

(General practitioner-2)

'...I guess, it could be [referring to community pharmacy involvement] but I have not had much input from the community pharmacy. So I don't have any comment on that.'

(General practitioner-3)

'... I would rather keep within the practice. But it depends on the way the system works. I can't see an advantage for having the community pharmacist within our small practice looking after rheumatology patients, because they would concentrate purely on drug, perhaps unfair but I think, to have... to bring in someone else for 2-3 patients with methotrexate, I can't see the advantage..'

(General practitioner-4)

On the other hand, community pharmacists had concerns about not being able to obtain medical information about their patients in order to support the care process more efficiently.

'...the main problem is we get the prescription and we don't know the diagnosis. So we have to assume the diagnosis..... It would be better if we knew more about the individual patient.... Anything else would develop from that, but really more to supply what patient's receiving, if they had the test things like we could obviously provide that secondary follow up for that.'

(Community pharmacist-2)

Moreover, lack of communication and inadequacy in the context of communication with other health care professionals explain reasons for a lack of opportunity for pharmacists to be involved in monitoring processes. Specific approaches may influence preferences of pharmacists being involved in the treatment process, such as provision of education and training for pharmacists on methotrexate therapy and its monitoring requirements and information materials available in pharmacy shop for patients.

'...we don't tend to have much involvement other than to check they're being monitored...we don't really have a set procedure for checking.....'

(Community pharmacist-1)

The Patient Medication Record (PMR) systems enable community pharmacists to keep records for their individual patients, however these systems may vary across pharmacies. Therefore, amount of information recorded for patients varies and pharmacists may need further information to be able to support patient care. It has been emphasised during the interviews that there is only a one-way form of communication being held at the pharmacy which is initiated by pharmacist and directed to GPs in order to obtain missing details on prescriptions. There is no formal arrangement established for communication and patient monitoring process. Hence pharmacists perceived that they have a lack of opportunity to judge the prescriptions.

'...we don't really probably have enough formal set up for that [referring to communication]... We get the prescription with the dose that has already been judged by someone '

(Community pharmacist-1)

'...we would supply whatever strength the GP requests sort of.. GP request 2.5 and we would supply 2.5mg tablets. It depends on what the GP wants.'

(Community pharmacist-2)

Health care professionals also raised concerns about the use of parenteral methotrexate in community settings. Although medical professions are concerned about giving this drug in a community setting, it has been recommended that the involvement of community pharmacists could resolve the problems. It has been suggested that medical and nursing staff should also be provided with information sheets about parenteral methotrexate therapy.

One of the nurse specialists suggested that understanding the roles among health care professionals would help to channel problems into appropriate health care profession. There is also a need for establishing a systematic way for transferring information between health care providers, where access to computers should be available for all health care providers.

2.7.2 Characteristics of patient population and the management of rheumatoid arthritis

Interviews with rheumatology specialists also highlighted the importance of a patient's beliefs, attitudes and their educational needs on self-management during methotrexate therapy. Patients' understanding about drug therapy and its complications, awareness on monitoring parameters and necessity of carrying the monitoring card are important issues for second line drug treatments, particularly in methotrexate therapy. Variation in patients' concerns about drug side effects that may be opposed to taking drug is also affected by their perceptions about drug treatment. Patients perceive methotrexate as an anti-cancer and toxic drug, which causes reluctance in starting the treatment (decision making about their treatment) and willingness to take an active role in their drug monitoring processes.

> *'...patients have focused too much on the side effects and haven't given them balance from the information about likely the benefits'*
>
> *(Consultant rheumatologist-2)*

> *'...they are naturally very anxious. The anxiety can be channelled into one or two ways either anxiety of drug side effects, that may well depend on their prior experience about the drugs or close relatives, or friends, or that anxiety can be channelled into a worry about disability or rising from their arthritis, so the psychological profile has an impact but it may be not predictable how it affects the outcome...'*
>
> *(Consultant rheumatologist-2)*

The nurse specialists indicated that patients' concerns and anxiety do increase with increased dose or addition of other second line agents to the therapy. Therefore specialist nurses intended to provide information according to patient's age and required level of information which is judged by questions that patients ask. It is believed that increased patient's awareness and knowledge would allow them to work in partnership with health care providers.

> *'...sometimes they are a bit apprehensive....I think most patients or many patients who have great difficulties with taking the second line agents so they have to be on drugs the rest of their lives, they are on a powerful drug*

which actually harm them....trying to explain it is a balancing act all the time, side effects versus condition.'

(Nurse specialist-2)

'...you really have to gauge what level they want information. Some people really, you know, when you start to talk to them and they aren't really able to take them, that's maybe because of the time that we are given the information, perhaps it is too close to their diagnosis and they are a bit shocked about that.... perhaps we are giving too much information in one day..'

(Nurse specialist-2)

Patients' attitudes also change in time and they become less vigilant in their monitoring process. They are more likely to ask for information at initiation of the therapy, but less likely to use the given information in time. It is indicated that there is also variation in types and amount of information required by patients which is more likely to be affected by patient's educational status, age, perceptions and beliefs and duration of treatment.

'...largely the patients are well aware that ESR falling is a good thing and ESR being high is a bad thing. We tend to go through at the beginning, when we give them the card, what haemoglobin is, what the white blood cells do, what platelets do...we don't find the problem at the beginning, most patients are very concerned at the beginning of the treatment, but when their disease is better and they feel well then they forget about the potential risk of the drugs and they perceive the drug is much less risky...but the patients become less vigilant...and so for them, observing the drug side effects is just a pure pain, so their whole attitude changes.'

(Consultant rheumatologist –1)

'...we would counsel them very firmly about monitoring at every visit....we wouldn't remind them of all the potential risks unless they either well-being monitored or they've come across difficulties.'

(Consultant rheumatologist –1)

'...the patient who has no interest in the likely future- they want the doctor to recommend the treatment and I will take it, thank you very much. There are

people who want to have an extremely in-depth understanding of the rational side effects and likely benefits....it is actually quite difficult to detect as a clinician how much information the patient wants.'

(Consultant rheumatologist-2)

'...I think educational status may have an impact in terms of type of information that the patient requires and the way it needs to be presented...It's quite a strong impact of age, the elderly are much more likely to accept our recommendations uncritically.'

(Consultant rheumatologist-2)

The findings of the interviews are summarised in Panel 2.1 below.

Panel 2.1 Emerged themes from the interviews

- Variation in health care providers' perceptions of their responsibility in the management process
- Lack of opportunity for community pharmacist to get involved
- Need for clearly designed monitoring guideline across different Trusts
- Need for increased patient awareness and education
- Need for education of primary care health care providers

2.7.3 Discussion on overall research approach

At the time that interviews were undertaken, the research pharmacist was not accustomed to routine of current practice and was enthusiastic to explore any relevant issues regarding rheumatoid arthritis and its treatment strategies. The interview contents were particularly focused on issues regarding methotrexate treatment and problems that health care providers have challenged. In this small exploratory study, it was feasible to approach only ten health care providers from different professions. The researcher also considered to approach other health care providers such as practice nurses at GP surgeries but interviews with the nurses could not be achieved during the time period. It was also considered to approach other health care providers who are involved in the management of rheumatoid arthritis such as physiotherapists or occupational therapists but the researcher's intent was to investigate such

issues particularly regarding methotrexate treatment. Therefore, interviewing with other professions would not have allowed a focus on the purpose of the study.

In addition, results of interviews were also considered in the light of pre-structured interviews, which were undertaken with patients diagnosed with rheumatoid arthritis (28 patients), and attending hospital outpatient clinics (details of these interviews have not been included in this chapter). However the interviews aimed to highlight important issues and potential problems in the current care system, results may not be applicable for all situations but may be considered valuable for future studies.

According to Miles and Huberman the quality of qualitative studies can be assessed through judgement on the following criteria; objectivity/confirmability, reliability/dependability/auditability, internal validity/credibility/authenticity, external validity/transferability/fittingness, utilisation/application/action orientation.[234]

In qualitative research, particularly with interviewing method, it may be difficult to maintain objectivity in a study since the process and analysis of results are candidates for exposing researcher bias, which occurs reciprocally between researcher and the case being studied. An objective stance was maintained throughout this study by using pre-structured interview guides and inductive content analysis of the results. It was inevitable that interview guides reflect the researcher's interests/intents on the subject. However it is believed that opportunities given to interviewees in order to express their further feelings produced an objective perspective in the study.

Reliability (reproducibility) of findings is generally not an applicable issue in qualitative studies because the researcher is interested in responses and interpretations which enable him/her to understand a context at a certain time point. It has been argued that using a standardised protocol for data gathering from interviews or agreement among coders ensures unbiased measurement in qualitative studies.

The validity of qualitative studies can be sustained by using pertinent approaches such as using probing questions during interviews to overcome ambiguity (content validity), using audio-taping, transcribing interviews verbatim and then undertaking the coding process by independent researchers. The humanistic perspective argues that validity of interviews relies on 'deep' understanding, to allow meaningful and mutual understanding of a participant and wholeness in inquiry. In this study, open-ended questions were preferred during the

interviews, because they allowed participants to define their experiences in their unique ways and raise important issues, which was not included in the interview guide. Transferability of the findings appeared to be somehow limited because of the small numbers of people being interviewed and existing variations in practice pattern, even across the same geographical location.

In this study, interview transcripts were coded and analysed by the research pharmacist manually. It might be argued that using computer software systems (such as the Ethnograph, MAX, ATLAS/ti, and NUD*IST) reduce analysis time and labour, ensure systematic and explicit procedures undertaken and give flexibility and revision in analysis.[234, 236] In fact, such systems are considered useful for case-oriented researchers where exploring relationships/links between interrelated events are the main intention and when vast numbers of interviews were undertaken and data handling manually was problematic for a researcher. However, software systems are not capable of establishing links between theory and data and do not help researchers in the move towards generating hypotheses.[233] Therefore, the researcher believed that it was not necessary to use a computer software package for the analysis of ten interviews in this study.

2.8 Conclusion

The management of rheumatoid arthritis is based on a multidisciplinary teamwork. Although management of the disease with methotrexate treatment seems efficient, there are potential gaps identified within the system of care. Lack of opportunities for community pharmacists to be involved in the disease management, lack of established effective communication pathways between health care providers and variation in health care providers' perceptions on their responsibility within monitoring process are the issues to be considered in the concept of continuity of care for this patient population.

Therefore there is a need for established effective communication pathways, to involve community pharmacists in the management of rheumatoid arthritis. Provision of relevant patient medical information and education and training regarding methotrexate therapy for pharmacists in the community settings seems to be required in order to maintain continuity of care.

Chapter 3: A retrospective study on the use of methotrexate in an arthritis population in relation to other disease modifying anti-rheumatic drugs

3.1 Introduction

Rheumatoid arthritis is a chronic, longstanding condition and requires long-term therapy. Recently, health care professionals have move towards initiating disease modifying anti-rheumatic drugs (DMARDs) therapy in the early stages of the disease in order to prevent further erosions in joints, slow down progression of the disease and improve clinical outcomes. Disease modifying anti-rheumatic drugs have a wide range of toxicity profiles which might be affected by various factors such as patients' characteristics, disease duration and co-morbid conditions.[150, 165]

Methotrexate is an immunosuppressive agent and its use as a disease modifying anti-rheumatic agent in the long term treatment of inflammatory arthritis has increased as evidence has emerged of the benefits of early aggressive treatment.[147] Much research has been undertaken in order to identify its effectiveness and explore complications of methotrexate treatment.

Methotrexate toxicity, including gastro-intestinal effects, liver enzyme abnormalities, haematological and pulmonary effects, is a major concern that can limit the length of treatment. It has been reported that the proportion of patients discontinuing treatment within 12 months has varied in studies from 14% to 30%.[237-239] A study conducted in the UK indicated that methotrexate is the DMARD most likely to be continued long term where less than 45% of patients had discontinued after 8 years of treatment.[240] Methotrexate treatment requires close clinical monitoring and places self-monitoring demands on patients. Patients' social circumstances may affect their response to these demands. Measures of the health impact of rheumatoid arthritis vary according to the rheumatoid patient's socio-economic status.[20]

This chapter intended to identify the pharmaceutical care needs of patients treated with oral methotrexate, explore discontinuation patterns of disease modifying anti-rheumatic drugs and relate findings to patients' social environment.

3.2 Aim of the study

To investigate the patterns of methotrexate use in the treatment of rheumatic diseases in a perspective of differences in socioeconomic environments.

3.3 Objectives

- To identify the patients who have received methotrexate therapy in the treatment of rheumatic diseases by using two hospitals' databases.
- To describe the use of other disease modifying anti-rheumatic drugs (DMARDs) in the treatment of rheumatic diseases by using two hospitals' databases.
- To identify the patterns of methotrexate use in patients diagnosed with rheumatic diseases in different socioeconomic environments.

3.4 Methodology

This study was undertaken retrospectively and consisted of database and case notes reviews. The data collection process is explained in further sections.

3.5 Subjects and settings

The researcher identified potential patients through hospital rheumatology outpatient databases in Southern General Hospital and Gartnavel General Hospital in Glasgow. The patients were considered eligible if they:

- have used methotrexate treatment for their rheumatic conditions
- started their methotrexate treatment between 1992 and 1999
- have their residential postcode indicated in the hospital databases

The researcher also identified the patients who have received other disease-modifying anti-rheumatic drugs for treatment of their rheumatic diseases between 1992-1999 and were registered in the hospital rheumatology outpatient databases.

3.6 Data collection procedures

The researcher had access to the two hospitals' rheumatology outpatient clinic databases and searched for the potential methotrexate users who were registered in the databases and continue to attend the hospital outpatient clinics. The patients' demographics and previous

second-line therapy histories were recorded. The clinical status of patients, those who had discontinued treatment during the proposed study period were obtained from their medical notes and recorded on a standard data collection form (Appendix 3.1). The patients were identified as living in a 'non-deprived' or a 'deprived' community if they were domiciled in postcodes of Carstairs category 1,2 or 6,7 respectively.

3.7 Results and analysis

Three hundred and thirty seven patients started on methotrexate treatment (received 351 treatment courses) 1992-1999 were identified from two hospitals' rheumatology outpatient clinic databases. Of those, 91% were diagnosed with rheumatoid arthritis, 6% with psoriatic arthritis and 3% with other rheumatological conditions. Demographics of patients are summarised in Table 3.1 and the pattern of discontinuation of methotrexate treatments are summarised in Table 3.2.

Table 3.1 Demographics of methotrexate patients population

	Total MTX users (n= 337)	**Past MTX users (n=91)**
Age (mean ±SD) years	59.7 ± 13.6	60.7 ± 13.1
Disease duration in 1999 (mean ±SD) years	13.7 ± 8.4	14.4 ± 8.7
Median (IQR)	12 (7.7-18.0)	13 (8.0-18.0)
Female (%)	77.4	80.2
MTX dose (mean ±SD) mg/week	10.2 ± 4.6	7.7 ± 3.7

Table 3.2 Methotrexate discontinuations according to the socio-economic patient groups by residential postcode (*Carstairs classification*)

	'Non-deprived' *(1,2)*	'Deprived' *(6,7)*	'Middle' *(3,4,5)*	All Patients
Patients started on MTX	n=75	n=110	n=152	n=337
courses of MTX	n=80	n=115	n=156	n=351
Patients stopped therapy	20 (27%)	29 (26%)	42 (28%)	91 (27%)
courses of MTX stopped	22 (28%)	33 (29%)	43 (28%)	98 (28%)
Dose, mean (SD) of stopped MTX courses	9.3 (3.9)	6.4 (3.6)	8.2 (3.2)	7.7 (3.7)
Age, mean yrs (SD) at start of MTX	58.0 (12.7)	58.3 (12.3)	55.4 (13.8)	56.9 (13.1)
Disease duration, mean yrs (SD) at MTX start	12.5 (6.3)	11.6 (8.9)	11.3 (8.9)	11.9 (8.3)
DMARDs used prior to MTX, median	3	3	2	3

Patients in the 'non-deprived' and 'deprived' groups were similar in terms of mean age, disease duration and median weekly dose of methotrexate. The proportions (95% CI) of patients in those commenced on methotrexate who were 'non-deprived' and 'deprived' were 22% (18%, 27%) and 33% (28%, 38%) respectively. The proportions in these groups of those who discontinued during the study period were similar (Chi-square test, $p>0.05$) at 22% (13%, 30%) and 32% (22%, 41%). The proportions of courses discontinued ≤12 months after commencing methotrexate among the 'non-deprived' and 'deprived' patients were similar (Chi-square test, $p>0.05$) at 19% (10%, 27%) and 17% (10%, 24%) respectively. The mean (95% CI) weekly methotrexate dose at discontinuation in the 'deprived' group was 6.4mg (5.0, 6.8) which was 2.9mg (0.8, 4.9) lower ($p<0.05$) than that in the 'non-deprived' group at 9.3mg (7.6, 11.1).

Ninety one (27%) patients had 98 (28%) treatment courses discontinued during the study period. There were 99 reasons for discontinuation identified. Of those, 85 (86%) were due to drug toxicity, 9 (9%) were due to lack of effectiveness and 5 (5%) were due to patients' choice. In 7/91 (8%) of patients, the reason for discontinuation was not clearly defined. The

most common drug toxicities were gastro-intestinal problems (39%), liver enzyme abnormalities (21%), pulmonary toxicity (12%), infection (8%) and haematological complications (6%).

Detailed information regarding past methotrexate treatments were available in 82 out of 91 (90%) patients which indicated 89 (91%) treatment courses. Among those patients, 81% were female and 93% were diagnosed with rheumatoid arthritis. There were 200 other co-morbid conditions identified, the mean (SD) value per patient was 2.4 (1.9). Of those 16% were gastrointestinal and related disorders, 15% were nutrition and blood related, 13% were cardiovascular disorders, 11% were musculoskeletal conditions, 10% were respiratory, 7% were the central nervous system and 6% were endocrine related disorders and 22% were other diseases. Thirty-three percent of those patients were domiciled in 'deprived' and 25% were in 'non-deprived' areas. Table 3.3 and Table 3.4 indicate patients' laboratory results during methotrexate treatment. There were no statistically significant differences between three socio-economic groups in terms of mean value of laboratory results (ANOVA test, $p>0.05$).

Among those 89 past methotrexate treatment courses, reasons for discontinuations were not specified in four (4.5%) treatment courses. Among the specified reasons for discontinuation 81% were due to drug toxicity and 12% were due to lack of drug efficacy. Only six (7%) treatments were stopped because of patient's preferences. The most common toxicities were gastro-intestinal problems (32%), liver enzyme abnormalities (25%), pulmonary toxicity (12%), infection (9%) and haematological complications (6%). There were 12 (17%) other toxicities led to discontinuation of treatment.

Table 3.3 Medication and laboratory data at the time of discontinuation for 82 patients who discontinued MTX therapy (n=89 treatment courses)

	Socio-economic classification			
	'Non-deprived' *(1,2)*	**'Deprived'** *(6,7)*	**'Middle'** *(3,4,5)*	**All past users**
Weekly dose of MTX, mean ± SD	9.1 ± 4.2 (n=21)	7.8 ± 4.2 (n=32)	9.6 ± 4.8 (n=28)	8.8 ± 4.5 (n=81)
Weekly dose of Folic acid, mean ± SD	6.5 ± 2.4 (n=13)	6.7 ± 2.4 (n=24)	6.4 ± 2.3 (n=28)	6.5 ± 2.3 (n=65)
	Laboratory results, mean ±SD			
Haemoglobin (g/dL)	10.9 ± 1.4 (n=13)	11.7 ± 1.9 (n=19)	11.6 ± 1.4 (n=27)	11.5 ± 1.5 (n=60)
WCC ($x10^9$/L)	7.3 ± 2.2 (n=13)	7.6 ± 1.7 (n=19)	8.4 ± 3.6 (n=27)	7.9 ± 2.8 (n=60)
Platelets ($x10^9$/L)	351.2 ± 110.0 (n=13)	316.8 ± 105.3 (n=19)	375.5±200.9 (n=27)	354.0 ± 157.3 (n=60)
Lymphocytes ($x10^9$/L)	1.8 ± 0.7 (n=12)	1.8 ± 0.8 (n=19)	2.5 ± 3.9 (n=25)	2.1 ± 2.6 (n=57)
Neutrophils ($x10^9$/L)	4.6 ± 1.8 (n=9)	5.1 ± 1.3 (n=10)	6.3 ± 4.4 (n=13)	5.5 ± 3.0 (n=33)
MCV (fL)	83.4 ± 8.3 (n=12)	87.8 ± 8.9 (n=19)	85.8 ± 14.5 (n=26)	86.0 ± 11.5 (n=57)
ESR (mm/hr)	41.7 ± 23.6 (n=6)	60.4 ± 34.4 (n=12)	42.6 ± 28.1 (n=14)	49.1 ± 30.3 (n=32)

Table 3.3 (cont.) Medication and laboratory data at the time of discontinuation for 82 patients who discontinued MTX therapy (n=89 treatment courses)

	Socio-economic classification			
	'Non-deprived' *(1,2)*	**'Deprived'** *(6,7)*	**'Middle'** *(3,4,5)*	**All past users**
		Laboratory results, mean ±SD		
ALT (iu/L)	100.7 ± 170.8 (n=7)	24.5 ± 20.6 (n=18)	49.9 ± 64.2 (n=14)	46.4 ± 82.7 (n=40)
AST (iu/L)	72.1 ± 139.1 (n=11)	28.7 ± 25.1 (n=22)	28.8 ± 27.4 (n=24)	36.6 ± 65.1 (n=57)
Alk Phos. (iu/L)	350.0 ± 270.3 (n=9)	361.3 ± 323.1 (n=13)	314.4 ± 336.9 (n=23)	332.5 ± 311.6 (n=46)
Gamma GT (iu/L)	124.7 ± 155.4 (n=7)	94.0 ± 92.5 (n=10)	90.6 ± 178.9 (n=21)	96.3 ± 151.4 (n=39)
Albumin (g/L)	38.7 ± 4.4 (n=9)	38.8 ± 7.8 (n=21)	40.3 ± 5.3 (n=24)	39.5 ± 6.2 (n=55)
Urea (mmol/L)	6.7 ± 2.3 (n=9)	6.9 ± 2.1 (n=18)	6.4 ± 1.6 (n=24)	6.6 ± 1.9 (n=52)
Creatinine (μmol/L)	76.8 ± 15.3 (n=9)	79.0 ± 25.5 (n=18)	78.3 ± 17.3 (n=24)	78.1 ± 19.7 (n=52)

** the 'all past users' column included one more patient than the total of three deprivation categories rows because the patient's residential postcode could be either Carstairs category '4' or '7'.*

Table 3.4 Medication and laboratory data at the time of 6 months prior to discontinuation of 82 patients who discontinued MTX therapy (n=89 treatment courses)

	Socio-economic classification			
	'Non-deprived' *(1,2)*	**'Deprived'** *(6,7)*	**'Middle'** *(3,4,5)*	**All past users**
	Laboratory results, mean ±(SD)			
Haemoglobin (g/dL)	12.1 ± 1.4 (n=13)	11.4 ± 2.2 (n=21)	11.7 ± 1.1 (n=25)	11.7 ± 1.6 (n=60)
WCC ($x10^9$/L)	8.2 ± 2.0 (n=13)	7.9 ± 2.3 (n=20)	7.6 ± 2.3 (n=25)	7.8 ± 2.2 (n=59)
Platelets ($x10^9$/L)	339.5 ± 92.2 (n=13)	362.7 ± 154.3 (n=21)	354.4 ± 119.2 (n=25)	352.5 ± 125.8 (n=60)
Lympocytes ($x10^9$/L)	2.1 ± 1.1 (n=12)	1.9 ± 0.8 (n=17)	1.6 ± 0.6 (n=25)	1.8 ± 0.8 (n=55)
Neutrophils ($x10^9$/L)	5.5 ± 2.1 (n=8)	6.2 ± 2.01 (n=9)	5.7 ± 2.4 (n=11)	5.7 ± 2.1 (n=29)
MCV (fL)	85.9 ± 7.9 (n=10)	87.5 ± 8.7 (n=17)	87.9 ± 7.4 (n=22)	87.5 ± 7.9 (n=50)
ESR (mm/hr)	42.3 ± 21.2 (n=4)	47.8 ± 22.0 (n=10)	51.9 ± 24.8 (n=15)	49.1 ± 22.9 (n=29)
ALT (iul/L)	19.7 ± 8.3 (n=7)	20.2 ± 12.6 (n=13)	17.2 ± 14.3 (n=17)	18.5 ± 12.4 (n=38)
AST (iul/L)	20.3 ± 6.3 (n=10)	26.1 ± 17.9 (n=19)	26.2 ± 24.1 (n=21)	24.9 ± 18.9 (n=51)

Table 3.4 (cont.) Medication and laboratory data at the time of 6 months prior to discontinuation of 82 patients who discontinued MTX therapy (n=89 treatment courses)

	Socio-economic classification			
	'Non-deprived' *(1,2)*	**'Deprived'** *(6,7)*	**'Middle'** *(3,4,5)*	**All past users**
		Laboratory results, mean ±(SD)		
Alk Phos.(iul/L)	332.0 ± 240.4 (n=10)	356.3 ± 363.7 (n=13)	315.7 ± 304.2 (n=19)	329.3 ± 300.8 (n=43)
Gamma GT (iul/L)	36.1 ± 21.9 (n=8)	92.5 ± 86.4 (n=13)	67.9 ± 128.8 (n=20)	68.5 ± 101.9 (n=42)
Albumin (g/L)	41.7 ± 3.5 (n=7)	40.4 ± 5.9 (n=18)	40.8 ± 4.9 (n=21)	40.9 ± 4.9 (n=50)
Urea (mmol/L)	6.6 ± 1.8 (n=7)	7.4 ± 2.4 (n=13)	6.1 ± 1.7 (n=18)	6.6 ± 1.9 (n=39)
Creatinine (μmol/L)	72.0 ± 12.4 (n=7)	83.2 ± 24.7 (n=13)	73.6 ± 16.3 (n=18)	76.1 ± 19.2 (n=39)

** the 'all past users' column included one more patient than the total of three deprivation categories rows because the patient's residential postcode could be either Carstairs category '4' or '7'.*

A Kaplan-Meier survival analysis in overall methotrexate population revealed continuation rates of 80% (SE 2%) and 70% (SE 3%) at 1 year and 2 years respectively after the start of treatment (Figure 3.1). There were no statistically significant differences in discontinuation rates in the 'deprived' and 'non-deprived' groups at 1 or 2 years (Log rank test, $p>0.05$) (Figure 3.2). The analysis of the toxicity patterns of methotrexate indicated that over two-thirds of methotrexate toxicity occurred within the first year of the therapy as a reason for discontinuation of the therapy (see Table 3.5).

Table 3.5 Methotrexate toxicity patterns during different stages of the therapy

MTX side effects	<1 year	1-2 year	>2 year
Gastro-intestinal	29%	6%	4%
Haematological	5%	-	1%
Hepatic	12%	9%	-
Pulmonary	6%	5%	1%
Infection	6%	-	2%
Other	9%	2%	2%
Total	67%	22%	11%

Figure 3.1 Methotrexate discontinuations in total patient population (n=337)

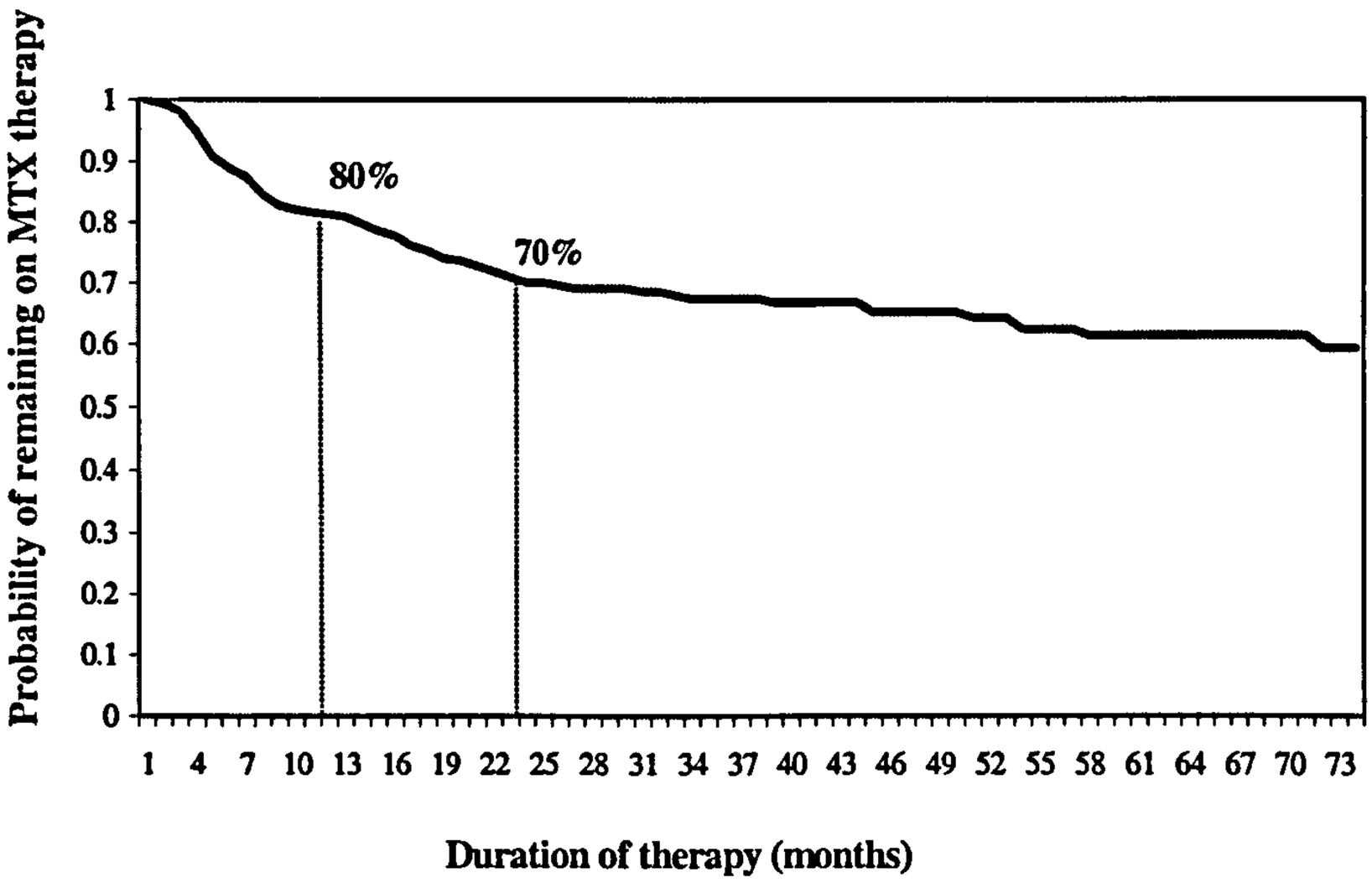
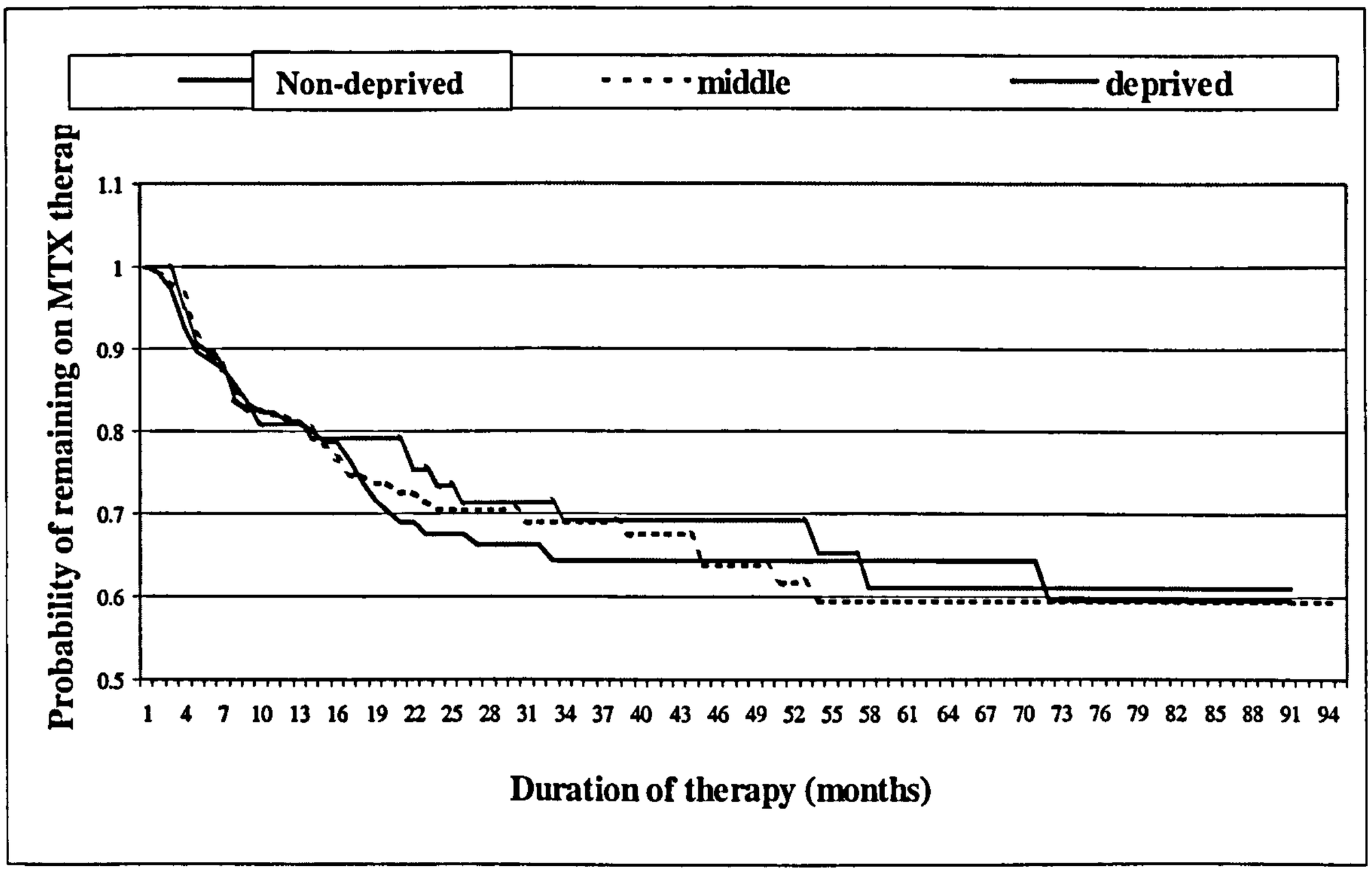


Figure 3.2 Methotrexate discontinuations in patient population according to socioeconomic classification



A search undertaken for other DMARD therapies from the two hospitals' rheumatology outpatient clinic databases showed different patterns for use of other DMARD treatments. The results are summarised in the next section under the heading of each disease modifying anti-rheumatic drugs.

Gold injections

Five hundred and thirty-three patients on gold treatment identified from two hospitals' rheumatology outpatient clinic databases received 546 treatment courses between 1992-99. Of those patients, 76% were female, 17% were domiciled in the 'non-deprived' and 36% were domiciled in the 'deprived' area. Of those treatment courses, 284 (52%) were discontinued. Discontinuations of the 284 treatment courses and in 264 reason for discontinuation was recorded; 10 (4%) out of 264 reasons were not clearly specified in the databases. Among the specified reasons for discontinuations, 159 (63%) were drug toxicity and 87 (34%) were lack of drug efficacy. Three (1%) treatment courses were stopped due to other reasons including planning pregnancy (1) and patient's choice (2). The remaining five (2%) courses were discontinued due to remissions during the therapy.

Table 3.6 Gold therapy discontinuations according to the patients' socio-economic classification

	Socio-economic patient groups by residential postcode (Carstairs classification)			
	'Non-deprived' *(1,2)*	**'Middle' *(3,4,5)***	**'Deprived' *(6,7)***	**All Patients**
Patients started on Gold	74	206	156	533
Courses of Gold started*	76	210	158	546
Courses of Gold stopped*	38	116	78	284
Age, mean (SD) yrs at the end of study period	67.1 (9.7)	59.9 (15.1)	61.4 (13.2)	61.0 (14.3)

* *Row totals of non-deprived, middle and deprived groups do not match with the 'all patients' total because Carstairs categories were not available for all patients*

The proportions (95% CI) of patients in those commenced on gold who were 'non-deprived' and 'deprived' were 17% (9%, 25%) and 36% (28%, 43%) respectively. The proportions of 'non-deprived' and 'deprived' groups in those who discontinued during the study period showed a similar patterns ($p > 0.05$) 16% (5%, 23%) and 34% (23%, 44%) respectively. The mean (SD) duration of the discontinued treatment courses were 15.1 (16.1) months (median, 8 months).

One hundred and fifty-nine treatment courses were discontinued due to side effects of gold therapy. Of those, 58 (37%) treatments were stopped due to rash, 38 (24%) due to proteinuria, 24 (15%) due to GI complications, 23 (15%) due to haematological toxicity, 4 (3%) due to skin reactions, 3 (2%) due to hepatotoxicity, 3 (2%) due to pulmonary toxicity and 6 (4%) due to other side effects including fever (1), intercurrent illness (1), central nervous system side effect (1) and renal complications (3).

Hydroxychloroquine (HYCQ)

Four hundred and ninety-eight patients identified from two hospitals' rheumatology outpatient clinic databases who received 521 treatment courses between 1992-99, of those 225 (43%) were discontinued. Of those patients 90% were female, 20% were domiciled in the 'non-deprived' and 30% were domiciled in the 'deprived' area. Discontinued 225 treatment courses indicated 192 reasons for discontinuation, of those six reasons (3%) were not clearly specified in databases. Moreover, discontinuations were occurred because of patients' preferences in 5 (3%) treatment courses, lack of drug efficacy in 109 (58%) and drug toxicity in 60 (32%) treatment courses. Seven (4%) treatment courses were stopped due to achieving optimum/maximum time on therapy, 3 (2%) due to pregnancy and 2 (1%) due to addition of another therapy.

Table 3.7 Hydroxychloroquine therapy discontinuations according to the patients' socio-economic classification

	Socio-economic patient groups by residential postcode (Carstairs classification)			
	'Non-deprived' *(1,2)*	**'Middle' *(3,4,5)***	**'Deprived' *(6,7)***	**All Patients**
Patients started on HYCQ	81	198	117	498
Courses of HYCQ started*	86	205	123	521
Courses of HYCQ stopped*	37	94	50	225
Age, mean (SD) yrs at the end of study period	61.3 (11.9)	55.5 (13.2)	52.9 (13.5)	55.4 (13.9)

** Row totals of non-deprived, middle and deprived groups do not match with all patients total because Carstairs categories were not available for all patients*

The proportions (95% CI) of patients in those commenced on hydroxychloroquine who were 'non-deprived' and 'deprived' were 21% (12%, 29%) and 30% (22%, 38%) respectively. The proportions of these groups in those who discontinued during the study period were

similar (p> 0.05) at 20% (8%, 33%) and 28% (15%, 40%). The mean (SD) duration of discontinued treatment courses were 13.6 (14.5) months (median, 8.8 months).

The toxicity profile of hydroxychloroquine indicated that discontinuations occurred due to gastrointestinal complications in 13 (22%) courses, rash in 21 (35%), ocular problems in 11 (18%), central nervous system side effects in 10 (17%), hepatotoxicity in 1 (2%) and other toxicities in 4 (7%) treatment courses including intercurrent illness (1), teratogenic (1), proteinuria (1) and renal complication (1).

Penicillamine (PEN)

Three hundred and ninety patients identified from two hospitals' rheumatology outpatient clinic databases who received 396 treatment courses between 1992-99, of those 206 (52%) were discontinued. Of those patients, 80% were female, 22% were domiciled in the 'non-deprived' and 33% were domiciled in the 'deprived' area. Discontinued two hundred and six treatment courses indicated 177 reasons for discontinuation, of those 7 (4%) reasons were not clearly specified in the databases. The treatments were discontinued due to drug toxicity in 107 (63%), lack of drug efficacy in 57 (34%), patient's choice in 4 (2%) and change of therapy and pregnancy in one (1%) occasion each.

Table 3.8 Penicillamine therapy discontinuations according to the patients' socio-economic classification

	Socio-economic patient groups by residential postcode (Carstairs classification)			
	'Non-deprived' *(1,2)*	**'Middle' *(3,4,5)***	**'Deprived' *(6,7)***	**All Patients**
Patients started on PEN	65	136	101	390
Courses of PEN started*	67	137	102	396
Courses of PEN stopped*	37	72	56	206
Age, mean (SD) yrs at the end of study period	62.4 (12.8)	61. 7 (13.9)	62.6 (12.5)	63.2 (13.1)

** Row totals of non-deprived, middle and deprived groups do not match with all patients total because Carstairs categories were not available for all patients*

The proportions (95% CI) of patients in those commenced on penicillamine who were 'non-deprived' and 'deprived' were 22% (12%, 32%) and 33% (24%, 42%) respectively. The proportions of these groups in those who discontinued during the study period were similar

(p>0.05) at 22% (21%, 36%) and 34% (22%, 46%). The mean (SD) duration of discontinued treatment courses was 23.9 (22.1) months (median, 16.1 months).

The toxicity profile of penicillamine treatment indicated that GI problems were the reason for discontinuation of the treatment in 32 (30%) treatment courses, proteinuria was in 31 (29%), rash in 21 (20%), haematological toxicity in 17 (16%) and other side effects in 6 (6%) treatment courses.

Sulphasalazine (SSZ)

One thousand five hundred and seventy five patients identified from two hospitals' rheumatology outpatient clinic databases who received 1621 treatment courses between 1992-99, of those 673 (42%) were discontinued. Of those patients, 70% were female, 19% were domiciled in the 'non-deprived' and 33% were domiciled in the 'deprived' area. The discontinued six hundred and seventy three treatment courses indicated 626 reasons for discontinuation, of those 5 (1%) reasons were not clearly specified in the databases. Thirteen (2%) treatments were discontinued due to patient's choice, 258 (42%) were due to lack of drug efficacy, and 342 (55%) were due to drug toxicity. Three treatments were discontinued due to poor patient compliance and two treatment courses were discontinued due to remissions at the end of sulphasalazine therapy.

The main toxicities observed as a reason for discontinuation during sulphasalazine treatments were gastrointestinal problems in 167 treatment courses (49%), rash in 63 courses (18%), haematological toxicity in 49 courses (14%), hepatotoxicity in 26 courses (8%) and central nervous system side effects in 10 courses (3%). There were other side effects of sulphasalazine treatment identified in 27 (8%) courses including allergy (3), angio-oedema (1), palpitations (1), flu-like symptoms (2), pulmonary (3), glomerulonephritis (1), malaise (1), swelling (1), cholecystitis (1), haematuria (1), proteinuria (4), Stevens Johnson Syndrome (2), patient feeling unwell (3) and other non-specified side effects (3).

Table 3.9 Sulphasalazine therapy discontinuations according to the patients' socio-economic classification

	Socio-economic patient groups by residential postcode (Carstairs classification) 'Non-deprived' *(1,2)*	'Middle' *(3,4,5)*	'Deprived' *(6,7)*	All Patients
Patients started on SSZ	245	632	440	1575
Courses of SSZ started*	255	644	456	1621
Courses of SSZ stopped*	104	259	204	673
Age, mean (SD) yrs at the end of study period	58.4 (14.4)	58.2 (14.6)	58.6 (14.7)	58.8 (14.9)

** Row totals of non-deprived, middle and deprived groups do not match with all patients total because Carstairs categories were not available for all patients*

The proportions (95% CI) of patients in those commenced on sulphasalazine who were 'non-deprived' and 'deprived' were 19% (14%, 24%) and 34% (29%, 38%) respectively. The proportions of these groups in those who discontinued during the study period were similar (p>0.05) at 18% (11%, 26%) and 36% (29%, 43%). The mean (SD) duration of the discontinued treatment courses was 17.5 (19.2) months (median, 9.9 months).

Azathioprine (AZA)

Two hundred and eighteen patients identified from two hospitals' rheumatology outpatient clinic databases who received 226 treatment courses between 1992-99, of those 95 (42%) were discontinued. Of those patients, 76% were female, 23% were domiciled in the 'non-deprived' and 30% were domiciled in the 'deprived' area. The ninety-five discontinued treatment courses indicated 81 reasons for discontinuations, of those 4 (5%) were not clearly specified in the databases. One (1%) treatment course was discontinued due to patient's choice, 17 (22%) were due to lack of drug efficacy and 59 (77%) were due to drug toxicity. The toxicity profile of azathioprine indicated that 32 (54%) treatment courses were stopped due to GI toxicity, 10 (17%) were due to hepatotoxicity, 9 (15%) were due to haematological toxicity, 7 (12%) were due to infections/intercurrent illness and 1 (2%) were due to rash.

Table 3.10 Azathioprine therapy discontinuations according to the patients' socio-economic classification

	Socio-economic patient groups by residential postcode (Carstairs classification) 'Non-deprived' *(1,2)*	'Middle' *(3,4,5)*	'Deprived' *(6,7)*	All Patients
Patients started on AZA	40	81	53	218
Courses of AZA started*	41	103	21	226
Courses of AZA stopped*	21	37	21	95
Age, mean (SD) yrs at the end of study period	54.7 (15.4)	55.9 (13.9)	54.7 (15.4)	55.0 (14.5)

** Row totals of non-deprived, middle and deprived groups do not match with all patients total because Carstairs categories were not available for all patients*

The proportions (95% CI) of patients in those commenced on azathioprine who were 'non-deprived' and 'deprived' were 21% (8%, 33%) and 28% (16%, 40%) respectively. The proportions of these groups in those who discontinued during the study period were not statistically significant different ($p>0.05$) at 27% (17%, 36%) and 27% (17%, 36%). The mean (SD) duration of discontinued treatment courses was 11.7 (14.1) months (median, 8.0 months).

Prednisolone (PRED)

Five hundred and forty-two patients identified from two hospitals' rheumatology outpatient clinic databases who received 552 treatment courses between 1992-99, of those 115 (21%) were stopped. Of those patients, 74% were female, 21% were domiciled in the 'non-deprived' and 33% were domiciled in the 'deprived' area. One hundred and fifteen discontinued treatment courses indicated 26 reasons for discontinuation; 2 reasons (8%) were not clearly specified in the databases and one treatment course was discontinued because of the patient was no longer alive. The treatments were discontinued due to lack of drug efficacy in 2 (9%), duration of optimum/maximum treatment course in 7 (30%), control of disease/improvement in 7 (30%), remission in 4 (17%) and drug toxicity in 2 (9%) which were not specified in the databases. One (4%) treatment course was discontinued due to chest disease.

Table 3.11 Prednisolone therapy discontinuations according to the patients' socio-economic classification

	Socio-economic patient groups by residential post-code (Carstairs classification) 'Non-deprived' *(1,2)*	'Middle' *(3,4,5)*	'Deprived' *(6,7)*	All Patients
Patients started on PRED	77	166	118	542
Courses of PRED started*	78	170	118	552
Courses of PRED stopped*	19	52	19	115
Age, mean (SD) yrs at the end of study period	58.3 (18.4)	61.6 (16.1)	60.6 (16.4)	62.1 (16.7)

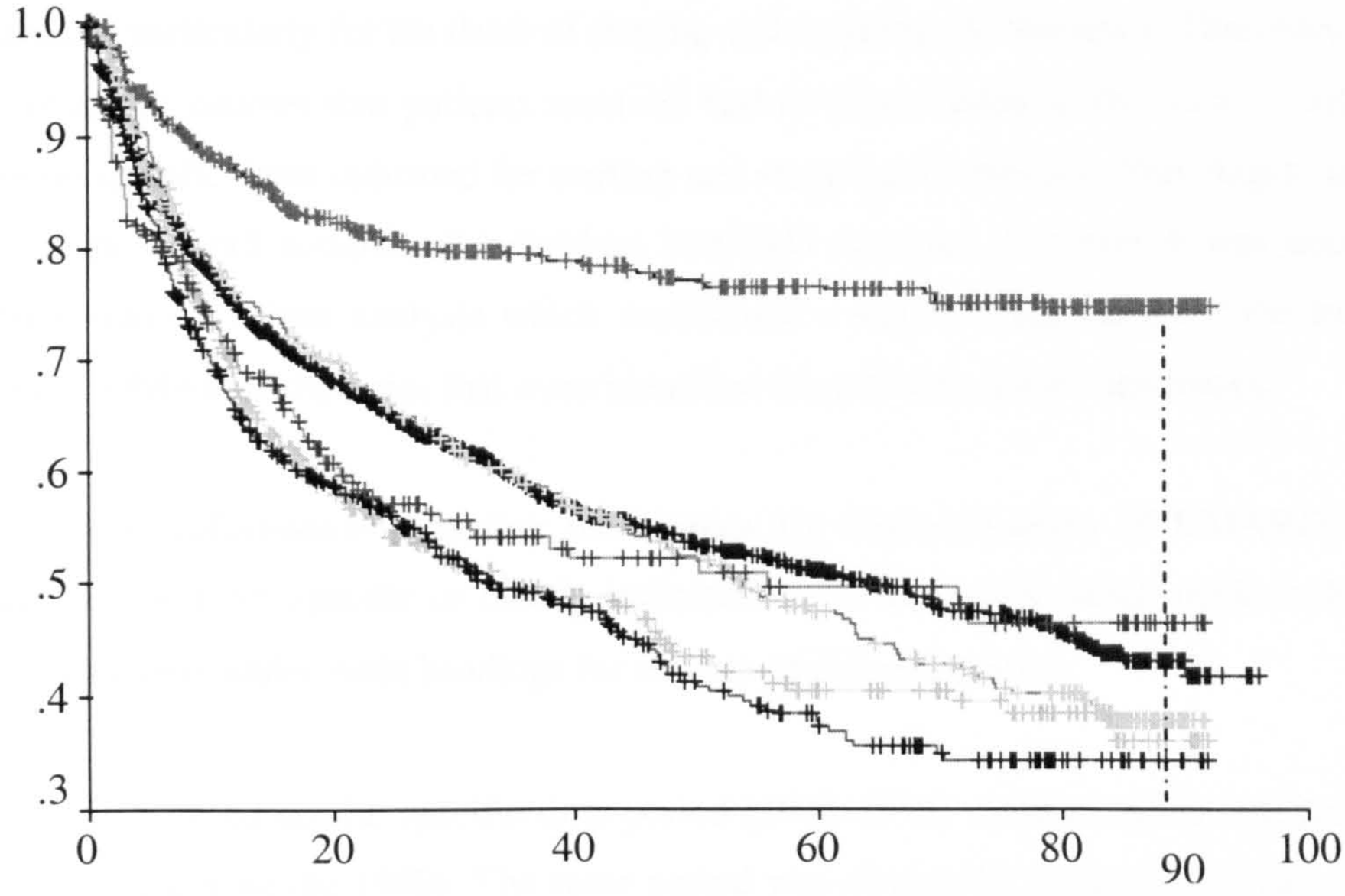
** Row totals of non-deprived, middle and deprived groups do not match with all patients total because Carstairs categories were not available for all patients*

The proportions (95% CI) of patients in those commenced on prednisolone who were 'non-deprived' and 'deprived' were 21% (12%, 30%) and 32% (24%, 41%) respectively. The proportions of these groups in those who discontinued during the study period were not statistically significant different (p>0.05) at 21% (3%, 40%) and 21% (3%, 40%). The mean (SD) duration of discontinued treatment courses was 15.4 (16.8) months (median, 9.2 months).

Table 3.12 Summary of discontinuation patterns of DMARDs between 1992-99 (n= treatment courses)

DMARDs	*n*	*Treatment courses discontinued*	*Lack of drug efficacy*	*Remission*	*Drug toxicity*
Gold	546	52%	33%	2%	60%
Hydroxychloroquine	521	43%	58%	-	32%
Penicillamine	396	52%	34%	-	63%
Sulphasalazine	1621	42%	42%	-	55%
Azathioprine	226	42%	22%	-	77%
Prednisolone	552	21%	8%	17%	13%
Methotrexate	**351**	**28%**	**9%**	**-**	**86%**

Figure 3.3 The treatment survivals of the DMARD therapies*



**From top line through the bottom at the time of 90 months is; steroids, azathioprine, sulphasalazine, penicillamine, hydroxychloroquine and gold therapies.*

3.8 Justification for the research

The study faced the common limitations of the retrospective study design. Variations in information stored in the hospitals' databases and the use of different software packages at the two sites have caused difficulties in data collection and interpretation.

The information about the treatment courses of DMARD therapies was patchy in the hospital databases, particularly for the dates of starting and stopping the therapies. Therefore, some of the treatment courses that patients received had to be excluded in the analysis since there were no specific dates indicated for starting and stopping the therapy. This might have led to bias in the overall patterns of individual DMARD therapies, however it was necessary in order to have a robust analysis which maintained a standard approach for the analysis of patients' DMARDs therapies that were identified from two hospitals' databases.

Once again, information regarding the reasons for discontinuation of DMARD therapies sometimes was not specific or clearly indicated in the databases which made it difficult to categorise them under main headings for reasons of discontinuation.

The study focused on the specific time period (1992-1999) since methotrexate therapy was widely used during the 1990s. The same period was chosen for collection of data regarding other DMARDs therapies in order to have comparison for the patterns of methotrexate use and the use of other DMARD therapies. Therefore, the results presented in this chapter for the patterns of the use of DMARDs should be interpreted cautiously in the light of the chosen time period and the study settings.

The data collection was limited by two hospitals' rheumatology clinic databases. It would have been a larger scale study if the researcher could have had access to the information regarding the patients attending other rheumatology clinics in Glasgow. However, there are four main hospitals in Glasgow serving the rheumatology patient population and of those, two did not have a database/computer system facilities in order to identify those patients.

The treatment survivals for DMARDs therapies were presented by using Kaplan-Meier survival analysis. Although this analysis was widely used in the prospective studies, the time period for the search of DMARDs therapies was pre-defined, therefore the censored data were not affected by any circumstances introduced by the researcher or by the study design.

The effect of social deprivation on the treatment courses of DMARD therapies were explored by using Carstairs Deprivation Category and the main comparisons were made between the two groups of patients who were categorised as 'non-deprived' and 'deprived'. Therefore, it should be remembered that selection of different groupings of Carstairs Deprivation Categories, such as Carstairs Category 1, 2 and 3 for 'non-deprived' and 4, 5, 6 and 7 for 'deprived' group might have led to different conclusions. The categorisation used in this study was selected in order to compare distinctly different groups of patients resident in the two extremes of 'socially deprived' settings.

3.9 Conclusion

The discontinuation rates among methotrexate-treated arthritic patients in the UK have been previously reported by survival analysis and this study provides useful data for future comparisons. It has been found that there was no statistically significant differences between the 'non-deprived' and the 'deprived' groups of patients in terms of discontinuation rates for methotrexate therapy; however, the identification of a lower methotrexate dose at discontinuation among patients living in the lower socio-economic environments deserves further study.

The discontinuation patterns of methotrexate revealed valuable information regarding the therapy. Almost 90% of the discontinuations occurred due to drug toxicity which emphasised the importance of patient monitoring during the treatment processes. There have been numerous studies indicating the toxicity profile of methotrexate in the treatment of arthritic patients which were similar to the results that have been found in this study. The gastro-intestinal toxicity appeared to be the main reason for discontinuation due to side effects of methotrexate therapy, followed by hepatotoxicity as the next most common reason.

Methotrexate was the potentially toxic drug among the other disease-modifying anti-rheumatic drug therapies, given the fact that it had the highest proportion of treatment discontinuations due to drug toxicity. However, methotrexate treatment courses were least likely to terminate due to lack of efficacy and the proportion of discontinued treatment courses were lower than the other DMARD therapies.

This study confirmed that methotrexate has the highest efficacy: toxicity profile amongst DMARD therapies which makes it preferable among the other disease-modifying anti-rheumatic drugs. Although the prevalence of serious side effects of methotrexate treatment is

low, the toxicity of the drug is still the main cause for discontinuation of the treatment in patients with rheumatoid arthritis. Therefore, it is important for the patients and health care professionals to be vigilant throughout the treatment processes.

It can be concluded that although the new biological agents, such as infliximab and etanercept, appeared to be promising in the treatment of rheumatoid arthritis, methotrexate therapy still has a potential and wider acceptance in the rheumatology arena. Therefore, a standard system for monitoring of drug therapy should be designed and implemented in order to get the best out of methotrexate treatment, which would also help to increase and maintain both patients' and health care professionals' awareness throughout the treatment process.

Chapter 4: Development of a consensus on requirements in methotrexate prescribing, monitoring and patients self-management processes in the treatment of rheumatoid arthritis : The Delphi study

4.1 Introduction

Methotrexate (MTX) therapy has been increasingly used in the treatment of rheumatoid arthritis in the 1990s. Recently, the possibility of involving multi-disciplinary health care providers within the treatment process has generated a wide interest in the rheumatology arena.

Guidelines are available for the management of rheumatoid arthritis and monitoring of disease-modifying anti-rheumatic drug (DMARD) therapies. The American College of Rheumatology (1996), the Royal College of Physicians (1992) and the Scottish Intercollegiate Guidelines Network (SIGN) (2000) have published guidelines for the management of rheumatoid arthritis.[151, 157, 158] The British Society for Rheumatology issued a guideline in July 2000 on the monitoring of DMARD therapies.[168] However, those guidelines do not reflect the findings of recent studies that have prompted new strategies for the treatment of rheumatoid arthritis, in particular trends in the use of disease-modifying drugs and the development of the patient self-management concept.

Self-management is a concept that has been recognised and exploited in strategies for chronic disease management. The implementation of the principles of self-management within chronic disease management has yielded a new perspective for patient-centred and multidisciplinary health care approaches, which emphasise the patient's participation. However, published guidelines do not explicitly reveal the importance of patient self-management, particularly in methotrexate therapy.

Chapter 2 and 3 highlighted the problems and identified several research questions regarding disease management and methotrexate therapy in patients diagnosed with rheumatoid arthritis. This chapter aims to identify health care professionals' opinions regarding the use of methotrexate therapy and the patient self-management concept in the treatment of rheumatoid arthritis.

4.2 Aim of the study

This study aimed to achieve a consensus amongst rheumatology specialists in Scotland on the concept of prescribing and monitoring of methotrexate therapy and the principles of patient self-management processes in the treatment of rheumatoid arthritis.

4.3 Objectives

- To identify the population of rheumatology specialists in Scotland
- To identify potential problems and concerns of rheumatology specialists regarding methotrexate therapy in the treatment of rheumatoid arthritis
- To design a conceptual framework that ascertains issues to be discussed by the group of experts in the rheumatology arena
- To obtain recommendations about good practice standards for methotrexate use in the treatment of rheumatoid arthritis

4.4 Methodology

4.4.1 Consensus Building Methods

Consensus is primarily defined as 'general or widespread agreement of opinion', 'majority view' or 'collaborative opinion'.[241]

The consensus building method is a collaborative and unanimous approach, which is used to deal with situations where conflicts and disputes have arisen in particular circumstances. It is convenient to have consensus decisions when the solution to a particular problem is not immediately recognised by all people affected. This process involves contributions from interested parties and/or individuals in order to identify common concepts and/or concerns, which would be solved through the way shown to be acceptable to each party involved.

Conflicts might occur due to misunderstandings or opposing beliefs or attitudes towards particular situations. Uncertainties on critical issues may cause disharmony where lack of direct and regular communication exists, therefore a need for co-operation and an agreement on specific problems arises in practice. A means of co-operation allows explicit understanding of problems, recognition of mutual interests, sharing of information deliberately via frequent contacts and networking and the addressing and meeting of the needs of interested parties. Although consensus methods allow a certain degree of agreement

to be achieved among participants, they are also valuable in terms of identifying disparities and issues for further research.

The consensus methods enhance decision-making, enable development of policies, allow proposal, revision and quality assessment of quality indicators, support clinical governance and identify, quantify and measure areas where uncertainty, controversy or incomplete evidence exists. These methods have been used in the health arena since the 1950s.[242] The use of a structured consensus method originates from the idea of overcoming potential disadvantages of group discussion where the desire to reach agreement prevents appropriate attention to accuracy of results, allows potential effects of social and group pressure on individuals' views and leads to likelihood of dominance of existing individual or group views.

Moore suggested various techniques for achieving a consensus which range from informal discussion through to use of legitimate use of powers among participants.[243] In the latter, the process can be costly, time-consuming and inefficient for other participants in terms of having little control over the outcome. Hence, all techniques require an independent and/or objective means of framing a proposal after receiving information about everyone's concerns.

The consensus building process involves pre-determined procedures to ensure equity. The process leads to;[243]

- an increased understanding of problems involved
- improved relationships between interested parties
- greater commitment to and control of outcome by interested parties
- savings in terms of time and money

Although it has potential advantages as described above, the consensus-building process might expose some difficulties. The presence of non-negotiable beliefs that are held by participants, the excessive authority of powerful parties, under-representation of some interests or the need for extended time to achieve agreement may cause difficulties during the process. The consensus-building process should be balanced to cover the agenda of interested parties, to secure the involvement of interested parties and ensure their representation within the whole process.

Selection of an appropriate method for achieving a consensus requires consideration of certain features, such as;

- anonymity
- clear objectives
- concept of 'expert'
- feedback
- iteration
- response rate
- sample size
- specificity
- definition of consensus
- validity and reliability

A consensus in decision making is dependent on the key features summarised in Table 4.1, which should be well established before the process even starts.

Table 4.1 Key features of the decision making process

Features	Issues to be considered....
Agenda	The purpose
Define the problem/issue	Nature of the issue
Determine feasible outcome	Issues to be covered
	Broad/narrow perspective
	Sufficiently rich but manageable information
Select and approach	The process design
Identify process steps	How it should be generated
Consider other components	Which methods to use
	How to interpret findings
Participants and representations	All relevant/interested parties included
Identify participants	Balanced representation of each party at each level
	Choice of participants with each party
Authority and use of power	Delegated to the group?
Clarify roles	Relative power between parties
	How to avoid one or more individual dominating?
Information	Available to all parties
	Objective
	Balanced
Involvement	Whole process open to all parties
	Degree of involvement
	Types of relationships among participants
Implementation	Cost of bringing people together
	Tendency to treat group decision as unanimous
Vision for the future	Applicable outcomes for the real circumstances

Adapted from [243]

The consensus-building process requires participants to express their own version of the relevant facts which are consistent with their definition of the problem and their perception of potential solutions that can be adopted for particular circumstances. Brainstorming is an important element of the consensus-building process, which should be used to generate issues and relevant solutions by a subcommittee or the full group of participants.

In the field of business or management sciences, it is conceivable that somehow achieving a consensus within a permanent organisation is easier than in a temporary group. The participants share the same interests, common values and possible ways of handling concerns for a long term, therefore the themes emerged through the consensus-building process are more likely to be accepted for a certain time period.

According to Carpenter there is no unique way to accomplish a consensus-building strategy, the process should be tailored in order to meet the demands of each circumstance.[244] Ideally, consensus-based approaches involve participants' ownership of the design of a process. Participants should be similarly affected by the particular problem and share a common interest in the issues. It is also likely that a neutral party initiates the design of a consensus building process through their approach to organisations or groups that are interested. Regardless of the position/perspective of initiatives for building a consensus process, it is inevitable that participants should broadly agree on the definition of a problem and potential solutions.

The development of a consensus process generally starts with problem solving approach where participants are able to clarify and agree on the definition of the problem that they aim to resolve. Decisions are made as the process evolves. Information regarding the nature of the problem becomes available for participants and participants are allowed to generate solutions in the light of different perspectives. It is recommended that it is always useful to ask 'what do we have?', 'what do we want?' or 'how do we achieve it?' questions to start with in order to identify strengths and weakness of the present problem and to share possibilities of the most appropriate strategies to solve the problem.[244] These initial steps generate a list of pre-determined issues for participants to achieve an agreement while seeking to accomplish a consensus. The approaches for developing issues are described in Table 4.2.

Table 4.2 The approaches for the development of issues for a consensus-building process

	Stylised, rhetorical	Interactional, communicative	Dynamic, transformative
Purpose is...	sharing information	sharing information and creation of new ideas	To seek agreement and solve the problem
Interaction...	is one way and scripted	is more complex and requires more management	requires clear articulation and must be structured
The process requires...		focus on acquiring knowledge, solving problems, making decisions or visioning desired future	systematic analysis of causes and its potential solutions through multiple meetings

Adapted from [245]

Two consensus-building methods that are commonly adopted in medical, nursing and health service arenas: the Nominal Group Technique (NGT) and the Delphi process, which are summarised in Table 4.3. In addition to those techniques, the consensus development conference has also been suggested, which is less frequently used. All three methods aim to achieve a certain degree of agreement (consensus measurement) and to resolve disagreement (consensus development).

The other methods for consensus-building were also described as the staticised group, the social judgement analysis and the structured discussion.[242] These methods are less likely to use mailed questionnaires and formal feedback processes, except in the social judgement analysis. Like the Delphi and the nominal group technique, the staticised group method uses an explicit aggregation for analysis, which involves statistical methods but the participants have no opportunity for interaction in order to discuss issues that are presented. The social judgement analysis is perceived as a method of feedback rather than a comprehensive consensus building method. It aims to identify reasons that are behind an individual's decision and to provide this information as a 'cognitive feedback' to the participants, therefore focus of discussion becomes logically facilitated towards the judgement. This method might be helpful when the researcher aims to understand the reasons for lack of consensus on a particular topic.

Table 4.3 Comparison of the two main consensus-building methods

	The Delphi	NGT
Process		
Initial review of literature/evidence	Yes	Rarely
Formulation and presentation of the questions	Review of literature and evidence ***OR*** Asking participants to generate	Silent process for generating
Develop questionnaire statements	Yes	Yes
Piloting	Yes	No
Rounds and feedback	Through postal contact Individual feedback	In the meeting Group feedback
Meeting for group discussion for clarification	No	Yes
Participants	Large, heterogeneous sample (4-3000)	Usually 9-12 people to allow face to face discussion
Analysis	Quantitative/ qualitative	Quantitative/ qualitative

4.4.2 The Nominal Group Technique

The nominal group technique (NGT) was developed by Delbecq and Van de Ven in 1968 and has been used to enhance committee decision making in different fields.[246] The technique consists of two rounds of structured meetings to allow experts to rate or prioritise their agreement for the questionnaire statements.

The nominal group technique aims to gather information from relevant experts through highly structured meetings, which are facilitated by an expert (the Delbecq technique) or credible non-expert person (Glaser technique) on the subject.[246-248] The process starts with thinking of possible questions and issues regarding the proposed subject where the research questions are not clearly defined. The participants are invited to spend a certain amount of time and then they are asked to write down their opinions. With assistance of a facilitator, each participant is then asked to raise their views in turn to the group. The facilitator is in a position to record the emerging issues, usually on flip charts, and groups them together where appropriate until no more new ideas have emerged. After generating and clarifying the

ideas and issues, participants are expected to rank each idea privately. The ranking is tabulated and presented to the group by the facilitator. The overall ranking is discussed and re-ranked in the subsequent round. The final ranking is analysed and the results are fed back to the participants. The technique may be perceived as another version of focus group interviewing but the former focuses on a single topic/concept and is less likely to take into account the qualitative analysis processes.

The modifications have also been applied to the procedures in the nominal group technique. The most commonly used method for the clinical guideline development was 'modified NGT' which was develop by the RAND Corporation during 1970s and 1980s and also referred as 'modified Delphi'.[242] In this process, the participants express their views independently via mailed questionnaire. The results of the questionnaire are collated and fed back to the respondents when they are assembled to discuss their views. They re-consider or re-rate their views in private. The nominal group technique can also be conducted by a single meeting or can be initiated by post and followed by a face to face discussion for ratings. The researcher/facilitator can also provide initial background about the issue for the discussion.[248]

The nominal group technique has been used for development of clinical guidelines, criteria for appropriateness, quality of life measures and to identify strategies for the practices and health priorities.[242, 249-252]

The features of the consensus building process and the Delphi technique that are discussed in the following section are also applicable to the nominal group technique.

4.4.3 The Delphi Technique

The Delphi technique was first introduced in the 1950s by the RAND Corporation in the United States. The process gathered its name from the Delphic oracles in Greece, which were known for their skills of interpretation and foresight but also associated with the ambiguity of their interpretation.

The Delphi technique and the Nominal Group Technique are both perceived as modified versions of the RAND method. The RAND method was generated in 1963 and is a formal group consensus process which provides combined expert opinion and scientific evidence to the participants and asks them to rate the statements, rather than asking them to generate

ideas in the first place. The final agreement is achieved through conducting a meeting to discuss and a re-rating of the statements.

Janis defined the Delphi process as a 'mode of thinking that people engage in when they are deeply involved in a cohesive in-group, when the members' strivings for unanimity override their motivation to realistically appraise alternative courses of action'.[253]

The Delphi technique is applicable when the following circumstances exist:[254]

- the research problem cannot be analysed by analytical techniques
- diversity in experiences, assumptions or information leading to practice in different ways among study population
- contact face to face with potential people in terms of time, cost and logistics is impractical

There are standard guidelines established for conducting a Delphi study. The technique has been variously classified in its applications as 'modified Delphi', 'policy Delphi', 'real-time Delphi', 'reactive Delphi' and 'decision Delphi'.[246, 253, 254] The 'decision Delphi' technique does not focus on facts or the use of specific application experts, but only considers decision-making in fields that are strongly susceptible to change. Unlike the conventional Delphi, 'quasi-anonymity' exists in implementation of this technique, which describes that the status of the participants is known by the researcher, but not by the other participated respondents.[255]

The Delphi technique consists of structured, isolated, indirect iterative rounds (preferably two to three rounds[254, 255]), which aggregates expert opinion on particular concepts. It enables participants to consider/judge their opinion in the light of a group response and creates an opportunity for them to change their responses throughout the process. The 'expert' people who are knowledgeable and have experiences on the proposed subject are invited to express their opinions. The emerged opinion in this qualitative stage that covers a wide range of perspectives are categorised under a certain number of headings and groups the statements to be delivered to the participants through a questionnaire. At that time, the participants are asked to rank their agreements with each statement in the questionnaire. The rankings are analysed, summarised and included in the repeat version of the questionnaire in order to be sent to the respondents in the subsequent round. In the following round, the participants are asked to re-rank their agreements with each questionnaire statement in the light of the group response, which is provided by the analyst. The re-rankings are re-analysed, summarised and

assessed for a degree of consensus. The additional rounds can be anticipated where an intended agreement has not been achieved.

Although the Delphi technique enables a researcher to reach a large number of people by a most convenient way in a short time, the analysis and feedback processes can be overwhelmingly laborious and time consuming. Avoidance of face to face interactions of participants in a meeting can be more convenient for some participants who feel insecure about raising their views within the whole 'expert' group.[248] Moreover, this approach can eliminate discussions and challenges amongst participants, which can be considered advantageous in the consensus building processes; whereas it can also yield hidden issues not yet emerged which are relevant to the topic.

One of the main concerns in conducting a robust Delphi process is the definition of the 'expert' group.[242] The composition of participants is important and mainly depends on the researcher's intention and the prospects of the study in consensus building processes. The participants should reflect interests of other relevant parties and should have had knowledge, experiences and perspectives on the proposed subject. Therefore, the definition of 'expert' remains between the persons who generate the evidence (academics and specialists) and those who apply it in practice (practitioners).[248]

The feedback process is perceived as a crucial stage in the Delphi technique because achieving a consensus on a particular topic partly depends on what has been fed back to the respondents between the subsequent rounds. The feedback process can either be qualitative in form which anonymously summarises the comments made by the participants (content analysis) or can be quantitative in form by provision of means, medians (central tendency), frequencies and interquartile range (dispersion) statistically addressing the questions being asked. The researchers have the opportunity to use both feedback methods mutually within the same study. Provision of qualitative feedback to the respondents may decrease the number of rounds required for the Delphi in the process of achieving a consensus as it provides clarifications for opinions suggested.

The Delphi technique has been used in various forms in the literature, and it has been criticised in terms of different methodological aspects.[242, 246, 247, 254, 256]

The composition of the study sample and its optimum size have been a focus of discussions.[255] It is suggested that the technique is more appropriate if a group of

heterogeneous participants are available and they are geographically distributed.[246] The composition and the size of the panel members mainly depend on the purpose of the study, available resources and members' willingness to participate. In the published literature, it has been shown that the sample size for the Delphi technique varies between 4 to 3000.[248] A random sample may be drawn to be able to represent the whole population if potential numbers of 'experts' is high.[255] Multi-professional composition of the panel allows discussion of issues through different perspectives, however if the purpose is to achieve a consensus, which will be applicable in a particular profession's practice, a uni-disciplinary group might be considered most appropriate. The selection of the 'experts' is mainly purposive and depends on the criteria that have been sought, therefore representativeness/representation is not necessarily sought or assured.

The response rate is another aspect that requires attention from the researchers. Since the Delphi technique uses postal questionnaires and continuous follow-up, it is not always possible to maintain the same response rate throughout the subsequent rounds. There may be dropouts during the late rounds of the technique, which provoke a 'fatigue' factor. An achievement of a high response rate requires continuous support and enthusiasm from the panel members. High initial interests of the panel members and preferred follow-up procedures may increase the response rate for the study.[255]

The Delphi technique is an anonymous way of gathering data. Although participants might be aware of the composition of the panel, they are not informed about identity of the responses. Therefore it is sometimes acknowledged as a 'semi/quasi- anonymous' technique. The responses to the questionnaire are only known to the researcher in order to follow up and feedback to the respondents during the study processes.

There has been a debate about definition of consensus and it has been suggested that consensus can be defined as maintaining stability of responses rather than achieving a certain level of agreement. Consensus should be achieved amongst participants within a particular round and also between the rounds (also refered to stability which is defined as no statistically significant difference between two subsequent rounds). Therefore it is sometimes necessary that the researcher should make a decision in advance about the number of rounds to be used for the study and report the level of agreement achieved. The literature demonstrates miscellaneous numbers of rounds that have been applied in the Delphi survey, which has ranged from two to six or more. The number of rounds depends on the amount of time available and should be sufficient and/or adequate enough to provide meaningful

results. Since there is no established guide available, the level of consensus is defined according to the sample size, resources available and the purpose of the research. Level of consensus has been quoted in the literature from lowest 50% up to 80%.[254]

The Delphi technique has been widely accepted not only within health service research but also in technology assessment, policy prioritisation, prescribing research, development of educational curricula, assessment of quality indicators, identifying research priorities, strategies and recommendations for proposed programmes.[242, 253, 257-261] The technique assumes that accurate and reliable information can be achieved through consulting a group of 'experts' in the area and accepts achievement of a consensus as the best solution.

In reviewing the use of the Delphi technique in pharmacy practice research and associated health service research, Desselle identified community pharmacists' perceptions on the feasibility of implementation of pharmaceutical care practice standards and its relevance to improving therapeutic outcomes while comparing 'experts' and 'practising pharmacists' opinions using the Delphi technique.[262] The Delphi has also been used to develop an initial list of the pharmaceutical care standards which formed the basis of the American Pharmaceutical Association's 'Principle of Practice' report. Desselle identified several pharmaceutical care standards including evaluations of pharmaceutical care plans, documentation and patient assessments, perceived as feasible by the pharmacists. The use of only one round for the Delphi technique, which did not allow respondents to re-consider their own judgements, and involved a relatively low response rate (22%) for participation are shortcomings of this study.

Williard et al explored various health care professionals' opinions regarding comprehensive drug therapy management (CDTM) and its importance in the health care system.[263] The authors anticipated three iterative rounds for the Delphi study involving 66 respondents. The first round questionnaire consisted of nine open-ended questions and intended to gather opinions on the definition of CDTM, barriers to its implementation, responsibilities and competencies of practitioners. The second and third round questionnaires, which included 200 items, allowed respondents to rate their agreements with each statement generated in the first round on a five point scale. Although a response rate of at least 70% was achieved throughout the three rounds (83%, 70% and 76% for the first, second and the third rounds respectively), the study did not reach a high level of consensus regarding ways of developing and evaluating CDTM which indicated a need for specific actions to be taken for individual circumstances.

Green and her colleagues examined the problems regarding general practitioners' information requirements.[264] They used three iterative rounds of the Delphi technique participated in by 150 general practitioners. Like Williard et al the authors initiated the first round questionnaire with open-ended questions which were based on the Royal College of General Practitioner report in 1994 known as 'Patient Care and the General Practitioner' and asked respondents to rate their agreement with each statement in the subsequent rounds. As a result, the study identified four main areas that have been problematic for the GPs, namely computer use; communication; resources and staffing; and clinical information.

Chocholik et al applied six rounds of the Delphi technique in order to identify appropriate criteria for selection of an automated patient care information system and included ten panel members.[253] In the first round, the participants were asked about their opinion by open-ended questions, however on the following rounds they were asked to rank the importance of criteria on a 100 point scale ranging from 0 (no relevance) to 100 (maximum relevance). The study indicated that there was the possibility of a 'fatigue factor' amongst respondents after the six repetitive rounds, which should have been considered in the Delphi design.

Campbell et al used two rounds of the Delphi to identify prescribing indicators for general practitioners in the UK.[265] There were 51% and 79% response rates achieved after the first and the second rounds respectively. 'Disagreement' was defined as 30% or more scores in both the bottom (1-3) and top (6-9) tertile of the 9-point Likert scale. Only two indicators were rated as valid and reliable for cost and quality by over 50% of the respondents.

Cantrill et al assessed the appropriateness of long-term prescribing indicators involving 100 general practitioners (GPs) and 100 community pharmacists in two rounds of the Delphi processes.[266] They pre-defined achievement of consensus for the statements (items) rated on 7-point Likert scale as 'item is retained if it is scored ≥ 5 by the $\geq 75\%$ of the respondents, whereas it is excluded if the item scored ≤ 3 by the $\geq 75\%$ of the respondents'. The GP's response rates were 85% and 62% for the first and the second rounds respectively. In the community pharmacist population, the response rate was 82% and 57% for the first and the second rounds respectively. At the end of the second round of the Delphi, 30 items representing 18 indicators were retained in the consensus, which were considered as serving the purpose of a practical tool for measuring quality for further studies.

Hearnshaw et al identified desirable characteristics of review criteria for quality improvement in health care.[267] Following a literature review process, two rounds of the

Delphi survey were implemented. Thirty-eight out of 49 (77.5%) panel members agreed to participate in the study and rated their opinions on a 7-point scale. The respondents received the questionnaires by e-mail and post. The items were included in the following round where a minimum 80% of the respondents rated a 5 or more score for importance and 4 and more score for the feasibility items. Disregarded items in the first round were also included in the second round in order to confirm respondents' ratings.

Peters and her colleagues explored the views of nurses on their current and future roles in the community for the care of patients with type 2 diabetes.[268] A Delphi technique that consisted of two rounds was used. They included specialist nurses and practice nurses in order to compare both groups' views using the randomised stratified sampling method. The response rate for the second round was 93% for the practice nurses and 86% for the specialist nurses. The first round questionnaire was based on literature review and allowed nurses to express their feelings on generated broad statements along with a short set of closed questions. In the second round, respondents were fed back about the results of the first round and were asked to rate their opinion for collated issues from the 1st round on a five-point scale. There were >80% agreement established by 85% of the respondents for 165 items in the questionnaire. They concluded that participants identified roles for the management of diabetes care but also the implementation of these shifting roles to improve the effectiveness of care. Co-ordination between primary and secondary care, community orientation with a move to community based care and increased availability of information were the issues that were identified by the respondents in the study.

Granas and Bates used the Delphi technique to assess the significance of the drug-related problems identified by a community pharmacist.[269] They included ten GPs to indicate their opinions on representative samples of 75 drug-related problems during two subsequent rounds. The response rate was 80% for the first round and 100% for the second round. The GPs identified three categories that were considered significant and could result in a clinical improvement in patient care; adding a medicine, drug interaction, monitoring and counselling.

Sachs et al surveyed experts' opinions in order to bridge the gaps between research evidence and key clinical decision in the treatment of bipolar diseases.[270] They used the RAND Corporation 9-point scale technique for rating the appropriateness of medical decisions amongst sixty-five national experts in the USA. The response rate was reasonably high (89%). Consensus was achieved on 89% (950/1065) of the treatment options included in the

study. The experts also identified strategies in acute and preventive treatment for bipolar disorders and approaches to manage the complications of treatment.

Although the technique is widely used in the health arena, Loveridge et al surveyed communities' views in business, science and technology regarding future developments in markets and technologies and aimed to inform these communities about implementation of the Technology Foresight Programme.[258]

4.4.4 The Consensus Development Conference

The consensus development conference was introduced by the National Institute of Health in the USA in 1977. Unlike the Delphi and the nominal group technique, the consensus development conference aims to provide a public forum for discussion of issues.[242]

The consensus development conference has been used in various topics in the health field such as in the treatment of stroke, arrhythmias, lyme disease, early stage of breast cancer, and otitis media, assessing dementia, management of hypertension, establishing therapeutic strategies for schizophrenic psychoses and diagnosis and treatment of early melanoma and depression.[242]

In this technique, a selected group of approximately ten people assembles to reach a consensus on a particular issue through a few days of meetings. The participants are asked to consider the questions or issues after the evidence is presented by experts or various interested groups. The meetings are chaired, the participation of audience is permitted and the group members are allowed to ask questions during these meetings. This group interaction also allows the minority and alternative views to be discussed by the group members.

The implementation of this technique can be difficult in terms of arrangements of venue, participants and resources. It may require sponsorship and various contributions from other organisations and societies. Therefore, it might preferably be conducted during the specialised conference.

After an overview of the consensus building techniques, the following section focuses on the processes that were undertaken for this study.

4.5 Subjects, settings and data collection procedures

The Delphi technique was chosen for a consensus building process in order to achieve an agreement on the prescribing and monitoring of methotrexate and the patient self-management concept in the treatment of rheumatoid arthritis. The study was initiated in July 2001 and initially three rounds were anticipated.

The participants:

The 'expert' population for this Delphi survey included rheumatology specialists, who;

- have considerable amount of experience in rheumatology area
- still continue to practise in the current health care system in Scotland
- have considerable amount of knowledge and experience about methotrexate treatment and its complications

The consultant rheumatologists were considered as 'experts' in the treatment of rheumatoid arthritis because they are trained and specialised in rheumatological diseases, are in a position to give advice to general practitioners (GPs) to initiate the methotrexate therapy for patients diagnosed with rheumatoid arthritis, and expect co-operation on the patient monitoring during the treatment process.

The consultant rheumatologists were identified from the 'Scottish Society for Rheumatology' mailing list. There were 38 consultant rheumatologists identified in Scotland. The potential participants were contacted by the researcher via letter, which explained the purpose of the study, the Delphi technique and the proposed time required for completion of the survey. The acknowledgement letter and a copy of the 1st round questionnaire were included along with a self-addressed pre-paid envelope. They were asked to return an acknowledgement letter in order to indicate their decisions for participation in the study.

Development of the questionnaires:

The questionnaire for the 1st round of the Delphi survey was initially drafted by the researcher in collaboration with hospital pharmacists, rheumatology specialists and independent academic researchers. The researcher identified potential issues regarding methotrexate therapy and patient self-management from the literature reviews, available guidelines and also from the emergent themes in previously undertaken exploratory study. The conceptual framework for the first round of the Delphi survey was drafted and discussed

with various health care professionals (three hospital pharmacists, one specialist nurse and two consultant rheumatologists) in July 2001. Discussions with health care professionals were undertaken in order to clarify the researcher's ideas and enable them to be adapted according to the concept of current health care practices. The researcher also had contacts with an independent academic researcher (in August 2001), who have had previous experience with the Delphi technique and who was considered an eligible person to discuss methodological issues in order to gather opinions regarding the study.

Following several revision processes, the questionnaire for the first round of the Delphi survey was structured and the final version consisted of 13 multiple choice questions which covered two main areas in methotrexate treatment; prescribing and dose increments, and patient monitoring (Appendix 4.1). The questionnaire also encouraged the participants to express their further opinions regarding each question in a space provided. This allowed the researcher to identify previously hidden or uncovered issues as they emerged from the subsequent rounds.

The second round of the Delphi questionnaire was designed by the researcher in the light of the result from the 1st round and was discussed with two consultant rheumatologists and two independent researchers in February 2002. There were 32 questions, which were grouped under three headings; prescribing and dose increments, patient monitoring and patient self-management (Appendix 4.2). The second round questionnaire also allowed the participants to expose their opinions about their current practice when necessary.

In the third round, the same questionnaire that was posted in the 2nd round was sent to the participants including quantitative feedback regarding the results of the previous round (Appendix 4.3).

The process:

The first round of the Delphi questionnaire was sent in November 2001 and expected to be returned by December 2001. The non-responders were followed up by telephone and a reminder of 1st round questionnaire has been re-sent when required.

The second round of the Delphi questionnaire was sent in March 2002 and expected to be returned in two weeks time (in beginning of April 2002). The non-responders were followed up by telephone and a copy of the 2nd round questionnaire was re-sent when required.

In May 2002, the third round of the Delphi questionnaire was sent to the participants, who had replied to the 2nd round questionnaire, and they were asked to return the 3rd round questionnaire in two weeks time (by June 2002). The non-responders were followed up by telephone and a copy of 3rd round questionnaire was re-sent when necessary.

Although the researcher intended to do only three rounds for the Delphi survey, the fourth and the last round questionnaire was sent in August 2002 and the participants were asked to return by September 2002. The last round questionnaire was sent to the participants who replied to the previous round and follow-ups were undertaken by telephone when necessary.

4.6 The results and analysis

Analysis of the 1st round:

The analysis of the first round of the Delphi survey has been completed in January 2002 and the results were as follows.

There were 28 out of 38 (74%) questionnaires returned at the end of the first round. Five non-participating specialists indicated their reasons for not accepting the invitation; lack of time for full commitment (2), not seeing any patients with rheumatoid arthritis therefore not using methotrexate (1) and being retired (2). Five other specialists did not return the questionnaire or the acknowledgement letter.

The results of each item in the first round questionnaire are summarised in Table 4.4 and Table 4.5 as follows.

Table 4.4 The results of the first round: A. Methotrexate prescribing and dose increments (n= 28 respondents overall)

Questionnaire items (number of respondents)	Percentage (number) of respondents
Initial MTX dose (28)	
2.5mg/week	11 (3)
5mg/week	14 (4)
7.5mg/week	75 (21)
Dose increments for MTX (28)	
2.5mg	100 (28)
5mg	-
Intervals for dose increments (26)	
Every 2 weeks	23 (6)
Every 4 weeks	46 (12)
Other	31 (8)
Max MTX dose (28)	
20mg/week	18 (5)
25mg/week	46 (13)
30mg/week	25 (7)
Max tolerated dose	7 (2)
Other	4 (1)
Max MTX dose for combination therapy (25)	
20mg/week	32 (8)
25mg/week	36 (9)
30mg/week	8 (2)
Max tolerated dose	16 (4)
Other	8 (2)
Weekly MTX dose timing (25)	
Single daily	72 (18)
Splitting over 2 times a day	24 (6)

Splitting over 3 times a day	4 (1)
Other	-

Table 4.4 (cont.) The results of the first round: A. Methotrexate prescribing and dose increments (n= 28 respondents overall)

Questionnaire items (number of respondents)	Percentage (number) of respondents
MTX dose frail elderly (26)	
Max 5mg/week	4 (1)
Max 7.5mg/week	4 (1)
Max 10mg/week	42 (11)
Other	50 (13)
Folic acid use (27)	
Yes	100 (27)
No	-
Usual dose of folic acid (27)	
5mg	96 (26)
10mg	4 (1)
Other	-
Frequency of folic acid (27)	
Daily	7 (2)
Weekly	85 (23)
Other	7 (2)
Timing of folic acid (27)	
3-4 days after MTX dose	63 (17)
Every day except the day of MTX	11 (3)
One day after MTX dose	15 (4)
Other	11 (3)

Table 4.4 (cont.) The results of the first round: A. Methotrexate prescribing and dose increments (n= 28 respondents overall)

Questionnaire items (number of respondents)		Percentage (number) of respondents
Prefer to avoid NSAIDs (27)		
	Yes	4 (1)
	No	96 (26)
If YES, any particular NSAID to avoid (1)		
	Yes	-
	No	4 (1)
	Not applicable	96 (26)
If NO, any preferences for choosing NSAID (23)	Yes	13 (3)
	No	83 (19)
	Not applicable	4 (1)

Patient factors when considering to <u>START</u> MTX as a <u>first choice DMARD</u>

% (number) of respondents	Unlikely	Possibly	Probably	Definitely
Age ≥75 yrs (26)	19.2 (5)	46.2 (12)	15.4 (4)	19.2 (5)
Reproductive risk (26)	7.7 (2)	11.5 (3)	15.4 (4)	65.4 (17)
Co-morbidities (26)	7.7 (2)	11.5 (3)	34.6 (9)	46.2 (12)
Length of time since diagnosis (25)	76.0 (19)	24.0 (6)	-	-
Severe arthritis (26)	26.9 (7)	23.1 (6)	26.9 (7)	23.1(6)
Has had previous DMARD (24)	29.2 (7)	16.7 (4)	33.3 (8)	20.8 (5)
Previous methotrexate experience (22)	4.5 (1)	27.3 (6)	13.6 (3)	54.5 (12)
Difficult social circumstances (26)	34.6 (9)	30.8 (8)	26.9 (7)	7.7 (2)
Low educational capacity (25)	20.0 (5)	40.0 (10)	12.0 (3)	28.0 (7)
Alcohol consumption / drug misuse (26)	7.7 (2)	-	15.4 (4)	76.9 (20)
Patient's physical disability/ poor functional status (26)	30.8 (8)	26.9 (7)	26.9 (7)	15.4 (4)
Patient's judgement (26)	7.7 (2)	19.2 (5)	19.2 (5)	53.8 (14)
Compliance with previous DMARD therapies (25)	12.0 (3)	24.0 (6)	24.0 (6)	40.0 (10)

Table 4.4 (cont.) The results of the first round: A. Methotrexate prescribing and dose increments (n= 28 respondents overall)

Patient factors in assessing if a patient is at increased risk of MTX unwanted effects					
% (number) of respondents		**Not so Important**	**Probably important**	**Fairly important**	**Very important**
Age ≥75 yrs (28)		14.3 (4)	39.3 (11)	35.7 (10)	10.7 (3)
Gender (28)					
	Female	85.7 (24)	10.7 (3)	-	3.6 (1)
	Male	92.9 (26)	7.1 (2)	-	-
Dose of MTX (28)		3.6 (1)	28.6 (8)	53.6 (15)	14.3 (4)
Duration of MTX therapy					
	<6 months (26)	57.7 (15)	23.1 (6)	11.5 (3)	7.7 (2)
	6-12 months (24)	66.7 (16)	29.2 (7)	4.2 (1)	-
	13-24 months (25)	56.0 (14)	36.0 (9)	8.0 (2)	-
Severe arthritis (27)		77.8 (21)	18.5 (5)	3.7 (1)	-
Co-morbidities (27)		3.7 (1)	22.2 (6)	48.1 (13)	25.9 (7)
Frailty (27)		14.8 (4)	37.0 (10)	44.4 (12)	3.7 (1)
Previous toxicity to other DMARDs (28)		50.0 (14)	25.0 (7)	25.0 (7)	-
MTX combined with sulphasalazine (27)		55.6 (15)	22.2 (6)	18.5 (5)	3.7 (1)
MTX combined with other DMARDs (other than sulphasalazine) (27)		18.5 (5)	51.9 (14)	25.9 (7)	3.7 (1)
Previous side effects during MTX therapy (28)		-	10.7 (3)	25.0 (7)	64.3 (18)
Difficult social circumstances (28)		21.4 (6)	42.9 (12)	32.1 (9)	3.6 (1)
Low educational capacity (28)		21.4 (6)	46.4 (13)	28.6 (8)	3.6 (1)
Alcohol consumption / drug misuse (28)		-	10.7 (3)	25.0 (7)	64.3 (18)
Compliance with MTX therapy (27)		11.1 (3)	11.1 (3)	40.7 (11)	37.0 (10)
Patient's physical disability/poor functional status (28)		50.0 (14)	32.1 (9)	17.9 (5)	-
Patient's judgement (27)		11.1 (3)	40.7 (11)	18.5 (5)	29.6 (8)

Table 4.5 The results of the first round: B. Methotrexate monitoring (n= 28 respondents overall)

	Actions in response to the following patient events reported during methotrexate therapy (%)								
Patient event (number of respondents)	Split MTX dose	Reduce MTX dose	Monitor and review	Withhold treatment until problem resolves	Discontinue treatment permanently	Increase folic acid dose	No action/ observe	Switching oral to parenteral	Other
1. Symptoms:									
Nausea (28)	60.7	50.0	32.1	21.4	14.3	21.4	17.9	46.4	32.1
Vomiting (28)	39.3	57.1	25.0	39.3	17.9	14.3	7.1	53.6	25.0
Diarrhoea (26)	19.2	61.5	53.8	46.2	19.2	3.8	11.5	23.1	-
Mouth ulceration (26)	7.7	61.5	30.8	50.0	15.4	26.9	19.2	11.5	19.2
Anorexia (26)	30.8	46.2	53.8	26.9	11.5	19.2	15.4	19.2	3.8
Fever/infection (28)	-	7.1	17.9	96.4	14.3	-	14.3	-	7.1
Dry cough (28)	-	10.7	42.9	60.7	17.9	-	7.1	-	32.1
Breathlessness (28)	-	-	10.7	75.0	21.4	-	3.6	3.6	53.6
Rash (27)	3.7	22.2	40.7	59.3	22.2	7.4	7.4	-	-
Hair thinning (24)	4.2	37.5	62.5	20.8	20.8	4.2	25.0	-	4.2
2. Lab tests:									
ALT/AST;									
2-3 x normal (28)	3.6	39.3	57.1	46.4	10.7	-	10.7	-	3.6
>3 x normal (27)	-	14.8	7.4	70.4	44.4	-	-	-	3.7
Alk Phos;									
1-2 x normal(27)	7.4	3.7	74.1	3.7	3.7	-	37	-	-
>2 x normal (28)	7.1	25.0	57.1	2.6	10.7	-	17.9	-	14.3
γ GT raised (27)	7.4	11.1	63.0	7.4	7.4	-	44.4	-	3.7
Alb<35g/L (25)	4.0	12.0	48.0	8.0	8.0	-	60.0	4.0	8.0
Leucopenia (27)	3.7	55.6	33.3	74.1	40.7	-	14.8	-	14.8

Table 4.5 (cont.) The results of the first round: B. Methotrexate monitoring (n= 28 respondents overall)

	Actions in response to the following patient events reported during methotrexate therapy (%)								
Patient event (number of respondents)	Split MTX dose	Reduce MTX dose	Monitor and review	Withhold treatment until problem resolves	Discontinue treatment permanently	Increase folic acid dose	No action/ observe	Switching oral to parenteral	Other
Plalelets low (28)	3.6	39.3	32.1	71.4	46.4	-	10.7	-	-
Anaemia (28)	3.6	3.6	71.4	3.6	3.6	-	28.6	3.6	14.3
Macrocytosis (25)	-	12.0	60.0	8.0	-	16.0	24.0	-	32.0
Neutropenia (28)	-	28.6	21.4	71.4	53.6	3.6	7.1	-	-
Renal function; (28)									
Cr 1-2x normal	-	46.4	60.7	10.7	14.3	-	17.9	-	3.6
Cr >2x normal	-	53.6	28.6	39.3	28.6	-	7.1	-	10.7

3. Investigations:

Normal practice for routine monitoring and frequency of monitoring during methotrexate treatment % (number)

	Before the treatment	*Induction phase (i.e. during dose increments)*			*Maintenance phase (i.e. during stable dose)*	
	% (n)	**Weekly**	**Fortnightly**	**Every 4 weeks**	**Every 2 weeks**	**Every 4 weeks**	**Every 8 weeks**
FBC	100 (27)	11.5 (26)	84.6 (26)	-	-	88.0 (25)	12.0 (25)
ESR and CRP	96.3 (27)	-	32.0 (25)	12.0 (25)	-	37.5 (24)	12.5 (24)
U & E's	100 (26)	-	30.8 (26)	7.7 (26)	-	32.0 (25)	28.0 (25)
Creatinine	100 (27)	-	40.0 (25)	8.0 (25)	-	45.8 (24)	25.0 (24)
LFTs	100 (27)	7.7 (26)	73.1 (26)	7.7 (26)	-	72.0 (25)	16.0 (25)
Chest X-ray	73.1 (26)				**Yes**		
Do you do routine follow up for chest X-ray? (24)					8.3		
Do you recommend chest X-ray thereafter? (26)					15.4		

The results of the first round questionnaire were also categorised according to the degree of agreement that has been achieved amongst participants and indicated in Table 4.6 and Table 4.7 as follows. The items were included in the subsequent rounds if were rated by ≥70% but less than 85% of respondents. If ≥85% of respondents agreed, achieving greater consensus was not thought necessary and such items were excluded from the next round. The items that have achieved less than 70% of responses were disregarded in the following rounds unless they were considered ambiguous by the rheumatology specialists and warranted a need to be explored in detail.

Table 4.6 Summary of the first round of the Delphi study: Methotrexate prescribing and dose increments (n=28 overall)

Methotrexate prescribing and dose increments			
AGREEMENT	**Very Good ≥85%**	**Good 70-84%**	**Less Good <70%**
Methotrexate start 7.5mg/week		75%	
Dose increment 2.5mg/week	100%		
Dose increases at 4 weeks			46%
Maximum dose 25mg/wk			64%
Maximum dose in frail elderly, up to 10mg/wk			42%
Use as single dose/week		72%	
Folic acid dose, 5mg	96%		
Folic acid, weekly	85%		
Folic acid, 3-4 days after MTX dose			63%
NSAIDs not avoided	96%		
***Factors to consider in the process of* Starting MTX (n=22,28);**			
Alcohol consumption/drug misuse		77%	
Reproductive risk			65%
Previous MTX experience			55%
Patient's judgement			54%
Assessing risk of MTX unwanted effects (n=22,28);			
Previous side effects during MTX therapy	89%		
Alcohol consumption/drug misuse	89%		
Compliance with MTX therapy		78%	
Co-morbidities		74%	
Dose of MTX			68%

Table 4.7 Summary of the first round of the Delphi study: Patient monitoring (n=28 overall)

AGREEMENT	Very Good ≥85%	Good 70-84%	Less Good <70%
Patient monitoring: Investigation			
Before starting MTX;			
FBC, U&E's, Creatinine, LFTs	100%		
ESR and CRP	96%		
Chest X-ray		73%	
Induction phase (during dose increments); fortnightly tests			
FBC	85%		
LFTs		73%	
Creatinine			40%
ESR and CRP			32%
U&E's			31%
Maintenance phase (during stable dose); tests every 4 weeks			
FBC	88%		
LFTs		72%	
Creatinine			46%
ESR and CRP			38%
U&E's			32%
Perform routine Chest X-ray			8%
Recommend routine chest X-ray			15%
Patient monitoring: MTX unwanted effects			
ALT/AST >3x normal			
Withhold treatment	70%		
Discontinue permanently			44%
WCC/Platelets below normal			
Monitor and review			32%
Discontinue permanently	71%		
Anaemia (Hb<9 g/dL)			
Monitor and review	71%		
Mouth Ulceration			
Reduce MTX dose			62%
Increase folic acid dose			27%
Cr>2x normal			
Reduce MTX dose			54%
Withhold treatment			39%
Hair thinning			
Monitor and review			63%
Reduce MTX dose			38%

Analysis of the 2nd round:

The second round Delphi questionnaires were sent to 28 consultant rheumatologists who replied to the previous round and 25 (89%) questionnaires were returned at the end of the second round. The reasons for not participating in the second round were not indicated by three rheumatology specialists.

In the second round, the participants were asked to indicate their agreements for each statement (42 statements in total including the subheadings of question 32) in the questionnaire on a 9-point Likert scale which ranged from strongly disagree (1) to strongly agree (9).

The results of the 2nd round of the Delphi study is summarised in Table 4.8.

Table 4.8 The results of the second round of the Delphi study (n=25 overall)

Questionnaire items (number of respondents)	*% (number)* of respondents who rated for each scores on a 9-point Likert Scale Strongly Disagree (1)								Strongly Agree (9)	
	1	2	3	4	5	6	7	8	9	Group Median (IQR)
Prescribing and dose increments										
Initial dose of MTX is 7.5mg/week (25)	-	4 *(1)*	12 *(3)*	4 *(1)*	4 *(1)*	8 *(2)*	24 *(6)*	32 *(8)*	12 *(3)*	7.0 (5.5-8.0)
Max. dose of MTX is no more than 25mg/week (25)	12 *(3)*	8 *(2)*	20 *(5)*	16 *(4)*	-	24 *(6)*	4 *(1)*	16 *(4)*	-	4.0 (3.0-6.0)
Weekly MTX is given as single daily dose (24)	-	-	21 *(5)*	13 *(3)*	8 *(2)*	8 *(2)*	13 *(3)*	21 *(5)*	17 *(4)*	6.5 (4.0-8.0)
The GP decides on the tablet strength (25)	36 *(9)*	4 *(1)*	12 *(3)*	8 *(2)*	24 *(6)*	4 *(1)*	4 *(1)*	4 *(1)*	4 *(1)*	3.0 (1.0-5.0)
The GP prescribes only 2.5mg tablet strength (25)	8 *(2)*	12 *(3)*	8 *(2)*	8 *(2)*	12 *(3)*	4 *(1)*	16 *(4)*	4 *(1)*	28 *(7)*	6.0 (3.0-9.0)
The dose is changed by rheumatologist (25)	-	-	16 *(4)*	8 *(2)*	4 *(1)*	20 *(5)*	28 *(7)*	4 *(1)*	20 *(5)*	7.0 (4.5-7.5)
The dose may be changed by the GP (25)	-	8 *(2)*	12 *(3)*	8 *(2)*	8 *(2)*	24 *(6)*	32 *(8)*	-	8 *(2)*	6.0 (4.0-7.0)
The dose changes is delegated to another health care professional (25)	4 *(1)*	8 *(2)*	24 *(6)*	4 *(1)*	8 *(2)*	16 *(4)*	28 *(7)*	4 *(1)*	4 *(1)*	6.0 (3.0-7.0)
The dose changes is delegated to a GP practice nurse (25)	36 *(9)*	20 *(5)*	20 *(5)*	12 *(3)*	4 *(1)*	4 *(1)*	4 *(1)*	-	-	2.0 (1.0-3.5)
The dose changes is delegated to a specialist nurse (25)	-	8 *(2)*	4 *(1)*	8 *(2)*	4 *(1)*	20 *(5)*	28 *(7)*	20 *(5)*	8 *(2)*	7.0 (5.5-8.0)
The dose changes is delegated to a community pharmacist (25)	52 *(13)*	24 *(6)*	-	12 *(3)*	8 *(2)*	-	4 *(1)*	-	-	1.0 (1.0-3.0)
The dose changes is delegated to a primary care pharmacist (25)	44 *(11)*	16 *(4)*	8 *(2)*	12 *(3)*	16 *(4)*	-	4 *(1)*	-	-	2.0 (1.0-4.0)

Table 4.8 (cont.) The results of the second round of the Delphi study (n=25 overall)

Questionnaire items (number of respondents)	*% (number)* of respondents who rated for each scores on a 9-point Likert Scale Strongly Disagree (1)							Strongly Agree (9)		
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**Group Median (IQR)**
The dose changes is delegated to a hospital pharmacist (24)	42 *(10)*	17 *(4)*	8 *(2)*	4 *(1)*	13 *(3)*	8 *(2)*	8 *(2)*	-	-	2.0 (1.0-5.0)
The dose changes delegated to patient (25)	32 *(8)*	16 *(4)*	20 *(5)*	-	8 *(2)*	12 *(3)*	4 *(1)*	-	8 *(2)*	3.0 (1.0-5.5)
Patient monitoring										
Withheld treatment when AST/ALT level >3xnormal (25)	4 *(1)*	-	-	-	4 *(1)*	4 *(1)*	12 *(3)*	28 *(7)*	48 *(12)*	8.0 (7.5-9.0)
Monitor patient when Alk. Phos. level 1-2x normal (25)	-	8 *(2)*	24 *(6)*	12 *(3)*	8 *(2)*	8 *(2)*	16 *(4)*	12 *(3)*	12 *(3)*	5.0 (3.0-7.5)
Withheld treatment when WCC<4x10^9/L (25)	-	4 *(1)*	-	4 *(1)*	4 *(1)*	16 *(4)*	36 *(9)*	8 *(2)*	28 *(7)*	7.0 (6.0-9.0)
Withheld treatment when neutrophils <2x10^9/L (25)	-	4 *(1)*	8 *(2)*	-	4 *(1)*	8 *(2)*	12 *(3)*	12 *(3)*	52 *(13)*	9.0 (6.5-9.0)
Withheld treatment when platelets <150x10^9/L (25)	-	-	-	12 *(3)*	8 *(2)*	24 *(6)*	28 *(7)*	16 *(4)*	12 *(3)*	7.0 (6.0-8.0)
Monitor patient when Hb<9g/dL (25)	4 *(1)*	8 *(2)*	12 *(3)*	8 *(2)*	8 *(2)*	16 *(4)*	24 *(6)*	-	20 *(5)*	6.0 (3.5-7.0)
Hb<9g/dL is attributable to MTX (25)	4 *(1)*	20 *(5)*	20 *(5)*	8 *(2)*	8 *(2)*	20 *(5)*	16 *(4)*	4 *(1)*	-	4.0 (2.5-6.0)
Perform LFTs fortnightly at induction phase (25)	4 *(1)*	8 *(2)*	12 *(3)*	-	12 *(3)*	4 *(1)*	12 *(3)*	20 *(5)*	-	7.0 (4.0-9.0)
Perform LFTs every 4 weeks at maintenance phase (25)	4 *(1)*	4 *(1)*	12 *(3)*	4 *(1)*	12 *(3)*	8 *(2)*	12 *(3)*	20 *(5)*	24 *(6)*	7.0 (4.5-8.5)
Perform chest X-ray only before treatment (24)	4 *(1)*	-	-	-	4 *(1)*	8 *(2)*	46 *(11)*	13 *(3)*	25 *(6)*	7.0 (7.0-8.8)

Table 4.8 (cont.) The results of the second round of the Delphi study (n=25 overall)

Questionnaire items (number of respondents)	*% (number)* of respondents who rated for each scores on a 9-point Likert Scale Strongly Disagree (1)							Strongly Agree (9)		Group Median (IQR)
	1	2	3	4	5	6	7	8	9	
Community pharmacist clarifies patients' expectation of their MTX therapy (25)	20 *(5)*	20 *(5)*	8 *(2)*	16 *(4)*	16 *(4)*	-	12 *(3)*	8 *(2)*	-	4.0 (2.0-5.0)
Important to show monitoring card to the community pharmacist (25)	20 *(5)*	16 *(4)*	16 *(4)*	12 *(3)*	12 *(3)*	-	16 *(4)*	4 *(1)*	4 *(1)*	3.0 (2.0-6.0)
Verification of the monitoring card for dispensing MTX prescription (25)	28 *(7)*	12 *(3)*	16 *(4)*	4 *(1)*	16 *(4)*	4 *(1)*	8 *(2)*	8 *(2)*	4 *(1)*	3.0 (1.0-5.5)
More attention for appropriate monitoring (25)	-	4 *(1)*	16 *(4)*	8 *(2)*	4 *(1)*	28 *(7)*	32 *(8)*	4 *(1)*	4 *(1)*	6.0 (4.0-7.0)
Routine enquiries from HCPs between clinic visits (25)	8 *(2)*	8 *(2)*	16 *(4)*	8 *(2)*	16 *(4)*	12 *(3)*	24 *(7)*	4 *(1)*	4 *(1)*	5.0 (3.0-7.0)
Patient self-management										
Dosage alteration in response to mild unwanted GI effects (25)	4 *(1)*	8 *(2)*	4 *(1)*	16 *(4)*	12 *(3)*	24 *(6)*	20 *(5)*	8 *(2)*	4 *(1)*	6.0 (4.0-7.0)
Withholding treatment in response to unwanted GI effects (25)	4 *(1)*	-	12 *(3)*	4 *(1)*	20 *(5)*	32 *(8)*	8 *(2)*	20 *(5)*	-	6.0 (5.0-7.0)
Arranging blood sampled in response to GI side effects (25)	4 *(1)*	16 *(4)*	36 *(9)*	8 *(2)*	20 *(5)*	-	8 *(2)*	8 *(2)*	-	3.0 (3.0-5.0)
Withholding treatment in response to bruising (25)	-	4 *(1)*	8 *(2)*	8 *(2)*	4 *(1)*	20 *(5)*	16 *(4)*	12 *(3)*	28 *(7)*	7.0 (5.5-9.0)
Arranging blood sampled in response to bruising (24)	-	8 *(2)*	4 *(1)*	-	-	8 *(2)*	13 *(3)*	33 *(8)*	33 *(8)*	8.0 (7.0-9.0)

Table 4.8 (cont.) The results of the second round of the Delphi study (n=25 overall)

Questionnaire items (number of respondents)	*% (number)* of respondents who rated for each scores on a 9-point Likert Scale Strongly Disagree (1)							Strongly Agree (9)		Group Median (IQR)
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	
Withholding treatment in response to fever (24)	-	8 *(2)*	4 *(1)*	8 *(2)*	4 *(1)*	13 *(3)*	29 *(7)*	8 *(2)*	25 *(6)*	7.0 (5.3-8.8)
Arranging blood sampled in response to infection (24)	8 *(2)*	8 *(2)*	-	-	17 *(4)*	17 *(4)*	17 *(4)*	21 *(5)*	13 *(3)*	6.5 (5.0-8.0)
Seeking professional advice in response to infection (24)	-	-	-	4 *(1)*	-	4 *(1)*	17 *(4)*	38 *(9)*	38 *(9)*	8.0 (7.3-9.0)
Stopping MTX in response to breathlessness (24)	-	13 *(3)*	8 *(2)*	4 *(1)*	-	4 *(1)*	17 *(4)*	21 *(5)*	33 *(8)*	8.0 (4.5-9.0)
Checking blood results (24)	-	4 *(1)*	13 *(3)*	13 *(4)*	25 *(6)*	21 *(5)*	8 *(2)*	8 *(2)*	8 *(2)*	5.0 (4.0-6.8)
Self-administration of parenteral MTX (24)	8 *(2)*	-	4 *(1)*	-	17 *(4)*	4 *(1)*	17 *(4)*	17 *(4)*	33 *(8)*	7.5 (5.0-9.0)

Analysis of the 3rd round:

The third round of the Delphi questionnaires were only sent to the participants who have already replied to the 2nd round (25 specialists), and 24 (96%) questionnaires were returned. The reasons for not returning the questionnaire for the third round were not indicated by the non-respondents.

In the third round, the participants were asked to re-rate their agreements for each statement (42 statements in total) in the questionnaire on a 9-point Likert scale which ranged from strongly disagree (1) to strongly agree (9). They were provided feedback about the results of the 2nd round, including the group median (interquartile range-IQR), the percentages of responses for the top three/four Likert scale scores and the participants' previous ratings for each statement.

The results of the 3rd round of the Delphi study is summarised in Table 4.9.

Table 4.9 The results of the third round of the Delphi study (n=24 overall)

Questionnaire items (number of respondents)	*% (number)* of respondents who rated for each scores on a 9-point Likert Scale Strongly Disagree (1)								Strongly Agree (9)	
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**Group Median (IQR)**
Prescribing and dose increments										
Initial dose of MTX is 7.5mg/week (24)	-	-	13 *(3)*	8 *(2)*	4 *(1)*	4 *(1)*	25 *(6)*	33 *(8)*	13 *(3)*	7.0 (5.25-8.0)
Max. dose of MTX is no more than 25mg/week (24)	8 *(2)*	-	13 *(3)*	21 *(5)*	-	17 *(4)*	29 *(7)*	13 *(3)*	-	6.0 (4.0-7.0)
Weekly MTX is given as single daily dose (22)	-	-	17 *(4)*	13 *(3)*	13 *(3)*	4 *(1)*	17 *(4)*	21 *(5)*	17 *(4)*	7.0 (4.0-8.0)
The GP decides on the tablet strength (24)	41 *(9)*	5 *(1)*	18 *(4)*	5 *(1)*	18 *(4)*	9 *(2)*	-	5 *(1)*	-	3.0 (1.0-5.0)
The GP prescribes only 2.5mg tablet strength (22)	5 *(1)*	-	9 *(2)*	14 *(3)*	18 *(4)*	5 *(1)*	9 *(2)*	14 *(3)*	27 *(6)*	6.5 (4.0-9.0)
The dose is changed by rheumatologist (22)	-	-	5 *(1)*	5 *(1)*	5 *(1)*	23 *(5)*	36 *(8)*	9 *(2)*	18 *(4)*	7.0 (6.0-8.0)
The dose may be changed by the GP (23)	-	4 *(1)*	13 *(3)*	13 *(3)*	13 *(3)*	13 *(3)*	44 *(10)*	-	-	6.0 (4.0-7.0)
The dose changes is delegated to another health care professional (23)	-	4 *(1)*	26 *(6)*	9 *(2)*	4 *(1)*	17 *(4)*	35 *(8)*	-	4 *(1)*	6.0 (3.0-7.0)
The dose changes is delegated to a GP practice nurse (23)	35 *(8)*	30 *(7)*	26 *(6)*	-	9 *(2)*	-	-	-	-	2.0 (1.0-3.0)
The dose changes is delegated to a specialist nurse (23)	-	-	4 *(1)*	9 *(2)*	4 *(1)*	22 *(5)*	39 *(9)*	17 *(4)*	4 *(1)*	7.0 (6.0-7.0)
The dose changes is delegated to a community pharmacist (23)	61 *(14)*	17 *(4)*	9 *(2)*	4 *(1)*	9 *(2)*	-	-	-	-	1.0 (1.0-2.0)
The dose changes is delegated to a primary care pharmacist (24)	46 *(11)*	21 *(5)*	17 *(4)*	4 *(1)*	13 *(3)*	-	-	-	-	2.0 (1.0-3.0)

Table 4.9 (cont.) The results of the third round of the Delphi study (n=24 overall)

Questionnaire items (number of respondents)	*% (number)* of respondents who rated for each scores on a 9-point Likert Scale Strongly Disagree (1) Strongly Agree (9)									
	1	2	3	4	5	6	7	8	9	Group Median (IQR)
The dose changes is delegated to a hospital pharmacist (24)	46 *(11)*	17 *(4)*	13 *(3)*	4 *(1)*	17 *(4)*	4 *(1)*	-	-	-	2.0 (1.0-3.75)
The dose changes delegated to patient (24)	29 *(7)*	21 *(5)*	29 *(7)*	-	8 *(2)*	4 *(1)*	4 *(1)*	-	4 *(1)*	2.5 (1.0-3.0)
Patient monitoring										
Withheld treatment when AST/ALT level >3xnormal (24)	-	-	-	-	-	-	8 *(2)*	25 *(6)*	67 *(16)*	9.0 (8.0-9.0)
Monitor patient when Alk. Phos. level 1-2x normal (24)	-	8 *(2)*	25 *(6)*	8 *(2)*	8 *(2)*	8 *(2)*	21 *(5)*	8 *(2)*	13 *(3)*	5.5 (3.0-7.0)
Withheld treatment when WCC<$4x10^9$/L (24)	-	-	-	-	-	4 *(1)*	50 *(12)*	13 *(3)*	33 *(8)*	7.0 (7.0-9.0)
Withheld treatment when neutrophils <$2x10^9$/L (24)	-	-	-	-	4 *(1)*	-	4 *(1)*	25 *(6)*	67 *(16)*	9.0 (8.0-9.0)
Withheld treatment when platelets <$150x10^9$/L (24)	-	-	-	8 *(2)*	4 *(1)*	17 *(4)*	42 *(10)*	17 *(4)*	13 *(3)*	7.0 (6.0-8.0)
Monitor patient when Hb<9g/dL (24)	-	4 *(1)*	8 *(2)*	13 *(3)*	13 *(3)*	25 *(6)*	21 *(5)*	4 *(1)*	13 *(3)*	6.0 (4.25-7.0)
Hb<9g/dL is attributable to MTX (23)	4 *(1)*	22 *(5)*	26 *(6)*	13 *(3)*	17 *(4)*	13 *(3)*	4 *(1)*	-	-	3.0 (2.0-5.0)
Perform LFTs fortnightly at induction phase (24)	4 *(1)*	4 *(1)*	4 *(1)*	4 *(1)*	21 *(5)*	4 *(1)*	8 *(2)*	25 *(6)*	25 *(6)*	7.5 (5.0-8.75)
Perform LFTs every 4 weeks at maintenance phase (24)	4 *(1)*	-	4 *(1)*	13 *(3)*	8 *(2)*	13 *(3)*	4 *(1)*	21 *(5)*	33 *(8)*	8.0 (5.0-9.0)

Table 4.9 (cont.) The results of the third round of the Delphi study (n=24 overall)

Questionnaire items (number of respondents)	*% (number)* of respondents who rated for each scores on a 9-point Likert Scale Strongly Disagree (1)							Strongly Agree (9)		
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**Group Median (IQR)**
Perform chest X-ray only before treatment (24)	4 *(1)*	-	-	-	8 *(2)*	4 *(1)*	38 *(9)*	21 *(5)*	25 *(6)*	7.0 (7.0-8.75)
Community pharmacist clarifies patients' expectation of their MTX therapy (24)	21 *(5)*	25 *(6)*	8 *(2)*	25 *(6)*	21 *(5)*	-	-	-	-	3.0 (2.0-4.0)
Important to show monitoring card to the community pharmacist (24)	21 *(5)*	8 *(2)*	25 *(6)*	8 *(2)*	21 *(5)*	-	13 *(3)*	-	4 *(1)*	3.0 (2.0-5.0)
Verification of the monitoring card for dispensing MTX prescription (24)	29 *(7)*	4 *(1)*	25 *(6)*	8 *(2)*	21 *(5)*	4 *(1)*	4 *(1)*	-	4 *(1)*	3.0 (1.0-5.0)
More attention for appropriate monitoring (24)	-	4 *(1)*	4 *(1)*	8 *(2)*	8 *(2)*	21 *(5)*	46 *(11)*	4 *(1)*	4 *(1)*	7.0 (5.25-7.0)
Routine enquiries from HCPs between clinic visits (24)	4 *(1)*	4 *(1)*	21 *(5)*	4 *(1)*	21 *(5)*	13 *(3)*	29 *(7)*	-	4 *(1)*	5.0 (3.0-7.0)
Patient self-management										
Dosage alteration in response to mild unwanted GI effects (24)	-	8 *(2)*	8 *(2)*	8 *(2)*	13 *(3)*	33 *(8)*	17 *(4)*	8 *(2)*	4 *(1)*	6.0 (4.25-7.0)
Withholding treatment in response to unwanted GI effects (24)	-	4 *(1)*	-	4 *(1)*	33 *(8)*	29 *(7)*	13 *(3)*	17 *(4)*	-	6.0 (5.0-7.0)
Arranging blood sampled in response to GI side effects (24)	4 *(1)*	8 *(2)*	54 *(13)*	13 *(3)*	8 *(2)*	4 *(1)*	4 *(1)*	4 *(1)*	-	3.0 (3.0-4.0)
Withholding treatment in response to bruising (24)	-	-	4 *(1)*	4 *(1)*	-	25 *(6)*	21 *(5)*	17 *(4)*	29 *(7)*	7.0 (6.0-9.0)

Table 4.9 (cont.) The results of the third round of the Delphi study (n=24 overall)

Questionnaire items (number of respondents)	*% (number)* of respondents who rated for each scores on a 9-point Likert Scale Strongly Disagree (1)								Strongly Agree (9)	
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**Group Median (IQR)**
Arranging blood sampled in response to bruising (24)	-	-	-	-	4 *(1)*	-	25 *(6)*	29 *(7)*	42 *(10)*	8.0 (7.0-9.0)
Withholding treatment in response to fever (24)	-	4 *(1)*	-	4 *(1)*	4 *(1)*	13 *(3)*	38 *(9)*	13 *(3)*	25 *(6)*	7.0 (6.3-8.8)
Arranging blood sampled in response to infection (24)	4 *(1)*	4 *(1)*	-	4 *(1)*	13 *(3)*	17 *(4)*	25 *(6)*	25 *(6)*	8 *(2)*	7.0 (5.25-8.0)
Seeking professional advice in response to infection (24)	-	-	-	-	4 *(1)*	-	17 *(4)*	38 *(9)*	42 *(10)*	8.0 (8.0-9.0)
Stopping MTX in response to breathlessness (24)	-	8 *(2)*	4 *(1)*	-	8 *(2)*	4 *(1)*	8 *(2)*	29 *(7)*	38 *(9)*	8.0 (6.25-9.0)
Checking blood results (23)	-	4 *(1)*	17 *(4)*	9 *(2)*	30 *(7)*	17 *(4)*	9 *(2)*	9 *(2)*	4 *(1)*	5.0 (4.0-6.0)
Self-administration of parenteral MTX (24)	-	-	-	8 *(2)*	17 *(4)*	17 *(4)*	17 *(4)*	17 *(4)*	42 *(10)*	8.0 (5.5-9.0)

Analysis of the 4th round:

The fourth round Delphi questionnaires were only sent to the participants who have replied to the 3rd round (24 specialists), and 23 (96%) questionnaires were returned at the end of the fourth round. The reasons for not participating in the fourth round were not indicated by non-respondent specialists.

In the fourth round, the participants were asked to re-rate their agreements for each statement (42 statements in total) in the questionnaire on a 9-point Likert scale which ranged from strongly disagree (1) to strongly agree (9). They were provided feedback about the results of the 3rd round, including the group median (interquartile range-IQR), percentages of responses for the top three/four Likert scale scores and the participants' previous ratings for each statement.

The results of the 4th round of the Delphi study is summarised in Table 4.10.

Table 4.10 The results of the fourth round of the Delphi study (n=23 overall)

Questionnaire items (number of respondents)	% *(number)* of respondents who rated for each scores on a 9-point Likert Scale Strongly Disagree (1)							Strongly Agree (9)		Group Median (IQR)
	1	2	3	4	5	6	7	8	9	
Prescribing and dose increments										
Initial dose of MTX is 7.5mg/week (23)	-	-	13 *(3)*	4 *(1)*	9 *(2)*	4 *(1)*	22 *(5)*	35 *(8)*	13 *(3)*	7.0 (5.0-8.0)
Max. dose of MTX is no more than 25mg/week (23)	9 *(2)*	-	9 *(2)*	9 *(2)*	9 *(2)*	17 *(4)*	30 *(7)*	17 *(4)*	-	6.0 (4.0-7.0)
Weekly MTX is given as single daily dose (23)	-	-	13 *(3)*	17 *(4)*	4 *(1)*	-	22 *(5)*	30 *(7)*	13 *(3)*	7.0 (4.0-8.0)
The GP decides on the tablet strength (23)	48 *(11)*	9 *(2)*	13 *(3)*	4 *(1)*	26 *(6)*	-	-	-	-	2.0 (1.0-5.0)
The GP prescribes only 2.5mg tablet strength (23)	4 *(1)*	-	9 *(2)*	17 *(4)*	17 *(4)*	4 *(1)*	17 *(4)*	9 *(2)*	22 *(5)*	6.0 (4.0-8.0)
The dose is changed by rheumatologist (23)	-	-	4 *(1)*	9 *(2)*	4 *(1)*	17 *(4)*	44 *(10)*	9 *(2)*	13 *(3)*	7.0 (6.0-7.0)
The dose may be changed by the GP (23)	-	-	17 *(4)*	9 *(2)*	9 *(2)*	26 *(6)*	35 *(8)*	4 *(1)*	-	6.0 (4.0-7.0)
The dose changes is delegated to another health care professional (23)	-	-	22 *(5)*	13 *(3)*	9 *(2)*	22 *(5)*	35 *(8)*	-	-	6.0 (4.0-7.0)
The dose changes is delegated to a GP practice nurse (23)	30 *(7)*	39 *(9)*	22 *(5)*	4 *(1)*	-	4 *(1)*	-	-	-	2.0 (1.0-3.0)
The dose changes is delegated to a specialist nurse (23)	-	-	-	4 *(1)*	13 *(3)*	22 *(5)*	39 *(9)*	22 *(5)*	-	7.0 (6.0-7.0)
The dose changes is delegated to a community pharmacist (23)	57 *(13)*	30 *(7)*	9 *(2)*	-	4 *(1)*	-	-	-	-	1.0 (1.0-2.0)
The dose changes is delegated to a primary care pharmacist (23)	48 *(11)*	26 *(6)*	13 *(3)*	4 *(1)*	9 *(2)*	-	-	-	-	1.0 (1.0-3.0)

Table 4.10 (cont.) The results of the fourth round of the Delphi study (n=23 overall)

Questionnaire items (number of respondents)	*% (number)* of respondents who rated for each scores on a 9-point Likert Scale Strongly Disagree (1)								Strongly Agree (9)	
	1	2	3	4	5	6	7	8	9	Group Median (IQR)
The dose changes is delegated to a hospital pharmacist (23)	48 *(11)*	17 *(4)*	4 *(1)*	9 *(2)*	13 *(3)*	9 *(2)*	-	-	-	2.0 (1.0-4.0)
The dose changes delegated to patient (23)	30 *(7)*	35 *(8)*	17 *(4)*	4 *(1)*	9 *(2)*	4 *(1)*	-	-	-	2.0 (1.0-3.0)
Patient monitoring										
Withheld treatment when AST/ALT level >3xnormal (23)	-	-	-	-	-	-	4 *(1)*	13 *(3)*	83 *(19)*	9.0 (9.0-9.0)
Monitor patient when Alk. Phos. level 1-2x normal (23)	-	9 *(2)*	30 *(7)*	-	9 *(2)*	22 *(5)*	22 *(5)*	4 *(1)*	4 *(1)*	6.0 (3.0-7.0)
Withheld treatment when WCC<4x10^9/L (23)	-	-	-	-	-	-	52 *(12)*	17 *(4)*	30 *(7)*	7.0 (7.0-9.0)
Withheld treatment when neutrophils <2x10^9/L (23)	-	-	-	-	-	-	-	35 *(8)*	65 *(15)*	9.0 (8.0-9.0)
Withheld treatment when platelets <150x10^9/L (23)	-	-	-	4 *(1)*	9 *(2)*	22 *(5)*	30 *(7)*	22 *(5)*	13 *(3)*	7.0 (6.0-8.0)
Monitor patient when Hb<9g/dL (22)	-	-	9 *(2)*	9 *(2)*	18 *(4)*	36 *(8)*	18 *(4)*	5 *(1)*	5 *(1)*	6.0 (5.0-7.0)
Hb<9g/dL is attributable to MTX (23)	4 *(1)*	26 *(6)*	30 *(7)*	4 *(1)*	30 *(7)*	4 *(1)*	-	-	-	3.0 (2.0-5.0)
Perform LFTs fortnightly at induction phase (23)	-	-	-	4 *(1)*	22 *(5)*	17 *(4)*	4 *(1)*	17 *(4)*	35 *(8)*	8.0 (5.0-9.0)
Perform LFTs every 4 weeks at maintenance phase (23)	-	-	4 *(1)*	4 *(1)*	9 *(2)*	9 *(2)*	9 *(2)*	26 *(6)*	39 *(9)*	8.0 (6.0-9.0)
Perform chest X-ray only before treatment (22)	-	-	-	-	9 *(2)*	-	41 *(9)*	27 *(6)*	23 *(5)*	7.5 (7.0-8.25)

Table 4.10 (cont.) The results of the fourth round of the Delphi study (n=23 overall)

Questionnaire items (number of respondents)	*% (number)* of respondents who rated for each scores on a 9-point Likert Scale Strongly Disagree (1)								Strongly Agree (9)	
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**Group Median (IQR)**
Community pharmacist clarifies patients' expectation of their MTX therapy (23)	17 *(4)*	26 *(6)*	26 *(6)*	17 *(4)*	13 *(3)*	-	-	-	-	3.0 (2.0-4.0)
Important to show monitoring card to the community pharmacist (23)	13 *(3)*	13 *(3)*	35 *(8)*	9 *(2)*	22 *(5)*	-	4 *(1)*	-	4 *(1)*	3.0 (2.0-5.0)
Verification of the monitoring card for dispensing MTX prescription (23)	17 *(4)*	13 *(3)*	35 *(8)*	4 *(1)*	22 *(5)*	4 *(1)*	-	-	4 *(1)*	3.0 (2.0-5.0)
More attention for appropriate monitoring (23)	-	4 *(1)*	4 *(1)*	4 *(1)*	13 *(3)*	13 *(3)*	52 *(12)*	4 *(1)*	4 *(1)*	7.0 (5.0-7.0)
Routine enquiries from HCPs between clinic visits (23)	-	4 *(1)*	22 *(5)*	4 *(1)*	22 *(5)*	4 *(1)*	39 *(9)*	-	4 *(1)*	5.0 (3.0-7.0)
Patient self-management										
Dosage alteration in response to mild unwanted GI effects (23)	-	4 *(1)*	9 *(2)*	13 *(3)*	13 *(3)*	39 *(9)*	13 *(3)*	4 *(1)*	4 *(1)*	6.0 (4.0-6.0)
Withholding treatment in response to unwanted GI effects (23)	-	4 *(1)*	-	4 *(1)*	35 *(8)*	35 *(8)*	9 *(2)*	13 *(3)*	-	6.0 (5.0-6.0)
Arranging blood sampled in response to GI side effects (23)	4 *(1)*	4 *(1)*	65 *(15)*	9 *(2)*	13 *(3)*	-	-	4 *(1)*	-	3.0 (3.0-4.0)
Withholding treatment in response to bruising (23)	-	-	-	-	4 *(1)*	26 *(6)*	22 *(5)*	13 *(3)*	35 *(8)*	7.0 (6.0-9.0)
Arranging blood sampled in response to bruising (23)	-	-	-	-	4 *(1)*	-	17 *(4)*	30 *(7)*	48 *(11)*	8.0 (8.0-9.0)

Table 4.10 (cont.) The results of the fourth round of the Delphi study (n=23 overall)

Questionnaire items (number of respondents)	% *(number)* of respondents who rated for each scores on a 9-point Likert Scale Strongly Disagree (1)							Strongly Agree (9)		Group Median (IQR)
	1	2	3	4	5	6	7	8	9	
Withholding treatment in response to fever (23)	-	4 *(1)*	-	-	4 *(1)*	13 *(3)*	30 *(7)*	22 *(5)*	26 *(6)*	7.0 (7.0-9.0)
Arranging blood sampled in response to infection (23)	4 *(1)*	-	-	-	4 *(1)*	17 *(4)*	44 *(10)*	26 *(6)*	4 *(1)*	7.0 (6.0-8.0)
Seeking professional advice in response to infection (23)	-	-	-	-	-	-	13 *(3)*	39 *(9)*	48 *(11)*	8.0 (8.0-9.0)
Stopping MTX in response to breathlessness (23)	-	4 *(1)*	4 *(1)*	-	4 *(1)*	9 *(2)*	4 *(1)*	30 *(7)*	44 *(10)*	8.0 (7.0-9.0)
Checking blood results (23)	-	9 *(2)*	9 *(2)*	9 *(2)*	52 *(12)*	4 *(1)*	4 *(1)*	9 *(2)*	4 *(2)*	5.0 (4.0-5.0)
Self-administration of parenteral MTX (23)	-	-	4 *(1)*	-	22 *(5)*	-	9 *(2)*	13 *(3)*	52 *(9)*	9.0 (5.0-9.0)

Table 4.11 The results of the Delphi questionnaire throughout the four consecutive rounds

Questionnaire items	2nd round		3rd round		4th round	
	Group median (IQR)	*% scored ≥7*	*Group median (IQR)*	*% scored ≥7*	*Group median (IQR)*	*% scored ≥7*
Prescribing and dose increments						
Initial dose of MTX is 7.5mg/week	7.0 (5.5-8.0)	68%	7.0 (5.25-8.0)	71%	**7.0 (5.0-8.0)**	70%
Max. dose of MTX is no more than 25mg/week	4.0 (3.0-6.0)	20%	6.0 (4.0-7.0)	42%	6.0 (4.0-7.0)	48%
Weekly MTX is given as single daily dose	6.5 (4.0-8.0)	50%	7.0 (4.0-8.0)	54%	**7.0 (4.0-8.0)**	65%
The GP decides on the tablet strength	3.0 (1.0-5.0)	12%	3.0 (1.0-5.0)	5%	2.0 (1.0-5.0)	-
The GP prescribes only 2.5mg tablet strength	6.0 (3.0-9.0)	48%	6.5 (4.0-9.0)	50%	6.0 (4.0-8.0)	48%
The dose is changed by rheumatologist	7.0 (4.5-7.5)	52%	7.0 (6.0-8.0)	64%	**7.0 (6.0-7.0)**	65%
The dose may be changed by the GP	6.0 (4.0-7.0)	40%	6.0 (4.0-7.0)	44%	6.0 (4.0-7.0)	39%
The dose changes is delegated to another health care professional	6.0 (3.0-7.0)	36%	6.0 (3.0-7.0)	39%	6.0 (4.0-7.0)	35%
The dose changes is delegated to a GP practice nurse	2.0 (1.0-3.5)	4%	2.0 (1.0-3.0)	-	2.0 (1.0-3.0)	-
The dose changes is delegated to a specialist nurse	7.0 (5.5-8.0)	56%	7.0 (6.0-7.0)	61%	**7.0 (6.0-7.0)**	61%
The dose changes is delegated to a community pharmacist	1.0 (1.0-3.0)	4%	1.0 (1.0-2.0)	-	1.0 (1.0-2.0)	-
The dose changes is delegated to a primary care pharmacist	2.0 (1.0-4.0)	4%	2.0 (1.0-3.0)	-	1.0 (1.0-3.0)	-
The dose changes is delegated to a hospital pharmacist	2.0 (1.0-5.0)	8%	2.0 (1.0-3.75)	-	2.0 (1.0-4.0)	-
The dose changes delegated to patient	3.0 (1.0-5.5)	12%	2.5 (1.0-3.0)	8%	2.0 (1.0-3.0)	-
Patient monitoring						
Withheld treatment when AST/ALT level >3x normal	8.0 (7.5-9.0)	88%	9.0 (8.0-9.0)	100%	**9.0 (9.0-9.0)**	100%

Table 4.11 (cont.) The results of the Delphi questionnaire throughout the four consecutive rounds

Questionnaire items	2nd round		3rd round		4th round	
	Group median (IQR)	*% scored ≥7*	*Group median (IQR)*	*% scored ≥7*	*Group median (IQR)*	*% scored ≥7*
Monitor patient when Alk. Phos. level 1-2x normal	5.0 (3.0-7.5)	40%	5.5 (3.0-7.0)	42%	6.0 (3.0-7.0)	
Withhold treatment when WCC<4x10^9/L	7.0 (6.0-9.0)	72%	7.0 (7.0-9.0)	96%	**7.0 (7.0-9.0)**	100%
Withhold treatment when neutrophils <2x10^9/L	9.0 (6.5-9.0)	76%	9.0 (8.0-9.0)	96%	**9.0 (8.0-9.0)**	100%
Withhold treatment when platelets <150x10^9/L	7.0 (6.0-8.0)	56%	7.0 (6.0-8.0)	71%	**7.0 (6.0-8.0)**	65%
Monitor patient when Hb<9g/dL	6.0 (3.5-7.0)	44%	6.0 (4.25-7.0)	38%	6.0 (5.0-7.0)	27%
Hb<9g/dL is attributable to MTX	4.0 (2.5-6.0)	20%	3.0 (2.0-5.0)	4%	3.0 (2.0-5.0)	-
Perform LFTs fortnightly at induction phase	7.0 (4.0-9.0)	60%	7.5 (5.0-8.75)	58%	**8.0 (5.0-9.0)**	57%
Perform LFTs every 4 weeks at maintenance phase	7.0 (4.5-8.5)	56%	8.0 (5.0-9.0)	58%	**8.0 (6.0-9.0)**	74%
Perform chest X-ray only at baseline	7.0 (7.0-8.75)	83%	7.0 (7.0-8.75)	83%	**7.5 (7.0-8.25)**	91%
Community pharmacist clarifies patients' expectation of their MTX therapy	4.0 (2.0-5.0)	20%	3.0 (2.0-4.0)	-	3.0 (2.0-4.0)	-
Important to show monitoring card to the community pharmacist	3.0 (2.0-6.0)	24%	3.0 (2.0-5.0)	17%	3.0 (2.0-5.0)	9%
Verification of the monitoring card for dispensing MTX prescription	3.0 (1.0-5.5)	20%	3.0 (1.0-5.0)	8%	3.0 (2.0-5.0)	4%
More attention for appropriate monitoring	6.0 (4.0-7.0)	40%	7.0 (5.25-7.0)	54%	**7.0 (5.0-7.0)**	61%
Routine enquiries by HCPs between clinic visits	5.0 (3.0-7.0)	32%	5.0 (3.0-7.0)	33%	5.0 (3.0-7.0)	43%
Patient self-management						
Dosage alteration in response to mild unwanted GI effects	6.0 (4.0-7.0)	32%	6.0 (4.25-7.0)	29%	6.0 (4.0-6.0)	21%
Withholding treatment in response to unwanted GI effects	6.0 (5.0-7.0)	28%	6.0 (5.0-7.0)	29%	6.0 (5.0-6.0)	22%

Table 4.11 (cont.) The results of the Delphi questionnaire throughout the four consecutive rounds

Questionnaire items	**2nd round**		**3rd round**		**4th round**	
	Group median (IQR)	*% scored ≥7*	*Group median (IQR)*	*% scored ≥7*	*Group median (IQR)*	*% scored ≥7*
Arranging blood sampling in response to GI side effects	3.0 (3.0-5.0)	16%	3.0 (3.0-4.0)	8%	3.0 (3.0-4.0)	4%
Withholding treatment in response to bruising	7.0 (5.5-9.0)	56%	7.0 (6.0-9.0)	67%	**7.0 (6.0-9.0)**	70%
Arranging blood sampling in response to bruising	8.0 (7.0-9.0)	79%	8.0 (7.0-9.0)	95%	**8.0 (8.0-9.0)**	96%
Withholding treatment in response to fever	7.0 (5.25-8.75)	63%	7.0 (6.25-8.75)	75%	**7.0 (7.0-9.0)**	78%
Arranging blood sampling in response to infection	6.5 (5.0-8.0)	50%	7.0 (5.25-8.0)	58%	**7.0 (6.0-8.0)**	74%
Seeking professional advice in response to infection	8.0 (7.25-9.0)	92%	8.0 (8.0-9.0)	96%	**8.0 (8.0-9.0)**	100%
Stopping MTX in response to breathlessness	8.0 (4.5-9.0)	71%	8.0 (6.25-9.0)	75%	**8.0 (7.0-9.0)**	78%
Checking blood results	5.0 (4.0-6.75)	25%	5.0 (4.0-6.0)	22%	5.0 (4.0-5.0)	17%
Self-administration of parenteral MTX	7.5 (5.0-9.0)	67%	8.0 (5.5-9.0)	75%	**9.0 (5.0-9.0)**	74%

4.7 Discussion

Criteria for good practice in methotrexate therapy have been identified on particular issues at the end of the fourth round. According to the definitions by the RAND Corporation, the statements are considered as 'valid' when the group's median reached between the score 7 and 9 on a nine-point Likert scale without any disagreement. The statements generated in this Delphi study, which achieved an agreement amongst the rheumatology specialists are indicated in bold characters for their median values in Table 4.11.

Therefore, it has been indicated that methotrexate therapy should be initiated at the dose of 7.5mg/week for the patients with rheumatoid arthritis and the weekly MTX dose should not be given by splitting the dose throughout the day. The participating rheumatology specialists agreed that the dose changes in methotrexate therapy should only be decided by the rheumatologist; however, there was a belief in favour of delegation of this responsibility to a nurse specialist within a protocol.

The study showed that the rheumatology specialists were reluctant about delegation of particular care responsibilities to the primary care health providers (except the GPs) in the management of rheumatoid arthritis with methotrexate treatment. It is believed that the GP should be advised to prescribe methotrexate therapy only with 2.5mg tablet strength regardless of the weekly dose of MTX that the patient needs to take. However, despite the fact that there are reported incidents of confusion with methotrexate tablets in the community, this recommendation did not reach a strong agreement amongst the rheumatology specialists.

There was a strong emphasis on patient monitoring during methotrexate therapy. The participants agreed with most of the criteria that have been suggested in the Delphi questionnaire and further acknowledged a general need for more attention to appropriate monitoring of methotrexate treatment. Interestingly, a haemoglobin level less than 9g/dL appeared to be problematic for the rheumatology specialists; they do not consider this condition necessarily attributable to methotrexate toxicity.

There was a substantial disagreement amongst the participants in regards to the community pharmacists' involvement in the monitoring processes. The community pharmacist's role in the monitoring processes was not emphasised by the participants and received lower scores

throughout the rounds despite the fact that pharmacists are involved in the dispensing processes for methotrexate prescriptions. This lack of consensus might arise due to absence of evidence supporting the pharmacist's contribution, therefore it has major implications for planning and the use of health service resources in future.

Remarkably, the participants are in a broad agreement about the patient self-management strategies, which achieved high scores on the Likert-scale by the participants and highlighted the importance of these strategies in methotrexate treatment. Therefore, the rheumatology specialists believed that the patients are in a position to take control over their disease management in their methotrexate therapy, which supports the emerging concept of patient empowerment in chronic disease management.

Moreover, a degree of consensus that emerged from this Delphi study can also be interpreted by using the definitions from Baumann et al[271] They defined a consensus at different levels. The definitions are summarised in Table 4.12

Table 4.12 Definitions for a degree of consensus

	Definition
Perfect consensus	All respondents agree on an answer
Very good consensus	Median and IQR of respondents are found at one integer or 80% of respondents are within one integer of the median
Good consensus	50% of respondents are within one integer of the median or 80% of the respondents are within two integers of the median
Some consensus	50% of respondents are within two integers of the median or 80% of respondents are within three integers of the median

Adapted from [271]

In the light of those definitions, the recommendations for good practice in methotrexate therapy that have been suggested in this Delphi study can be categorised as summarised in Table 4.13. 'Good consensus' was achieved on six out of 14 (43%) of the 'prescribing and dose increments' items; 7 out of 15 (47%) of the 'monitoring' items and 7 out of 11 (64%) of the 'self-management' items. The 'very good consensus' was achieved on only one item (7%) in the 'prescribing and dose increments' recommendations; 3 (20%) in the 'monitoring' and 3 (27%) in the 'self-management' recommendations.

Table 4.13 Degree of consensus achieved for each recommendation

	Degree of consensus		
	Some	Good	V.good
Prescribing and dose increments			
Initial dose of MTX is 7.5mg/week		✓	
Maximum dose of MTX is no more than 25mg/week		✓	
Weekly MTX is given as single daily dose		✓	
The GP decides on the tablet strength			
The GP prescribes only 2.5mg tablet strength	✓		
The dose is changed by rheumatologist		✓	
The dose may be changed by the GP		✓	
The dose changes is delegated to another HCPs		✓	
The dose changes is delegated to a GP practice nurse			
The dose changes is delegated to a specialist nurse			✓
The dose changes is delegated to a community pharmacist			
The dose changes is delegated to a primary care pharmacist			
The dose changes is delegated to a hospital pharmacist			
The dose changes delegated to patient			
Patient monitoring			
Withheld treatment when AST/ALT level >3x normal			✓
Monitor patient when Alk. Phos. level 1-2x normal		✓	
Withhold treatment when WCC<$4x10^9$/L		✓	
Withhold treatment when neutrophils <$2x10^9$/L			✓
Withhold treatment when platelets <$150x10^9$/L		✓	
Monitor patient when Hb<9g/dL		✓	
Hb<9g/dL is attributable to MTX			
Perform LFTs fortnightly at induction phase		✓	
Perform LFTs every 4 weeks at maintenance phase		✓	
Perform chest X-ray only at baseline			✓
Community pharmacist clarifies patients' expectation of their MTX therapy			
Important to show monitoring card to the community pharmacist			
Verification of the monitoring card for dispensing MTX prescriptions			
More attention for appropriate monitoring		✓	
Routine enquiries by HCPs between clinic visits	✓		
Patient self-management			
Dosage alteration in response to mild unwanted GI effects		✓	
Withholding treatment in response to unwanted GI effects		✓	
Arranging blood sampling in response to GI side effects			
Withholding treatment in response to bruising		✓	
Arranging blood sampling in response to bruising			✓
Withholding treatment in response to fever		✓	
Arranging blood sampling in response to infection			✓
Seeking professional advice in response to infection			✓
Stopping MTX in response to breathlessness		✓	
Checking blood results		✓	
Self-administration of parenteral MTX		✓	

4.8 Justification for the study

The Delphi technique was chosen for this study in order to achieve a consensus on methotrexate prescribing and monitoring and on the patient self-management processes in treatment of rheumatoid arthritis. Although there is no standard framework or algorithm established for how to process the Delphi technique, the researcher intended to apply the suggestions and recommendations made in the textbooks and literature, but some limitations were inevitable in the study.

It has been suggested that questionnaires can be piloted in order to ensure the content, construct and face validity before the Delphi processes start.[248] Because there were only 38 rheumatology specialists identified in Scotland as the 'expert' population, another group of rheumatology specialists could not easily be achieved in order to pilot the questionnaire for this study. However, the questionnaires were designed by the researcher in collaboration with different health care professionals and academic researchers in order to resolve ambiguities and misunderstandings on the statements included. The RAND Corporation's definition was used in order to assess the validity of the statements included in the questionnaire. According to this definition, a 9-point Likert scale is broken down into three tertiles; the statements are scored between 1-3 considered 'invalid', scored between 4-6 is 'equivocal' and scored between 7-9 is 'valid'. Therefore, 19 out of 42 statements (45%) were considered valid in this study, which could help to initiate the design of guidelines on methotrexate treatment.

An analysis of agreement for the consensus development processes has been defined in the literature according to the extent which respondents agree with the issue under consideration (rated on a scale) and the extent which respondents agree with each other (statistical measures of mean and dispersion).[247] It has been suggested that the mean value (central tendency) is an indicator of a group agreement and a low standard deviation value represents strong agreement amongst participants.[256] However, it is indicated that the use of median and interquartile range (IQR) values are more robust where more than eight participants are available and the distribution is not markedly bimodal.[242] Furthermore, giving more attention on what is happening between the rounds allows understanding on whether an agreement has been maintained throughout the rounds and is reached in the final round, which reflects the reliability of the final decision.[256]

The number of rounds that have been used in this Delphi study was comparable with other studies reported in the literature.[248, 254] Since the first round intended to explore the ideas in detail and did not ask respondents to rank their opinion on each statement included in the questionnaire, the researcher aimed to allow respondents to re-consider their opinions during at least two more rounds of the Delphi study. Therefore, the Delphi processes was initiated as three rounds, but was completed after the fourth round.

4.9 Conclusion

The formal consensus method can be used as an acceptable alternative to the evidence-based approach when developing guidelines in situations in which evidence is scarce, and which the guideline is intended as an aid in linking different stages of care.

This Delphi study was a systematic attempt to develop an instrument of general applicability for the management of rheumatoid arthritis with regards to methotrexate therapy. The study indicated that there are variations in opinions of rheumatology specialists in Scotland on the use of methotrexate therapy in patients with rheumatoid arthritis even though established guidelines are available for current health practice. It can be concluded from this Delphi study that the study is highly relevant to informing the content, structure and operationalisation of protocols and/or guidelines associated with the management of rheumatoid arthritis, in particular with methotrexate prescribing and patient self-management processes in the treatment of rheumatoid arthritis.

In conclusion, the recommendations emerged from this consensus building processes are summarised in the Panel 4.1 below.

Panel 4. 1 Recommendations on prescribing and monitoring of methotrexate (MTX) and patient self-management strategies in the treatment of rheumatoid arthritis

Prescribing;

- The MTX therapy should be initiated in a dose of 7.5mg/week
- The weekly MTX dose should be given as a single daily dose
- The MTX dose changes should be decided only by a rheumatologist
- The dose changes can safely be delegated to a rheumatology specialist nurse within a protocol

Monitoring;

- MTX treatment should be withheld until problem resolves, when
  AST/ALT level >3x normal
  WCC < $4x10^9$/L
  Neutrophils < $2x10^9$/L
  Platelets <$150x10^9$/L

- LFTs should be monitored fortnightly at the induction phase (during the dose increments) and every 4 weeks at the maintenance phase (during stable dose) of MTX therapy
- Chest X-ray should only be performed before the MTX therapy, but not thereafter in the absence of chest symptoms

Patient self-management strategies;

- Patients should **withhold the treatment** in response to increased bruising and fever
- Patients should **arrange to go to get their blood sampled for laboratory tests** in response to increased bruising, any infection
- Patients should **seek professional advice** in response to any infection
- Patients should **immediately stop** MTX in response to breathlessness
- Patients should be thought to self-administer their parenteral MTX dose

Chapter 5: An evaluation of methotrexate prescribing patterns in Scotland

5.1 Introduction

The Department of Health indicated in the report of 'NHS Performance Indicators, National Figures: February 2002' that more people with chronic conditions are being looked after in primary care rather than hospitals.[272] The results of the report reflect the fact that chronic disease management should be largely maintained in primary care with the intention of avoidance of potential hospitalizations. Therefore, medicines management, prescribing and dispensing policies within primary care practices might contribute to the goal of reducing hospitalizations.

The Scottish Executive highlighted the importance of appropriate utilisation of medicines in the report of 'A Strategy for Pharmaceutical Care in Scotland' and aimed to develop and achieve standards for electronic prescribing and electronic transfer of prescriptions across NHS Scotland by 2005 in terms of creating new opportunities for improving the quality of patient care.[273]

It has been reported that over 66 million prescriptions were dispensed in Scotland in the year 2002, which approximates 12 prescriptions per person. The number of prescription items dispensed in Scotland by community pharmacies, dispensing doctors and appliance suppliers has increased from 40 million to 66 million items over the past fourteen years with an average annual 3.7% growth. This growth reflects not only the availability of new or more effective medicines, but also increasing patient expectation and demographic changes. The rate of increase in prescription volume has been higher in 2001/02 compared to the previous years. The total prescription items for the 'rheumatic diseases and gout' is estimated at 2.5 million, which is 3.8% of the total prescription items dispensed in Scotland for all BNF categories.

Considering the increased volume of prescriptions, the National Prescribing Centre for England & Wales indicated in the 2001-2002 annual report that they aim 'to facilitate the promotion of high quality, cost-effective prescribing and medicines management through a co-ordinated and prioritised programme of activities aimed at supporting all relevant professionals and senior managers working in the modern NHS'.[274] It is apparent that a provision of local and/or national guidance for prescribing and medicines management for the health care professionals would ensure a standard and effective way for the delivery of medicines to patients.

Therefore, development of local and/or national policies and quality assurance indicators in prescribing process has been an aim of research into health care services.

It has been suggested by Cantrill and her colleagues that 'prescribing indicators potentially might provide a standardised means of measuring both 'quantitative' activity and change within a targeted healthcare area. Information derived from such indicators then has the potential to be presented (or misrepresented) as either a 'performance monitoring' or 'quality assessing' tool'.[275]

Although these indicators allow a very restricted assessment of overall prescribing patterns, they can be used for monitoring of prescribing activity.

It is previously identified that prescribing of methotrexate tablets in the Greater Glasgow Health Board (GGHB) in Scotland has been increased over the years. It has been estimated that just over five hundred scripts were issued for methotrexate in the period of June-August 1998 whereas this figure increased to six hundred and fifty scripts during the period of March-May 1999. During the period of June 1998-May 1999, approximately 8.6% of the total methotrexate prescriptions in Scotland are dispensed in GGHB area (Personal communication from The Prescribing Advisers Department, Glasgow Royal Infirmary, September 1999).

The figures for the proportion of number of prescribed items in GGHB and in Scotland in the year 1998/1999 were also estimated according to the BNF categories (Personal communication with W.Gold at ISD in September 1999). Therefore, it has been shown that the number of prescribed items in GGHB for methotrexate is about 12% of the prescribed items in Scotland; 10% of the items for auranofin; 30% of the items for hydroxychloroquine; 19% of the items for penicillamine and 25% of the items for the sodium aurothiomalate. An overall figure for the prescribed items in GGHB for the BNF Section 10.1.3 for the "drugs which suppress the rheumatic disease process" is about 25% of the prescribed items for the same section in Scotland.

Following the brief information regarding the figures for prescribing and dispensing of medicines in Scotland, this chapter focuses on the current prescribing and dispensing activities in methotrexate treatment in particular, within a specific time scale and gives descriptive data for the patterns and quality of methotrexate prescribing.

5.2 Aim of the study

To evaluate the patterns of methotrexate prescribing and dispensing in the Local Health Care Co-operative (LHCC) environments in Scotland.

5.3 Objectives

- To identify the trend of methotrexate use in the last decade in Scotland
- To propose criteria for good prescribing and dispensing practice policy for methotrexate use
- To assess the quality of methotrexate prescribing according to pre-defined criteria
- To characterise examples of deviations from good prescribing and dispensing practice

5.4 The study design and data collection process

The data on methotrexate prescriptions were gathered from the Information & Statistics Division (ISD) Scotland after an agreement on the confidentiality issues. The annual data were collected for the years between 1991-2001 for both 2.5mg and 10mg tablet strengths of methotrexate prescriptions issued in Scotland.

The sample size calculation was undertaken on the basis of previous reports from the ISD and the Prescribing Advisers Department in Greater Glasgow Health Board for methotrexate prescriptions in Scotland. It is suggested that in a descriptive survey, the size of the sample is determined by a defined 'margin of error' and a specified 'degree of confidence'.[276]

$$\text{Absolute margin of error (e\%)} = \frac{\sqrt{Z^2 p(1-p)/n}}{0.01}$$

z: 1.96 for 95% confidence

p: proportion in the sample expressed as fraction

n: sample size

According to the equation is indicated above, the following assumptions on the sample size have been made;

	e (95% Confidence Interval) number of prescription=200
10%	4.2 (5.8%, 14.2%)
25%	6.0 (19.0%, 31.0%)
50%	6.9 (43.1%, 56.9%)

It has been identified that approximately 4000 methotrexate prescriptions are issued per month in Scotland, which approximates 4000 patients assuming a one month prescription interval. Therefore, the sampling process available through ISD provided the opportunity to extract the prescription sample from the sources of the prescriptions, that is the pharmacies (approximately 1150 in Scotland). Since using this approach meant that no pharmacy provided more than one prescription sample, a 5% prescription sample (n=200) of 2.5mg tablet strength would be derived from a 17.4% sample of pharmacies in Scotland.

The search on the ISD database was physically undertaken by the staff (Lorna Ramage) at the ISD unit, because of the confidentiality issues. Random sampling of overall 10-20% of Scottish monthly methotrexate prescriptions was conducted by prescriptions sorted by health board and then the prescriptions were chosen according to the tablets strength of methotrexate prescriptions in order to obtain an equal number of prescriptions with 2.5mg and 10mg tablet strength of methotrexate respectively.

The copies of actual methotrexate prescriptions were anonymised for the patient's name, address and postcodes. The prescriptions were then sent to the researcher for further analysis. The prescribers' and the pharmacies' identities were not recorded. All the prescription data were entered anonymously in the computer by the researcher.

5.5 Results and analysis

5.5.1 Prescribing patterns of Methotrexate between 1991-2001

The data on prescribing of methotrexate tablets were gathered for 2.5mg and 10mg tablet strengths individually for available brands from different manufacturers. The results are summarised in Table 5.1 and Table 5.2.

Table 5.1 Total prescribing of 2.5mg tablet strength in Scotland between 1991-2001

Year	Number of prescription items	Quantity dispensed	Cost (£)
1991	3,377	111,380	12,080.02
1992	4,450	142,691	15,485.12
1993	5,600	177,585	19,188.82
1994	7,450	222,523	23,558.75
1995	10,255	302,016	31,864.54
1996	13,028	397,713	44,783.67
1997	16,247	481,216	50,453.05
1998	20,501	617,333	64,742.48
1999	25,862	789,188	94,396.76
2000	30,680	953,334	114,205.50
2001	36,847	1,150,706	128,491.80

Table 5.2 Total prescribing of 10mg tablet strength in Scotland between 1991-2001

Year	Number of prescription items	Quantity dispensed	Cost (£)
1991	130	3,487	1,691.24
1992	244	6,606	3,203.99
1993	386	8,088	3,907.09
1994	510	6,317	2,987.16
1995	689	9,397	4,426.16
1996	1,068	13,747	6,538.76
1997	1,530	18,516	8,828.61
1998	2,087	26,357	12,558.01
1999	3,134	39,653	18,902.88
2000	4,581	57,448	27,044.02
2001	6,613	83,979	39,752.42

Figure 5.1 The distribution of prescription items between 1991-2001

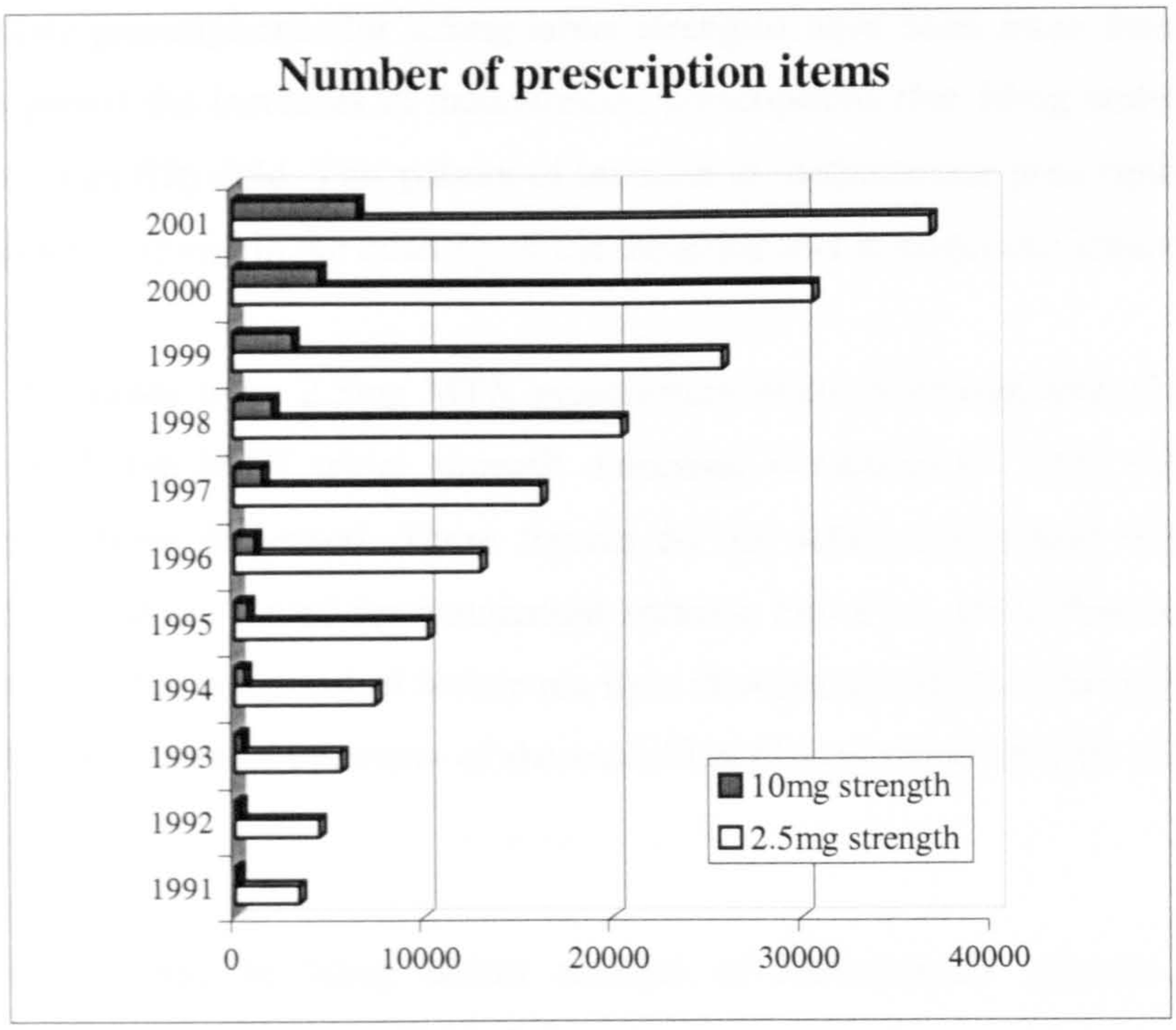
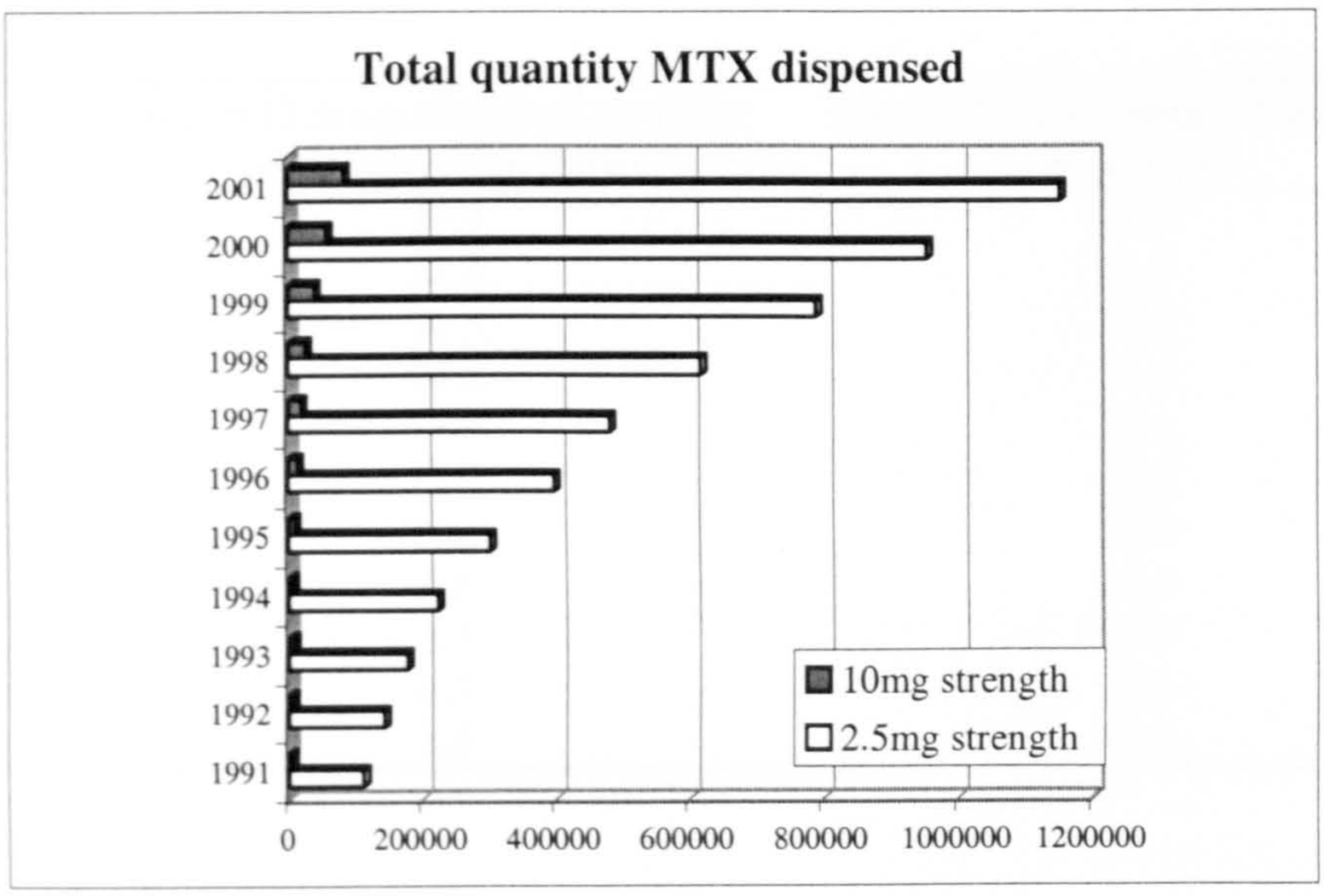


Figure 5.2 The distribution of quantities dispensed between 1991-2001



As it can be seen from Figure 5.1 and Figure 5.2 above, methotrexate prescription volume has been increasing remarkably over the last decade. From 1991 to 2001 the increases in methotrexate prescriptions (for 2.5mg tablet strength) have been more than ten-fold. Over the same period the increases in methotrexate prescriptions (for 10mg tablet strength) have been more than fifty-fold. This pattern of increase in methotrexate prescriptions has led to a more than ten-fold rise in the quantity of the medicine that is dispensed annually.

In 2001, 5.6 times more 2.5mg MTX prescription items dispensed and 13.7 times greater quantity of 2.5mg MTX tablet strength dispensed compared to 10mg tablet strength of methotrexate were dispensed. These figures do not solely correspond with methotrexate prescriptions that are issued for rheumatoid arthritis. However, given that oral methotrexate is only used for the treatment of leukaemia for a short period of time, these figures represent essentially the pattern of treatment of rheumatoid and/or psoriatic arthritis with methotrexate therapy.

The ratio of 2.5mg to 10mg tablets strength of methotrexate quantity dispensed and prescription items are shown in Table 5.3.

Table 5.3 Ratio of dispensed forms of methotrexate tablet strengths (2.5mg and 10mg) over the last decade in Scotland

Year	Ratio (2.5mg:10mg) of number of prescription items	Ratio (2.5mg:10mg) of quantity dispensed
1991	25.9	31.9
1992	18.2	21.6
1993	14.5	21.9
1994	14.6	35.2
1995	14.9	32.1
1996	12.2	28.9
1997	10.6	25.9
1998	9.8	23.4
1999	8.3	19.9
2000	6.7	16.6
2001	5.6	13.7

5.5.2 Quality of Methotrexate prescribing and dispensing

The criteria for quality assessment on good prescribing and dispensing of oral methotrexate for RA are proposed as follows, following group discussion with a clinical pharmacist and an academic researcher.

For methotrexate items prescribed;

1. The dose of methotrexate is not written 'as directed'
2. The dose of methotrexate is clearly indicated as 'weekly'
3. The dose of methotrexate is clearly indicated as 'weekly' when only one tablet is intended to be taken (or prescribed)
4. An instruction exists for tablets to be taken on the same day when two or more tablets are intended to be taken (or prescribed)
5. An instruction exists for tablets to be taken on the same day when two different tablet strengths are prescribed
6. No bad handwriting/misleading/confusing statement exists on the prescription about MTX
7. The tablet strengths are indicated for methotrexate
8. The amount of methotrexate tablets to be dispensed is indicated
9. No more than 3 months supply is requested for methotrexate tablets
10. No combination of two different tablet strengths is used for doses of ≥15mg/week methotrexate

For folic acid items prescribed;

11. The dose of folic acid is not written 'as directed'
12. The directions for folic acid tablets to be taken according to the MTX dose is indicated
13. No bad hand writing/misleading/confusing statement exist for folic acid dosing
14. The tablet strength is indicated for folic acid
15. The amount of folic acid tablets to be dispensed is indicated

Four hundred chosen methotrexate prescriptions that were issued in Scotland during the period of February 2001 and March 2002 were exposed to quality assessment analysis according to the criteria outlined above. After revisions of the prescriptions, the researcher identified that some of the prescriptions had been duplicated by photocopying in error, therefore the duplicates were excluded from the suggested analysis. Therefore, the analysis was undertaken on a total of 372 methotrexate prescriptions.

Among the chosen methotrexate prescriptions, 300 out of 360 (83.3%) were issued in February 2002 and 46 (13%) were in January 2002. One hundred and seventy six (47.3%)

prescriptions prescribed only the 2.5mg tablet strength, 123 (33.1%) the 10mg and 72 (19.4%) a combination tablet strengths of methotrexate. Only one (0.03%) prescription did not include any information regarding the tablet strength for the prescribed dose of methotrexate, therefore it was included in assessment of the total prescriptions, however disregarded in Table 5.5-Table 5.7.

The dose of methotrexate was indicated in 296 (80%) out of 372 prescriptions and the mean (SD; Median) weekly dose of methotrexate was 14.6 (16.7; 12.5) mg overall in the prescriptions. The dose of methotrexate is indicated according to the use of different tablet strengths of methotrexate in the prescriptions as follows; the mean (SD; Median) weekly dose of methotrexate was 11.6 (8.0; 10.0) mg, 16.6 (21.2; 10.0) mg and 18.9 (22.2; 15.0) mg in the prescriptions, which include only 2.5mg, only 10mg and the combination of the two tablet strengths, respectively. The information regarding the dose of weekly methotrexate is summarised in Table 5.4.

Table 5.4 The patterns of the prescribed methotrexate doses (n=296 prescriptions)

Dose of 'weekly' methotrexate prescribed, mg	Dose prescribed as in only one tablet strength (2.5mg)	Dose prescribed as in only one tablet strength (10mg)	Dose prescribed as in a combination of two tablet strengths
2.5	9	-	-
5.0	15	-	-
7.5	38	-	-
10.0	18	64	-
12.5	13	-	15
15.0*	28	2	21
17.5	7	-	10
20.0	8	27	1
22.5	1	-	1
25.0	1	-	3
30.0	-	5	-
>30.0	3	3	2
Total	141	101	53

**the tablet strength was not specified in one prescription for methotrexate at the dose of 15mg/week*

Two hundred and forty eight prescriptions included 2.5mg tablet strengths of methotrexate and the mean (SD; Median) quantity prescribed was 32.9 (35.8; 20) tablets while one hundred and ninety five prescriptions included 10mg tablet strength of methotrexate and the mean (SD; Median) quantity prescribed was 13.3 (13.2; 10) tablets. The total ratio of 2.5mg:10mg tablet strength of quantity dispensed for prescribed methotrexate was 3.1:1.

In terms of duration of supplies for the two tablet strengths of methotrexate, one hundred and ninety four prescriptions provided information for 2.5mg and the mean (SD; Median) duration of supply was 7.9 (6.4; 6) weeks while one hundred and fifty four prescriptions provided information for 10mg and the mean (SD; Median) duration of supply was 9.1 (7.0; 8) weeks.

Ninety-three (25%) out of 372 prescriptions included folic acid tablets items in the scripts, of those eighty-two (88%) indicated the dose for folic acid. The mean (SD; Median) weekly dose of folic acid was 12.7 (12.3; 5) mg. Ninety-two prescriptions indicated the amount of folic acid tablets to be dispensed where the mean (SD; Median) number of tablets was 23.6 (20.9; 18). The following paragraphs indicated the prescribing of folic acid according to the use of different tablet strengths of methotrexate in the prescriptions.

In the prescriptions only including 2.5mg tablet strength: The mean (SD; Median) dose of folic acid was 13.8 (13.1; 5.0) mg/week and the mean amount of tablets to be dispensed was 22.1 (20.0; 13.5).

In the prescriptions only including 10mg tablet strength: The mean (SD; Median) dose of folic acid was 9.6 (9.6; 5.0) mg/week and the mean amount of tablets to be dispensed was 21.3 (17.9; 12.0).

In the prescriptions including combination of 2.5mg and 10mg tablet strengths: The mean (SD; Median) dose of folic acid was 14.4 (12.9; 5.0) mg/week and the mean amount of tablets to be dispensed was 29.8 (21.6; 28).

Forty-four prescriptions (12%) indicated co-prescribing of non-steroidal anti-inflammatory drugs (NSAIDs) on the scripts. There was one prescription with Acemetacin, nine with Diclofenac, one with Etodolac, three with Flurbiprofen, four with Ibuprofen, eleven with Indomethacin, one with Ketoprofen, four with Nabumetone, eight with Naproxen (one is co-prescribed with indomethacin), two with Piroxicam and one with Sulindac. Furthermore,

selective COX-2 inhibitors were also prescribed; 11 prescriptions included Celecoxib (one is co-prescribed with an NSAID, two with paracetamol, one with dihydrocodeine), 13 included Rofexocib and 3 included Meloxicam on the same prescription as methotrexate.

The analysis on the quality assessment of methotrexate prescriptions was performed according to the criteria, which were proposed for the study and the results are summarised from Table 5.5 to Table 5.7.

Table 5.5 Quality assessment of prescriptions including only 2.5mg tablet strength (n=176)

Quality criterion (n)*	number (%) of prescriptions meeting the criterion
For MTX items	
Dose is not written 'as directed'(n=176)	150 (85.2)
Dose is clearly indicated as 'weekly' (n=176)	5 (2.8)
intended weekly dose should be indicated when one tablet is intended to be taken (n=14)	10 (71.4)
instruction exists for tablets to be taken on the same day when ≥2 tablets are intended to be taken (n=144)	52 (36.1)
no bad handwriting/misleading/confusing statement exist (n=176)	159 (90.3)
Tablet strengths are indicated (n=176)	175 (99.4)
Amount of tablets to be dispensed is indicated (n=176)	174 (98.9)
no more than 3 months supply is requested (n=148)	132 (89.2)
Folic acid items (n=57)	
Dose is not written 'as directed'	55 (96.5)
instruction exists for tablets to be taken according to the MTX dose	37 (64.9)
no bad handwriting/misleading/confusing statement exist	55 (96.5)
Tablet strength is indicated	56 (98.2)
amount of tablets to be dispensed is indicated	56 (98.2)

* *numbers in brackets indicate the potential number of eligible prescriptions for the assessment on each criterion)*

Table 5.6 Quality assessment of prescriptions including only 10mg tablet strength (n=123)

Quality criterion (n)*	Number (%) of prescriptions meeting the criterion
For MTX items	
Dose is not written 'as directed'(n=123)	105 (85.4)
Dose is clearly indicated as 'weekly' (n=123)	3 (2.4)
intended weekly dose should be indicated when one tablet is intended to be taken (n=79)	64 (81.0)
instruction exists for tablets to be taken on the same day when ≥2 tablets are intended to be taken (n=40)	10 (25.0)
no bad handwriting/misleading/confusing statement exist (n=112)	112 (100)
Tablet strengths are indicated (n=123)	123 (100)
Amount of tablets to be dispensed is indicated (n=123)	123 (100)
no more than 3 months supply is requested (n=111)	95 (85.6)
Folic acid items (n=26)	
Dose is not written 'as directed'	24 (92.3)
instruction exists for tablets to be taken according to the MTX dose	10 (38.5)
no bad handwriting/misleading/confusing statement exist	21 (80.8)
Tablet strength is indicated	26 (100)
amount of tablets to be dispensed is indicated	26 (100)

** numbers in brackets indicate the potential number of eligible prescriptions for the assessment on each criterion)*

Table 5.7 Quality assessment of prescriptions including a combination of tablet strengths (n=72)

Quality criterion (n)*	number (%) of prescriptions meeting the criterion
For MTX items	
Dose is not written 'as directed'(n=72)	57 (79.2)
Dose is clearly indicated as 'weekly' (n=72)	2 (2.8)
intended weekly dose should be indicated when one tablet is intended to be taken (n=58)	47 (81.0)
instruction exists for tablets to be taken on the same day when ≥2 tablets are intended to be taken (n=47)	15 (31.9)
instruction exists for tablets to be taken on the same day when 2 tablet strengths are prescribed (n=70)	12 (17.1)
no bad handwriting/misleading/confusing statement exist (n=72)	67 (93.1)
Tablet strengths are indicated (n=72)	72 (100)
amount of tablets to be dispensed is indicated (n=72)	70 (97.2)
no more than 3 months supply is requested (n=61)	53 (86.9)
Folic acid items (n=9)	
Dose is not written 'as directed'	9 (100)
instruction exists for tablets to be taken according to the MTX dose	6 (66.7)
no bad handwriting/misleading/confusing statement exist	7 (77.8)
Tablet strength is indicated	9 (100)
amount of tablets to be dispensed is indicated	9 (100)

** numbers in brackets indicate the potential number of eligible prescriptions for the assessment on each criterion)*

Approximately 80-85% of the prescriptions met the criteria suggested for methotrexate dose not being indicated 'as directed', where any prescribing and/or dispensing error could be prevented by this action. However, 97% of the prescriptions did not clearly indicate methotrexate dose regimen as 'weekly' on the scripts, which might have been helpful for other health care providers who are involved in the treatment of the patients and unfamiliar with the weekly dosage of certain medications.

In the event that 'only one' methotrexate tablet is intended to be taken by patient for the treatment -such as one 10mg tablet strength for 10mg/week dose of methotrexate- 151 (41%) out of 372 prescriptions were able to be interpreted in terms of the criterion for the existence of a clear indication for a 'weekly' MTX dose regimen. Of those, 71-81% prescriptions did include the instruction for methotrexate to be taken as a 'weekly' regimen where the tablet should not be taken every day.

Two hundred and thirty-one (62%) out of 372 prescriptions showed that ≥2 tablets are intended to be taken by the patient for the prescribed dose of methotrexate (such as 3x2.5mg tablet strength for the dose of 7.5mg/week methotrexate). An instruction for those tablets to be taken on the same day existed in 25-36% of the prescriptions.

Seventy two (19%) out of 372 prescriptions verified that two different tablets strength are prescribed for an intended weekly methotrexate dose (such as 2x2.5mg and 1x10mg for 15mg/week MTX dose regimen). An indication for those tablets to be taken on the same day existed in 12 (17.1%) prescriptions, however it did not exist in 58 (83%) prescriptions. There was an additional 2 (3%) prescriptions where the conditions cannot be judged because of unknown methotrexate dose.

Methotrexate was prescribed at the dose of ≥15mg/week in 124 (33%) out of 372 prescriptions. Among those prescriptions, the tablet strength of prescribed methotrexate dose is unknown in one prescription, therefore these scripts could not be assessed in regard to use of combination tablet strengths. The combination of two different tablet strengths for the dose of ≥15mg/week methotrexate has been used in 38 (31%) prescriptions where the possibility of the patients taking a wrong amount of tablets from the unintended tablet strength exists which may lead to a high dose of methotrexate therapy.

The tablet strengths for prescribed methotrexate dose and the amount of tablets to be dispensed were indicated in 371 (99.7%) out of 372 prescriptions. In terms of the supply of methotrexate tablets, the proposed criteria suggested that the duration of the supply should not exceed 3 months, which would ensure patients having contacts with community pharmacists between clinic visits. A supply of methotrexate tablets lasting more than 3 months existed in 11-14% prescriptions.

Two hundred and seventy nine (75%) out of 372 prescriptions do not include folic acid items on the methotrexate prescriptions. Among the 92 prescriptions, which indicated the folic acid prescribing pattern, the dose of folic acid is not written "as directed" in over 90% of the prescriptions. Given the fact that folic acid tablets should be taken 3-4 days after the methotrexate dose is taken, guidance for folic acid tablets to be taken according to the MTX dose is indicated in 39-67% of the prescriptions. The tablet strength and the amount of tablets to be dispensed for folic acid items were indicated in almost all prescriptions.

Bad handwriting and/or misleading statements existed in 7-10% of the prescriptions for MTX items and in 4-22% of the prescriptions for folic acid items.

No statistically significant difference was found between the prescriptions including only 2.5mg and only 10mg tablet strengths of methotrexate in terms of quality assessment criteria for methotrexate items (Chi-square test, $p>0.05$). Among the methotrexate prescriptions which also included folic acid items in the scripts, the quality assessment revealed that the instruction for folic acid tablets to be taken according to the methotrexate dose is more likely to exist in the prescriptions including only the 2.5mg tablet strength of methotrexate compared to the prescriptions including only the 10mg tablet strength (Chi-square test, $p<0.05$). Moreover, the prescriptions including only the 2.5mg tablet strength were less likely to have bad handwriting/misleading/confusing statements for folic acid items compared to the prescriptions including only the 10mg tablet strength of methotrexate (Chi-square test, $p<0.05$).

5.6 Discussion and conclusion

Prescribing and dispensing criteria for methotrexate therapy have not been explicitly established in the treatment of rheumatoid arthritis despite the fact that the drug has been increasingly used since the 1990s. Increased responsibility of secondary care health care professionals for the disease management and patient monitoring processes demands effective collaboration from the primary care health providers. Even though the rheumatology specialists have different preferences for the monitoring requirements of methotrexate therapy, they tend to rely on the decisions made by primary care health care providers on the effective and safe prescribing and dispensing of the drug. Lack of evidence-based guidelines on the process of prescribing and dispensing of methotrexate and availability of two different tablet strengths of this potentially toxic drug generates problems and may lead to difficulties in co-ordination among the health care providers in the care of the patients with rheumatoid arthritis.

Although, the overall study sample was not representative of the relative frequency of prescription of 2.5mg and 10mg tablet strength the national figures in Scotland, the study provided valuable information regarding prescribing and dispensing of the two tablet strengths of methotrexate in practice.

The mean (median) durations of dispensed quantity of methotrexate tablets (for 2.5mg and 10mg) were 8-9 (6-8) weeks. These data revealed a large minority (approximately 25%) of patients receiving prescriptions less frequently than every 12 weeks. The findings provide evidence that the patients often are having to undertake blood tests in between receiving their methotrexate prescriptions. This is a missed opportunity for the community pharmacists to be actively involved in verifying a) that the patient's blood has been sampled according to the guidelines and b) that blood tests values are consistent with continuation of treatment at the prescribed dose. It would be a simple change to synchronise the issue of the prescription from the doctor with a taking of a blood sample. If the dispensing pharmacist expects that synchronisation he/she can usefully make a verbal verification with the patient that laboratory monitoring follows agreed local guidelines.

Almost all prescriptions did not clearly indicate the methotrexate dose regimen as 'weekly' (even though prescriptions might indicate the day of the week the tablet should be taken). A clearly stated weekly regimen is preferred in order to guide patients and other health care providers who are not familiar with this treatment regimen. Furthermore, 15-21% of prescriptions instructed the patient to take the dose of methotrexate 'as directed' in this study. The ambiguities were especially worrying given the scenario of medication errors occurring not only because of patients' misinterpretation but also because of ambiguity to other health care providers.

Another reason for occurrence of medication errors due to inappropriate/improper prescribing and dispensing of methotrexate is the use of two different tablet strengths (which at the time of writing were visually similar dose forms), particularly for the dose of ≥15mg/week. It has been shown in this study that approximately 10% of the prescriptions included a combination of two different tablet strengths for the methotrexate doses prescribed ≥15mg/week. However, recommendation for these tablets to be taken on the same day was not indicated in 83% of the prescriptions, which might lead patients to take the tablets on different days throughout the week, unless the patients are familiar with the dosage regimen.

Recently, the manufacturers of methotrexate tablets have changed the appearance of the tablets for the 2.5mg and 10mg tablet strengths. They are no longer similar in terms of the tablet shape, which would help patients to differentiate the tablet strengths for an intended methotrexate dose.

Nevertheless, it is difficult to draw a conclusion on the overall quality of prescribing of methotrexate by only looking at the results of this study. The information regarding the duration of methotrexate therapy, the patient's diagnosis, the type of prescription (repeat or once off) and the level of patients' and pharmacists' involvement in the dispensing process were not further considered because of the unavailability of this information, although such considerations might affect the assessment of the quality of the process of prescribing and dispensing of methotrexate treatment.

Furthermore, the criteria suggested for the study were not previously validated and they were different in concept from the other indicators of quality that have been used in different studies. Since no such indicators had previously suggested for the assessment of methotrexate prescribing, the researcher attempted to generate the criteria in order to give structured descriptive data on the patterns of methotrexate prescribing and dispensing processes in Scotland. Given the fact that the criteria were generated in collaboration with another research pharmacist who had previous experience in the hospital setting, it is believed that the criteria were not solely an academic researcher's attempts but also reflect the actual circumstances in prescribing processes. The process of generating quality criteria could have been performed in a more structured way, such as using the nominal group or the Delphi technique[265, 266] but the availability of time and resources did not allow such study for only this purpose. However, the results of the Delphi study on the 'methotrexate prescribing, monitoring and patient self-management processes in treatment of rheumatoid arthritis' (see chapter 4) guided the development of quality criteria for this study. Considering that the Delphi was undertaken amongst the rheumatology specialist, it would have been valuable to consider general practitioners' and pharmacists' views on the prescribing and dispensing of methotrexate which would have helped to generate quality criteria.

It would have been interesting to explore the variations in prescribing and dispensing processes of methotrexate in different socio-economic environments, which might have developed the arguments made in the previous chapters regarding different patients' needs that may be associated with socio-economic deprivation. However, such information was not available for the analysis.

The implementation of computer-generated prescription systems in general medical practices has the potential to detect and prevent medication errors, but is insufficiently reliable in the absence of practitioners' awareness.[216] The patient care information system should be available whenever users need it to manage patient care and wherever decisions about care

are made.[277] Knowing the fact that the electronic transfer of prescriptions is on the agenda of the Scottish Executive in order to be completed in 2005, particular attention should be drawn to the issues around the safe and effective prescribing and dispensing.

It can be concluded that there is a need for a standard policy on the good prescribing and dispensing of methotrexate in order to provide safe and effective health care services for patients. In addition, the health care systems should also support the health care professionals through widespread provision and application of information technologies.

Chapter 6: Design and evaluation of a standard pharmacist monitoring programme for methotrexate users in the arthritic population -a study at the primary and the secondary care interface-

6.1 Introduction

In the light of previously reported medication errors with oral methotrexate (MTX) treatment (see section 1.9.1), it has been recently recognised that there is a need for more attention by health care providers on potential problems with methotrexate therapy in the hospital and in the community settings among the arthritic population.

Although a weekly dosage regimen of methotrexate therapy in the treatment of rheumatoid arthritis is well established, there are still unknown factors about the treatment process, mainly in the community settings. The availability of two different tablets strengths (2.5mg and 10mg) of methotrexate, use of a 'weekly' dosage regimen and unfamiliarity of primary care health providers about the overall treatment processes might contribute explanations about why problems occur in the current health care provision with this drug.

The management of rheumatoid arthritis with oral methotrexate therapy in the UK is currently undertaken by a shared care arrangement between rheumatology specialists in the hospital settings and general practitioners in the community settings. The involvement of the nursing profession within the processes is maintained through provision of education and counselling for patients and follow-up for blood monitoring in the hospital (by a nurse specialist) and in the community (by a practice nurse based in the surgery). Pharmacists are engaged with medication review activities in those patients who are admitted to the hospital and also in the dispensing of methotrexate prescriptions in the community settings. However, the role of community pharmacists in the management of rheumatoid arthritis with methotrexate therapy has not been fully defined or exploited within the health care system. The study undertaken by Osterhaus et al[278] has indicated that assessment of patient's health outcomes can also be undertaken in community pharmacy settings.

This chapter focuses on an intervention study, which was designed to approach the management of rheumatoid arthritis from a pharmacist's point of view through the establishment of a shared system among health care providers in primary and secondary care settings in order to maintain the continuity of care.

6.2 Aim of the study

To implement and evaluate patient monitoring processes within community settings in order to ensure continuity of care by involving community pharmacists with patients diagnosed with arthritic conditions who receive oral methotrexate therapy.

6.3 Objectives

6.3.1. To characterise four Local Health Care Co-operative (LHCC) populations of those served by two rheumatology clinics (Southern General Hospital and Gartnavel General Hospital) in Glasgow.

6.3.2. To design a standard monitoring plan for the patients who receive oral methotrexate therapy and test it in the four LHCC environments. In order to follow this process, the following objectives were defined;

- to revise the shared care protocol for the use of methotrexate
- to revise the patient-held monitoring card for methotrexate therapy
- to design a rheumatology care plan for the monitoring of methotrexate therapy

6.3.3. To prepare education and training sessions for the pharmacists and evaluate the effect of community pharmacist involvement in patient monitoring processes on the patient's perceptions related to their self-monitoring of methotrexate therapy.

6.3.4. To investigate any influence of socio-economic environment on the disease management and self-monitoring processes.

6.3.5. To identify methotrexate prescribing and dispensing patterns in the patient population.

6.4 The study design

The study was a short-term randomised controlled trial to evaluate the effect of self-monitoring support to patients on MTX provided via their community pharmacists.

The main outcome measures were patients' attitudes towards their medication and the patient's desire for information for their methotrexate treatment.

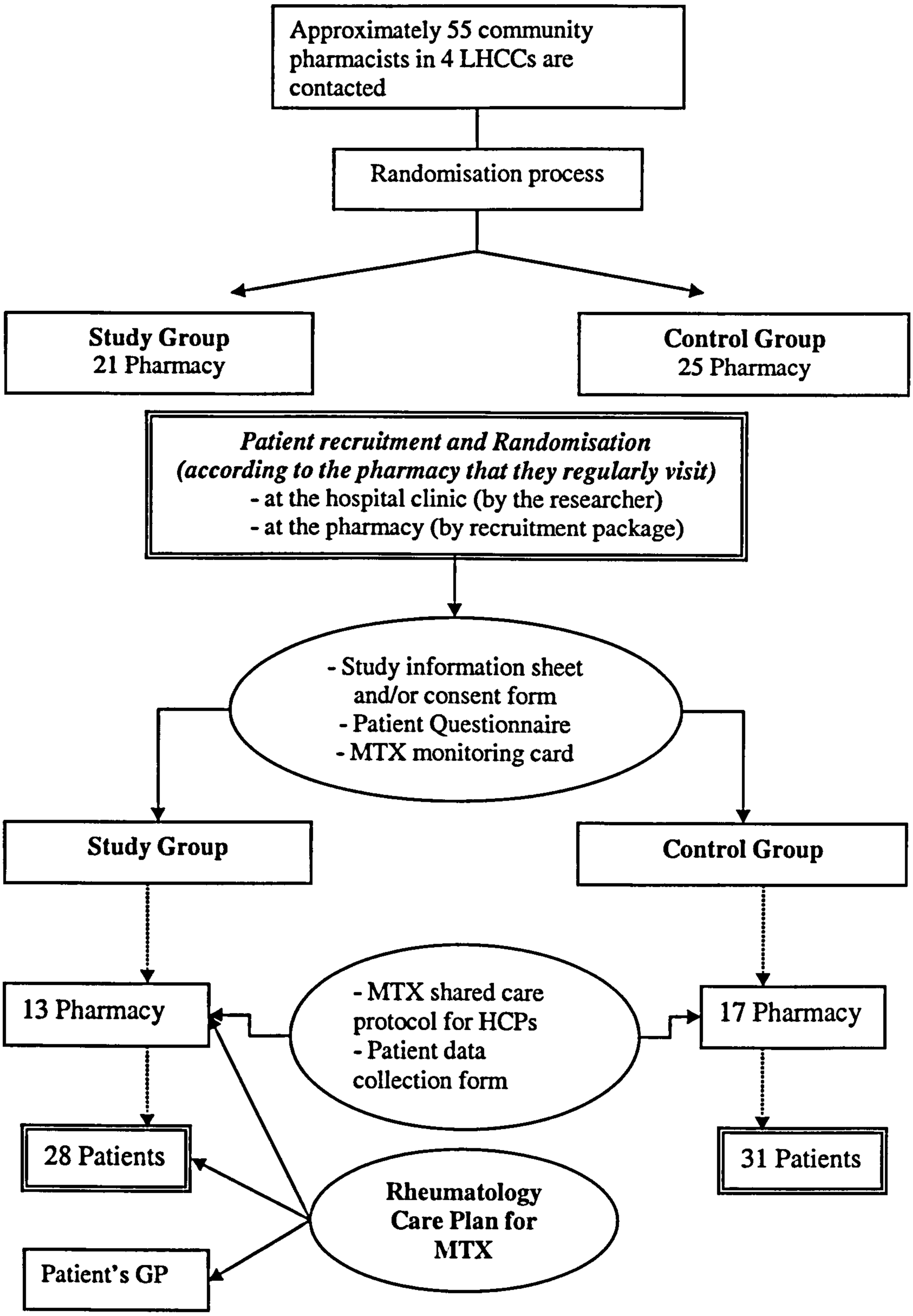
The unit of randomisation was the community pharmacists nominated by the patients who agreed to enter the study. Sampling was stratified to ensure similar numbers of community pharmacies in postcode sectors identified as 'deprived' compared with sectors identified as 'non-deprived'.

Community pharmacists in participating LHCCs were randomly assigned to the study group. The study group pharmacies were intended to receive an MTX care plan issued by the rheumatology specialist which is designed to enable the pharmacist to support the general practitioner (GP) in the patient monitoring role. The first phase of the study (Months 1-6) aimed to compare outcome assessments in the patients served by the study group against those served by the control group. The second phase of the study (Months 7-12), aimed to allow the duration of the care plan evaluation to be extended to 12 months and would widen the experience to all participating pharmacists in the LHCCs (see Table 6.1). The randomisation and recruitment processes are summarised in Figure 6.1.

Table 6.1 Design of the study

	Phase 1 ***(1-6 months)***	***Phase 2*** ***(7-12 months)***
Group A	Study	Study
Group B	Control	Study
Baseline assessment	*Assessment after 6 months*	*Assessment after 12 months*

Figure 6.1 The randomization and recruitment processes during the study



6.4.1 Estimation of sample size for the patient population

A sample size calculation was based on the questionnaire results that have been previously reported by the original authors of two previously validated questionnaire instruments for discriminating differences in patients' attitudes to their medicines.[279-281] A total sample size of 88-112 was calculated as the total number of patients required, demonstrating, with 80% power, the following changes in the outcome measures;

- *Intrinsic Desire for Information (IDI)*: 50% of patients recording ≤30 on the IDI scale (anticipated in the pre test) reducing to 25% (at the post test). (n=112)

- *Beliefs About Medicines - NECESSITY*: 34% of patients recording ≤18 on the specific 'NECESSITY' scale (anticipated in the pre test) reducing to 10% (at the post test). (n=88)

- *Beliefs About Medicines - CONCERNS*: 33% of patients recording >16 on the specific 'CONCERNS' scale (anticipated in the pre test) reducing to 10% (at the post test). (n=94)

6.4.2 Study Settings

The identified four LHCC environments were chosen because their populations were served by the two hospital rheumatology clinics involved in the study. The LHCCs were Anniesland/Bearsden/Milngavie LHCC, Eastwood LHCC, Drumchapel LHCC and South West Glasgow LHCC. These LHCC environments were characterised in terms of Carstairs deprivation category based on postcodes, practice population, number of GPs and community pharmacies located within their boundaries. Approximately 55 community pharmacists were identified in the four LHCC environments as shown in Table 6.2. Their ranges indicate some uncertainty about some pharmacies situated on LHCC boundaries.

Table 6.2 Characteristics of the identified Local Health Care Co-operative (LHCC) environments*

Carstairs category†	LHCC	Practice population	Number of GPs	Number of GP surgery	Number of pharmacies
Non-deprived	Anniesland/ Bearsden/Milngavie	50,321	36-39	8	14
	Eastwood	59,185	29-39	11	12-15
	Total	**109,506**	**53-67**	**22-27**	**19-23**
Deprived	Southwest Glasgow	99,719	72	21	25
	Drumchapel	20,728	14-16	6	5
	Total	**120,447**	**86-91**	**16-19**	**27-30**

** Numbers in the table were approximation which were based on different sources, therefore do not add up the totals*

† Carstairs category 1,2 and 3 indicates the 'non-deprived' population; 4,5,6 and 7 indicates the 'deprived' population

Recruitment process for the community pharmacists

The community pharmacies were identified from the Greater Glasgow Health Board (GGHB) list. The pharmacies were considered eligible if they were located in any of the identified four LHCC environments and were nominated by a patient who agreed to take part in the study. The pharmacists were initially contacted by telephone and were asked an appropriate time for them to be visited by the researcher in order to explain the project in detail. Thereafter, the researcher along with one of the collaborators arranged a visit to the pharmacy to discuss the study with the pharmacist in charge and to seek consent of the pharmacists for agreeing to participate in the study. They were even informed that they might not necessarily be required to participate in the study unless they were nominated by at least one recruited patient from the outpatient clinics. They were given information about the study, were shown a copy of a new 'methotrexate monitoring card', the 'shared care monitoring protocol', the 'rheumatology care plan' and the 'patient data collection form' and asked to co-operate in confirming the patients under their care from their patient medication records. They were asked to provide information about themselves and their dispensed MTX prescriptions, and these data were collected and manipulated in an anonymised form. The community pharmacists who agreed to participate in the study were asked to complete the form with their personal details and to sign a written agreement to participate and enter into the randomisation (Appendix 6.1 and Appendix 6.2). They were also invited to ask any questions about the study. All pharmacists were informed that in the event of them being randomised into the initial control group that they would receive all the potential benefits of

being in the study group in the second phase of the study. In this way no pharmacist would have cause to feel disadvantaged.

The recruitment process for the patients

The patients were recruited both in the community pharmacies and in the hospital outpatient clinics in the Southern General Hospital and Gartnavel General Hospital during the period of December 2001-May 2002.

Inclusion criteria: The patients were considered eligible if they met the following criteria:

- aged over 16 years
- able to read and understand the English language
- diagnosed with rheumatoid arthritis or psoriatic arthritis
- currently receiving oral methotrexate therapy
- residing in the identified LHCC environments

Exclusion criteria: The patients were excluded if they:

- nominate a community pharmacy that has not been agreed to participate
- do not reside in the designated LHCC environments
- have juvenile chronic arthritis, osteoarthritis or arthritic conditions other than rheumatoid arthritis or psoriatic arthritis
- are pregnant or part of a couple planning a pregnancy
- have learning difficulties, mental illnesses or life threatening disorders
- are identified by the rheumatologist as a patient who is otherwise unsuitable for inclusion

Recruitment at the outpatient clinics:

During the recruitment processes in the hospital outpatient clinics, the patients were invited to participate in the study by the researcher and their informed consent was sought only if their nominated pharmacist had already agreed to participate. The *'Patient Consent Form'* was given to all identified patients and they were asked whether they want to take part in the study (Appendix 6.3). The patients were given sufficient time to read the study information leaflets (Appendix 6.4) which explained the purpose of the study, the procedures and relevant information regarding the study. The patients who agreed to take part in the study were then asked to complete the consent form by signing an appropriate section and returning it to the research pharmacist. The patients were allocated in the control or the study group according to the results of the randomisation of their community pharmacy that they

had nominated. It was explained to the patients that a new MTX monitoring card is being introduced and that the purpose of the study was for the hospital to test how their community pharmacist can help to support the introduction of the card. They had been informed that this process involved the patients completing a questionnaire once every 6 months at the clinic and attending the same community pharmacy during the study period, therefore their treatment would be otherwise unaffected.

The inclusion in the study would involve their community pharmacist being sent a note from the rheumatologist with medical information that may help them to discuss the monitoring tests with the patient when they get their prescription dispensed at the pharmacy. Once the patient was accepted into the study, they were informed that they might or might not have their pharmacist participate in the first six months. All patients would eventually be able to benefit from their pharmacist receiving information from the rheumatologist during the one-year study.

Recruitment at the community pharmacy:

The participating community pharmacies were also asked to recruit eligible patients from their patient medical record (PMR) systems for the study, because the time period allowed for the recruitment process to be exceeded beyond the intended period. The pharmacists were provided with a recruitment package with self-addressed/pre-paid envelopes, which consisted of a copy of the study information leaflet for patients, a consent form, a copy of the patient questionnaire and a monitoring card from their hospital. The pharmacists, who were previously contacted by the researcher in person, were provided with a letter that explained inclusion/exclusion criteria for patients being able to participate in the study. They were asked to give this package to their named eligible patients and to invite the patient to send it back to the researcher with an envelope provided. After the consent had been sought, the eligible patients were asked to fill the patient questionnaire either at home or in the pharmacy while they were waiting for their prescriptions to be dispensed.

6.5 Ethics approvals

The study protocol and related documents were submitted to the Ethics Committee of the North and the South Glasgow University Hospitals NHS Trusts and also to the Greater Glasgow Community/Primary Care Local Research Ethics Committee. The approvals were granted in September/October 2001.

6.6 Methods

6.6.1 The chosen four LHCC environments were categorized according to the postcodes of their boundaries which were indicated as the 'deprived' and the 'non-deprived' population. The information regarding the practice population, the number of pharmacies, the number of GPs and the GP surgeries within their boundaries were gathered from the Greater Glasgow Health Board, the Scottish Health on the Web (SHOW) website and the LHCC co-ordinators.

6.6.2 Before the study commenced, currently used MTX shared care monitoring protocol and patient-held drug monitoring cards were updated and made generally available to all GPs and community pharmacists caring for the patients seen by the clinics for the study.

The researcher reviewed the shared care protocols for methotrexate treatment which were currently used in the hospital outpatient clinics in Glasgow (Glasgow Royal Infirmary, Victoria Infirmary, Southern General Hospital and Gartnavel General Hospital), in Edinburgh (Western General Hospital), in Perth (Perth Royal Infirmary) and in Wales (University Hospital of Wales) and also looked at the information sheet designed by the Arthritis Research Campaign and relevant literature on methotrexate treatment. The revision processes were undertaken in collaboration with two rheumatology specialists and a hospital pharmacist, and the protocol was finalized after an agreement was achieved by the panel members (Appendix 6.5).

The patient-held drug monitoring cards were also revised by the researcher after having discussion with two rheumatology specialists and the changes were made in the new format of the monitoring card (Appendix 6.6).

The rheumatology care plans for the monitoring of methotrexate therapy were designed by the researcher and academic collaborators in the study and were based on studies that have previously been undertaken in the arena of chronic disease management and management of rheumatoid arthritis (Appendix 6.7).

6.6.3 The education and training event on methotrexate therapy was conducted by the members of the project team and was coordinated by the researcher. The event was accredited by the Scottish Centre for Post Qualification Pharmaceutical Education. The aim of the event was to update community pharmacists on methotrexate therapy in rheumatic

diseases and to introduce a new shared care monitoring tool for this treatment. The objectives were set for the event as;

- to describe when methotrexate is used in the treatment of rheumatoid arthritis
- to identify side effects that patients may experience while on methotrexate therapy
- to contribute to the patient specific methotrexate care plan
- to collaborate in the transfer of patient specific methotrexate related information between primary and secondary care.

The community pharmacists were given didactic lectures on general features of methotrexate treatment (by an academic collaborator-AP/VK), when and how to use the drug in practice for the treatment of rheumatic diseases (by a rheumatology specialist-JH), practical problems with the drug that the patients experience (by a nurse specialist- DM) and medication errors with oral methotrexate therapy (by an academic collaborator- AP/VK and the researcher-AB).

The education and training event for the pharmacists also included the workshops, which were led by two hospital pharmacists (MW/VK and SB) and where the participants discussed the problems and/or solutions for methotrexate therapy on the illustrative cases that were prepared by the researcher. The participants were also allowed to raise their concerns and questions regarding methotrexate therapy and had an opportunity to discuss with other health care professionals who were involved in the patient care.

The community pharmacies in the four LHCC environments were identified from the Greater Glasgow Health Board list and the pharmacists were characterised in terms of their age, gender, years on the register, hours of Continuing Professional Development (CPD) and hours of Scottish Centre for Post Qualification Pharmaceutical Education (SCPPE) as information provided by the pharmacists themselves.

The community pharmacists were allocated either to the study or the control group by a stratified randomisation process with regard to the Carstairs deprivation category of the geographical location of pharmacies in which they practise.

Patient-specific monitoring requirements were initiated by the rheumatology specialist and conveyed to each patient's GP in the normal way by letter from the hospital clinic. For the patients who nominated a pharmacist assigned to the study group, the care plan was issued. The care plan was drawn up by the researcher and checked by a clinical pharmacist,

expanded if required, augmented and approved by the rheumatologist during consultation with the patient at the clinic. The care plan was issued to the community pharmacists, the GPs and patients themselves. The care plans were updated on the next hospital visit when the patient might have new care issues which were added; the new care plan replaced the old one and was issued as before.

The pharmacists had been informed about receiving the shared care monitoring protocol and the rheumatology care plans at appropriate times in the following 12 month period according to whether they had been allocated to the 'study' or the 'control' group. They were also asked to record on the patient data collection forms, the details of MTX prescriptions and any care issues that they address during the care of their patients (Appendix 6.8). The study group pharmacists were asked to attend an educational and training evening on methotrexate therapy in rheumatoid arthritis in November 2001. The pharmacists were also provided with information on how to use the patient data collection forms and the care plans for the methotrexate therapy. The consultant rheumatologists, rheumatology nurse specialist, hospital pharmacists and the researcher participated in this training evening, which was repeated in January 2003 for the pharmacists who were initially allocated in the control group.

- Study group of community pharmacists

The study group pharmacists were issued with a copy of the care plan for MTX monitoring from the rheumatologist, which included the contact details of the nominated pharmacists and the patient's medication details. They also received a copy of the shared care monitoring protocol, a programme of written educational support, a personal briefing and an invitation to two educational meetings during the 12 months of the intervention.

- Control group of community pharmacists

At the beginning of the study, the control group was informed about the intention that they would receive the care plan and the educational programme in the second six months of the study. The pharmacists assigned to the control group in Phase 1 were invited to participate in the Phase 2 extension as a study group. This was for the completion of the introduction of the MTX protocol and the care plan into the LHCCs.

All patients received a new MTX monitoring card and the patients' GPs received a letter from the rheumatology specialists explaining the study and they were also provided with a

copy of the shared care monitoring protocol and the care plans where appropriate during the study.

The participating community pharmacists received an *ex gratia* payment for their involvement in the study by the Primary Care NHS Trust in Glasgow.

6.6.4 The patients were included in the study for a 12 month period. During the first 6 months, half of the recruited patients' community pharmacists were assigned into the control group and the remaining half were into the study group. After the initial 6 months period, all recruited patients started to receive the same intervention procedures, therefore none of the patients or pharmacists was ultimately disadvantaged from having been entered into the control group during the study.

The patients were identified from the hospital outpatient clinic databases in terms of age, sex, duration of disease, duration of methotrexate therapy, number of previous disease modifying anti-rheumatic drugs (DMARDs), number of co-morbid conditions and socio-economic status of their place of residence. The patients were categorised as residing in a 'non-deprived' or 'deprived' area in terms of the Carstairs Category (the postcode of their place of residence).

The patients were given a copy of the questionnaire to complete with a help of the researcher where it is needed after they agreed to participate in the study (Appendix 6.9). The overall questionnaire was adapted from the previously validated questionnaires and laid out appropriately by the researcher in collaboration with other academic researchers. The administration of the questionnaire was piloted in order to ensure patient's acceptability on a sample of patients (n=20) at the rheumatology clinic not otherwise eligible for inclusion in the study. The questionnaire consisted of 35 questions, which were specified under three sections;

1. Patient's intrinsic desire for information (12 questions)
2. Patient's beliefs about their medicines (11 questions)
3. Patient's satisfaction about service that they receive at the community pharmacy (8 questions)

The answers for each question were categorised on a 5-point Likert scale from 'strongly disagree' (1) to 'strongly agree' (5) options. The further four questions were related with any

problems that patients may have experienced with their medication in the past. The questionnaire took approximately 15-20 minutes to complete. The patients were asked to complete the questionnaire independently, but with the supervision of the research pharmacist at the clinic while they were waiting for their consultations. The patients were also asked to indicate the name of the community pharmacy that they regularly visit.

The participating patients were asked to complete the same questionnaire after 6 months of the study period, where they received the questionnaire by post with a pre-paid, self-addressed envelope. They were asked to return the questionnaires to the researcher along with their methotrexate monitoring card which was given at the beginning of the study. The researcher photocopied the cards and returned the original to the patients in order to maintain its completion throughout the second phase of the study.

6.7 Results and analysis

6.7.1 Characteristics of the community pharmacist population

The community pharmacist population is characterised in terms of age, gender, number of years on the register and recorded CPD and SCPPE hours of the pharmacists who practise in the pharmacies located in the identified LHCC environments. Forty six out of fifty-five (83.6%) community pharmacies contacted provided a signed consent in order to participate in the study. Nine pharmacies did not want to take part in the study and the reasons were indicated as an increased workload (3), not returning follow-up calls therefore not given a consent form (5) and not having any patients on methotrexate treatment in their PMR system (1). Thirty pharmacies were nominated by the patients during the recruitment process, of those 13 were allocated in the 'study' and 17 in the 'control' group. However, only 23 out of 30 (76.6%) pharmacies provided information about themselves (Table 6.3 and Table 6.4).

Table 6.3 Characteristics of respondents to the questionnaire for 23 out of 30 participating pharmacies in the study

	Study (n=12)	Control (n=11)
Located in 'non-deprived' LHCC	4	5
Located in 'deprived' LHCC	8	6
Number of MTX patients on PMR;		
≤2 patients	7	5
3 or 4 patients	4	3
5 or 6 patients	1	3
Number of part-time pharmacists working >2days/week in the pharmacy;		
One pharmacist	9	10
Two pharmacists	3	1
Type of pharmacy:		
Independent	3	4
Small chain	5	3
Large chain	4	4
Location of pharmacy:		
In health centre	0	0
Close to GP surgery	8	7
In shopping centre	2	1
High street shop	1	3
Total number of pharmacists per pharmacy		
One pharmacist	12	10
Two pharmacists	0	1
Number of pharmacies with a pre-reg pharmacist;		
No pre-reg pharmacist	12	7
One pre-reg pharmacist	0	4
Number of other non-pharmacist staff;		
≤3 staff	7	5
4-7 staff	3	5
>7 staff	-	1
Number of R_x items dispensed/week:		
<500	0	0
500-1000	2	5
1000-2000	9	4
>2000	1	2

Table 6.4 Characteristics of respondents to questionnaire for 25 participating pharmacists in the study (in 23 pharmacies)

	Study (n=14)	Control (n=11)
Mean age, years (SD)	39.7 (11.4)	39.0 (9.4)
Female (%)	71.0	36.0
Mean number of years on register (SD)	15.8 (11.6)	14.8 (8.3)
Mean number of recorded CPD hours (SD)	22.3 (10.8)	22.5 (20.1)
Mean number of recorded SCPPE hours (SD)	8.8 (9.4)	10.2 (13.6)

6.7.2 Characteristics of the patient population

During the four months of the recruitment process, 59 patients responded to the questionnaire, of those 76% were female, 85% were diagnosed with rheumatoid arthritis, 14% with psoriatic arthritis and 1.7% with polyarthritis. Following the randomisation, 31 patients were in the control group and 28 patients were in the study group. Approximately 37% of the total patient population were domiciled in the Carstairs Category 1, 2 and 3 (referred to as 'non-deprived' population) and 63% were in category 4, 5, 6 and 7 (referred to as 'deprived' population) (Table 6.5).

One hundred and two other diagnoses were indicated in the hospital outpatient clinic databases for the 58 patients. Of those, 48 (47.1%) diagnoses identified from the 'study' group and 54 (52.9%) from the 'control' group patients. The mean (SD) number of other diagnoses was 1.8 (1.8) for the 'control' group and 1.7 (1.7) for the 'study' group. The frequency (distribution) of indicated diagnoses is summarised in Table 6.6. No statistically significant difference was found between the study and the control group patients in terms of diagnoses of other conditions (Chi-square tests or Fisher's exact test, $p>0.05$).

Table 6.5 Demographics of patients participating in the study (n=59)

	Study (n=28)	Control (n=31)	Total (n=59)
Mean age in years (SD)	60.7 (11.2)	59.5 (10.8)	60.1 (10.9)
Gender (female %)	75	77	76
Carstairs category;			
1, 2 and 3 ('non-deprived')	11	11	22
4, 5, 6 and 7 ('deprived')	17	20	37
Number of previous DMARD courses (number of patients);			
Sulphasalazine	25 (22)	28 (27)	53 (49)
Penicillamine	12 (12)	11 (11)	23 (23)
Gold	17 (17)	19 (19)	36 (36)
Azathioprine	3 (3)	3 (3)	6 (6)
Hydroxychloroquine	9 (9)	9 (8)	18 (17)
Chloroquine	3 (3)	2 (2)	5 (5)
Cyclosporin	1 (1)	-	1 (1)
Methotrexate	1 (1)	2 (2)	3 (3)
Prednisolone	2 (2)	1 (1)	3 (3)

Table 6.6 The frequency of other diagnoses (n=102) within the patient population (n=58)

	Study (n=28)	Control (n=30)
Cardiovascular	9 (32.1%)	7 (23.3%)
Other musculoskeletal conditions	6 (21.4%)	7 (23.3%)
Gastrointestinal disorders	6 (21.4%)	5 (16.7%)
Peripheral vascular diseases	4 (14.3%)	3 (10.0%)
Infectious diseases	3 (10.7%)	3 (10.0%)
Skin disorders	2 (7.1%)	2 (6.7%)
Endocrine disorders	2 (7.1%)	2 (6.7%)
Haematological	-	3 (10.0%)
Renal	2 (7.1%)	3 (10.0%)
Respiratory	1 (3.6%)	3 (10.0%)
Miscellaneous	6 (21.4%)	11 (36.7%)
Total diagnoses	48 (47%)	54 (53%)

6.7.3 Patient questionnaire findings- baseline assessment

The questionnaire results were anonymised for each patient and stored in the computer. The results of the two sets of questionnaires for each patient were analyzed by the Statistical Package for the Social Sciences (SPSS). The differences in responses between the time periods were analyzed by using the appropriate statistical tests for unpaired and paired data.

The findings for the patient questionnaire were examined for differences associated with patient characteristics including age and the socio-economic environment of the patients' residential addresses. The results are reported in the following sections in order to examine the baseline assessment data first, followed by the six months follow up data. Data were analysed for evidence of a normal distribution.

INTRINSIC DESIRE FOR INFORMATION QUESTIONNAIRE

The items of the Intrinsic Desire for Information Questionnaire are indicated in Panel 6.1 below.

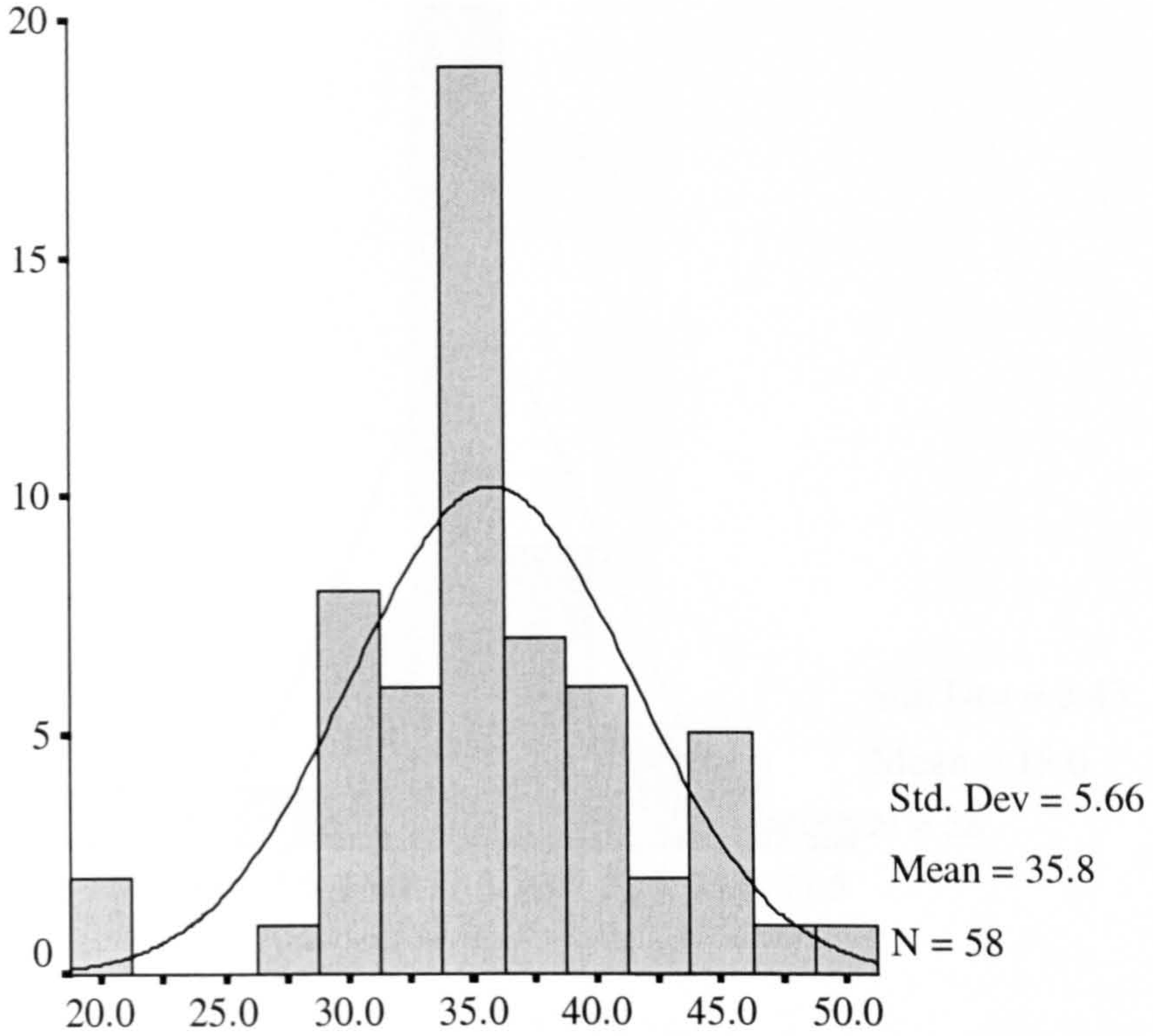
Panel 6.1 Intrinsic Desire for Information (IDI) questionnaire items[282]

1. I always speak to my pharmacist when I want information about my medicines
2. Sometimes I feel a little inhibited when I ask for information, I should know already
3. It's most convenient to ask at the surgery, if there is anything I need to know
4. It's not really my place to ask information, they have enough to do
5. People at the hospital can easily give me information when I go for my appointment
6. I need as much information about my medicines as possible
7. Too much knowledge is bad thing
8. You can never know enough about these things
9. I don't need any more knowledge
10. I read about my medicines and illness as much as possible
11. What you don't know doesn't hurt you
12. I find medical information confusing

The distribution of scores for the ***Intrinsic Desire for Information*** **(IDI)** scale is shown in Figure 6.2. The total score for the IDI scale ranged from 20 to 50. The mean (SD) score for the total population was 35.8 (5.7). Thirty-eight percent of the patients scored higher than and equal to the mean score (≥36) on the IDI scale. The original authors presented the results from a larger patient population (n=501) and indicated that the distribution of scores for IDI scale was bimodal and the mean (SD) value was 31.2 (12.5).[281] However, the distribution of

the scores for IDI scale in the patient population for the study showed normal distribution (Kolmogorov Smirnov test for normality, p=0.175)

Figure 6.2 Distribution of the total score for the Intrinsic Desire for Information Scale for the all patients baseline (n=58)

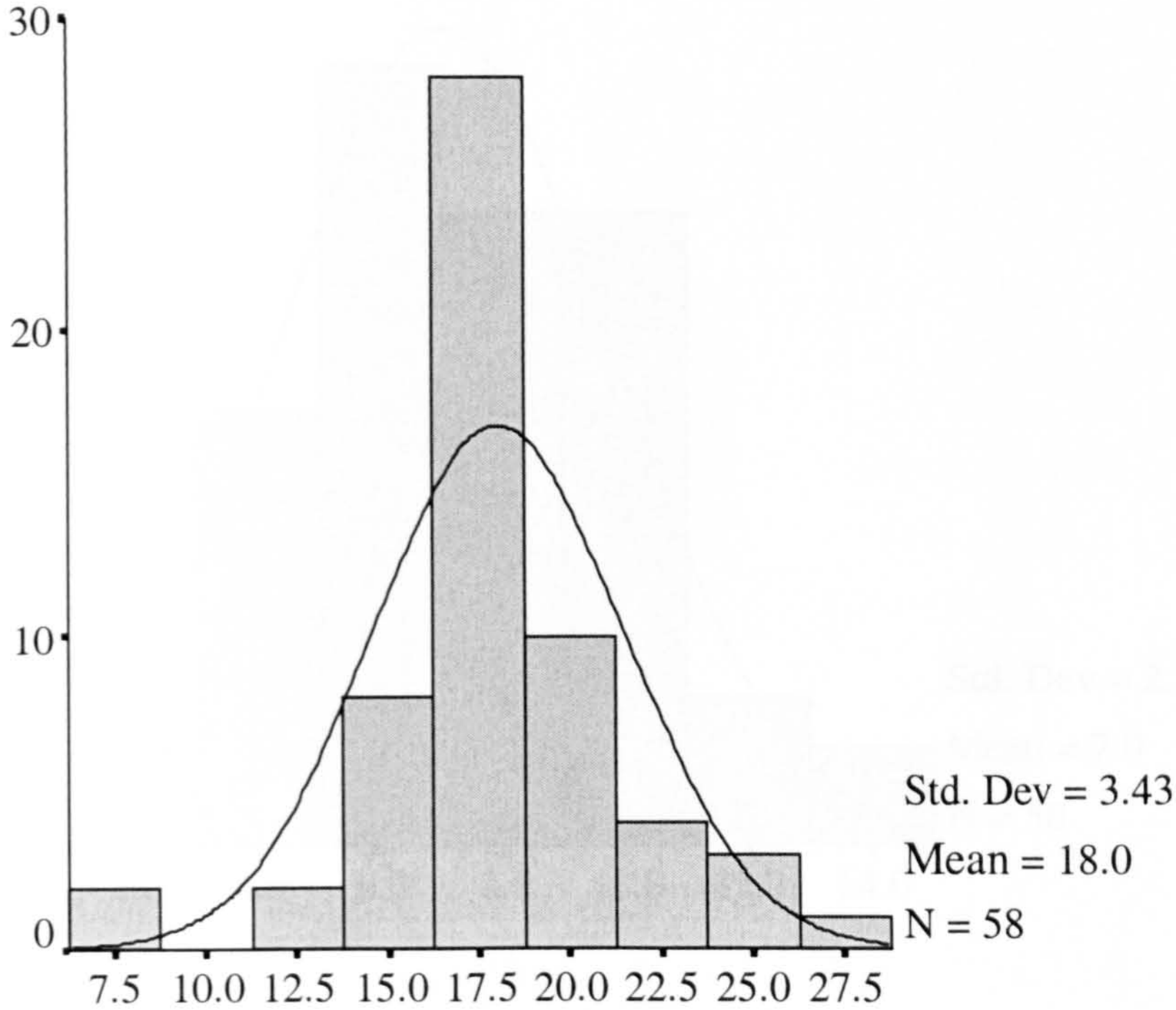


The ***Extent of Information Desired (EID)*** scale is derived from the Intrinsic Desire for Information scale on the basis of factor analysis. The authors extracted two factors; factor 1 consists of 6 items (items including Nos. 6-11 in the Panel 6.1 above) and indicates the extent of information desired (EID) by patients and was considered useful to identify receptive (high scorers) or refractory (low scorers) patients.[282] The validity of the scale had been tested in the population of 630 patients and the distribution of the total scores for the EID scale showed normal distribution. The high scorers were defined as those patients who had the factor score above the mean score of the population.

The distribution of the total scores for EID scale did not show normal distribution (Kolmogorov Smirnov test, p=0.000) and the mean (SD) score for the EID scale was 18.0 (3.4) for the total patient population (Figure 6.3). Thirty-one percent of the patients scored

>18 on the EID scale. No statistically significant difference was found between the control and the study group patients (Mann-Whitney U test, U= 394.00, p>0.05).

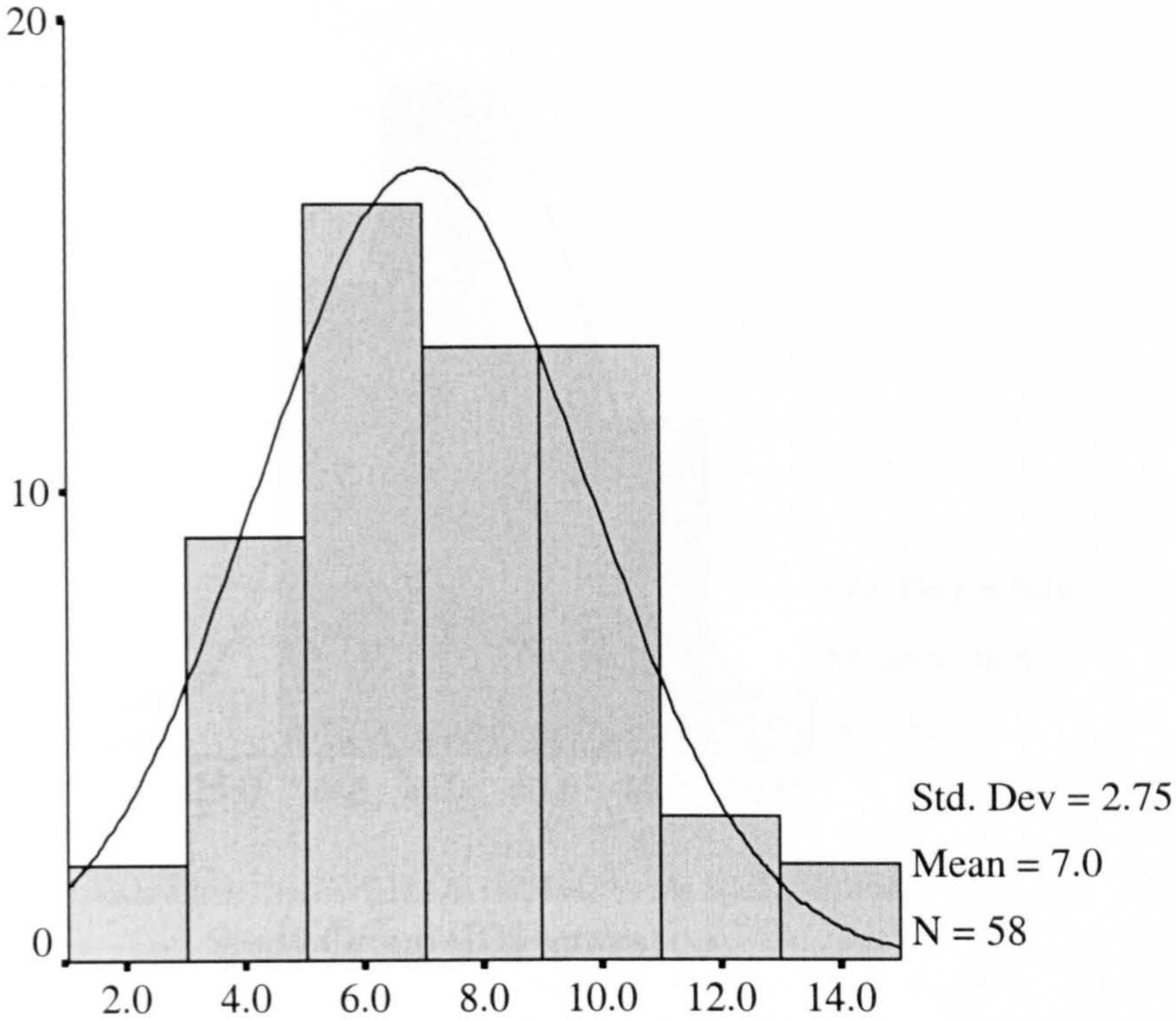
Figure 6.3 Distribution of the total score for the Extent of Information Desired (EID) scale for the all patients at baseline (n=58)



The factor 2 consists of three items (items including Nos.2, 4 and 11 in the Panel 6.1) and indicates the inhibited desire for knowledge about illness/drugs rather than the amount of information patients are concerned. The results from the sample of 299 patients indicated that the distribution of the total scores for the inhibited desire for knowledge scale was normally distributed and the mean value was 8.1. Furthermore, the authors indicated that the scale is significantly but weakly correlated with patient's age (Pearson r= 0.186).[283] However, the level of reliability was found to be low and further work is still in progress with regard to the reliability of the scale, therefore the authors considered that the results should be interpreted with caution.[282]

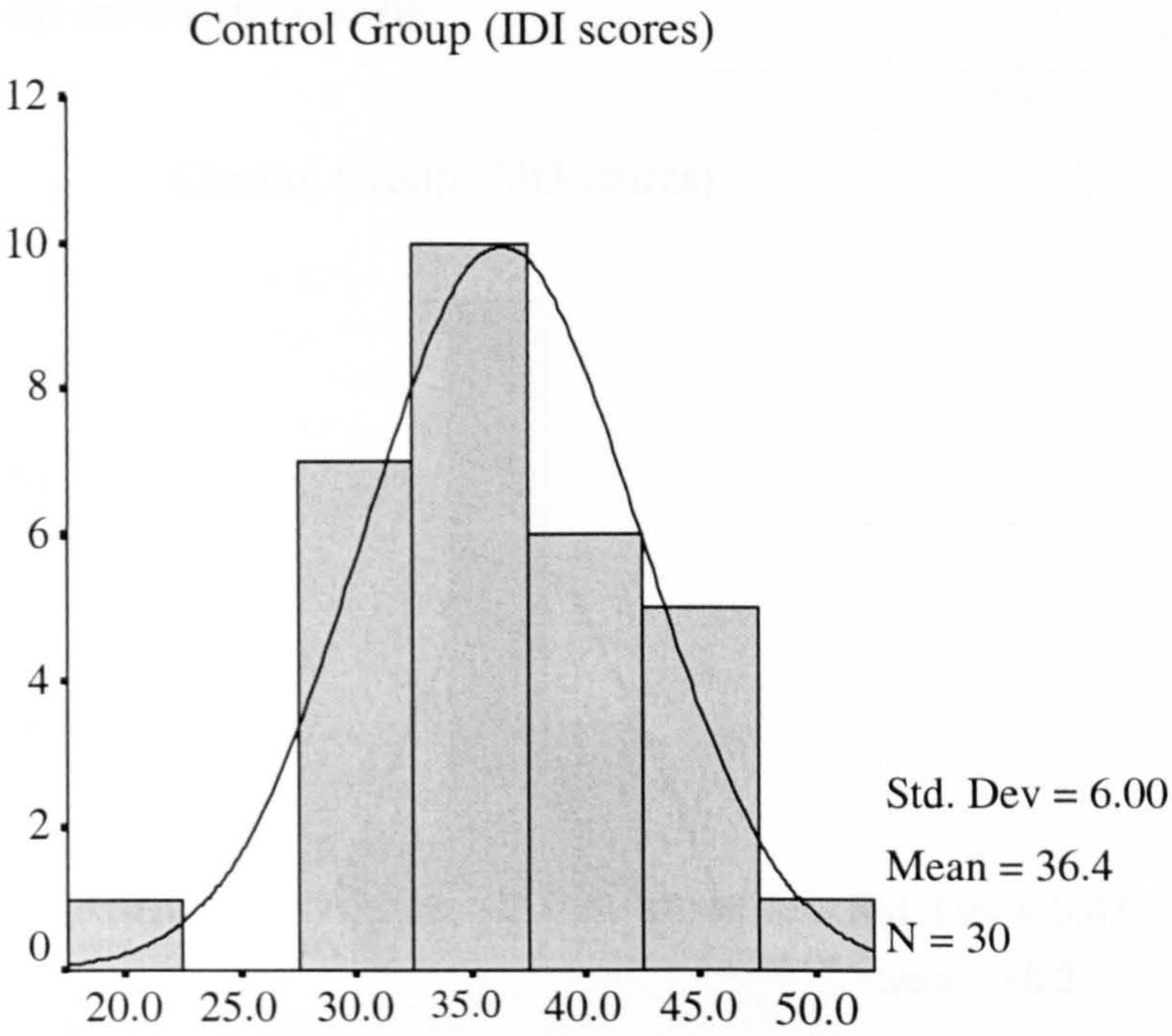
The distribution of the scores for the inhibited desire for knowledge scale was normally distributed and the mean (SD) score was 7.0 (2.7) in the total patient population and 55.2% of the patients scored ≤7 in this study (Figure 6.4).

Figure 6.4 Distribution of the total score for the inhibited desire for knowledge scale for the all patients at baseline (n=58)



The distribution of the total scores for the IDI scale and EID scale at baseline assessment for the control and the study group patients are shown in Figure 6.5 and Figure 6.6, and the results are summarised in Table 6.7.

Figure 6.5 Distribution of the IDI scores for the control (n=30) and the study (n=28) group at baseline



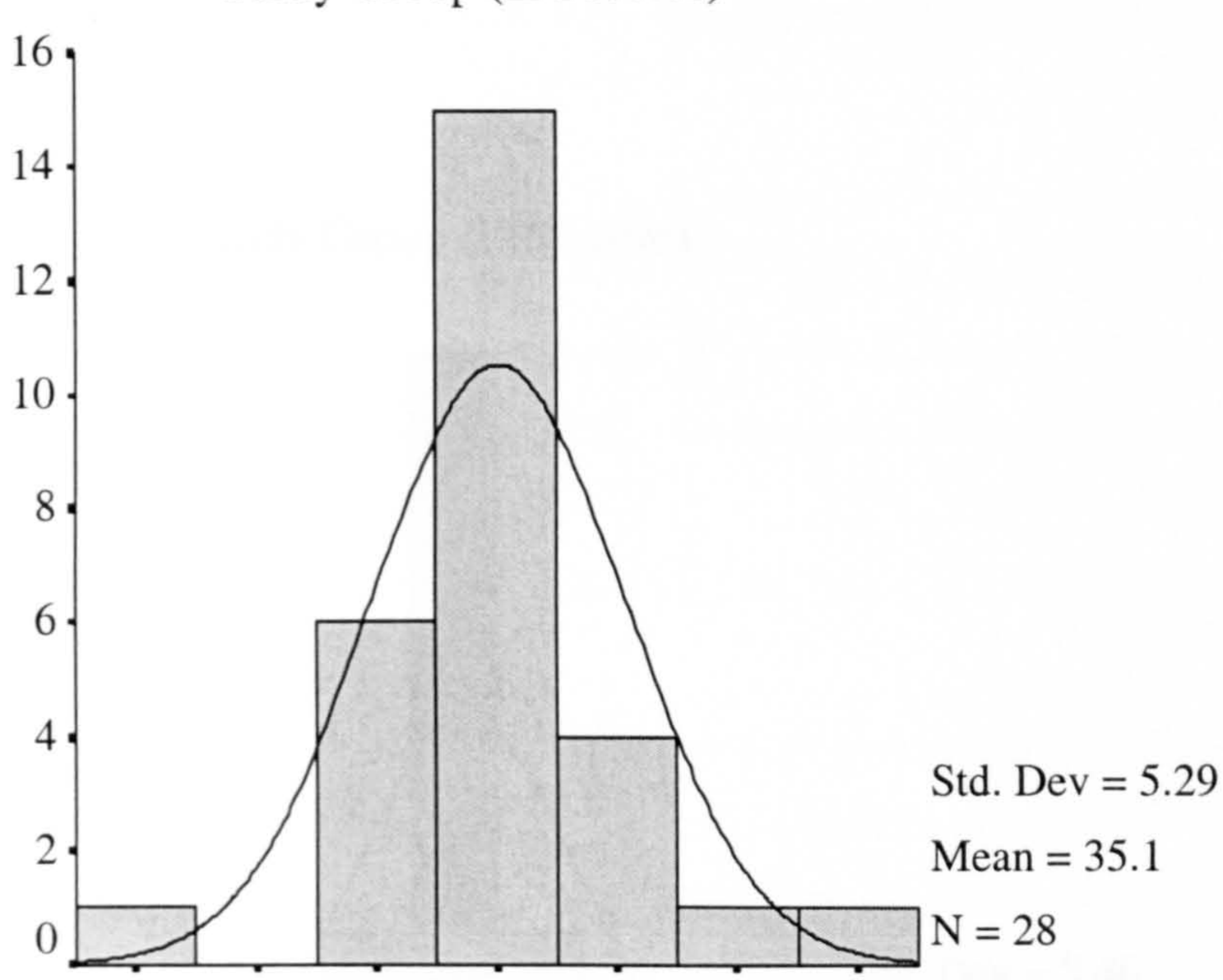
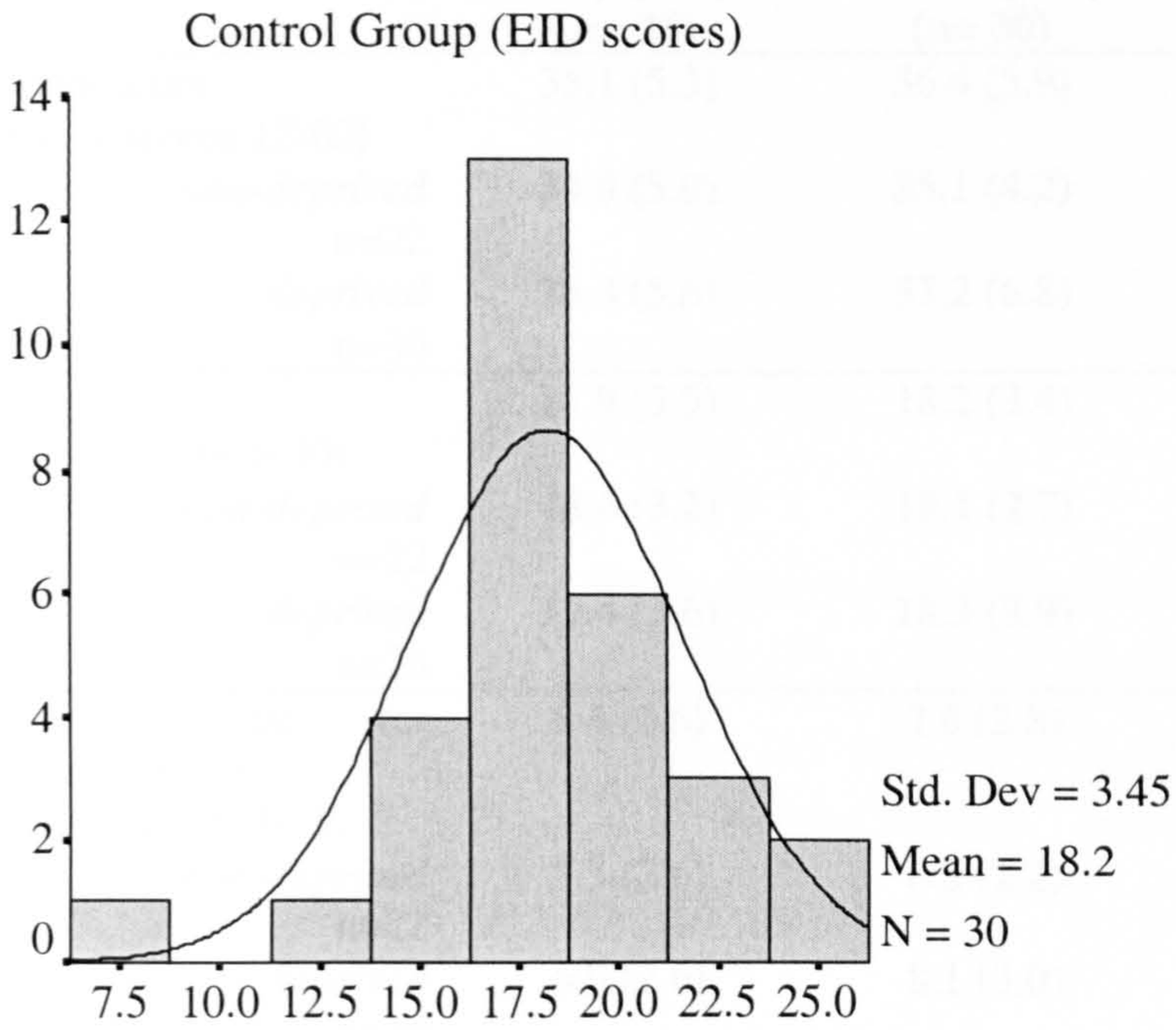


Figure 6.6 Distribution of the EID scores for the control (n=30) and the study group (n=28) at baseline



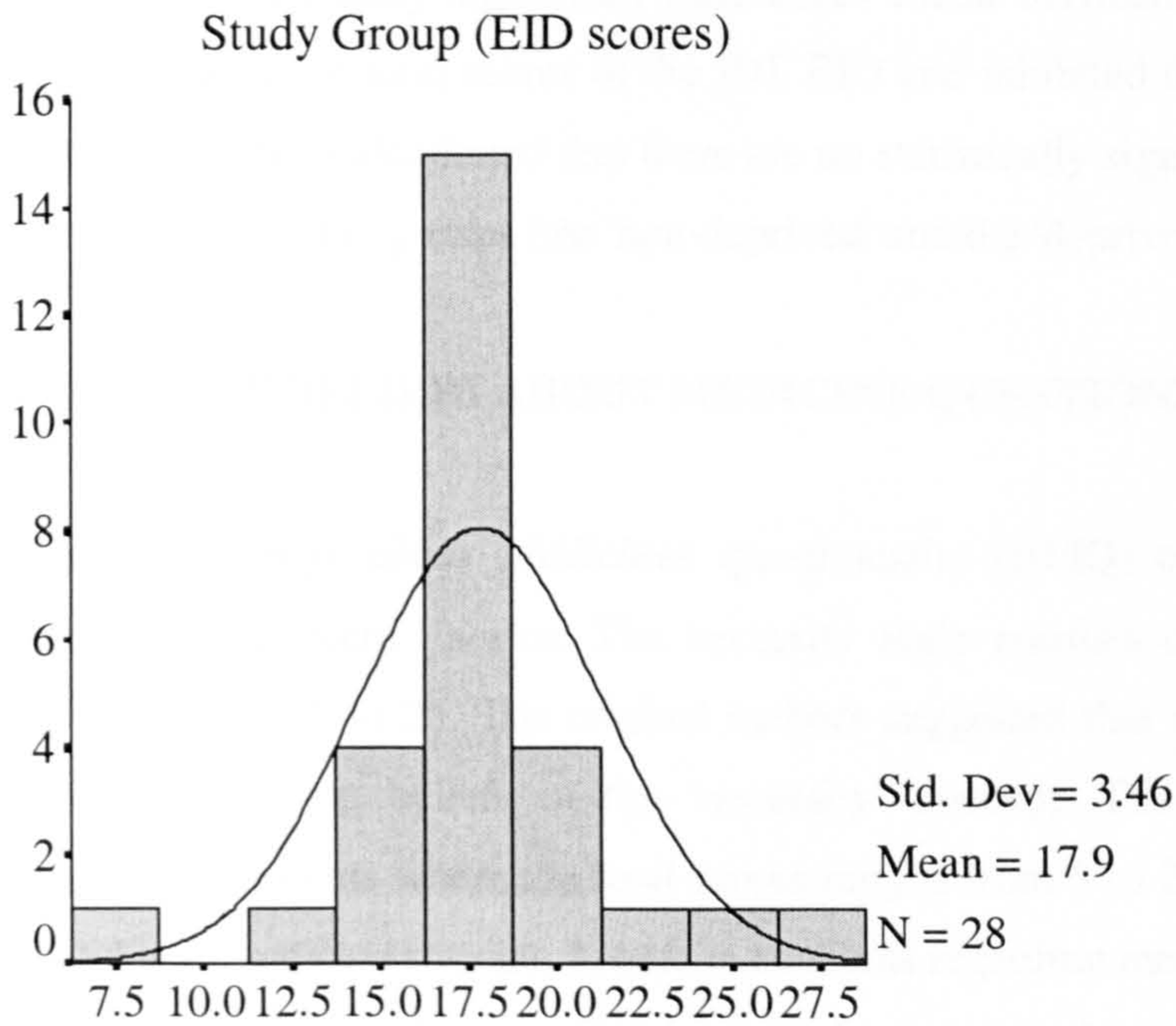


Table 6.7 The summary of results of the Intrinsic Desire for Information questionnaire at baseline assessment

	Mean score (standard deviation)			
	Study group **(n= 28)**	***Control group*** **(n= 30)**	***p value***	***All*** **(n=58)**
IDI total score (range of scores 12-60)	35.1 (5.3)	36.4 (5.9)	0.39*	35.8 (5.6)
non-deprived n=22	34.8 (5.0)	35.1 (4.2)	0.39*	34.9 (4.5)
deprived n=36	35.3 (5.6)	37.2 (6.8)		36.3 (6.3)
EID (range of scores 6-30)	17.9 (3.5)	18.2 (3.4)	0.68** (U=394.0)	18.0 (3.4)
non-deprived n=22	18.6 (3.2)	18.1 (2.7)	0.78** (U=378.5)	18.4 (2.9)
deprived n=36	17.4 (3.6)	18.3 (3.9)		17.8 (3.7)
Inhibited desire for knowledge scale (range of scores 3-15)	6.4 (2.6)	7.6 (2.8)	0.07*	7.0 (2.7)
non-deprived n=22	5.5 (2.6)	6.8 (2.2)	0.07*	6.2 (2.4)
deprived n=36	6.9 (2.6)	8.1 (3.0)		7.5 (2.8)

** Student t test ** Mann Whitney U test (appropriate test is chosen according to distribution of data)*

There are no statistically significant differences found between the control and the study group in terms of the total scores of the IDI, EID and inhibited desire for knowledge scales ($p>0.05$). It has been also found that there are no statistically significant differences between the two socioeconomic groups (the 'non-deprived' and the 'deprived') ($p>0.05$).

THE SPECIFIC BELIEFS ABOUT MEDICINE QUESTIONNAIRE

The specific ***Beliefs about Medicines*** questionnaire (BMQ) consists of two scales; the 'necessity' and 'concerns' scales. The necessity scale consists of five items and the total scores range from 5 to 25. The original authors suggested that scores above the mid scale point indicate strong beliefs in the 'necessity' concept. The 'concerns' scale initially consisted of five items where the total scores ranged from 5 to 25 and the scores above the scale mid point indicate stronger beliefs in concerns regarding medicines.[280] Furthermore, the authors suggested including another item in the 'concerns' scale and studied the internal consistency of the 6-items scale. As a result, they concluded that if Cronbach's alpha value

was >0.65, the new item can be included in the analysis which makes the total score for the 'concerns' scale range from 6-30 (Personal communication with R.Horne in March 2002).

The analysis for internal consistency, which was undertaken in the sampled patient population for this study, revealed that the Cronbach's alpha value for the five-items concerns scale was 0.42 and 0.47 for the six-items scale. It is indicated that the additional item increased the internal consistency of the concerns scale, therefore the 6th item was included in the further analysis of the 'concerns' scale. However, the results of the 5-items concerns scale were also reported in the following sections in order to allow comparison with the results from the original authors.

The distribution of the scores for the specific Beliefs about Medicines questionnaire scales for the 'necessity' and 'concerns' are shown in Figure 6.7. The mean (SD) score for the total patient population was 19.3 (3.3) for the 'necessity' scale (Kolmogorov Smirnov test for normality, p=0.062) and 18.6 (3.8) for the 6 items 'concern' scale (Kolmogorov Smirnov test for normality, p=0.004).

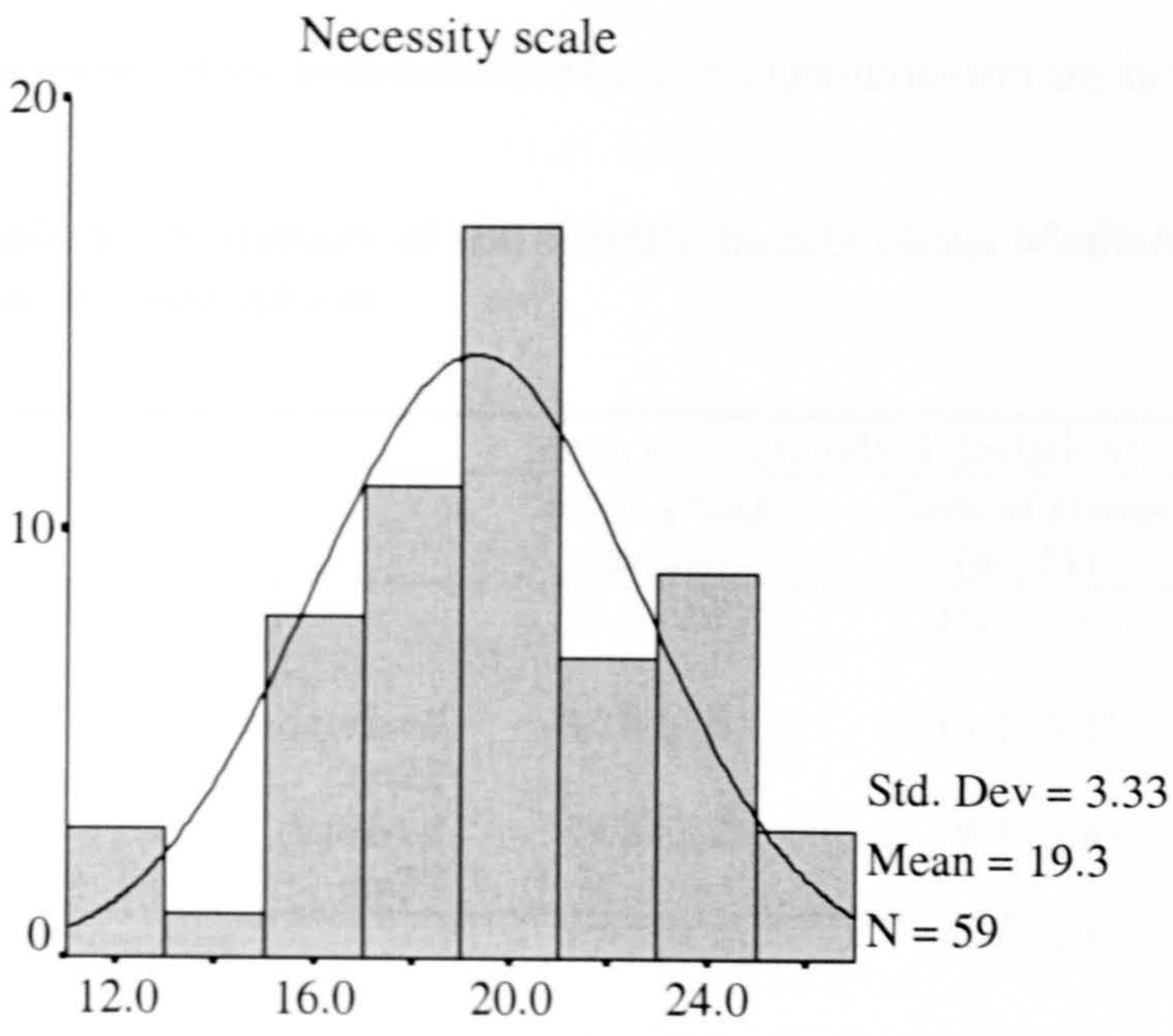
The results from the original authors in terms of the mean (SD) values for the 'necessity' and the 'concerns' scales across the different disease groups are as follows in the Panel 6.2;[280]

Panel 6.2 Mean (SD) values for the Beliefs about Medicines Questionnaire's scales reported by the original author

Patients group	Necessity Scale Mean (SD)	Concerns Scale* Mean (SD)
Asthmatic (n=78)	19.7 (3.2)	15.8 (4.1)
Diabetic (n=99)	21.3 (2.9)	12.9 (3.4)
Renal (n=47)	19.5 (2.8)	13.8 (4.3)
Cardiac (n=116)	18.7 (3.0)	13.9 (3.7)

* *The results are reported from the 5-items concerns scale*

Figure 6.7 Distribution of the total scores for the Beliefs about Medicine questionnaire scales for the 'necessity' and 'concerns' at baseline assessment (n=59)



Forty-nine percent of the total population scored ≤19 on the 'necessity' scale and 63% of the patient population scored ≤19 on the 'concerns' scale. There is no statistically significant difference between the control and the study group patients in regards to the 'necessity' (Student t test, p=0.18) and the 'concerns' scale (Mann-Whitney U test, U=311.0; p=0.06).

The results of the Beliefs about Medicines Questionnaire are summarised in Table 6.8.

Table 6.8 Summary of the specific Beliefs about Medicines Questionnaire at baseline assessment

	Mean score (standard deviation)			
	Study group **(n= 28)**	***Control group*** **(n= 31)**	***p value***	***All*** **(n=59)**
BMQ-necessity (range of scores 5-25)	19.9 (2.9)	18.7 (3.6)	0.18*	19.3 (3.3)
non-deprived n=22	20.0 (2.6)	19.5 (3.3)	0.44*	19.7 (2.9)
deprived n=37	19.8 (3.2)	18.4 (3.8)		19.0 (3.6)
BMQ-concerns (range of scores 6-30)	17.7 (3.8)	19.5 (3.7)	0.06**	18.6 (3.8)
non-deprived n=22	17.4 (3.2)	19.0 (3.2)	0.25** U=334.0	18.2 (3.2)
deprived n=37	17.9 (4.2)	19.8 (3.9)		18.9 (4.1)
BMQ- concern (initial 5 items scale) (range of scores 5-25)	15.2 (3.0)	16.9 (3.1)	0.06**	16.1 (3.2)
non-deprived n=22	14.5 (2.5)	16.5 (2.8)	0.08** U=295.5	15.5 (2.8)
deprived n=37	15.7 (3.3)	17.1 (3.4)		16.5 (3.4)

** Student t test ** Mann Whitney U test (appropriate test is chosen according to distribution of data)*

The analysis was also carried out on the BMQ scales in the comparison of the patient's socioeconomic status, which was characterised by Carstair Deprivation Index. There is no statistically significant difference between the non-deprived and the deprived groups in terms of BMQ 'necessity' and the 'concerns' scales (p=0.44 and p=0.25 respectively).

The results from the baseline assessment indicated that 51% of the patients scored higher than the mean value (>19) on the necessity scale and 37% of the patients scored higher than the mean value (>19) on the concerns scale.

The authors of the Beliefs about Medicine Questionnaire also suggested to calculate the 'necessity' and 'concerns' scales (five items) differential in order to indicate the relative importance of attitudes for individual patients. This is calculated as the difference between the 'necessity' and the 'concerns' scores and has a range of -20 to 20, where the positive value indicates that the patients perceive that the benefits of medication outweigh the risks [Personal communication]. At the baseline assessment, 86.4% of the total patient population have a positive value for the necessity and concerns differential.

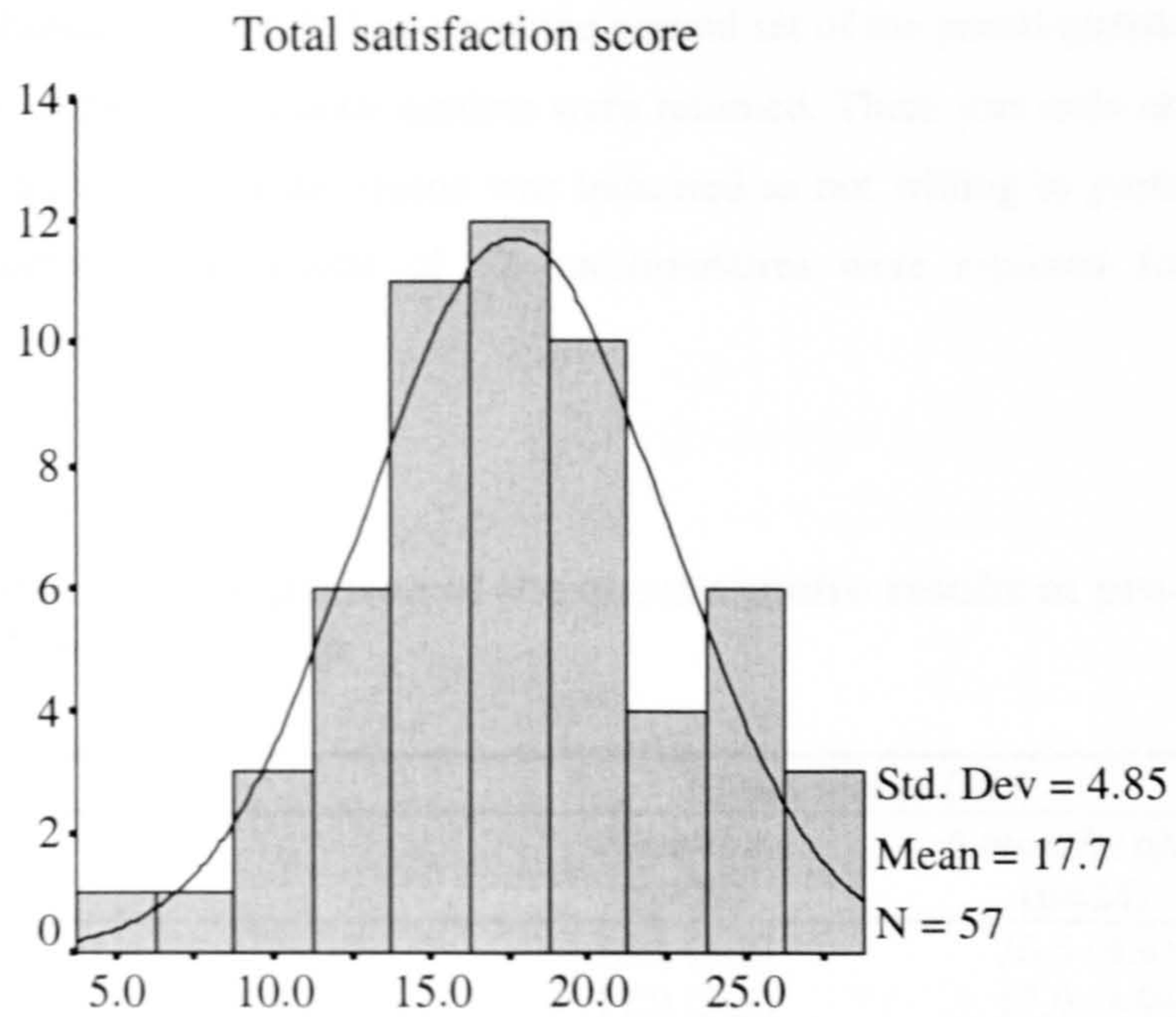
PATIENTS' ATTITUDES TO THE PHARMACY SERVICE AND THEIR MONITORING PROCESS

The analysis of the concept of overall patient *satisfaction with the pharmacy service* that they receive in their community pharmacy revealed that over half of the patient population (56.4%) are 'very satisfied' and 27.3% were 'fairly satisfied' with the service that they regularly receive.

The original seven items satisfaction questionnaire is related to a prescription service and provision of information in the pharmacy instrument previously piloted.[284] The total scores for the scale ranged from 6-28 and the mean (SD) value for the patient population was 17.7 (4.85) (Kolmogorov Smirnov test for normality, p=0.20). Fifty one percent of the population scored ≥18 (Figure 6.8).

No statistically significant differences were found between the 'non-deprived' and the 'deprived' patient groups (Student t test, p=0.71) in terms of satisfaction with the services that they receive in the pharmacy. However, the control group patients were more satisfied with the service at the pharmacy compared to the study group patients at baseline (Student t test, p=0.03)

Figure 6.8 Distribution of the total score of the satisfaction scale at baseline (n=57)



Twenty-eight (51%) patients indicated that they ***had problems with their medication in the past*** and of those 57% were domiciled in the 'non-deprived' and 43% in the 'deprived' community. For the 26 patients who further indicated their actions when they have problems with their medication; 5 (19%) contacted the GP, 2 (8%) contacted the rheumatologist (3 (12%) contacted GP and/or rheumatologist), 3 (12%) stopped medication completely, 3 (12%) medication withdrawn a while, 3 (12%) changed medication and 3 (12%) had taken no specific action and 1 (4%) had to return to hospital clinics.

Where would patients 'usually' seek advice?: 60% from the hospital clinics (14% 'sometimes'); 55% from the GP surgery (21% 'sometimes'); and 9% from the pharmacy (3% 'sometimes').

Where would patients 'usually' show their monitoring cards?; 71% at the hospital clinics (12% 'sometimes'); 66% at the GP surgery (7% 'sometimes'); and none at the pharmacy (none 'sometimes').

6.7.4 Patient questionnaire findings-comparison of the baseline and 6 months follow-up results

Subsequent to the follow-up of the second set of the postal questionnaires after 6 months, 52 out of 59 (88%) questionnaires were returned. There was only one patient who dropped out of the study and the reason was indicated as not willing to participate further in the study. Therefore, the results of 52 questionnaires were reported for the 6 month follow-up assessment.

Table 6.9 Comparison of the questionnaire results at pre- and post- assessments in the study group

	Mean scores (SD)		p value	
	Baseline (n=28)	*6 months after* (n=24)	*	**
IDI scale	35.1 (5.3)	36.5 (4.4)	0.096	0.085
EID scale	17.9 (3.5)	17.9 (1.9)	0.861	0.817
BMQ- necessity scale	19.9 (2.9)	20.1 (2.4)	0.861	1.000
BMQ- concerns scale	17.7 (3.8)	19.4 (2.4)	0.025	0.030
Satisfaction scale	15.7 (4.9)	17.8 (4.9)	0.178	0.176
Overall satisfaction	4.3 (1.2)	4.3 (0.9)	0.516	0.331

**Wilcoxon Signed Rank test ** Paired t test*

Four patients (14%) in the study group scored ≤30 on the IDI scale at baseline compared to one patient (4%) after 6 months of the study period, however this was not statistically significant (McNemar test, p=1.00). On the other hand, 16 (57%) of the patients scored higher than and equal to the mean value (≥35) at baseline whereas this proportion was 67% after 6 months assessment (McNemar test, p=0.73).

Seven (25%) patients in the study group scored higher than the mean value (>18) on the EID scale at baseline and eight (33%) scored after 6 months assessment (McNemar test, p=0.38).

The study group patients also indicated their beliefs about necessity of their MTX medication on the BMQ-necessity scale. Thirty nine percent of the patients scored ≤18 on the scale at baseline, which was reduced to 29% after 6 months of study period (McNemar test, p=0.63). The percentage of the patients who scored higher than the mean value (>20) was 43% at baseline and 42% after 6 months assessment.

The only statistically significant difference found in the comparison between the two different time periods was observed on the total scores of the BMQ concerns scale. Forty three percent of the study group patients scored ≤16 on the BMQ-concerns scale at baseline, which was reduced to 12.5% after 6 months study period (McNemar test, p=0.021). The percentage of patients who scored higher than the mean value (>18) at baseline vs 6 months after assessment was 43% at baseline and 58% at 6 months study period (McNemar test, p=0.508).

The patient satisfaction with the services that they receive in the pharmacy showed a trend to increase after 6 months of the study period, however it did not reach statistical significance (p=0.178).

Fifty two percent of the patients in the study group indicated that they had problems with their medications in the past at the baseline assessment compared to 64% did so after 6 months assessment. Of those who had problems with their medications in the past they also indicated their actions in response to the problems at baseline (n=12) and after 6 months (n=14) as follows;

Table 6.10 The self-management activities taken by the study group patients in response to medication problems in the past

	Baseline	6 months after
Contacted the GPs	3	2
Contacted rheumatologist	1	5
Contacted GP/ rheumatologist	1	3
Stopped medication	2	1
Changed medication	2	2
Admitted to the hospital	-	1
No specific action taken	3	-
Total	12	14

Considering the patients' actions in terms of seeking advice and showing their drug monitoring cards during their treatment process, the results showed the following pattern;

Table 6.11 The self-management activities taken by the study group patients during their monitoring process

	Baseline (n=28)		6 months after (n=24)	
	Usually	*Sometimes*	*Usually*	*Sometimes*
Advice seeking				
From the clinic	59%	15%	82%	5%
From the GP surgery	59%	15%	59%	14%
From the pharmacy	11%	4%	9%	23%
Show the card				
At the clinic	67%	15%	86%	5%
At the GP surgery	70%	4%	57%	14%
At the pharmacy	-	-	24%	5%

The following sections reported the results from the control group patients.

Table 6.12 Comparison of the questionnaire results at pre- and post- assessment in the control group

	Mean scores (SD)			
	Baseline **(n=30)**	***6 months after*** **(n=28)**	p value*	p value**
IDI scale	36.4 (5.9)	36.0 (4.9)	0.606	0.642
EID scale	18.2 (3.4)	17.3 (3.3)	0.150	0.216
BMQ- necessity scale	18.7 (3.6)	19.3 (3.7)	0.375	0.250
BMQ- concerns scale	19.5 (3.7)	20.2 (3.1)	0.624	0.435
Satisfaction scale	19.4 (4.1)	19.4 (5.7)	0.614	1.000
Overall satisfaction	4.2 (1.0)	4.2 (0.9)	0.837	0.861

* *Wilcoxon Signed Rank test* ** *Paired t test*

In contrast to the results from the study group, 6.7% of the control group patients scored ≤30 on the IDI scale at baseline and this proportion was increased to 10.7% after the 6 months period (McNemar test, p=0.63).

The differences between the scores of the IDI scales among the control group patients at baseline and after 6 months period did not show any statistical significance.

The results of the BMQ-concerns scale revealed that 23% of the control group patients scored ≤16 on the scale at baseline whereas this figure was reduced to 10.7% after the 6 months period (McNemar test, p=0.69) that indicates a trend towards increased concerns amongst the patients.

The control group patients also presented increased beliefs on the necessity of MTX therapy for their conditions. Forty eight percent of the patients scored ≤19 on the BMQ-necessity scale at baseline whereas this proportion was decreased to 43% after 6 months (McNemar test, p=0.63).

The control group patients' satisfaction with the services that they receive at the pharmacy remained at the same level at baseline and after 6 months.

Fifty percent of the patients in the control group indicated that they had problems with their medications in the past at the baseline assessment compared to 42% after 6 months assessment. Of those who had problems with their medications in the past also indicated their actions in response to the problems at baseline (n=14) and after 6 months (n=11) as follows;

Table 6.13 The self-management activities taken by the control group patients in case of medication problems in the past

	Baseline	6 months after
Contacted the GPs	5	4
Contacted rheumatologist	1	2
Contacted GP/ rheumatologist	2	1
Contacted nurse specialist	-	1
Stopped medication	1	-
Changed medication	1	-
Medication withdrawn	3	2
Admitted to the hospital	1	-
No specific action taken	-	1
Total	14	11

Considering the patients' actions in terms of seeking advice and showing their drug monitoring cards during their treatment process, the results showed the pattern as follows;

Table 6.14 The self-management activities taken by the control group patients in case of medication problems in the past

	Baseline (n=30)		6 months after (n=28)	
	Usually	*Sometimes*	*Usually*	*Sometimes*
Advice seeking				
From the clinic	61%	13%	59%	11%
From the GP surgery	52%	26%	56%	15%
From the pharmacy	6.5%	3%	19%	7%
Show the card				
At the clinic	74%	10%	63%	11%
At the GP surgery	61%	10%	78%	-
At the pharmacy	-	-	19%	7%

Table 6.15 The comparison of the study and the control group at the baseline and 6 months after assessments

	Mean (SD)					
	Study group			Control group		
Scales	**Pre (n=28)**	**Post (n=24)**	**p value***	**Pre (n=30)**	**Post (n=28)**	**p value***
IDI	35.1 (5.3)	36.5 (4.4)	0.085	36.4 (5.9)	36.0 (4.9)	0.642
EID	17.9 (3.5)	17.9 (1.9)	0.817	18.2 (3.4)	17.3 (3.3)	0.216
BMQ- necessity	19.9 (2.9)	20.1 (2.4)	1.000	18.7 (3.6)	19.3 (3.7)	0.250
BMQ- concerns	17.7 (3.8)	19.4 (2.4)	0.030	19.5 (3.7)	20.2 (3.1)	0.435
Satisfaction	15.7 (4.9)	17.8 (4.9)	0.176	19.4 (4.1)	19.4 (5.7)	1.000
Overall satisfaction	4.3 (1.2)	4.3 (0.9)	0.331	4.2 (1.0)	4.2 (0.9)	0.861

**Paired t test*

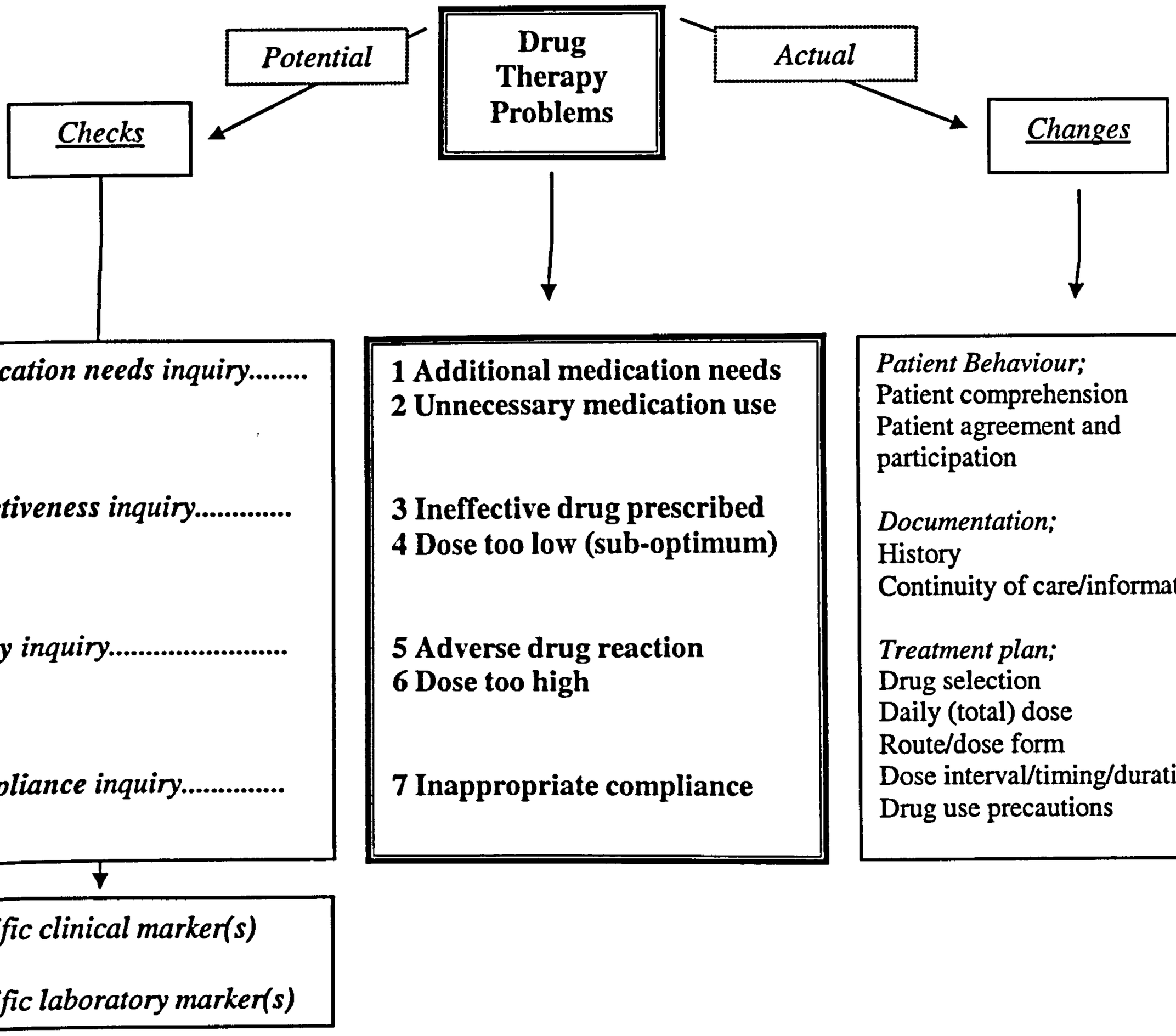
No statistically significant difference was found between the study and the control group patients' responses to the questionnaire at baseline and 6 months after assessment in terms of IDI, EDI and BMQ-necessity and BMQ-concerns scales (Mann Whitney U test, $p > 0.05$).

6.7.5 The results of drug therapy problems identified from the rheumatology care plans

During the period of December 2001-December 2002, fifty two rheumatology care plans were issued by the hospital clinics for 28 'study' group patients where 507 care issues were identified. Of those, three care issues were not valid at the time of the patient's visit to the hospital clinic and additional two care issues were related to a referral to the physiotherapy department and two were regarding information to the GPs/pharmacists. Therefore they were disregarded in the categorisation of care issues as they were not related to drug therapy problems. The mean (SD; Median) number of issued care plans was 1.9 (0.65; 2.0) and the mean (SD; Median) number of care issues identified per patient was 17.8 (9.3; 17). One patient (the study group) dropped out of the study after having been issued one rheumatology care plan.

Consequently, five hundred care issues were identified from the study group patients for the further analysis. The identified care issues were categorised according to the classification of drug therapy problems (DTPs) proposed by Strand et al[31] and adapted by McAnaw.[285] The categorisation system is schematized in below Figure 6.9.

Figure 6.9 Categorisation System for the Drug Therapy Problems



The results are summarised in Table 6.16, Table 6.17 and Table 6.18. It has been shown that there is a statistically significant difference between the 'non-deprived' and the 'deprived' patient groups in terms of the monitoring of specific laboratory markers for the medication needs (Chi-square test, p=0.003).

Table 6.16 The distribution (%) of drug therapy problems (DTPs) and monitoring inquiries identified at the hospital clinics for the all patients

Drug therapy problems	Potential	Actual
Medication needs	168 (33.9%)	4
Effectiveness	15 (3.0%)	-
Safety	142 (28.6%)	-
Compliance	171 (34.5%)	-
Total	496 (100%)	4

Table 6.17 The distribution of drug therapy problems (DTPs) identified at the hospital clinics for the 'non-deprived' (n=11) and the 'deprived' (n=17) patient population

	Drug therapy problems (per patient)			
Category	Non-deprived (n=11)	Deprived (n=17)	Total (n=28)	p value*
Medication needs	85 *(7.7)*	87 *(5.1)*	172 *(6.1)*	0.089
Effectiveness	9 *(0.8)*	6 *(0.4)*	15 *(0.5)*	
Safety	55 *(5.0)*	87 *(5.1)*	142 *(5.1)*	0.121
Compliance	72 *(6.5)*	99 *(5.8)*	171 *(6.1)*	0.496
Total	221	279	500	

* *Chi-square tests*

Table 6.18 The distribution of monitoring inquiries identified at the hospital clinics for the 'non-deprived' (n=11) and the 'deprived' (n=17) population

		Drug therapy problems (%)		
Monitoring inquiries		**Non-deprived (n=11)**	**Deprived (n=17)**	**Total (n=28)**
Medication needs		85 (38.5)	83 (30.2)	168 (33.9)
	Clinical	65 (29.4)	77 (28.0)	142 (28.6)
	Laboratory	20 (9.0)	6 (2.2)	26 (5.3)
Effectiveness		9 (4.1)	6 (2.2)	15 (3.0)
	Clinical	3 (1.4)	-	3 (0.6)
	Laboratory	6 (2.7)	6 (2.2)	12 (2.4)
Safety		55 (24.9)	87 (31.6)	142 (28.6)
	Clinical	26 (11.7)	34 (12.3)	60 (12.1)
	Laboratory	29 (13.1)	53 (19.3)	82 (16.5)
Compliance		72 (32.6)	99 (36.0)	171 (34.5)
	Clinical	30 (13.6)	40 (14.5)	70 (14.1)
	Laboratory	42 (19.0)	59 (21.5)	101 (20.4)
Total		**221 (100%)**	**275 (100%)**	**496 (100%)**

6.7.6 The laboratory results from the patient-held monitoring cards and the rheumatology care plans

The data for the laboratory results were collected from the rheumatology care plans and the drug monitoring cards for the 'study' group patients and from the drug monitoring cards for the 'control' group patients. There were 1673 blood test investigations identified; of those 1003 for the 'study' group patients and 670 for the 'control' group patients and the results are summarised in Table 6.19.

Table 6.19 The frequency of laboratory results reported for the 'study' and the 'control' group patients

	Number of investigations performed		
Investigations	**Study (n=28)**	**Control (n=31)**	**Total (n=59)**
Albumin	36	1	37
ALT	80	10	90
AST	80	10	90
Alk. Phosp.	2	-	2
Gamma GT	3	-	3
C reactive protein	24	-	24
Creatinine	107	49	156
Plasma urea	46	1	47
ESR	143	137	280
Haemoglobin	159	146	305
Platelets	159	145	304
WCC	159	146	305
Blood pressure	-	8	8
Urine	4	9	13
Ferritin	1	-	1
Total	*1003*	*670*	*1673*

6.7.7 The results of drug therapy problems identified in the community pharmacies

Thirty seven out of 59 (63%) data collection forms were returned by the pharmacists at the end of the 6 months period. The community pharmacists initiated/prompted one hundred and two queries for 10 'study' group patients and 15 'control' group patients, regarding their disease status and drug therapies during the period of December 2001-December 2002. Ninety out of 102 (88%) queries were specified on the data collection forms; however, the remaining 12 (12%) queries were not specified, because the pharmacist did not see the patient at the time the prescription was presented at the pharmacy. Among the indicated treatment issues/queries, 30 (33%) were to verify that the patient does not have any problems or confirmed the patient was feeling well at the time of the visit. Of those, 18 (60%) and 12 (40%) were for the 'study' group and the 'control' group patients respectively.

Sixty one queries were specified regarding drug therapy problems, of which 22 (36%) were from the 'study' group and 39 (64%) from the 'control' group patients (Chi-square test, p= 0.024). Eighteen (30%) care issues (7 from the 'study' and 11 from the 'control' group patients) were related to the potential ***'additional medication needs'*** of the patients; 4 (6.5%) indicated the potential prescribing of an ***'ineffective drug'*** (2 from the 'study' and 2 from the 'control' group patients); 3 (5%) indicated ***'sub-optimum dose'*** (2 from the 'study' and 1 from the 'control' group patients) and 3 (5%) indicated ***'high dose'*** of intended drug therapy (1 from the 'study' and 2 from the 'control' group patients).

Twenty (33%) care issues (7 from the 'study' and 13 from the 'control' group patients) showed the potential ***'adverse drug reactions'*** that the patients might be experiencing at the time of the visit. Moreover, thirteen (21%) care issues explored the potential ***'inappropriate compliance'*** (3 from the 'study' and 10 from the 'control' group patients).

Table 6.20 Distribution (%) of drug therapy problems (DTPs) identified in the community pharmacy settings

DTPs	Study (n=10)	Control (n=15)	All (n=25)	p value*
Medication needs	7 (32)	11 (28)	18 (30)	0.494
Effectiveness	4 (18)	3 (8)	7 (11)	0.205
Safety	8 (36)	15 (38)	23 (38)	0.547
Compliance	3 (14)	10 (26)	13 (21)	0.222
Total	***22 (100%)***	***39 (100%)***	***61 (100%)***	

**Fisher's Exact test*

Consequently, sixty-one monitoring activities were recorded by the community pharmacists as shown in Table 6.21.

Table 6.21 Distribution of drug therapy problems (DTPs) identified as monitoring inquiries at the community pharmacy settings

Drug therapy problems *Monitoring inquiries*	Study (n=10 patients)	Control (n=15 patients)	Total (n=25 patients)
Medication needs	7 (32%)	11 (28%)	18 (30%)
Clinical	3	8	11
Laboratory	4	3	7
Effectiveness	4 (18%)	3 (8)	7 (11%)
Clinical	1	2	3
Laboratory	3	1	4
Safety	8 (36%)	15 (38%)	23 (38%)
Clinical	6	8	14
Laboratory	2	7	9
Compliance	3 (14%)	10 (26%)	13 (21%)
Clinical	2	4	6
Laboratory	1	6	7
Total	**22**	**39**	**61**

The comparison between the frequency of the identified drug therapy problems in the hospital and in the community settings showed that no statistically significant difference was found regarding the medication needs and safety problems (Chi-square test, $p>0.05$). However there were significantly more drug therapy problems identified in the hospital clinics for the effectiveness and compliance problems (Chi-square test, $p<0.05$) (see Table 6.16).

The community pharmacists also highlighted the potential medication errors that the prescriptions presented on six occasions. They were as follows;

- the dose of methotrexate had been changed by the hospital but was not changed on the prescription by the GP (2 occasions).
- the dose of methotrexate on the GP prescription was twice as high as it was supposed to be (1)
- the dose of methotrexate indicated 'as directed' on the prescription (1)
- the dose of methotrexate 10mg was not specified on the prescription (1)
- diclofenac was ordered instead of celecoxib which the patient was taking for a while (1)

6.7.8 The patterns of methotrexate prescriptions

Methotrexate prescribing and dispensing patterns are summarised below in terms of the number of prescriptions dispensed, the proportion of dispensed tablet strength and the amount of tablets dispensed over the time period.

The data for methotrexate prescriptions were collected by the participating community pharmacists between the period of December 2001 and December 2002 both for the control and the study group patients. Two hundred and forty seven prescriptions were presented by 37 patients (15 patients from the study group and 22 from the control group) within 12 months. The data are summarised in

Table 6.22 and Table 6.23.

The mean (SD; Median) dose of prescribed methotrexate was 12.4 (3.7; 12.5) mg/week and the mean (SD; Median) dose prescribed of folic acid was 5.2 (0.9; 5) mg/week for the patient population. The mean (SD; Median) amount of dispensed tablets of methotrexate per prescription was 9.8 (8.4; 8) for the 2.5mg tablet strength and was 7.4 (6.8; 4) for the 10mg tablet strength.

No statistically significant difference was found between the 'control and the 'study' group in terms of the number of prescriptions presented for methotrexate and for other medication during the data collection period (Chi-square test, $p>0.05$).

The pharmacists indicated in one hundred and twenty six visits that the mean (SD; Median) time that they spent with patients on each was 2.6 (2.3; 2) minutes in order to dispense the prescription presented and/or to discuss any problems that the patient may have at the time of the visit to the pharmacy.

Table 6.22 Methotrexate prescriptions details for the study and the control group patients

	Study group (n=15)	Control group (n=22)	Total (n=37)
Number of prescriptions presented	98	149	247
MTX only	9 (9%)	14 (9%)	23 (9%)
Other medication	53 (54%)	75 (50%)	128 (52%)
MTX and other medication	36 (37%)	60 (40%)	96 (39%)
Dose of MTX in prescriptions presented *indicated as;*	43	67	110
2.5mg/week	-	1 (2%)	1 (0.1%)
7.5mg/week	4 (9%)	17 (25%)	21 (19%)
10mg/week	6 (14%)	8 (12%)	14 (13%)
12.5mg/week	15 (35%)	28 (42%)	43 (39%)
15mg/week	10 (23%)	6 (9%)	16 (15%)
17.5mg/week	3 (7%)	5 (8%)	8 (7%)
20mg/week	3 (7%)	2 (3%)	5 (5%)
22.5mg/week	2 (5%)	-	2 (2%)
Number of prescriptions with only 2.5mg tablet strength prescribed	38 (86%)	61 (87%)	99 (87%)
Number of presciptions with only 10 mg tablet strength prescribed	-	-	-
Number of prescriptions with combination of tablet strengths prescribed	6 (14%)	9 (13%)	15 (13%)
Number of visits to pharmacy (per person)	98 (5.8)	149 (7.5)	247

Table 6.23 MTX prescriptions details for the patients in the 'non-deprived' and the 'deprived' group

	Non-deprived (n=15)	Deprived (n=22)	Total (n=37)
Number of prescriptions presented	92	155	247
MTX only	7 (7.6%)	16 (10.3%)	23 (9%)
Other medication	51 (55.4%)	77 (49.7%)	128 (52%)
MTX and other medication	34 (36.9%)	62 (40.0%)	96 (39%)
Dose of MTX in prescriptions presented			
indicated as;	38	72	110
2.5mg/week	-	1 (1%)	1
7.5mg/week	4 (10.5%)	17 (24%)	21
10mg/week	3 (8%)	11 (15%)	14
12.5mg/week	13 (34%)	30 (42%)	43
15mg/week	9 (24%)	7 (10%)	16
17.5mg/week	5 (13%)	3 (4%)	8
20mg/week	4 (10.5)	1 (1%)	5
22.5mg/week	-	2 (3%)	2
Number of prescriptions with only 2.5mg tablet strength prescribed	35	65	105
Number of prescriptions with only 10 mg tablet strength prescribed	-	-	-
Number of prescriptions with combination of tablet strengths prescribed	6	9	15

The results indicated that patients from the 'deprived' environment did not present more prescriptions than those from the 'non-deprived' environment (observed findings in the 'deprived' is 63% (expected 60%; Chi-square test, $p>0.05$). However, in regard to the indicated dose of methotrexate, the proportion of prescriptions presented by patients for methotrexate at the dose of ≥15mg/week was 18% in the 'deprived' group compared to 47.5% in the 'non-deprived' (Chi-square test, $p<0.05$).

6.8 Discussion

Discussion on the results of the questionnaire

One of the main aims of this study was to assess the patient's desire for information/knowledge about their disease or its treatment. The hypothesis was that the patient's desire for information would increase with them being engaged with self-management activities along with the involvement of their pharmacists in their treatment process.

The total patient population sampled for this study (in the control or the study group) already indicated a high desire for information about their medicine at the baseline assessment, which was not surprising considering that rheumatoid arthritis is a chronic condition that the patients have to live with. The results of the IDI and the EID scales did not change dramatically after 6 months assessment, which indicated that the patients sustained/maintained their attitudes towards willingness to have information about their medicines. The study group patients indicated a trend for a higher desire for information about their MTX therapy after 6 months, but it did not change significantly. On the other hand, the control group patients also indicated a higher desire for information at baseline assessment but it slightly decreased after 6 months of the study period, which might indicate the lack of pharmacist's input into their MTX therapy.

The original authors of the Intrinsic Desire for Information questionnaire had previously found that the total EID score was significantly associated with patient's age (Pearson r= -0.432), school leaving age (Pearson r= 0.115) and occupation (Spearman rho= -0.15), which indicates that older patients tend to desire less information than younger patients. Given the fact that the patients with rheumatoid arthritis are more likely to be older but still willing to have more information, the crucial point is to maintain their desire for information about their medicines in the long term. This study did not focus on the effect of the patient's occupation and age on the willingness to have information but it considered the potential impact of living within a socially deprived environment. Although the results of the IDI and EID scales from the pre and post assessments showed varying patterns, it was found that the patients from more deprived areas indicated a higher desire for information about their medicines. Although there was no statistically significant difference found in terms of patient's desire for information between the 'deprived' and the 'non-deprived' groups, the slightly observed trend may indicate that the patients from the deprived areas are more likely

to demand information regarding their treatment and may need more attention from the health care professionals. This is worthy of more investigation in a larger study.

The other outcome measure of the study was the assessment of patient's attitudes towards their medication. At the baseline assessment 49% percent of the total population scored ≤19 on the 'necessity' scale on the Beliefs about Medicine questionnaire, which indicated that half of the patient population is convinced that their MTX medication is necessary for maintaining or improving their health now and in the future. In the 'concerns' scale, 63% of the patient population scored ≤19 which indicates that over a third of the sample do not have strong concerns about potential side effects and risk of their MTX treatment.

However, after 6 months assessment, 60% of the total population scored ≤20 on the 'necessity' scale, which indicated that more than half of the patient population is convinced that their MTX medication is necessary for maintaining or improving their health now and in the future. There is no statistically significant difference found between the control and the study group patient population (Mann-Whitney U test, U=297.50 p= 0.48). In the 'concerns' scale, 56% of the patient population scored ≤20 which indicated that nearly over half of the sample do not have strong concerns about potential side effects and risk of their MTX treatment. There is no statistically significant difference between the control and the study group patient population (McNemar test, $p>0.05$).

The original authors of the Beliefs about Medicine questionnaire indicated that there is a strong association between the 'necessity' and the 'concerns' scales total scores and patient adherence to medication. The patients with stronger beliefs in the necessity of their medication (high scores on the BMQ-necessity scale) were significantly more adherent, whereas the patients with stronger concerns (high scores on the BMQ-concerns scale) were significantly less adherent.[82]

The results from the baseline assessment indicated that 51% of the patients scored higher than the mean value on the 'necessity' scale, which suggests that those patients are more likely to adhere to the treatment. However, 37% of the patients scored higher than the mean value on the 'concerns' scale which presumes that those patients are less likely to adhere to their MTX therapy.

Only fourteen percent of the total patient population have a negative value (less than '0') for the 'necessity' and 'concerns' differential, at baseline and 6 months-after assessments, which

indicated that the majority of the patients believe that the potential benefits of methotrexate therapy outweigh the risk of the treatment, indicating a direction of change associated with an increased likeliness to adhere to the therapy.

The patients in the study group expressed increased concerns about the methotrexate potential side effects and risk of the treatment after the 6 months period. In other words, involvement of the pharmacists in the monitoring processes might have caused patients to become more concerned about their treatment after 6 months, which presented an existing or even an increased awareness about their therapy.

Inevitably, there was a possibility of bias for the results of the specific Beliefs about Medicine questionnaire. The 'necessity' and the 'concerns' scales' questions were included in the whole questionnaire sequentially and consecutively in this study. Although, the original authors of the questionnaire suggested a different order for the questionnaire items, this information was not available for the researcher before the questionnaires were implemented in the study population. Therefore, it might be an explanation of why the patients' concerns were increased after 6 months assessment.

It has been found that the patients become more involved with their MTX monitoring process during the 6 months study period which was indicated by an increased proportion of showing of their drug monitoring card in the clinic, GP surgery and at the pharmacy and seeking advice when they have problems with their medication.

Discussions on the results of the drug therapy problems and identified care issues

The study also identified drug therapy problems of the patients in the study group who were exposed the pharmaceutical care intervention.

The purpose of reporting pharmaceutical care activities by the categorisation system used in this study was to reduce ambiguity and to produce more specific and focused themes for care issues. The care issues can be described as the 'drug therapy problems' or as the 'activities that must be performed'. It has been suggested that reducing the *actual* drug therapy problems may indicate better provision of pharmaceutical care, therefore allows increased quality of care. Moreover, reporting the 'actual drug therapy problems' per patient will help to identify the exact prevalence of drug therapy problems. [285]

The drug therapy problems identified in the hospital settings in this study were mostly 'potential' problems where the patient may experience reduced quality of care if preventative action is not taken in near future. The most common problems identified in the hospital setting were patient compliance, which was followed by the 'medication needs', 'safety' and 'effectiveness' drug therapy problems. The patients from the different socio-economic environments did present similar patterns for the drug therapy problems however, there were slightly more drug therapy problems identified for the patients in the 'deprived' environment (279 for the 'deprived' 16.4 per patient vs 221 for the 'non-deprived' 20.1 per patient) which may indicate the special group of patients who need additional contributions from the health care professionals.

On the other hand, the drug therapy problems that were identified in the community settings indicated that the most common problem are the 'safety', followed by the 'medication needs', 'compliance' and the 'effectiveness' categories of drug therapy problems. It was clear that the community pharmacists were apprehensive about the safety of drug therapy of their patients, which also emphasised the potential role of the community pharmacists in the monitoring of patient's drug therapy.

It was also found that the community pharmacists managed to identify six occasions that had a possibility of medication errors with methotrexate therapy and they took an action before those errors resulted in serious consequences. Therefore, the community pharmacists highlighted their impact on the maintenance of the safety of drug therapy for the patients.

Discussions on the results of the methotrexate prescriptions pattern

The results indicated that the patients in the control group presented more prescriptions compared to the patients in the study group (60% vs 40%, respectively), but the patterns of methotrexate prescriptions presented at the pharmacy were similar in the two groups. The proportion of patients who received methotrexate at the dose of ≥15mg/week was 43% in the study group whereas it was 21% in the control group. Even though the patients in the study group are receiving a higher dose regimen for the methotrexate treatment, the proportion of identified drug therapy problems was similar for both patient groups, which might indicate the potential contributions of the proposed model of care in this study.

Although it appeared that the patients from the 'deprived' group presented more prescriptions compared to the patients in the 'non-deprived' group, the patterns of methotrexate

prescriptions presented at the pharmacy was similar in the two groups of patients. However, the interesting finding was that the proportion of patients who received methotrexate at the dose of ≥15mg/week was higher in the 'non-deprived' group (47.5%) compared to the 'deprived' group (18%). This figure has raised the question of why patients in the relatively deprived areas were less likely to be put on the higher dose methotrexate regimens. This issue also occurred as a result of the retrospective study (see Chapter 3), therefore it might be considered that there is a potential effect of socio-economic environment on the treatment process of the patients who receive methotrexate therapy for their arthritic conditions. This question deserves further study.

The use of different strengths of methotrexate tablets was also confirmed through the prescriptions presented in the community pharmacy. The proportion of dispensed 2.5mg tablet strength of methotrexate was higher than the proportion of dispensed 10mg tablet strength, which verified the preferred use of the 2.5mg tablet strength in practice. It is because the use of 2.5mg strength allows easy dose titration throughout the methotrexate treatment and may reduce the likelihood of occurrence of medication errors. However, for the higher dose regimen of methotrexate therapy, 10mg tablet strengths are still available for patients who require to take fewer tablets in their medication regimens.

6.9 Limitations of the study

The study aimed to assess the contribution of the community pharmacists in the monitoring process of methotrexate treatment through implementation of the rheumatology care plans. However, the study encountered limitations in order to achieve its aim. These are described in the following section.

Lack of definition/expectations of patient services provided by the participating pharmacy:
In the intervention group, the community pharmacists were expected to be involved in patient care activities prompted by the care plans generated by the clinic. However, the variation in pharmacists' skills, their relationships with their patients and the intense workload of the pharmacy shops might have an effect on the activities that pharmacist might have taken during the data collection period and the number of care issues documented. The researcher was not able to optimise/standardise these processes for the whole patient population. This limitation is an inevitable problem in trying to evaluate an emerging form of practice.

Lack of control over the patients: The patients were asked to attend the same community pharmacy during the study period that they nominated at the beginning of the study. They were also provided with a new monitoring card which they were expected to bring to their pharmacist, the GP and the clinic. However, the researcher did not have control over this process, which may also have limited the opportunity for identification of the care issues in the community settings.

The patient recruitment process and the sample size: The sample from the patient population was achieved within a limited 3 month recruitment period, leading to a smaller sample size than anticipated. The study included only 59 patients, even though attempts to improve the recruitment process by extending identification of patients beyond the hospital clinics were put in place. The small sample size of the patient population also might have affected the ability of the study to demonstrate significant differences in outcome measures.

The duration of the study and the outcome measures: The sample size calculation was based on the previous results of the questionnaire scales. The main outcome of the study was to determine the changes in the patient's desire for information and their beliefs about their medication by the potential contribution of community pharmacist in the patient care process. Therefore, the measurements for outcome assessment were grounded on the patient's desire for information for their treatment, their beliefs about their medications and consequently their satisfaction with the service that they additionally receive at the pharmacy. The study hypothesised that the patients would desire more information about their treatments, would have increased beliefs about the necessity of their medications and become less concerned about the potential side effects of their therapies, with the involvement of their pharmacists in their monitoring processes. Therefore, their satisfaction with the services that they regularly receive at the pharmacy might have expected to increase at the end of the study period.

It can be assumed that a certain amount of time should be allowed for the patient population to demonstrate detectable changes that might occur in the outcome measures. The study was initially designed to last for 12 months, whereas the intervention period had to be limited to 6 months. Therefore, the intended time period might have not been sufficient to recognise the changes in the patients' beliefs, attitudes and opinion about the new care model proposed from the health care providers. Particularly, given the fact that the patients are generally seen by the consultants every 4-6 months and almost every month by their pharmacists, there would be a maximum of six contacts by their pharmacists during the intervention period of

the study which may not be enough to establish detectable change in the selected outcome measures.

Lack of control over contributions from the GPs: The study did not aim to identify impacts of contributions from the GPs in the patient care process. As the pharmacies were randomised, the GPs consequently have the patients from the 'control' and the 'study' group. Therefore, the researcher assumed that the patients received a similar care from their GPs. However, the study was unable to identify the additional care issues that might have been identified by the GPs or any actions that had been undertaken through liaison with the pharmacist, unless these care issues and actions were specified on the data collection forms by the community pharmacists.

6.10 Conclusion

The involvement of community pharmacist in the monitoring process of patients receiving methotrexate treatment has been evaluated in this study.

The treatment of rheumatoid arthritis involves the specialist treatment from the secondary care, surgical treatment, drug treatment, complementary/alternative treatment and exercise therapy. Furthermore, a collaborative approach with a multidisciplinary team care and engagement of patients with self-management activities would create opportunities for different roles and level of involvement.

It has been acknowledged that there is a need for a structured pro-active approach to disease management in rheumatoid arthritis.[120] This approach can be established through a well co-ordinated team of skilled health care providers and empowered patients, which further emphasise the importance of primary care in chronic disease management.

Improved outcomes in the management of rheumatoid arthritis, particularly with methotrexate therapy, can be achieved by close control and monitoring of the patients. Therefore, it can be concluded that the community pharmacists are in a position to support patient care through counselling on medications and potential side effects, giving advice on the purchase of over-the-counter (OTC) products, guidance on self-management activities and monitoring of the patient groups who potentially need extra vigilance in the community settings.

Chapter 7: Synthesis of Findings, General Discussion and Conclusions

7.1 Introduction

The disease management in chronic, long-term conditions generally begins with the (1) recognition of the disease by the primary care health care providers (2) a referral to a specialist in secondary care and (3) long term management by shared contributions from primary and secondary care health providers, social workers and lay health workers. The successful system must provide a comprehensive approach for the provision of health care through an integrated seamless system for prevention and care. The process utilises the health care services and focuses on outcomes for the specific patient population where the patients demand continuous and comprehensive care from the health care professionals.[286]

Recently, a growing body of evidence indicates that provision of care for patients with chronic diseases is well managed by specialists since those health care providers are more knowledgeable about the diseases, familiar with the emerged evidence and have authority and influence on implementation of new guidelines at their practices.

The shift towards a shared care model in chronic disease management should reduce any differentiation in the care provided by specialists (in secondary care) or by generalists (in primary care) by allowing each practitioner to provide their own type of patient support.

The various models of care that have been demonstrated in the literature have sought to improve chronic disease management and the medicines management in patient care processes.[287] Some of those suggest participation of relevant medical specialists beyond their usual roles and mediation of the specialist's input through nurses: whereas others favours the value of the visits to the primary care practices made by specialists, nurses or clinical pharmacists.

The design of a disease management model requires identification of a specific patient population which has a particular treatment priority, the assessment of available resources in the practice setting and definition of key indicators for the evaluation of the model using appropriate methods. In pharmaceutical care the targeted patient populations that are likely to be responsive and benefit from better integration of the pharmacist's contribution can include those patients with diseases that can be effectively controlled with improved patient adherence to medication, better education, and improved patient monitoring.

Regardless of the particular model of provision of patient care, the patient care process involves three stages which should be maintained in the delivery of pharmaceutical care to individual patients;[31, 33]

- assessment of pharmaceutical care issues for individual patients *(patient's needs assessment)*

- formulation of a pharmaceutical care plan *(design of the care plan)*

- implementation and monitoring the pharmaceutical care plan *(evaluation)*

The goal of co-ordinated disease management approaches and provision of pharmaceutical care is to provide additive effects on humanistic and economical outcomes. Audit of the impact of the new models is integral to the provision of health care.

Health services research, within which has emerged pharmacy practice research, has drawn attention to the role of primary care and the necessity of multidisciplinary teamwork on chronic disease management among health care professionals. Moving from the paternalistic thinking where the patient passively accepts the authority of doctors, new models are based on the aim of ensuring that patients have confidence and are skilled to self-manage their conditions in collaboration with other health care provides as necessary.

7.2 Summary of the main research findings

The main findings of this thesis can be summarised under five headings which cover different aspects of the health care provided for patients diagnosed with rheumatoid arthritis.

7.2.1 The management of rheumatoid arthritis: from the perspectives of the health care providers (and potential gaps at the primary and secondary care interface)

The management of rheumatoid arthritis is currently undertaken by the secondary care specialists in liaison with the primary care team according to the local shared care treatment protocols.

The inquiry into the perceptions of the different health care providers on the disease management provided unique understanding of the current system of health care for patients diagnosed with rheumatoid arthritis (see Chapter 2). The challenges for health care professionals in order to maintain the continuity of care are recognised and the potential gaps within the system are identified. The findings of the qualitative study envisaged the issues around the management of rheumatoid arthritis and explored the perceptions and expectations of health care providers.

Although a small number of interviews were conducted, sufficient information was gathered to supplement the literature review in order to construct the pharmaceutical care model for the arthritic patient population. Disclosure of the potential obstacles within ongoing processes revealed the need for solutions to overcome barriers and help health care providers to function in a more co-ordinated way in order to support patients more efficiently. The interviewees were particularly chosen from different health care environments in Glasgow in order to reflect issues on the health care system according to the different socio-economic environments. Therefore, the study was able to supplement the information from the literature on the strategies and systems for the management of rheumatoid arthritis in current practices.

The unforeseen finding of the study was that the community pharmacists do not receive any information from the hospitals or surgeries regarding the shared care protocols for the disease management of patients with rheumatoid arthritis. Furthermore some pharmacists are even not aware of the fact that the patients are given a card for the monitoring of disease-modifying anti-rheumatic drug therapies. Therefore, there are missed opportunities for community pharmacists to participate in the disease management of rheumatoid arthritis. These findings reflect communication drawbacks within the system, which should be addressed by the health care providers.

Another result of the study indicated that the general practitioners (GPs) do not necessarily see the patients every month when the patients make visits to the surgery for their blood tests to be done. This situation has an implication where the patients are not capable of identifying their potential needs and recognising any potential problems about their treatment. The assumptions by secondary care specialists that patients are closely monitored by primary care health providers seems to be overlooked by secondary care specialists, which may cause problems in the continuity of patient care. Moreover, this also emphasises the importance of patient self-management strategies in the chronic disease management of RA.

The local disease management protocols for the shared care process that have been used in the practices are slightly at variance with each other which has the potential to cause misunderstanding amongst the primary health care providers. Therefore additional, supportive education and training for those health care providers are necessary if further involvement in disease management is required.

A lack of a standard system for documentation of the care activities performed by the health care professionals appeared to be problematic in the provision of the seamless care that is intended for the patients.

7.2.2 Methotrexate therapy as a treatment choice in rheumatoid arthritis

Effective disease management in RA relies on a focus on drug therapy, which is central to the treatment of rheumatoid arthritis since the goal is disease modification. Almost all patients with rheumatoid arthritis receive disease-modifying anti-rheumatic drugs (DMARDs) at some stage of their disease and methotrexate is the second choice after sulphasalazine.

Although new drugs have been introduced in the treatment of rheumatoid arthritis, methotrexate preserves its value among the available treatment options. It has recently become established in the literature as a 'standard' comparative therapy in the assessment of new therapeutic agents, which verifies the importance of methotrexate therapy.

The findings of the retrospective study, which was undertaken as a part of this thesis (see Chapter 3), are consistent with the results from previously published studies. The discontinuation rates among methotrexate-treated arthritic patients in the UK have not previously been reported by survival analysis until the year 2001[240], thus this study provides useful data for future comparisons. Moreover, the comparison with the recent UK results showed similar patterns for methotrexate use in the arthritis population, where discontinuation rate is 20% and 30% at the end of first year and second year of the treatment, respectively. The results emphasised the fact that the majority of the patients who receive methotrexate have remained on the treatment beyond 5 years from initiation. Since unwanted effect of methotrexate can occur at any point after initiation, patients and health care providers should remain vigilant throughout this continuous care processes. The pattern of methotrexate toxicity also gives insights into potential problems that patients might

experience during their treatment and would help health care providers to identify the likelihood of unwanted effects of methotrexate therapy.

The study also examined the influence of social deprivation and its effects on the treatment continuation rate. Although published evidence suggests that measures of the health impact of rheumatoid arthritis vary according to the rheumatoid patient's socio-economic status, the study indicated no differences between the patient groups in terms of discontinuation rate for methotrexate therapy. However, identification of a lower methotrexate dose at the time of discontinuation among the patients living in the lower socio-economic environments deserves further study.

The investigation on DMARDs use in the arthritic population provides a perspective for future research. The retrospective data also showed the patterns for the use of other disease-modifying anti-rheumatic drug during the period of 1992-1999 where methotrexate predominantly is associated with toxicity as the reason for its discontinuation.

The findings of this retrospective study reflect the patterns of current health care practice particular to Glasgow between the years of 1992-1999. Therefore, further generalisation of these findings may not be appropriate. However, within the scope of the thesis the findings allowed the local use of methotrexate in rheumatoid arthritis to be described in the context of other similar work in the literature.

Nevertheless, time restriction, workloads of clerical staff at the hospitals and limited competency of hospital's database might have affected the quality of information that could be gathered during the study. This kind of research undertaken by one, like this researcher, who is external to the health care settings can be problematic and more time consuming since access to data requires special provisions and recognition that limitations are imposed by the workload of daily practice on clinical collaborators. Nevertheless in spite of the hurdles the level of co-operation of clinical and clerical staff was always high, instead of reliance on computerised profiles of patients, the study could have been accomplished by searching through patient's medical notes, which would have provided more depth and reliable information about patient's disease status at the time of any DMARD therapy. However, the process of accessing patients' medical notes would have been too time consuming and inconvenient to staff.

The practice of prescribing and monitoring methotrexate varies according to the preferences of specialists in different countries or even in the different settings in the same country, because the evidence base for its optimum use is incomplete. Therefore, achieving a clearer understanding of and agreement on good practice during the different stages of methotrexate therapy would create better opportunities for inclusion of the various health care providers contribute to better patient care and to better patient self management.

7.2.3 Health care needs of patients with rheumatoid arthritis

A part of the thesis focused on the health care needs of arthritic patients who receive methotrexate therapy. The pharmaceutical care needs of patients who receive disease modifying anti-rheumatic drug therapies have been previously identified by the study undertaken within the University of Strathclyde Pharmaceutical Care Research Group.[288] However, the patients' educational needs, their beliefs about their medications and their satisfaction with the pharmacy services have not been identified systematically or quantified in any way.

The education of patients and maintenance of their knowledge about their treatments are crucial elements of chronic disease management. Therefore, it is important to verify and assess the patients' desire for information about their therapies and their beliefs about their medications. Understanding of patients' beliefs and attitudes towards their disease management would provide an explicit framework for the self-management strategies (see Chapter 6). Furthermore, attention to the particular aspects of the various health belief models that were discussed in Chapter 1-section 1.7, would improve the understanding of patient's behaviour and attitudes in the self-management process. The study serves as a descriptive analysis of patients' behaviour and attitudes during chronic disease management which impact on patient empowerment and the patient's self- management role.

The results of the questionnaires confirmed that the patients are willing to receive information about their treatment although they hold concerns over the side effects of the methotrexate therapy. This was not unexpected given the fact that most of the patients with chronic diseases become an expert in their condition after living with it for a long period of time; particularly in patients diagnosed with rheumatoid arthritis where different treatment options are available and the majority of them encompass potential side effects in long and/or short term therapy.

The particular finding of the study which is not consistent with the perceptions of the health care providers was the absence of a demonstrable effect of social deprivation on the patient's desire for information or their beliefs about their medicines. However, the interpretation of these findings is limited by the small sample size. It has been shown from the previous studies that patients from different socio-economic backgrounds may present dissimilar preferences about information or show different attitudes and beliefs towards their medication.[279] Nevertheless, the hypothesised effect of social deprivation on the patient's desire for information and their concerns on methotrexate therapy has not been supported by the evidence from this study.

One of the findings that emerged from the patient questionnaire is that the patients perceive the hospital rheumatology clinic as a first call for information or help request regarding their diseases or treatments. This attitude is mainly because of the implementation of an established telephone helpline with a specialist nurse in order to help the patients with rheumatoid arthritis. The nurse specialist is delegated to help and solve any problems that the patients may have experienced during their treatments. Thus, the conventional system places a centralised workload, perhaps disproportionately, on one particular health care profession which may have the effect of restricting the initiative of patients to seek any help from other health care providers. The greater recognition of the community pharmacist's role, by the patients as well as the health care providers, within the system of monitoring of the patients would create an opportunity for responsibilities to be shared by the patients and the care providers.

7.2.4 Outstanding issues around methotrexate therapy

Although methotrexate therapy is well recognised in the treatment of rheumatoid arthritis, certain issues were still outstanding for the health care providers. The interviews with health care providers revealed the likelihood that different approaches are taken by the different health care specialists during both the initiation and the maintenance stages of methotrexate therapy. An inquiry on these varying issues helped to delineate a basic and acceptable framework for use of methotrexate by health care providers and for the reliance on certain patient self management skills during methotrexate therapy.

The consensus inquiry sought to obtain collective convergence of opinion on different aspects of methotrexate therapy, and benefit care by facilitating a co-ordinated approach by health care providers from the different professions.

The particular prescribing, the dose increments and the monitoring issues for methotrexate therapy were clearly identified by the participating rheumatology specialists. These issues have not previously been explored among the rheumatology specialist community. An unfortunate finding of the study was that there is a lack of recognition among the rheumatology specialists of the community pharmacists' role during the monitoring of patients with methotrexate therapy. These opinions may originate from the idea that the patients are monitored by blood sampling and patient held record card of laboratory results and the community pharmacists present position in the system does not provide an opportunity to contribute. This lack of belief in the pharmacist's contribution extends to the pharmacists' role in the patients' needs assessments, monitoring of potential side effects and patient education.

The rheumatology specialists are confident of the competency of the specialist nurses in patient monitoring, which is not surprising, given the fact that they work closely together in the same health care settings. Furthermore, the activities of the patient self-management strategies are also well appreciated and believed to have a great importance in the chronic disease management.

The degree of agreement and/or disagreement achieved at the end of the study enabled the issues to be brought up which were previously hidden beneath the system of current health care. And it also outlined some practical solutions for certain problems perceived by the health care professionals and generated by the practitioners themselves. Therefore, application of the suggested framework might be unconstrained by the beliefs of the professionals involved.

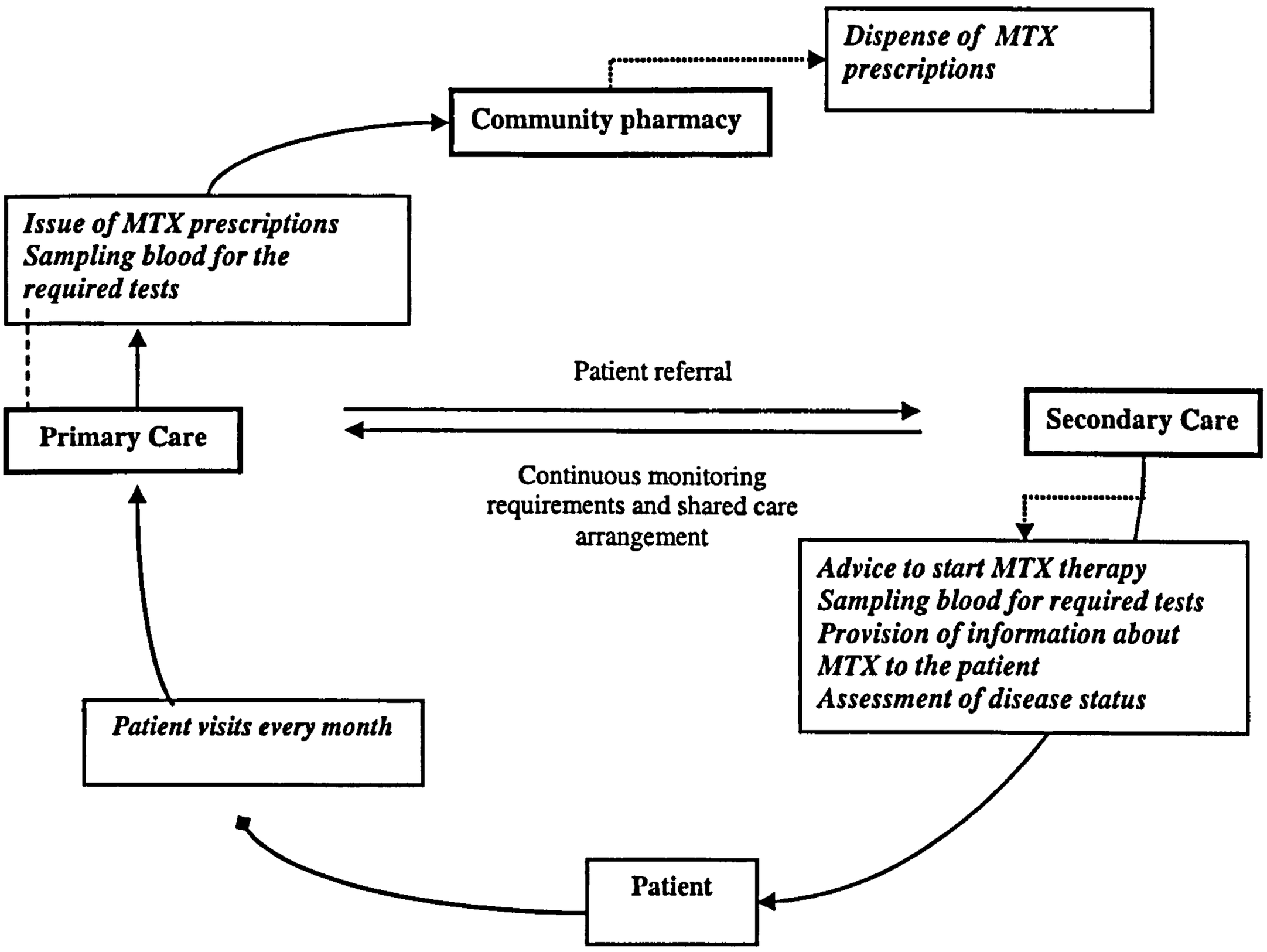
In spite of measurable effects on the chosen measures of patient's attitudes, the pharmacy intervention has been demonstrated to be feasible in practice and acceptable to both patients and specialists. The acceptability to the general practitioner remains to be investigated.

Although lack of beliefs existed among the rheumatology specialists in pharmacists' contribution in monitoring process of the patients with rheumatoid arthritis, the results from the study highlighted the potential opportunities for community pharmacists to be involved in the provision and process of a seamless care for the patients with RA. Therefore, further investigation of the role of the community pharmacists in disease management process which is undertaken among community pharmacist would or might demonstrate the benefits of the new model of shared care. Further work is needed to work up a model among

community pharmacists themselves and actually test the model in practice rather than seek a way forward by canvassing opinions. Identification of the potential roles and recognition of responsibilities of the pharmacists might lead to successful implementation of the new model in their practises.

Figure 7.1 summarises the current system for the delivery of care for the patients with rheumatoid arthritis in the light of study findings.

Figure 7.1 System of delivery of health care for the patients receiving methotrexate therapy



7.2.5 Developing a model of care for patients with rheumatoid arthritis

From exploration of the emerging themes from the earlier studies in the thesis, a new model of care has been designed and implemented for patients diagnosed with rheumatoid arthritis (see Chapter 6). The new shared care model involved active (collaborative or mutual) participation by the patients and their community pharmacists. The model proposed a continuous information flow between the health care providers who are involved in the patient care process. Delegation of responsibilities to the different health care providers and to the patients according to their capabilities in disease management would make the system more comprehensive and compatible with circumstances.

This study demonstrated the potential for active involvement by community pharmacists in the patient care process for patients diagnosed with rheumatoid arthritis. So far, the community pharmacists' involvement has not been identified in the patient monitoring process in rheumatoid arthritis, therefore the new model of care created an opportunity in the present health care system and within existing resources. The new model suggested a pathway for developing the present delivery of care rather than radically changing the shared care system.

Although a rather small number of patients and community pharmacists were finally included in the study and the period of intervention was necessarily limited, the results provided some encouraging findings among other equivocal findings. The patients' satisfaction with the services that they receive at the pharmacy is increased after the intervention period, whereas it has not been changed for the patients in the control group. The participating community pharmacists also acknowledged the advantages of receiving information about their patients' disease status and their medications. They ascertained that they could extend their roles beyond the dispensary by the provision of supportive information and knowledge about the chronic disease management and through reciprocal collaboration with other health care providers. It has been confirmed through the patient data collection forms that were gathered from community pharmacy that the pharmacists are able to identify the patients' needs about their medicines and their problems regarding methotrexate therapy in the assistance of the shared care protocol provided. They are also in a position to discuss any problems about the prescriptions with the GPs or any other health care providers who are involved in the patient care.

The proposed pharmaceutical care model is shown to be feasible to meet the health care professionals' as well as the patients' needs in the current health settings. The care plan does not demand extra time from the rheumatology specialists when it is issued during the consultation at the hospital clinics. The transfer of the care plan was undertaken by the researcher, but this can be done by the clerical staff at the hospitals without any further training or causing any extra workload. However, the care plans are initiated by the hospital pharmacists in collaboration with the rheumatology specialists, therefore the transfer of the care plans requires collaboration between the pharmacists at the hospital and in the community settings. Therefore, the practicality of the proposed model is reasonable which builds a link between the secondary and the primary care settings, particularly with community pharmacies.

7.3 Implications for pharmacy practice and the professional obligations for pharmacists in creating a system for quality of methotrexate use

The overall study was specially directed at the use of methotrexate therapy in patients diagnosed with rheumatoid arthritis. This was in order to study pharmaceutical care in a way which allowed clinical focus on a recognised area of clinical risk. However it was always intended that the various findings would help inform the development of patient services in general.

The qualitative study demonstrated that the pharmacists are willing to take more responsibilities in the chronic disease management if they are supported by relevant information, knowledge, education and training. The provision of relevant up-to-date patient information regarding medication and disease status, exchange of the local treatment protocols/guidelines between the primary and secondary health care settings and increased awareness on the drug information leaflets that have been issued for the patients would help pharmacists to fully integrate themselves into the chronic disease management processes. The pharmacists in the community settings are mostly perceived by the public as 'chemists' who mainly *dispense* the medicines. Contrary to the limited public perception the profession has its own education and training goals directed to the entire patient care process including the medication review, the counselling about medicines and health promotion and recently, disease screening activities for the patients such as those with hypertension or diabetes mellitus.

All those patient care activities that the pharmacist has the potential to deliver in the community setting are restricted by the barriers that the profession is exposed to. Increased workloads by the number of prescriptions to be dispensed, unfamiliarity with the shared care arrangements and protocols and the limited access to the patient's clinical information are the main reasons for pharmacists not being able to be fully involved in the disease management processes. Beyond these considerations, the current remuneration system does not encourage the profession to take specified actions or provide directed pharmaceutical care activities in the community setting. Appropriate time management and allocation of duties to the other pharmacy staff at the pharmacy will be needed to allow pharmacists to practise at levels that to which the profession aspires.

As the study showed, the pharmacists are able to provide pharmaceutical care for the patients with chronic disease in the community settings and in collaboration with hospitals. The provision of continuous care for the patients in need of collaborative support is well maintained by the transfer of the care plans from one setting to another. Therefore, the feasibility of such activities being routine is not unrealistic.

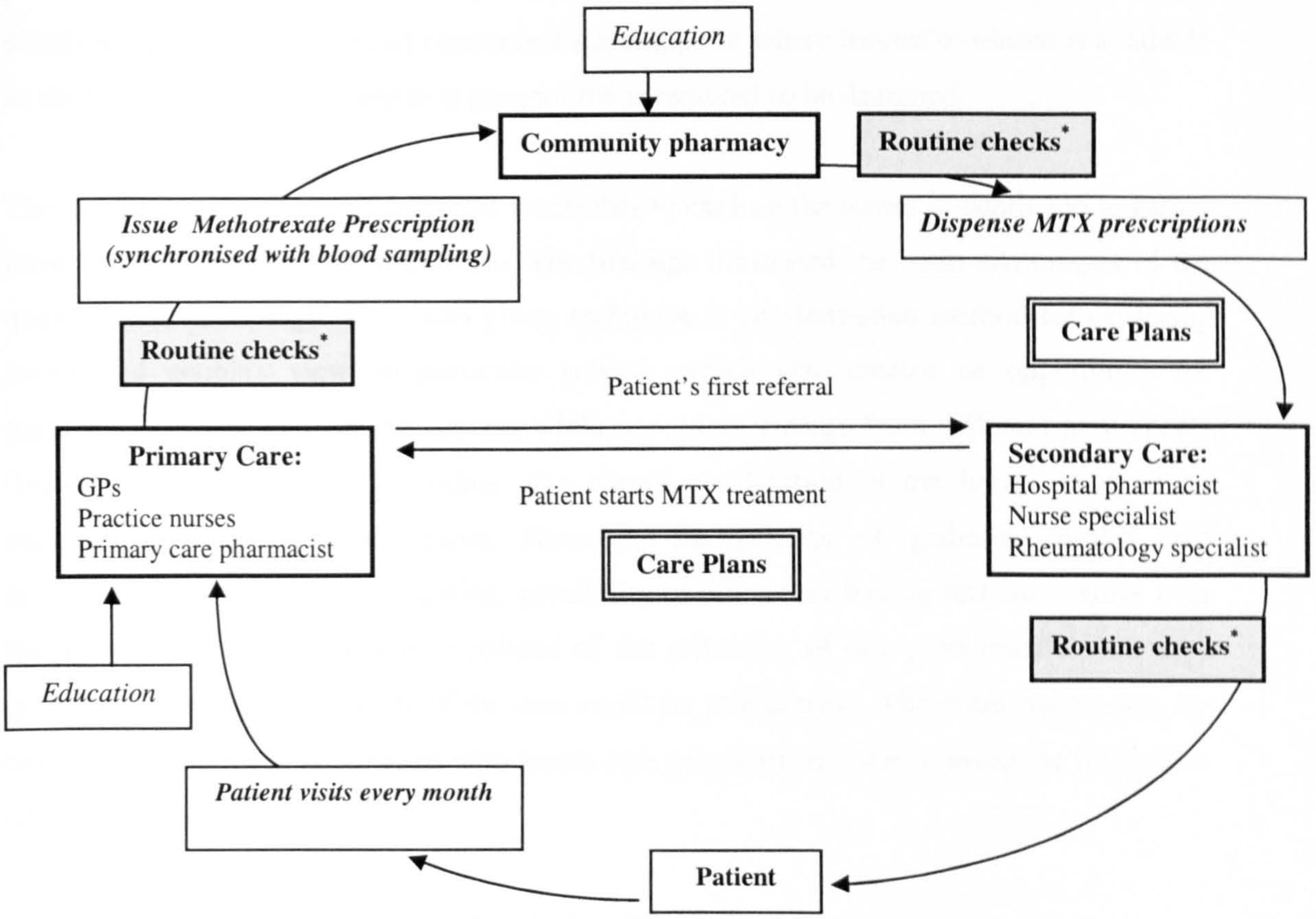
The concept of pharmacists' involvement in the management of chronic diseases is verified in the population of patients with diabetes and hypertension where continuous health screening is necessary. Although rheumatoid arthritis appears to be a condition that should be under specialist's care, the pharmacist can offer a range of activities to support the care of these patients in order to maintain safe care processes. The medication and prescription review, repeat prescription dispensing, counselling on pain control and purchase of over-the-counter medicines, encouragement and management on self-care activities and monitoring for the side effects of disease modifying anti-rheumatic drugs would expand the quality of patient care and maintain the continuity of care across the health care settings.

The findings from this thesis provide evidence for the good practice in the use of methotrexate therapy in the management of rheumatoid arthritis. The criteria for the prescribing, dispensing and monitoring processes of methotrexate therapy are established, therefore it would be helpful to use these criteria as a tool for the quality assessment in the patient care provided by health care professionals. In July 2003, during the writing-up stage of this thesis, a survey undertaken by Kerr and colleagues was published. This highlighted the lack of patient's awareness of the safety issues around methotrexate therapy.[289] At the same time, the National Patient Safety Agency emphasised the importance of the patient's active involvement in methotrexate therapy in order to prevent medication errors. There have

been 25 fatal incidents and 26 cases of serious harm linked to the use of oral methotrexate in the community setting over the last decade.[290] Therefore, mirroring the findings of this thesis, the safety issues of methotrexate therapy are a priority for the health service agenda. The importance of good prescribing, monitoring and dispensing practices with methotrexate treatment is highlighted.

The findings from the studies undertaken in this thesis regarding the provision of a new care model provided evidence for the pharmacy profession to improve quality of patient care. The further implementation of the tool or system suggested in this thesis would be valuable in audit of the profession in practice in order to demonstrate positive changes within the system by implementation of simple actions. The suggested changes in order to improve quality assurance system are summarised in Figure 7.2.

Figure 7.2 Suggested model of care for the patients with rheumatoid arthritis receiving methotrexate therapy



7.3.1 Implications for research practice

A combination of research methods has been used in this thesis in order to get greater insights from the various methods in the overall research project.

A retrospective data analysis provided a scope for further areas to focus on for the pharmacists and other health care providers. Although a retrospective study has its own disadvantages, it is a useful and convenient starting point where limited evidence is available in the field and an original research programme is required to be designed.

The qualitative interviews allowed the researcher to explore the issues in depth and to gather information about the current practice. The findings illustrated the main advantages of the qualitative methodology. The focus group technique is an alternative method for exploring issues and people's view on particular subject, which also creates an opportunity for participants to discuss over the concept while new ideas emerge from different participants (interactive interaction). The method also allows clarification of the issues emerged by encouragement of the participants. However, the process of gathering health care professionals together for the meeting, possibility of researcher having little/no control over the discussion/meeting and the likelihood of the reflection of one participant's view as a group view during the analysis of the data could be problematic. Therefore one-to-one, in-depth interviews were undertaken with health care providers in order to avoid the limitations of the other methods.

Another qualitative method, the Delphi technique, has been used to achieve a consensus on the issues around methotrexate treatment. The technique has been implemented in various arenas, including health care in general, pharmacy practice and social sciences. The process allows not only the gathering 'expert' opinions on subject areas in which conflicting views are systematically identified; it also seeks to formally identify potential areas of agreement. The Delphi technique is chosen for the consensus building process, because it allows relatively easy access to the all potential participants (particularly for the participants from different geographical locations), provides quantitative as well as qualitative data for the systematic analysis and demands less labour work compared to the other consensus building methods. Since the researcher did not have any previous experience as a facilitator/mediator in group discussions, it was more convenient to choose such a method which partly eliminates the influence/effect of the researcher as a facilitator.

The proposed research design for the intervention study to test the model of care has been commonly used in the research practice, because it allows one to compare the results from the two groups which are 'exposed' and 'not being exposed' to the intervention at different time periods (before and after the intervention). The randomised control trial as a study design is generally a preferable method to undertake a research; however, it is difficult to conduct such studies without having any limitations. Therefore, further implementation of the new care model in long-term might be conducted as a longitudinal, prospective study design as argued in the previous section.

7.4 Suggestions for further research

Since the evaluation of the proposed model of care has been continuing in order to complete the second phase of the study, further extension of the implementation of the care model would be useful for the long term comparison with other similar studies conducted in chronic disease management. The twelve months time period may not be adequate to achieve valid outcomes (or conclusions) for assessment of the proposed model, therefore long term results of the study are needed.

The implementation of the new care model in a larger scale, long-term study with frequent follow-up intervals would provide information regarding the changes occurring in the system and allow measuring the success in its implementation over time. The design of the future study might not be a randomised controlled trial, since the profession of pharmacy is moving forward and the pharmaceutical care is expected to be provided by all pharmacists. Therefore, given the fact that the patients should not get disadvantaged from the assessment of the proposed new care model according to the ethical obligations/concerns, having a control group in order to assess the effectiveness of the intervention might not be possible in real life circumstances. Identification of the measurable outcomes and the analysis of the trend would provide sufficient information regarding the quality of system for patient care. The longer treatment duration of patients to remain on methotrexate therapy without any complications would indicate the effectiveness of the care provided. A decrease in the number of inquiries that the specialist nurse receives from the patients may indicate that the disease is well-managed, the patient is closely monitored and his/her care needs are met at appropriate time during the monitoring process. Furthermore, the assessment of patients' quality of life (QoL), their beliefs about their medicines, their attitudes towards their disease management process, their satisfaction with the services provided by health care

professionals at different time period during the provision of care would give insights for the success of the new care model.

It might be argued that, the implementation of the new care model would be more successful if the provision of education and training for the community pharmacists is designed more intensively (such as a one week course) which familiarises pharmacists with the data collection forms and the care plans during the intervention period. The pharmacists and other health care providers should also be provided with the local guidelines and shared care arrangements. An exchange of information regarding the patient's treatment process would create opportunities for each health care professional to be closely involved in the disease management and would ensure continuity of care.

The implementation of such care models demands full commitments from the health care providers, particularly from the community pharmacists, given the fact that considerable amount of their time to provide patient care has consisted of the dispensing of medicines. The provision of such care models would need to re-inforced by an extra payment for the health providers in order to maintain continuity of care.

The synchronisation of the patient's blood sampling and MTX prescriptions at GP surgeries would allow all health care providers to contact the patient at regular basis, hence the patient would be closely monitored by primary health care providers in between his/her visits to the rheumatology clinic during the treatment process.

The standardisation of methotrexate prescriptions would also help community pharmacists to be more familiar with the treatment and able to help them to identify potential medication errors with methotrexate therapy, therefore they would be able to integrate themselves into the treatment process. The establishment of an electronic prescribing process or issuing of printed prescriptions by the GP surgery would minimise human errors in the process of prescribing and dispensing of methotrexate.

There is also a need for the patients to be actively involved in their disease management and treatment processes. The implementation of the patient self-management activities during methotrexate therapy which were identified/suggested in part of this thesis (see Chapter 4) would create opportunities for patients to have control in their treatment process and therefore facilitate them to work in collaboration with health care professionals. They would

become more knowledgeable about their medicines, the monitoring requirements of the drug therapies and the outcomes of the therapy.

Beyond the assessment of the proposed model of care, opinions of the participating health care providers can be explored after the study period, which gives an opportunity to evaluate their satisfaction with the implemented care model. Furthermore, conducting a focus group or in-depth interviews with those health care providers will help to identify any problems or barriers that they are exposed to during the study period which may be overcome by further research attempts.

The interesting finding of the research was the identification of discrepancies amongst the specialists on the monitoring requirements of methotrexate therapy. The Delphi study identified the beliefs and opinions of rheumatology specialists; however, it would be ideal to explore the other health care providers' opinions on the same concepts, including the patient self-management strategies. So far, the study managed to outline a basic framework for the self-management activities for the patients who receive methotrexate therapy. Along with the revision of the patient drug information leaflets, implementation and assessment of the value of this framework will provide insights for further research interests. There are also opportunities for pharmacists to be involved in these patient self-management activities as an activator and assessor in the community settings.

Having confirmed by the previous studies that the patient empowerment and education are crucial in the chronic disease management, the assessment of patient's educational needs and their expectations from the process of provision of self-care activities will be worthwhile to focus on in the future studies. Proposed model for the self-manaement strategy in rheumatoid arthritis should incorporate different aspects of health belief models discussed in Chapter-1. For such research, qualitative methods can be helpful in order to build a foundation for the further work.

The assessment of actual methotrexate prescriptions during the intervention period would have been useful in order to detect the impact of pharmacists being involved in the patient care process. It would have been advantageous if the patterns of methotrexate prescriptions could have been explored among the Local Health Care Co-operatives. This information would have provided specific information about the current practice pattern in the prescription and dispensing process of methotrexate. This approach would require the

agreement of individual prescribers in each setting in order to overcome barriers to data sharing.

There are other areas that the thesis indicates for further research in the pharmacy practice arena in general. Firstly, there is a need for a systematic way of provision of pharmaceutical care for the patients diagnosed with rheumatoid arthritis. So far, this concept has not been explicitly identified in rheumatoid arthritis population, therefore the study conducted in this thesis should be seen as an initial attempt to focus on the needs of these patient groups in depth.

Secondly, a standardised documentation of care activities and instant transfer of this information to the other health care practitioners is needed in the current system of delivery of care. The electronic transfer of care activities for individual patient is one way to share information regarding patient's health status and medications which would improve the quality of delivery care. However, this kind of system has dilemmas concerning the confidentiality issues, where the NHS could work in collaboration across the health care settings in order to find realistic solutions.

Thirdly, integration of pharmacists within the patient care process is required, not only by recognising them as an expert in medicines but also accepting the role for them being health care providers in hospital and community settings who are capable of identifying the needs of patients during the care processes.

Fourthly, evaluation of economic outcomes of such interventions may provide satisfactory answers in order to commence new approaches for delivery of care.

And lastly, further research is needed in order to show the effect of provision of a pharmaceutical care model on patient's disease outcomes. Although a recent study suggests that the assessment of patient's disease outcomes can be undertaken in the community settings in collaboration with pharmacists[278], there is a demand for such investigation on the UK practices which will be invaluable.

7.5 Conclusion

In conclusion, the thesis has added to the body of knowledge on the provision of pharmaceutical care of patients diagnosed with rheumatoid arthritis. The findings of the research provided insights for further areas to focus on and opportunities to expand the system for delivery of care for patients with chronic diseases.

The improved quality of patient care can be achieved by the provision of good evidence that encourages implementation of new developments in the patient care process. The unique contributions from health care professionals, either by academic way and/or provision of practice, will move the health care system towards more effective, safe, improved quality of patient-centred services.

It is important to remember that achievement of *'the best'* requires several attempts and the only way to reach there is to try constantly with enthusiasm and not be intimidated by the apparent drawbacks. Therefore, it is assumed that recognition of the limitations of the studies undertaken in this thesis will provide different perspectives for the researchers in the future studies in order to develop and achieve an improved quality of care for the patients diagnosed with rheumatoid arthritis.

Appendices

Appendix 2.1 The interview guide for rheumatology specialists

1. Can you tell me more about a routine rheumatology clinic in "X" hospital in terms of monitoring processes?
2. How many patients do you see in a clinic every week?
3. How many methotrexate (MTX) patients do you see in each clinic?
4. What would you say about the proportion of psoriasis patients and rheumatoid arthritis (RA) patients in each clinic?
5. How often does arthritis patient come to the clinic?
6. What would you say for MTX patients, how often they come to the clinic?
7. How much time do you spend with MTX patients?
8. What kind of information do you give them?
9. Do you give some specific or standard information to patients on each consultation?
10. Does this information differ across patients in terms of duration of disease, duration of treatment, age or educational level? (*Prompt:* If yes, what are the criteria for giving information in different ways?)
11. Do you use any written information materials to counsel with these patients? Or only verbal information is given during the consultation?
12. Do you also talk with partners of patients (if they attend to clinic together with the patient) in terms of education or counselling issues?
13. How often is the monitoring card updated? (*Prompt:* How accurate is it?)
14. Is it specifically for MTX patients or for other DMARDs therapies as well?
15. Who is responsible to fill this card?
16. Who designed MTX drug information sheet and when?
17. Can you tell me more about monitoring process for MTX patients? How often do you see these patients in terms of monitoring?
18. What are the monitoring intervals for MTX patients?
19. What are the critical stages for these patients in terms of drug complications/side effects?
20. How long does a patient can stay on MTX treatment without any complications?
21. What do you specifically consider during consultation in terms of MTX monitoring? (*Prompt:* What are the main criteria for monitoring of these patients?)
22. How do you document the monitoring processes?
23. Are there any information goes to any other health care professionals or exchanged between health care providers regarding MTX patient monitoring? (*Prompt:*GPs, pharmacy, nurse specialists in the clinic?)

24. Do you have any contact with patient's GP or pharmacist in terms of patient monitoring?
    (*Prompt-1:* If yes, what kind of contact do you have? Is it written or verbal communication?)
    (*Prompt-2:* If no, does it cause any problems or difficulties in the monitoring process?)
25. In your opinion, what are the main problems in monitoring process for MTX patients?
26. Can you tell me more about MTX prescribing as well? What is the source of MTX prescription, GP or consultant?
27. What is the dose, increment intervals, strength, number of tablets to be prescribed for MTX?
28. Are there any differences between psoriasis patients and RA patients in terms of MTX prescribing?

Appendix 2.2 The interview guide for general practitioners

1. Can you tell me more about a routine practice at the GP surgery for patients diagnosed with rheumatoid arthritis, especially who receives methotrexate therapy.
2. What is involved in visits of these patients? What is the journey of patients at the GP surgery?
3. How many rheumatology patients do you see in a week?
4. How many methotrexate (MTX) patients do you see in a week?
5. How often do you see arthritis patients at GP practice in terms of monitoring? (*Prompt-1:* How often do they come to the surgery?) (*Prompt-2*: Is the visit for repeat prescription or for monitoring?)
6. What would you say for MTX patients, how often do they come to the surgery?
7. How much time do you spend on average with these patients when they come to the surgery?
8. What are the monitoring intervals for MTX patients?
9. Is the instruction given by the rheumatology clinic in hospital for these patients clear enough in terms of monitoring intervals, dose increments etc?
10. If patients have one months supply for methotrexate tablets, do they still come to the GP surgery every month for blood monitoring?
11. How often is the monitoring card updated? (*Prompt*: How accurate is it?)
12. Who is responsible to fill this card?
13. When do you get blood results and when do you put the results on the card for methotrexate patients?
14. How do you document/archive the monitoring process for MTX patients?
15. What kind of information do you put in computer record in terms of patient monitoring?
16. Do you have any contact with patient's consultant or community pharmacist in terms of patient monitoring? (*Prompt-1:* If yes, what kind of contact do you have? Is it written or verbal communication?) (*Prompt-2:* If no, does it cause any problems or difficulties in the monitoring process?)
17. Are there any information goes to any other health care professionals or exchanged between health care providers regarding MTX patient monitoring? (*Prompt*: Such as pharmacy or nurse specialists in clinics or consultants)
18. What do you think about community pharmacy's involvement in general? Does it help you to monitor these patients?
19. What would you say about critical stages for these patients in terms of having drug complications/side effects?
20. In your opinion, what are the main problems in monitoring process for MTX patients?

21. Can you tell me more about MTX prescribing as well? What is the dose, increment intervals, strength, number of tablets to be prescribed for MTX?
22. How do you decide the dose, strength and number of tablets to be prescribed? (*Prompt:* Is it personal preference or depends on how often you would like to see the patient?)
23. Are there any differences between psoriasis patients and rheumatoid arthritis patients in terms of MTX prescribing?
24. What kind of information do you give them? What kind of information do you provide at the surgery for these patients?
25. How much information do you give on the disease (at the beginning or thereafter) or information on drug side effects?
26. Do you give some specific or standard information to these patients on each consultation?
27. Do you use any written information materials to counsel with these patients? Or only verbal information is given during the consultation?
28. How much information does patient able to use?
29. Does this information differ across patients in terms of duration of disease, duration of treatment, age or educational level? (*Prompt:* If yes, what are the criteria for giving information in different ways?)
30. How often do you check patient's perception?
31. Are there any education or training programme for practice nurses and GPs regarding rheumatoid arthritis and its treatment?

Appendix 2.3 The interview guide for community pharmacists

1. What is the routine procedure for prescription supply? (*Prompts*:
    a. How many prescriptions do you do in a week?
    b. How often would you say methotrexate (MTX) prescription comes in?
    c. Where do MTX prescriptions mainly come from, direct from a surgery or from patient/patient's representative?
    d. Where does repeat prescriptions mainly come from?
    e. How long do patients generally wait for prescriptions?
    f. How do you get repeat prescriptions back to patients?
2. In general, how often do you see patients who get repeat prescriptions?
3. Are there any differences between MTX prescription and other prescriptions in terms of medication supplying procedures? (*Prompts:*
    a. Are most methotrexate patients getting repeats or do they often get once offs?
    b. Do you know why some MTX patients get one months supply whereas others get 3 months?
    c. When and why do you sometimes supply all MTX with same strengths to make up total weekly dose but sometimes patients are given different strengths?
4. Can you follow-up or recognise MTX patients when they come to the pharmacy for their other medications?
5. Who is responsible for supplying methotrexate to these patients? Is it pharmacist or any other staff in the pharmacy?
6. Are MTX patients routinely given counselling or information – either verbal or written?
7. Do you have enough information/education on methotrexate as a pharmacist?
8. If any other staff in the pharmacy supply methotrexate, do they have any education on methotrexate (or any specific drug that requires close monitoring), its side effect profile or monitoring process?
9. How many people are working in this pharmacy? Number of pharmacists? Number of dispensers, counter staff?
10. Do you have any monitoring procedure for these patients?
11. Are you aware of monitoring parameters?
12. Do patients ever bring, discuss or show their monitoring cards to you?
13. In your opinion, what are the main problems in the monitoring processes for these patients?
14. Do you have any kind of contact with patients' GP or consultant in terms of patient monitoring or any problems (*Prompts:* you contact them or them contacting you?)
15. How are MTX prescriptions generally given back to patients?

16. When MTX patients are given their medicines in the pharmacy how much time do you generally spend with these patients? Do you counsel them regarding methotrexate side effects or adverse drug reactions or OTC consumption?
17. If a patient comes to pharmacy with a prescription, would you routinely register that they are on MTX?
18. Are you aware of main side effects and interactions to look out for with methotrexate?
19. Do you record OTC use in the PMR system?
20. Are you aware of warning signs of regular OTC use in a MTX user?
21. What do you generally do when you notice any kind of methotrexate side effects?
22. Do you have any monitoring procedures for any chronic disease groups such as patients with diabetes, cardiovascular disease? (*Prompt:* If yes, what is the monitoring process and parameters for these patients led by pharmacy?)

Appendix 2. 4 The interview guide for nurse specialists

1. Can you tell me more about a routine rheumatology outpatient clinic?
2. How often do you see rheumatoid arthritis (RA) patients who are currently on methotrexate (MTX) therapy?
3. Can they easily reach you whenever they want to talk?
4. Do you counsel with only rheumatology outpatients?
5. How much time do you spend on average for counselling who are on MTX therapy?
6. Do you generally talk to them only after the first/new prescription for MTX or is it a part of regular care for every visit to the clinic?
7. What kind of information do you give them during counselling (except explanations on drug information sheet)?
8. In your opinion, what do these patients specifically want to know?
9. Are there any specific indicators for educational needs of these patients who live in different socio-economic areas?
10. Is there any difference between MTX users in regards to educational needs or information request? (psoriatic arthritis patients and rheumatoid arthritis patients)
11. What is the main issue/problem/difference between MTX-RA patients and other medication-RA patients for counselling process/monitoring process?
12. Does it depend on prescription source (by GP/consultant)?
13. What are the critical stages for those patients in terms of having drug complications?
14. What kind of information or laboratory results do you consider for monitoring process?
15. What kind of information materials that you need during counselling process?
16. How do you document or archive the details of counselling process?
17. What kind of indicators you consider when you are monitoring the patient?
18. Do you monitor the patient's needs or monitoring process only includes clinical outcome measures?
19. How often do you counsel them for their clinical outcome measures?
20. How do you document or archive the monitoring process?
21. Do you have any contact or information sharing process with patients' pharmacist or GPs'?
22. Is there any system or pathways that allow other health care providers to share this monitoring details?
23. When you need information about specific drug, can you reach resources at the same time?

Appendix 3.1 Data collection form for the past MTX users

- PATIENT DATA COLLECTION FORM -

Demographics

Name:	**Unit No:**	**Patient Code:**
Address: **Phone:**		**Post code:** **Carstairs Index:**
DOB:	**Sex (F/M):**	**Smoker (S)/ non-smoker (NS):**
GP name and GP surgery:		

Medical History

Main diagnosis	*Year of diagnosis*	*Other diagnosis*	*Year of diagnosis*

2nd line therapies

Drug	*Date started*	*Date stopped*	*Reason for discontinuation*	*Dose*

Concomitant therapies while on MTX

1st line treatment (simple analgesic/ NSAIDs)			*2nd line treatment (DMARDs/ steroids)*			*Other treatment*		
Drug	*Date start*	*Dose*	*Drug*	*Date start*	*Dose*	*Drug*	*Date start*	*Dose*

- PATIENT DATA COLLECTION FORM -
(continue...)

Laboratory results and symptoms

	Results at the time of discontinuation	*Symptoms*	*Results 6 months prior to discontinuation*	*Symptoms*
Hb (g/dL)				
WCC ($X10^9$/L)				
Plt ($X10^9$/L)				
Lymph. ($X10^9$/L)				
MCV (fL)				
ESR (mm/h)				
LFTs				
ALT (iu/L)				
AST (iu/L)				
γ-GT (iu/L)				
Chest X-ray				
U&E				
Alb (g/L)				
Cr (µmol/L)				
Urea (mmol/L)				
Other				

Visits to outpatient clinic while on MTX therapy	**Comments / further information**

Appendix 4.1 The 1st round of the Delphi questionnaire

"1st Round of the Delphi"

Development of a consensus on requirements in methotrexate prescribing, monitoring and patient self-management processes in treatment of rheumatoid arthritis

'Methotrexate (MTX) prescribing and monitoring' and 'patient self-management processes' in treatment of rheumatoid arthritis

Questionnaire for Health Care Professionals' Opinions

The following statements have been generated by review of scientific literature, clinical guidelines, drug information leaflets and interviews with various health care providers. This questionnaire will take max.15-20 minutes to fill in. For each statement, can you please **describe your current practice** by choosing the appropriate box which is the most applicable. There are 13 questions and I have grouped them under the two headings; (i) Prescribing and Dose increments (ii) Patient Monitoring

I would appreciate if you could also add your further opinion and recommendation in the space provided after each statement.

Prescribing and dose increments

	2.5 mg/week	*5 mg/week*	*7.5 mg/week*	*Other*	*Please specify*
1. Usual initial MTX dose	☐	☐	☐	☐	

	2.5 mg	*5 mg*	*Other*	*Please specify*
2. MTX dose increments	☐	☐	☐	

	Every 2 weeks	*Every 4 weeks*	*Other*	*Please specify*
3. Intervals for dose increments	☐	☐	☐	

	20 mg/wk	*25 mg/wk*	*30 mg/wk*	*Max. tolerated dose*	*Other*	*Please specify*
4. Maximum MTX dose	☐	☐	☐	☐	☐	
5. Maximum MTX dose for switching to combination therapy with other DMARDs	☐	☐	☐	☐	☐	

	Single daily dose	*Dose split over 2 times a day*	*Dose split over 3 times a day*	*Other*	*Please specify*
6. Usual timing of giving *weekly* MTX	☐	☐	☐	☐	

	max. 5mg/wk	*max. 7.5mg/wk*	*max. 10mg/wk*	*Other*	*Please specify*
7. MTX dose use in frail elderly	☐	☐	☐	☐	

	Yes	*No*
8. Do you use folic acid supplementation?	☐	☐

	5 mg	*10 mg*	*Other*	*Please specify*
If **YES**, usual folic acid dose	☐	☐	☐	

	Daily	*Weekly*	*Other*	*Please specify*
If **YES**, usual *frequency*	☐	☐	☐	

	3-4 days after MTX dose	*Every day*	*Every day except the day of MTX*	*1 day after MTX dose*	*Other*	*Please specify*
If **YES**, usual timing	☐	☐	☐	☐	☐	

	Yes	*No*	
9. Do you prefer to avoid the use of NSAIDs in patients on MTX?	☐	☐	
If **YES**, are there any particular ones you avoid?	☐	☐	*If 'YES' Please specify*
If **NO**, do you have any preferences for choosing an NSAID for patients on MTX?	☐	☐	*If 'YES' Please specify*

10. How likely are you to take into account the following factors when considering to <u>START</u> MTX as <u>your first choice DMARD</u>?

Patient factor	***Unlikely*** **1**	***Possibly*** **2**	***Probably*** **3**	***Definitely*** **4**
Age ≥75 yrs	☐	☐	☐	☐
Reproductive risk	☐	☐	☐	☐
Co-morbidities	☐	☐	☐	☐
Length of time since diagnosis	☐	☐	☐	☐
Severe arthritis	☐	☐	☐	☐
Has had previous DMARD	☐	☐	☐	☐
Previous methotrexate experience	☐	☐	☐	☐
Difficult social circumstances	☐	☐	☐	☐
Low educational capacity	☐	☐	☐	☐

Alcohol consumption / drug misuse	☐	☐	☐	☐
Patient's physical disability/ poor functional status	☐	☐	☐	☐
Patient's judgement	☐	☐	☐	☐
Compliance with previous DMARD therapies	☐	☐	☐	☐

11. Please rate the importance of the following factors in assessing if a patient is at increased risk of MTX unwanted effects

Patient factor	*Not so important* 1	*Probably important* 2	*Fairly important* 3	*Very important* 4
Age ≥75 yrs	☐	☐	☐	☐
Gender				
Female	☐	☐	☐	☐
Male	☐	☐	☐	☐
Dose of MTX	☐	☐	☐	☐
Duration of MTX therapy				
<6 months	☐	☐	☐	☐
6-12 months	☐	☐	☐	☐
13-24 months	☐	☐	☐	☐
Severe arthritis	☐	☐	☐	☐
Co-morbidities	☐	☐	☐	☐
Frailty	☐	☐	☐	☐
Previous toxicity to other DMARDs	☐	☐	☐	☐
MTX combined with sulphasalazine	☐	☐	☐	☐
MTX combined with other DMARDs (other than sulphasalazine)	☐	☐	☐	☐
Previous side effects during MTX therapy	☐	☐	☐	☐
Difficult social circumstances	☐	☐	☐	☐
Low educational capacity	☐	☐	☐	☐
Alcohol consumption / drug misuse	☐	☐	☐	☐
Compliance with MTX therapy	☐	☐	☐	☐
Patient's physical disability/ poor functional status	☐	☐	☐	☐
Patient's judgement	☐	☐	☐	☐

(Please specify any other factors you think are important in the decision to start methotrexate)

If you have other comments on your usual practice of prescribing methotrexate and increasing the dose please add them here:

Patient Monitoring

12. Please indicate your opinion on your normal actions in response to the following patient events reported during methotrexate therapy (please remember to ✓ as many box/boxes as apply to each patient event)

Patient event	Split MTX dose	Reduce MTX dose	Monitor and review	Withhold treatment until problem resolves	Discontinue treatment permanently	Increase folic acid dose	No action/ observe	Switching oral to parenteral	Other
Nausea post MTX	☐	☐	☐	☐	☐	☐	☐	☐	
Vomiting post MTX	☐	☐	☐	☐	☐	☐	☐	☐	
Diarrhoea	☐	☐	☐	☐	☐	☐	☐	☐	
Mouth ulceration	☐	☐	☐	☐	☐	☐	☐	☐	
Anorexia	☐	☐	☐	☐	☐	☐	☐	☐	
ALT/AST									
2-3 x normal	☐	☐	☐	☐	☐	☐	☐	☐	
>3 x normal	☐	☐	☐	☐	☐	☐	☐	☐	
Alk Phos									
1-2 x normal	☐	☐	☐	☐	☐	☐	☐	☐	
>2 x normal	☐	☐	☐	☐	☐	☐	☐	☐	
γ GT raised	☐	☐	☐	☐	☐	☐	☐	☐	
Albumin<35g/L	☐	☐	☐	☐	☐	☐	☐	☐	
Leucopenia (WCC<4X10^9/L)	☐	☐	☐	☐	☐	☐	☐	☐	
Plalelets low (<150X10^9/L)	☐	☐	☐	☐	☐	☐	☐	☐	
Anaemia (Hb <9 g/dL)	☐	☐	☐	☐	☐	☐	☐	☐	
Macrocytosis	☐	☐	☐	☐	☐	☐	☐	☐	
Neutropenia (<2X10^9/L)	☐	☐	☐	☐	☐	☐	☐	☐	
Fever/infectious symptoms	☐	☐	☐	☐	☐	☐	☐	☐	
Dry cough	☐	☐	☐	☐	☐	☐	☐	☐	
Breathlessness	☐	☐	☐	☐	☐	☐	☐	☐	
Renal function									
Creatinine 1-2x normal	☐	☐	☐	☐	☐	☐	☐	☐	
Creatinine >2x normal	☐	☐	☐	☐	☐	☐	☐	☐	
Rash	☐	☐	☐	☐	☐	☐	☐	☐	
Hair thinning	☐	☐	☐	☐	☐	☐	☐	☐	

Any other comment you may have:

13. Please indicate your normal practice for routine monitoring and frequency of monitoring during methotrexate treatment

	Please ✓ if recommended	Please ✓ when recommended			Please ✓ when recommended		
	Before the treatment	Induction phase (i.e. during dose increments)			Maintenance phase (i.e. during stable dose)		
		Weekly	**Fortnightly**	**Every 4 weeks**	**Every 2 weeks**	**Every 4 weeks**	**Every 8 weeks**
Full blood count	☐	☐	☐	☐	☐	☐	☐
ESR and CRP	☐	☐	☐	☐	☐	☐	☐
Urea & Electrolytes	☐	☐	☐	☐	☐	☐	☐
Creatinine	☐	☐	☐	☐	☐	☐	☐
Liver function tests	☐	☐	☐	☐	☐	☐	☐
Chest X-ray	☐				*Yes*		*No*
Do you do routine follow up for chest X-ray?					☐		☐
Do you recommend chest X-ray thereafter?					☐		☐

Other *(please specify)*

Thank you.

Appendix 4.2 The 2nd round of the Delphi questionnaire

Development of a consensus on requirements in methotrexate prescribing, monitoring and patient self-management processes in treatment of rheumatoid arthritis

'Methotrexate (MTX) prescribing and monitoring' and 'patient self-management processes' in treatment of rheumatoid arthritis

The following statements have been generated by review of scientific literature, clinical guidelines, drug information leaflets, interviews with various health care providers and your responses in the first round. This questionnaire will take maximum 20-30 minutes to fill in. For each statement, can you please indicate **your degree of agreement or disagreement on 'good practice in methotrexate therapy'** by choosing the appropriate number which is the most applicable to your decision. There are "32" statements and I have grouped them under the three headings; (i) Prescribing and dose increments (ii) Patient Monitoring (iii) Patient self-management in their methotrexate therapy.

I would appreciate if you could also add your further opinion and recommendations in the space provided after each statement.

Prescribing and dose increments

Questions from the 1st round of the Delphi exercise

	Strongly Disagree 1	2	3	4	5	6	7	8	*Strongly Agree* 9
1. Methotrexate therapy should be initiated in a dose of 7.5mg/week	☐	☐	☐	☐	☐	☐	☐	☐	☐

Comments

	Strongly Disagree 1	2	3	4	5	6	7	8	*Strongly Agree* 9
2. The maximum methotrexate dose should be no more than 25mg/week	☐	☐	☐	☐	☐	☐	☐	☐	☐

Comments

	Strongly Disagree 1	2	3	4	5	6	7	8	*Strongly Agree* 9
3. A weekly methotrexate dose should be given as a single daily dose	☐	☐	☐	☐	☐	☐	☐	☐	☐

Comments

4. Please rank the following criteria to indicate the top 5 (ranked 1-5) in terms of importance when considering **STARTING** MTX as your first choice of DMARD

Reproductive risk	( )
Previous MTX experience	( )
Alcohol consumption/ drug misuse	( )
Patient's judgement	( )
Co-morbidities	( )
Has had previous DMARD	( )
Compliance with previous DMARD	( )
Severe arthritis	( )

5. Please rank the following criteria on a 5 point scale (ranked 1-5) in terms of importance when assessing if a patient is at risk of MTX unwanted effects

Previous side effects during MTX therapy	( )
Alcohol consumption/ drug misuse	( )
Dose of MTX	( )
Compliance with MTX	( )
Co-morbidities	( )

New questions for the 2nd round of the Delphi exercise

	Strongly Disagree								*Strongly Agree*
	1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*
6. The GP should decide on the tablet strength (2.5 or 10mg) to use	☐	☐	☐	☐	☐	☐	☐	☐	☐

Comments

	Strongly Disagree								*Strongly Agree*
	1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*
7. The GP should be advised to prescribe methotrexate only in 2.5mg tablet strength regardless of the weekly dose the patient needs to take	☐	☐	☐	☐	☐	☐	☐	☐	☐

Comments

	Strongly Disagree								*Strongly Agree*
	1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*
8. The dose changes should be decided only by a rheumatologist	☐	☐	☐	☐	☐	☐	☐	☐	☐

Comments

	Strongly Disagree								*Strongly Agree*
	1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*
9. The dose changes may be decided by the GP within a protocol	☐	☐	☐	☐	☐	☐	☐	☐	☐

Comments

	Strongly Disagree								*Strongly Agree*
	1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*
10. Prescribing of MTX dose changes can safely be delegated to another health care professional (within a protocol)	☐	☐	☐	☐	☐	☐	☐	☐	☐

Comments

	Strongly Disagree								*Strongly Agree*
	1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*
11. The dose changes can safely be delegated to a GP practice nurse (within a protocol)	☐	☐	☐	☐	☐	☐	☐	☐	☐

Comments

	Strongly Disagree								*Strongly Agree*
	1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*
12. The dose changes can safely be delegated to a rheumatology specialist nurse (within a protocol)	☐	☐	☐	☐	☐	☐	☐	☐	☐

Comments

	Strongly Disagree								*Strongly Agree*
	1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*
13. The dose changes can safely be delegated to a community pharmacist (high street pharmacist) (within a protocol)	☐	☐	☐	☐	☐	☐	☐	☐	☐

Comments

	Strongly Disagree								*Strongly Agree*
	1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*
14. The dose changes can safely be delegated to a primary care pharmacist (pharmacist working within the GP surgery) (within a protocol)	☐	☐	☐	☐	☐	☐	☐	☐	☐

Comments

	Strongly Disagree								*Strongly Agree*
	1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*
15.The dose changes can safely be delegated to the hospital pharmacist (within a protocol)	☐	☐	☐	☐	☐	☐	☐	☐	☐

Comments

	Strongly Disagree								*Strongly Agree*
	1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*
16. The dose changes can safely be delegated to the patient (within a protocol)	☐	☐	☐	☐	☐	☐	☐	☐	☐

Comments

Patient Monitoring

Questions from the 1st round of the Delphi exercise

	Strongly Disagree								*Strongly Agree*
	1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*
17. MTX treatment should be withheld until problem resolves, when AST/ALT level >3x normal	☐	☐	☐	☐	☐	☐	☐	☐	☐

Comments

	Strongly Disagree								*Strongly Agree*
	1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*
18. Patient should be monitored and reviewed when Alkaline Phosphatase level 1-2x normal level	☐	☐	☐	☐	☐	☐	☐	☐	☐

Comments

	Strongly Disagree								*Strongly Agree*
	1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*
19. MTX treatment should be withheld until the problem resolves, when WCC < $4X10^9/L$ (leucopenia)	☐	☐	☐	☐	☐	☐	☐	☐	☐

Comments

	Strongly Disagree								*Strongly Agree*
	1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*
20. MTX treatment should be withheld until the problem resolves, when Neutrophils <2 X $10^9/L$ (neutropenia)	☐	☐	☐	☐	☐	☐	☐	☐	☐

Comments

	Strongly Disagree								*Strongly Agree*
	1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*
21. MTX treatment should be withheld until the problem resolves, when Platelets < 150 X 10^9/L	☐	☐	☐	☐	☐	☐	☐	☐	☐

Comments

	Strongly Disagree								*Strongly Agree*
	1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*
22. The patient should be monitored and reviewed when anaemia (Hb< 9g/dL) occurs	☐	☐	☐	☐	☐	☐	☐	☐	☐

Comments

	Strongly Disagree								*Strongly Agree*
	1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*
23. Haemoglobin <9g/dL could be attributable to MTX	☐	☐	☐	☐	☐	☐	☐	☐	☐

Comments

	Strongly Disagree								*Strongly Agree*
	1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*
24. LFTs should be monitored fortnightly at the induction phase (during dose increments) of MTX therapy	☐	☐	☐	☐	☐	☐	☐	☐	☐

Comments

	Strongly Disagree								*Strongly Agree*
	1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*
25. LFTs should be monitored every 4 weeks at the maintenance phase (during stable dose) of MTX therapy	☐	☐	☐	☐	☐	☐	☐	☐	☐

Comments

	Strongly Disagree								*Strongly Agree*
	1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*
26. Chest X-ray should only be performed before the MTX therapy, not thereafter in the absence of chest symptoms	☐	☐	☐	☐	☐	☐	☐	☐	☐

Comments

New questions for the 2nd round of the Delphi exercise

	Strongly Disagree								*Strongly Agree*
	1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*
27. The community pharmacist (high street pharmacist) is in a position to clarify patients' expectations of their MTX therapy	☐	☐	☐	☐	☐	☐	☐	☐	☐

Comments

	Strongly Disagree								*Strongly Agree*
	1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*
28. It is important for patients to show their monitoring card to the community pharmacist (high street pharmacist)	☐	☐	☐	☐	☐	☐	☐	☐	☐

Comments

	Strongly Disagree								*Strongly Agree*
	1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*
29. Verification of the methotrexate monitoring card by the community pharmacist should be part of dispensing the MTX prescription	☐	☐	☐	☐	☐	☐	☐	☐	☐

Comments

	Strongly Disagree								*Strongly Agree*
	1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*
30. There is a general need for more attention to appropriate monitoring of patients on methotrexate therapy	☐	☐	☐	☐	☐	☐	☐	☐	☐

Comments

	Strongly Disagree								*Strongly Agree*
	1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*
31. Patients should routinely receive enquiries from health care professionals about MTX therapy in between clinic visits	☐	☐	☐	☐	☐	☐	☐	☐	☐

Comments

Patient self-management in their methotrexate therapy

**The implementation of the self-management concept is defined for this purpose: the creation of ways for patients to be responsible for actions that are consistent with desired beneficial outcomes.*

32. Education of the patients in self-management might include some of the following. Please indicate how much you agree with the following patient actions being included in a patient education and training programme.

	Strongly Disagree 1	2	3	4	5	6	7	8	*Strongly Agree* 9
(1) Patient's own dosage alteration in response to mild unwanted gastrointestinal (GI) effects	☐	☐	☐	☐	☐	☐	☐	☐	☐

Comments

	Strongly Disagree 1	2	3	4	5	6	7	8	*Strongly Agree* 9
(2) Patients withholding treatment due to unwanted GI effects	☐	☐	☐	☐	☐	☐	☐	☐	☐

Comments

	Strongly Disagree 1	2	3	4	5	6	7	8	*Strongly Agree* 9
(3) Patients responding to the GI side effects by arranging to go to get their blood sampled for laboratory tests	☐	☐	☐	☐	☐	☐	☐	☐	☐

Comments

	Strongly Disagree 1	2	3	4	5	6	7	8	*Strongly Agree* 9
(4) Patients withholding treatment due to increased bruising	☐	☐	☐	☐	☐	☐	☐	☐	☐

Comments

	Strongly Disagree								*Strongly Agree*
	1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*
(5) Patients responding to increased bruising by arranging to go to get their blood sampled for laboratory tests	☐	☐	☐	☐	☐	☐	☐	☐	☐

Comments

	Strongly Disagree								*Strongly Agree*
	1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*
(6) Patients withholding treatment due to fever	☐	☐	☐	☐	☐	☐	☐	☐	☐

Comments

	Strongly Disagree								*Strongly Agree*
	1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*
(7) Patients responding to any infection by arranging to go to get their blood sampled for laboratory tests	☐	☐	☐	☐	☐	☐	☐	☐	☐

Comments

	Strongly Disagree								*Strongly Agree*
	1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*
(8) Patients responding to any infection by seeking professional advice	☐	☐	☐	☐	☐	☐	☐	☐	☐

Comments

	Strongly Disagree								*Strongly Agree*
	1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*
(9) Patients responding to breathlessness by stopping MTX immediately	☐	☐	☐	☐	☐	☐	☐	☐	☐

Comments

	Strongly Disagree								*Strongly Agree*
	1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*
(10) Patients checking their own blood results within a protocol	☐	☐	☐	☐	☐	☐	☐	☐	☐

Comments

	Strongly Disagree								*Strongly Agree*
	1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*
(11) Patients' self-administration of parenteral MTX	☐	☐	☐	☐	☐	☐	☐	☐	☐

Comments

Appendix 4.3 The 3rd round of the Delphi questionnaire

'Methotrexate (MTX) prescribing and monitoring' and 'patient self-management processes' in treatment of rheumatoid arthritis

This questionnaire will take max. 20 minutes to fill in. For each statement, can you please indicate <u>your degree of agreement or disagreement on 'good practice in methotrexate therapy'</u> by choosing the appropriate number which is the most applicable to your decision. There are "32" statements and I have grouped them under the three headings; (i) Prescribing and dose increments (ii) Patient Monitoring (iii) Patient self-management in their methotrexate therapy.

In this third round questionnaire, you will find information on the median (cut off between the bottom/top 50% of responses), interquartile range-IQR- (the range of central 50% of responses), top three/four percentages of the group responses and your previous response in the 2nd round of the Delphi questionnaire for each question. Please re-rank your opinion in a light of information provided.

Prescribing and dose increments

	Strongly Disagree								*Strongly Agree*
	1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*
1. Methotrexate therapy should be initiated in a dose of 7.5mg/week	☐	☐	☐	☐	☐	☐	☐	☐	☐

% of response:									
Group Median (IQR):									
Your previous response:	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*

	Strongly Disagree								*Strongly Agree*
	1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*
2. The maximum methotrexate dose should be no more than 25mg/week	☐	☐	☐	☐	☐	☐	☐	☐	☐

% of response:									
Group Median (IQR):									
Your previous response:	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*

	Strongly Disagree								*Strongly Agree*
	1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*
3. A weekly methotrexate dose should be given as a single daily dose	☐	☐	☐	☐	☐	☐	☐	☐	☐

% of response:									
Group Median (IQR):									
Your previous response:	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*

4. Please re-rank the following criteria to indicate the top 5 (ranked 1-5) in terms of importance when considering **STARTING** MTX as your first choice of DMARD

		Group Median rank	*Your previous response*
Reproductive risk	( )		( )
Previous MTX experience	( )		( )
Alcohol consumption/ drug misuse	( )		( )
Patient's judgement	( )		( )
Co-morbidities	( )		( )
Has had previous DMARD	( )		( )
Compliance with previous DMARD	( )		( )
Severe arthritis	( )		( )

5. Please re-rank the following criteria on a 5 point scale (ranked 1-5) in terms of importance when assessing if a patient is at risk of MTX unwanted effects

		Group Median rank	*Your previous response*
Previous side effects during MTX therapy	( )		( )
Alcohol consumption/ drug misuse	( )		( )
Dose of MTX	( )		( )
Compliance with MTX	( )		( )
Co-morbidities	( )		( )

	Strongly Disagree								*Strongly Agree*
	1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*
6. The GP should decide on the tablet strength (2.5 or 10mg) to use	☐	☐	☐	☐	☐	☐	☐	☐	☐

% of response:									
Group Median (IQR):									
Your previous response:	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*

	Strongly Disagree								*Strongly Agree*
	1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*
7. The GP should be advised to prescribe methotrexate only in 2.5mg tablet strength regardless of the weekly dose the patient needs to take	☐	☐	☐	☐	☐	☐	☐	☐	☐

% of response:									
Group Median (IQR):									
Your previous response:	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*

	Strongly Disagree								*Strongly Agree*
	1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*
8. The dose changes should be decided only by a rheumatologist	☐	☐	☐	☐	☐	☐	☐	☐	☐

% of response:									
Group Median (IQR):									
Your previous response:	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*

	Strongly Disagree								*Strongly Agree*
	1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*
9. The dose changes may be decided by the GP within a protocol	☐	☐	☐	☐	☐	☐	☐	☐	☐

% of response:									
Group Median (IQR):									
Your previous response:	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*

	Strongly Disagree								*Strongly Agree*
	1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*
10. Prescribing of MTX dose changes can safely be delegated to another health care professional (within a protocol)	☐	☐	☐	☐	☐	☐	☐	☐	☐

% of response:									
Group Median (IQR):									
Your previous response:	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*

	Strongly Disagree								*Strongly Agree*
	1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*
11. The dose changes can safely be delegated to a GP practice nurse (within a protocol)	☐	☐	☐	☐	☐	☐	☐	☐	☐

% of response:									
Group Median (IQR):									
Your previous response:	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*

	Strongly Disagree								*Strongly Agree*
	1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*
12. The dose changes can safely be delegated to a rheumatology specialist nurse (within a protocol)	☐	☐	☐	☐	☐	☐	☐	☐	☐

% of response:									
Group Median (IQR):									
Your previous response:	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*

	Strongly Disagree								*Strongly Agree*
	1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*
13. The dose changes can safely be delegated to a community pharmacist (high street pharmacist) (within a protocol)	☐	☐	☐	☐	☐	☐	☐	☐	☐

% of response:									
Group Median(IQR):									
Your previous response:	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*

	Strongly Disagree								*Strongly Agree*
	1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*
14. The dose changes can safely be delegated to a primary care pharmacist (pharmacist working within the GP surgery) (within a protocol)	☐	☐	☐	☐	☐	☐	☐	☐	☐

% of response:									
Group Median (IQR):									
Your previous response:	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*

	Strongly Disagree								*Strongly Agree*
	1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*
15.The dose changes can safely be delegated to the hospital pharmacist (within a protocol)	☐	☐	☐	☐	☐	☐	☐	☐	☐

. ***% of response:***									
Group Median (IQR):									
Your previous response:	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*

	Strongly Disagree								*Strongly Agree*
	1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*
16. The dose changes can safely be delegated to the patient (within a protocol)	☐	☐	☐	☐	☐	☐	☐	☐	☐

% of response:									
Group Median (IQR):									
Your previous response:	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*

Patient Monitoring

	Strongly Disagree								*Strongly Agree*
	1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*
17. MTX treatment should be withheld until problem resolves, when AST/ALT level >3x normal	☐	☐	☐	☐	☐	☐	☐	☐	☐

% of response:									
Group Median (IQR):									
Your previous response:	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*

	Strongly Disagree								*Strongly Agree*
	1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*
18. Patient should be monitored and reviewed when Alkaline Phosphatase level 1-2x normal level	☐	☐	☐	☐	☐	☐	☐	☐	☐

% of response:									
Group Median IQR):									
Your previous response:	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*

	Strongly Disagree								*Strongly Agree*
	1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*
19. MTX treatment should be withheld until the problem resolves, when WCC< $4X10^9/L$ (leucopenia)	☐	☐	☐	☐	☐	☐	☐	☐	☐

% of response:									
Group Median (IQR):									
Your previous response:	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*

	Strongly Disagree								*Strongly Agree*
	1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*
20. MTX treatment should be withheld until the problem resolves, when Neutrophils< $2X10^9/L$ (neutropenia)	☐	☐	☐	☐	☐	☐	☐	☐	☐

% of response:									
Group Median (IQR):									
Your previous response:	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*

	Strongly Disagree 1	2	3	4	5	6	7	8	*Strongly Agree* 9
21. MTX treatment should be withheld until the problem resolves, when Platelets< 150X10^9/L	☐	☐	☐	☐	☐	☐	☐	☐	☐

% of response:									
Group Median (IQR):									
Your previous response:	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*

	Strongly Disagree 1	2	3	4	5	6	7	8	*Strongly Agree* 9
22. The patient should be monitored and reviewed when anaemia (Hb< 9g/dL) occurs	☐	☐	☐	☐	☐	☐	☐	☐	☐

% of response:									
Group Median (IQR):									
Your previous response:	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*

	Strongly Disagree 1	2	3	4	5	6	7	8	*Strongly Agree* 9
23. Haemoglobin <9g/dL could be attributable to MTX	☐	☐	☐	☐	☐	☐	☐	☐	☐

% of response:									
Group Median (IQR):									
Your previous response:	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*

	Strongly Disagree 1	2	3	4	5	6	7	8	*Strongly Agree* 9
24. LFTs should be monitored fortnightly at the induction phase (during dose increments) of MTX therapy	☐	☐	☐	☐	☐	☐	☐	☐	☐

% of response:									
Group Median (IQR):									
Your previous response:	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*

	Strongly Disagree 1	2	3	4	5	6	7	8	*Strongly Agree* 9
25. LFTs should be monitored every 4 weeks at the maintenance phase (during stable dose) of MTX therapy	☐	☐	☐	☐	☐	☐	☐	☐	☐

% of response:									
Group Median (IQR):									
Your previous response:	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*

	Strongly Disagree 1	2	3	4	5	6	7	8	*Strongly Agree* 9
26. Chest X-ray should **only** be performed before the MTX therapy, not thereafter in the absence of chest symptoms	☐	☐	☐	☐	☐	☐	☐	☐	☐

% of response:									
Group Median (IQR):									
Your previous response:	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*

	Strongly Disagree 1	2	3	4	5	6	7	8	*Strongly Agree* 9
27. The community pharmacist (high street pharmacist) is in a position to clarify patients' expectations of their MTX therapy	☐	☐	☐	☐	☐	☐	☐	☐	☐

% of response:									
Group Median (IQR):									
Your previous response:	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*

	Strongly Disagree 1	2	3	4	5	6	7	8	*Strongly Agree* 9
28. It is important for patients to show their monitoring card to the community pharmacist (high street pharmacist)	☐	☐	☐	☐	☐	☐	☐	☐	☐

% of response:									
Group Median (IQR):									
Your previous response:	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*

	Strongly Disagree 1	2	3	4	5	6	7	8	*Strongly Agree* 9
29. Verification of the methotrexate monitoring card by the community pharmacist should be part of dispensing the MTX prescription	☐	☐	☐	☐	☐	☐	☐	☐	☐

% of response:									
Group Median (IQR):									
Your previous response:	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*

	Strongly Disagree								*Strongly Agree*
	1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*
30. There is a general need for more attention to appropriate monitoring of patients on methotrexate therapy	☐	☐	☐	☐	☐	☐	☐	☐	☐

% of response:									
Group Median (IQR):									
Your previous response:	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*

	Strongly Disagree								*Strongly Agree*
	1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*
31. Patients should routinely receive enquiries from health care professionals about MTX therapy in between clinic visits	☐	☐	☐	☐	☐	☐	☐	☐	☐

% of response:									
Group Median (IQR):									
Your previous response:	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*

Patient self-management in their methotrexate therapy

The implementation of the self-management concept is defined for this purpose: the creation of ways for patients to be responsible for actions that are consistent with desired beneficial outcomes.

32. Education of the patients in self-management might include some of the following. Please indicate how much you agree with the following patient actions being included in a patient education and training programme.

	Strongly Disagree 1	2	3	4	5	6	7	8	*Strongly Agree* 9
(1) Patient's own dosage alteration in response to mild unwanted gastrointestinal (GI) effects	☐	☐	☐	☐	☐	☐	☐	☐	☐

% of response:									
Group Median (IQR):									
Your previous response:	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*

	Strongly Disagree 1	2	3	4	5	6	7	8	*Strongly Agree* 9
(2) Patients withholding treatment due to unwanted GI effects	☐	☐	☐	☐	☐	☐	☐	☐	☐

% of response:									
Group Median (IQR):									
Your previous response:	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*

	Strongly Disagree 1	2	3	4	5	6	7	8	*Strongly Agree* 9
(3) Patients responding to the GI side effects by arranging to go to get their blood sampled for laboratory tests	☐	☐	☐	☐	☐	☐	☐	☐	☐

% of response:									
Group Median (IQR):									
Your previous response:	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*

	Strongly Disagree 1	2	3	4	5	6	7	8	*Strongly Agree* 9
(4) Patients withholding treatment due to increased bruising	☐	☐	☐	☐	☐	☐	☐	☐	☐

% of response:									
Group Median (IQR):									
Your previous response:	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*

	Strongly Disagree								*Strongly Agree*
	1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*
(5) Patients responding to increased bruising by arranging to go to get their blood sampled for laboratory tests	☐	☐	☐	☐	☐	☐	☐	☐	☐

% of response:									
Group Median (IQR):									
Your previous response:	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*

	Strongly Disagree								*Strongly Agree*
	1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*
(6) Patients withholding treatment due to fever	☐	☐	☐	☐	☐	☐	☐	☐	☐

% of response:									
Group Median (IQR):									
Your previous response:	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*

	Strongly Disagree								*Strongly Agree*
	1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*
(7) Patients responding to any infection by arranging to go to get their blood sampled for laboratory tests	☐	☐	☐	☐	☐	☐	☐	☐	☐

% of response:									
Group Median (IQR):									
Your previous response:	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*

	Strongly Disagree								*Strongly Agree*
	1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*
(8) Patients responding to any infection by seeking professional advice	☐	☐	☐	☐	☐	☐	☐	☐	☐

% of response:									
Group Median (IQR):									
Your previous response:	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*

	Strongly Disagree								*Strongly Agree*
	1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*
(9) Patients responding to breathlessness by stopping MTX immediately	☐	☐	☐	☐	☐	☐	☐	☐	☐

% of response:									
Group Median (IQR):									
Your previous response:	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*

	Strongly Disagree								*Strongly Agree*
	1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*
(10) Patients checking their own blood results within a protocol	☐	☐	☐	☐	☐	☐	☐	☐	☐

% of response:									
Group Median (IQR):									
Your previous response:	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*

	Strongly Disagree								*Strongly Agree*
	1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*
(11) Patients' self-administration of parenteral MTX	☐	☐	☐	☐	☐	☐	☐	☐	☐

% of response:									
Group Median (IQR):									
Your previous response:	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*

- Thank you -

Appendix 6.1 The community pharmacies information sheet

Identification code:

COMMUNITY PHARMACIES INFORMATION SHEET

Methotrexate Project

Date : ../ .. / ....

Pharmacy Premises Details

Pharmacy Address:		**Post Code:**
Contact Telephone Number:	**Fax:**	**E-mail:**

Pharmacists Names:	**working > 2 days in a week**
1)	❒
2)	❒
3)	❒
4) Other locum:	❒

Type of Pharmacy Independent ❒ Small chain (5-15 local branches) ❒ Large chain ❒

Normal number of staff at dispensing/medicine counter Registered Pharmacist [....] Pre-registration pharmacist [....] Other non-pharmacist staff [....]

Approximate number of prescription items dispensed in a week:

< 500 ❒
500-1000 ❒
1000-2000 ❒
>2000 ❒

Number of frequent users on oral methotrexate therapy in PMR system: [.....]

Is your pharmacy involved in any other project or model/schemes?

Yes ❒ (if YES, please indicate) .....

No ❒

Location of Pharmacy:

In health centre ❒ Close to GP surgery ❒ In shopping centre ❒ High street shop ❒

Pharmacist Details

Pharmacist-1

Name:		
D.O.B (year):	Gender:	Female ❒ Male ❒
Years on the register:		
Recorded hours of Continuing Professional Development (CPD) (during last 12 months):.....		
Recorded hours of SCPPE (during last 12 months):		

Pharmacist-2

Name:		
D.O.B (year):	*Gender:*	*Female* ❒ Male ❒
Years on the register:		
Recorded hours of Continuing Professional Development (CPD) (during last 12 months):.....		
Recorded hours of SCPPE (during last 12 months):		

Pharmacist-3

Name:		
D.O.B (year):	Gender:	Female ❒ Male ❒
Years on the register:		
Recorded hours of Continuing Professional Development (CPD) (during last 12 months):.....		
Recorded hours of SCPPE:		

Pharmacist-4

Name:		
D.O.B (year):	Gender:	Female ❒ Male ❒
Years on the register:		
Recorded hours of Continuing Professional Development (CPD) (during last 12 months):.....		
Recorded hours of SCPPE:		

Appendix 6.2 The community pharmacist consent forms

Agreement to Participate (Study Group)

Design and evaluation of a standard pharmacist monitoring programme for methotrexate users in the arthritic population

-A study at the primary and secondary care interface-

Pharmacist's name(s):.....

Work Address:.....

- I agree to participate in this study.
- I have discussed any questions I have regarding this study with the research pharmacist.
- I agree that each time a patient on this study comes to my pharmacy, I will make simple records of the service that I provide.
- I understand that from .../.../... , I will be receiving information from the patients' rheumatology consultant.
- I understand that for the purposes of evaluation, I will be asked to keep a written record of the problems I encounter and discussions I have with patients and healthcare professionals on methotrexate therapy.

Date: .../.../.....

Signature:

Contact name:- Ailsa Power, Research Fellow, University of Strathclyde.
Tel- 0141 548 3568

Agreement to Participate (Control Group)

Design and evaluation of a standard pharmacist monitoring programme for methotrexate users in the arthritic population

-A study at the primary and secondary care interface-

Pharmacist's name(s):.....

Work Address:.....

- I agree to participate in this study.
- I have discussed any questions I have regarding this study with the research pharmacist.
- I agree that each time a patient on this study comes to my pharmacy, I will make simple records of the service that I provide.
- I understand that from .../.../... (in 6 months), I will be receiving information from the patients' rheumatology consultant.
- I understand that for the purposes of evaluation, I will be asked to keep a written record of the problems I encounter and discussions I have with patients and healthcare professionals on methotrexate therapy.

Date: ..../..../.....

Signature:

Contact name:- Ailsa Power, Research Fellow, University of Strathclyde.
Tel- 0141 548 3568

Appendix 6.3 The study consent form for patient

Consent Form

Design and evaluation of a standard pharmacist monitoring programme for methotrexate users in the arthritic population

-A study at the primary and secondary care interface-

First Name:.....

Surname:.....

- I have read and understood the patient information sheet provided
- I have discussed any other concerns have raised regarding this study with the research pharmacist
- I understand that I am free to withdraw from the study at any time without having to give a reason for my withdrawals and that not affect any future medical care
- I understand the questionnaire will be completed with a help of the research pharmacist during the hospital clinic visit

Date: ..../..../.....

Signature:

Appendix 6.4 Study information sheet

-Study information sheet-

Design and evaluation of a standard pharmacist monitoring programme for methotrexate users in the arthritic population -A study at the primary and secondary care interface-

We invite you to take part in a study of Methotrexate use, patients' problems and their needs in rheumatoid arthritis.

- **WHY are we doing this study?**

We are working with the rheumatology specialists who are treating your arthritis. This study is trying to find out about methotrexate use, patients' understanding about their drug therapy and their needs in relation to their treatment. The reason for doing this study is to ensure an extra safety check during your methotrexate therapy. Our study may allow us to improve the way your doctors and your pharmacists can work with you in the management of your arthritis.

- **WHO is doing this study?**

This study is being carried out by **Aygin Bayraktar,** a researcher at the Rheumatology Clinic and based at the University of Strathclyde, Department of Pharmaceutical Sciences.

The study will include your community pharmacist, your rheumatologist and your general practitioner (GP).

- **WHO CAN PARTICIPATE in this study?**

We have identified interested community pharmacists in particular areas of Glasgow. If your pharmacist is on our list, and you attend either the Southern General Hospital Rheumatology clinic or Gartnavel General Hospital Rheumatology clinic, you can participate.

- **WHAT WILL HAPPEN if I decide to participate in the study?**

Depending on your allocated pharmacy, you will either be put into the intervention group or the non-intervention group. If you are in the intervention group, more detailed information about your drug treatment (e.g. information about your past arthritis medicines, the reasons you stopped taking these medicines, any ailments that you may have, your blood results and your prescribed medicines) will be passed to your community pharmacy now. If you are in the control group this information will be transferred in 6 months time. For the study we would also like to interview you and will help you to complete a questionnaire. We will repeat this twice (6 months and 12 months later). If you agree to participate in the study the researcher will contact you to explain more about the study. First you should first fill in the consent form to say that you agree to take part in the study.

While you are taking part in the study, you do not have to do anything additional. You will continue your regular visit to the hospital clinic, GP surgery and your chemist. For the duration of the study you will be required to go to the same local pharmacist. We will ask you to indicate and attend one particular community pharmacy during the study period. You are free to attend any community pharmacy after the study period.

We will give you a new 'drug monitoring card' and new 'drug information sheet' about methotrexate therapy and ask you to bring your 'drug monitoring card' and show it to your doctors, nurses or your chemist whenever you visit them.

Your GP will be informed that you are taking part in this study.

- **WILL this study AFFECT MY TREATMENT?**

This study **WILL NOT** affect your treatment. Your treatment will continue to be under the care of your rheumatologist and your GP.

- **HOW LONG the study will take?**

The study will continue for 12 months from October/November 2001 until October/November 2002.

The questionnaire will take a maximum 20 minutes to complete and the researcher will help you to fill it in.

- **WHO WILL SEE this information?**

The information obtained from you will be confidential and anonymous. Names and addresses will only be used to contact you.

If you do not want to be a part of this study or feel later that you wish to withdraw you are free to not enter or to stop at any time.

It will not affect your medical care in the future in any way.

If you have any further questions, now or at any time in the future, please do not hesitate to contact me.

Aygin Bayraktar *Telephone: 0141 548 45 71*

Appendix 6.5 Shared Care Protocol

METHOTREXATE

SHARED CARE PROTOCOL FOR HEALTH CARE PROFESSIONALS IN METHOTREXATE PRESCRIBING AND MONITORING

Patient's Name: ..... D.O.B:.....

Hospital Unit No:.....

GP name/ contact number: .....

Pharmacy name/ contact number: .....

Methotrexate (MTX) is an immunosuppressive drug which is used in the treatment of rheumatoid arthritis as a disease modifying anti-rheumatic drug (DMARD). The treatment is potentially hazardous but if certain precautions are taken, most patients tolerate methotrexate without serious complications and can stay on the treatment for a longer period of time than other DMARDs.

Close monitoring is essential during the treatment. **If you have any concerns about methotrexate toxicity please contact other health care professionals as soon as possible.** Please monitor the patient according to the shared care protocol along with *"Methotrexate Monitoring Card"* and *"Rheumatology Patient Care Plan for Methotrexate Treatment"* (when appropriate) which is provided by the hospital.

- Prescribing issues -

Absolute contra-indications

✗ Hepatic diseases ✗ Moderate/ severe renal impairment ✗ Excess alcohol Ingestion

Drug interactions

- Sulphonamides, trimethoprim and co-trimoxazole should not be used without consultation with rheumatologist.
- Other drugs may potentate such as tetracyclines, diuretics, hypoglycaemics, penicillins, phenytoin, pyrimethamine, cyclosporin

Methotrexate (MTX) tablets are available in 2.5mg and 10mg strengths and they **look very similar** (same size and shape; vary slightly in colour). Usual prescribed dose varies between 5-25 mg/week.

- It is safest to use only one tablet strength for the prescribed methotrexate dose until maintenance dose is stable

FOR YOUR PATIENT

Initial stage — Initial dose is ..... mg **ONCE A WEEK**

Dose increments ..... mg

Intervals
- every **2** weeks ☐ until a response seen/ patient stabilised
- every **4** weeks ☐ until a response seen/ patient stabilised
- other intervals ☐ .....

Maintenance — Maintenance dose is usually between 5-20 mg **ONCE A WEEK**

Please co-prescribe with Folic acid 5 mg midweek which should be taken 3-4 days after methotrexate dose

- Dispensing issues -

- If used please make sure that patients keep two tablet strengths separate unless pre-dispensed in a dosette box.
- Please check patient's home supplies of MTX tablets before dispensing the repeat prescription

Recommendations including those as a result of Cambridgeshire Health Authority inquiry

- Please make sure that the patient MTX prescription details in your computer database and in medical records are updated regularly
- Please make an explicit explanation for MTX dose changes when necessary
- Patients may still need analgesics and NSAIDs during therapy. Please make sure that the patient does not take any other OTC medication of painkillers. In the treatment of rheumatic diseases co-prescribing of MTX with NSAIDs is the norm.
- Contraception advice should be given to patients who are planning to be pregnant or whose partner is planning to be pregnant during treatment and 6 months post treatment.
- Make sure that the patient knows what dose of MTX he/she is taking
- Make sure that the patient knows which tablet strength he/she is taking
- Make sure that the patient brings the "MTX Monitoring Card" with him/herself and the blood results are documented into it.

- Monitoring issues -

PLEASE ENTER THE LAB. RESULTS IN "PATIENT DRUG MONITORING CARD"

Laboratory Tests

☛ Before starting the treatment:

Full Blood Count (FBC), ESR
Urine & Electrolytes (U&E's)
Urinanalysis
Liver Function Tests (LFTs)

☛ During the treatment:

ESR, FBC and differential **WEEKLY** until the dose is stable thereafter **EVERY 4 WEEKS**

U&E's and LFTs **EVERY 4 WEEKS**

Please be cautious about the following features during methotrexate therapy !

☹ Side Effects	☛ Action to be taken
Gastrointestinal:	Folic acid supplementation generally helps to reduce these symptoms
Nausea (mainly occurs within 24-48 hrs post MTX dose) Vomiting Diarrhoea Mouth Ulcers (stomatitis)	Split the weekly MTX dose throughout a day, if symptoms still continue reduce the weekly dose by 2.5mg and consider prescribing an anti-emetic. If it still continues refer to rheumatology specialist
Haematological:	Stop treatment and refer to the hospital when; WCC < 4 $X10^9$/L Neutrophils < 2 $X10^9$/L Platelets < 150 $X10^9$/L Hb < 9 g/dL MCV >100 fL (check B12 and folate level and monitor MVC)
Leukopenia, Neutropenia Thrombocytopenia Pancytopenia (may be precipitated by renal impairment or co-prescription of another folate antagonist)	
Hepatic:	
2x upper limit of normal ALT/AST (hepatic fibrosis and cirrhosis may occur)	Stop if AST and/or ALT >2x upper limit of normal and re-check If improved, re-start at lower dose and increase monitoring
Pulmonary:	
Dyspnoea Dry cough, Pneumonitis (cough associated with progressive dyspnoea) (interstitial fibrosis and eosiniphilia may occur)	Stop therapy and refer to rheumatology specialist
Mucocutaneous:	
Alopecia Rash Skin ulceration	If in doubt refer to the rheumatology specialist

☛ **Please be cautious about any symptoms of infection and seek medical advice.**

Appendix 6.6 Methotrexate Monitoring Card

What you can do for yourself in methotrexate therapy monitoring

Methotrexate is a drug used to treat your rheumatoid arthritis. It comes as two tablet strengths, 2.5mg tablets and 10mg tablets.

These two tablets strengths look very similar.
Please check the strength on your bottle and especially when your doctor has made a change in your dose of methotrexate.

Please be aware of the following events that might happen during your methotrexate therapy and report them to any health care providers if any of the following occur;

Symptoms you may experience that you should report;

- Mouth ulcers
- Bleeding gums
- Easy bruising
- Fever

- Cough
- Sore throat
- Breathlessness
- Skin rash

Lab. results on your monitoring card:

- White Cell count drops to 4 $\times 10^9$/L
- Platelets <150 $\times 10^9$/L
- Haemoglobin <9 g/dL

You MUST AVOID ALCOHOL while on methotrexate therapy

You should continue your anti-inflammatory drug unless advised otherwise by your doctor.

You should get advice from your pharmacist when buying any medicines at the chemist or from the general store.

METHOTREXATE MONITORING CARD

Pharmacy Project

Southern General Hospital
☎ 0141 201 1100
☎Help line: 0141 201 1118

Patient Name:

Hospital No.:

Consultant name:
GP name:
Community Pharmacy:

PLEASE ALWAYS BRING THIS MONITORING CARD WITH YOU WHEN YOU GO TO THE CLINIC or YOUR GP SURGERY or YOUR PHARMACY

METHOTREXATE
DOSE EACH WEEK:
WHEN IT IS TO BE TAKEN:
THE TABLET STRENGTH:

FOLIC ACID
DOSE :
WHEN IT IS TO BE TAKEN:

Your blood tests should be done EVERY MONTH or more often if your doctor instructs.
Blood tests will normally be taken at your GP surgery and the results should be recorded in this monitoring card at each visit

Laboratory Results **Date of Issue........................**

Prescribed MTX	
Date of issue *dd/mm/yy*	Prescribed dose *mg/week*

Haematological					Renal	Other Relevant Tests	
Date blood taken *dd/mm/yy*	White Cell count *$X10^9$/L*	Platelets *$X10^9$/L*	Haemo-globin *g/dl*	ESR *mm/hr*	Creatinine *µmol/L*	Name	Result

Appendix 6.7 The Rheumatology Care Plan

Date Issued	Next Clinic Visit

RHEUMATOLOGY PATIENT CARE PLAN
Methotrexate treatment monitoring

Surname	Forename	Gender	Date of Birth	Consultant
Patient address	**Rheumatology Nurse Specialist Help-line☎:**		**Community Pharmacist/Address ☎:**	
Social History			**General Practitioner ☎:**	

Relevant medical history					
Date		Rheumatology	Date		Other co-morbidities
1			6		
2			7		
3			8		
4			9		
5			10		
Known Drug Sensitivities					

Previous DMARD therapy		Reasons for Discontinuation
1		
2		
3		
4		
Patient's use of Complementary Therapies		

ROUTINE LABORATORY MONITORING					PRESCRIBED MEDICATION		*start*	*stop*
Test	Last Result		Monitor before next clinic visit?		*1*			
	Date	*Result*	*Yes*	*Frequency*	*2*			
Plasma Urea mmol/L			☐		*3*			
Creatinine (Cr) μmol/L			☐		*4*			
Estimated Cr Clearance ml/min			☐		*5*			
White Cell count x10⁹/L			☐		*6*			
Platelet count x10⁹/L			☐		*7*			
Haemoglobin d/L			☐		*8*			
Albumin g/L			☐		*9*			
ESR mm/hr			☐		*10*			
C-Reactive Protein mg/L			☐		**Medicines Regularly Purchased**			
Liver Function Tests ALT/AST (IU/L)			☐		*1*			
Other investigations/comments					*2*			
					3			
					4			

☐ **Care Issues/Actions advised** **MONITORING PLAN**

Pain and symptom control	Checking signs & symptoms of unwanted effects	Patient comprehension and treatment continuity
1 Signed Start	1 Signed Start	1 Signed Start
2 Signed Start	2 Signed Start	2 Signed Start
3 Signed Start	3 Signed Start	3 Signed Start
4 Signed Start	4 Signed Start	4 Signed Start
5 Signed Start	5 Signed Start	5
6 Signed Start	6 Signed Start	6 Signed Start

Other care issues/...care issues continued..

1		Signed	Start
2			
3			
4			
5			
6			

Other Comments/Additional Information

Appendix 6.8 Community Pharmacist Data Collection Form

Identification code:	

COMMUNITY PHARMACIST DATA COLLECTION FORM
Methotrexate Patient

Patient Demographics

Surname	Forename	Gender	Date of Birth
Address		☎:	Postal Code
GP ☎:	Consultant ☎:	Help line ☎:	

Patient Medication Details

Visit 1 (Date): .....

	Methotrexate (MTX) details if applicable			
Prescription(s) presented	Dose of MTX on R_x (mg/week)	Dispensed MTX tablet strength (e.g. 2x2.5mg plus 1x10mg)	Dispensed number of MTX tablets	Approx. time spent with patient (min.)
MTX prescription only ❒				
No MTX and other medication ❒				
Other medication (no MTX) ❒				

Identified care issues related MTX		**Signature**

Please specify other medications

Visit 2 (Date): .....

	Methotrexate (MTX) details if applicable			
Prescription(s) presented	Dose of MTX on R_x (mg/week)	Dispensed MTX tablet strength (e.g. 2x2.5mg plus 1x10mg)	Dispensed number of MTX tablets	Approx. time spent with patient (min.)
MTX prescription only ❒				
No MTX and other medication ❒				
Other medication (no MTX) ❒				

Identified care issues related MTX		**Signature**

Please specify other medications

Visit 3 (Date): .....

	Methotrexate (MTX) details if applicable			
Prescription(s) presented	Dose of MTX on R_x (mg/week)	Dispensed MTX tablet strength (e.g. 2x2.5mg plus 1x10mg)	Dispensed number of MTX tablets	Approx. time spent with patient (min.)
MTX prescription only ❒				
No MTX and other medication ❒				
Other medication (no MTX) ❒				
Identified care issues related MTX				**Signature**

Please specify other medications

Appendix 6.9 Patient Questionnaire

Identification Number:.....

Interview Date:.....

Interview Location: **at the clinic ❐** **home visit ❐**

Interviewer:.....

Interview with

Patient Name:.....

Patient Code:.....

Date of Birth:.....

Address and Post code:.....

.....

.....

Name of community pharmacy:.....

Name of general practitioner:.....

Please read before filling in the questionnaire

Dear Ms/Miss/Mr.....

This questionnaire is to help us appreciate your thoughts on the medicines you are using to treat your rheumatoid arthritis. **The questionnaire takes no more than 10-15 minutes to complete.** Results of the questionnaire will be kept anonymously and your responses will **not** be stored in your medical records. Please do not hesitate to ask the interviewer if you do not understand the questions or need help to fill in the questionnaire.

The questionnaire consists of 35 questions in total. Please indicate your agreement by ticking (✓) the appropriate box for each question. The word used 'pharmacist/pharmacy' in the questions refers your local chemist. Please consider 'your methotrexate treatment' when you are answering the questions about your medicines.

The first part of the questionnaire (Question No.1- No.12) will ask you about your desire for education and information about your medicines. The second part (Question No.13- No.23) will include questions about your opinion and your beliefs about your medicines and how that affects you. The third part (Question No.24- No.27) will ask questions about any problems that you have with your medicines and how you cope with them. The last part (Question No.28- No.35) will ask you about your satisfaction with the service that you receive from the pharmacy.

Please do not hesitate to ask to the interviewer if you do not understand the questions.

PATIENT QUESTIONNAIRE

YOUR VIEWS ABOUT
DESIRE FOR EDUCATION & INFORMATION FOR YOUR METHOTREXATE THERAPY

There are no right or wrong answers.
We are interested in your personal views

Please indicate by ticking (✓) in the appropriate box (❒) to show how much you agree or disagree with the statements to do with information about your medicines

	Strongly Disagree *1*	***Disagree*** *2*	***Uncertain*** *3*	***Agree*** *4*	***Strongly Agree*** *5*
1. I always speak to my pharmacist when I want information about my medicines	❒	❒	❒	❒	❒
2. Sometimes I feel a little inhibited when I ask for information, I should know already	❒	❒	❒	❒	❒
3. It's most convenient to ask at the surgery, if there is anything I need to know	❒	❒	❒	❒	❒
4. It's not really my place to ask for information, they have enough to do	❒	❒	❒	❒	❒
5. The people at the hospital can easily give me information when I go for my appointment	❒	❒	❒	❒	❒
6. I need as much as information about my medicines as possible	❒	❒	❒	❒	❒
7. Too much knowledge is bad thing	❒	❒	❒	❒	❒
8. You can never know enough about these things	❒	❒	❒	❒	❒
9. I don't need any more knowledge	❒	❒	❒	❒	❒
10. I read about my medicines and illness as much as possible	❒	❒	❒	❒	❒
11. What you don't know doesn't hurt you	❒	❒	❒	❒	❒
12. I find medical information confusing	❒	❒	❒	❒	❒

For researcher *use only*

Score

YOUR VIEWS ABOUT
METHOTREXATE PRESCRIBED FOR YOU

- We would like to ask you about your personal views about methotrexate prescribed for you.
- These are statements other people have made about their medicines.
- Please show how much you agree or disagree with them by ticking the appropriate box.

There are no right or wrong answers.
We are interested in your personal views

Views about METHOTREXATE PRESCRIBED FOR YOU:	***Strongly Disagree***	***Disagree***	***Uncertain***	***Agree***	***Strongly Agree***
	1	*2*	*3*	*4*	*5*
13. My health, at present, depends on these medicines	❒	❒	❒	❒	❒
14. Having to take medicines worries me	❒	❒	❒	❒	❒
15. My life would be impossible without these medicines	❒	❒	❒	❒	❒
16. I sometimes worry about long-term effects of these medicines	❒	❒	❒	❒	❒
17. Without these medicines I would be very ill	❒	❒	❒	❒	❒
18. These medicines are a mystery to me	❒	❒	❒	❒	❒
19. My health in the future will depends on these medicines	❒	❒	❒	❒	❒
20. These medicines disrupt my life	❒	❒	❒	❒	❒
21. I sometimes worry about becoming too dependent on these medicines	❒	❒	❒	❒	❒
22. These medicines protect me from becoming worse	❒	❒	❒	❒	❒
23. This medicine gives me unpleasant side effects	❒	❒	❒	❒	❒

For researcher use only
Score

YOUR VIEWS ABOUT
ANY PROBLEMS WITH YOUR METHOTREXATE MEDICINES AND YOUR SATISFACTION WITH SERVICES THAT YOU RECEIVED AT PHARMACY

There are no right or wrong answers.
We are interested in your personal views

24. Have you had any problems with your medicines in the past? Yes ❒ No ❒

25. If so, what did you do about it?

.....
.....
.....
.....
.....
.....

26. If you found you had a problem with your medicines, where would you seek advice

	No or Not Usually	Sometimes	Yes, Usually
The Rheumatology clinic	❒	❒	❒
The Doctor's surgery	❒	❒	❒
The Community Pharmacy	❒	❒	❒

27. When do you show your monitoring card

	No or Not Usually	Sometimes	Yes, Usually
At the Rheumatology clinic	❒	❒	❒
At the Doctor's surgery	❒	❒	❒
At the Community Pharmacy	❒	❒	❒

Please indicate by ticking (✓) in the appropriate box (❒) to show how much you agree or disagree with the statements to do with <u>how you feel when you visit your regular pharmacy</u>

	Strongly Disagree 1	*Disagree* 2	*Uncertain* 3	*Agree* 4	*Strongly Agree* 5
28. You sometimes feel like you are just a number	❒	❒	❒	❒	❒
29. You sometimes feel that the pharmacist could be more understanding	❒	❒	❒	❒	❒
30. You feel that the prescription service at the pharmacy could be improved	❒	❒	❒	❒	❒
31. Usually they hand your medicine over without providing any additional information	❒	❒	❒	❒	❒
32. You are rarely provided with additional written information about your medicines	❒	❒	❒	❒	❒
33. The pharmacist at the pharmacy is usually too busy to give you any personal attention	❒	❒	❒	❒	❒
34. You are usually provided with good information about your prescriptions at the pharmacy	❒	❒	❒	❒	❒

For researcher

use only

Score

Please indicate by ticking (✓) in the appropriate box (❒) to show how much you agree or disagree with the statements to do with <u>your satisfaction with the pharmacy service</u>

	Very Dissatisfied *1*	Fairly Dissatisfied *2*	Neither satisfied nor dissatisfied *3*	Fairly Satisfied *4*	Very Satisfied *5*	*For the researcher use only* Score
35. How satisfied are you with the service that you receive in the pharmacy?	❒	❒	❒	❒	❒	

THANK YOU
FOR HELPING US BY FILLING IN YOUR PATIENT QUESTIONNAIRE

If you have any queries about the questions you have been asked or about our study, please let us know before you return the completed questionnaire.

Appendix 6.10 The results of the patient questionnaire after the 6 months follow-up

Figure A. Distribution of the IDI scores for the study (n=24) and the control (n=28) group after 6 months assessment

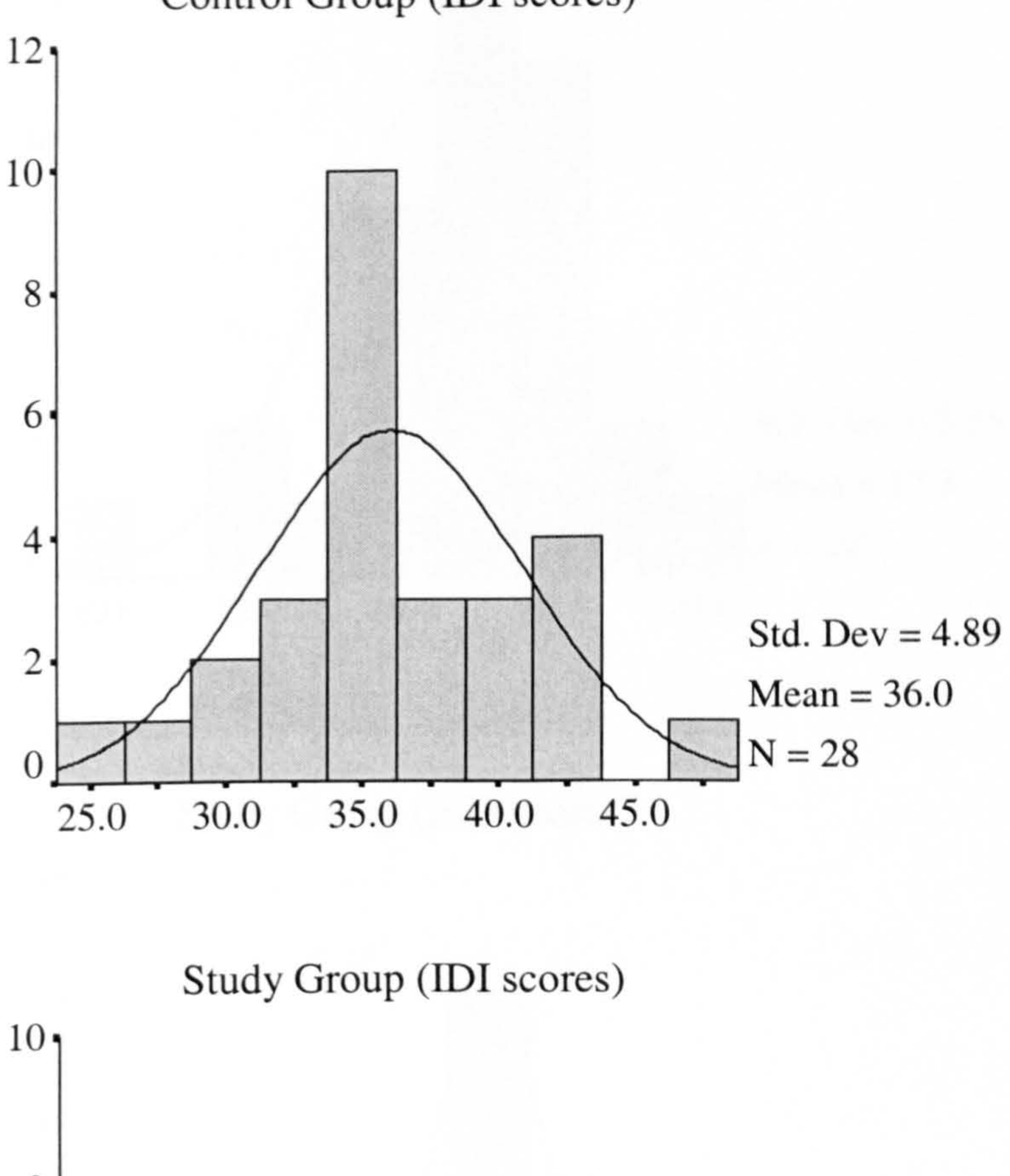
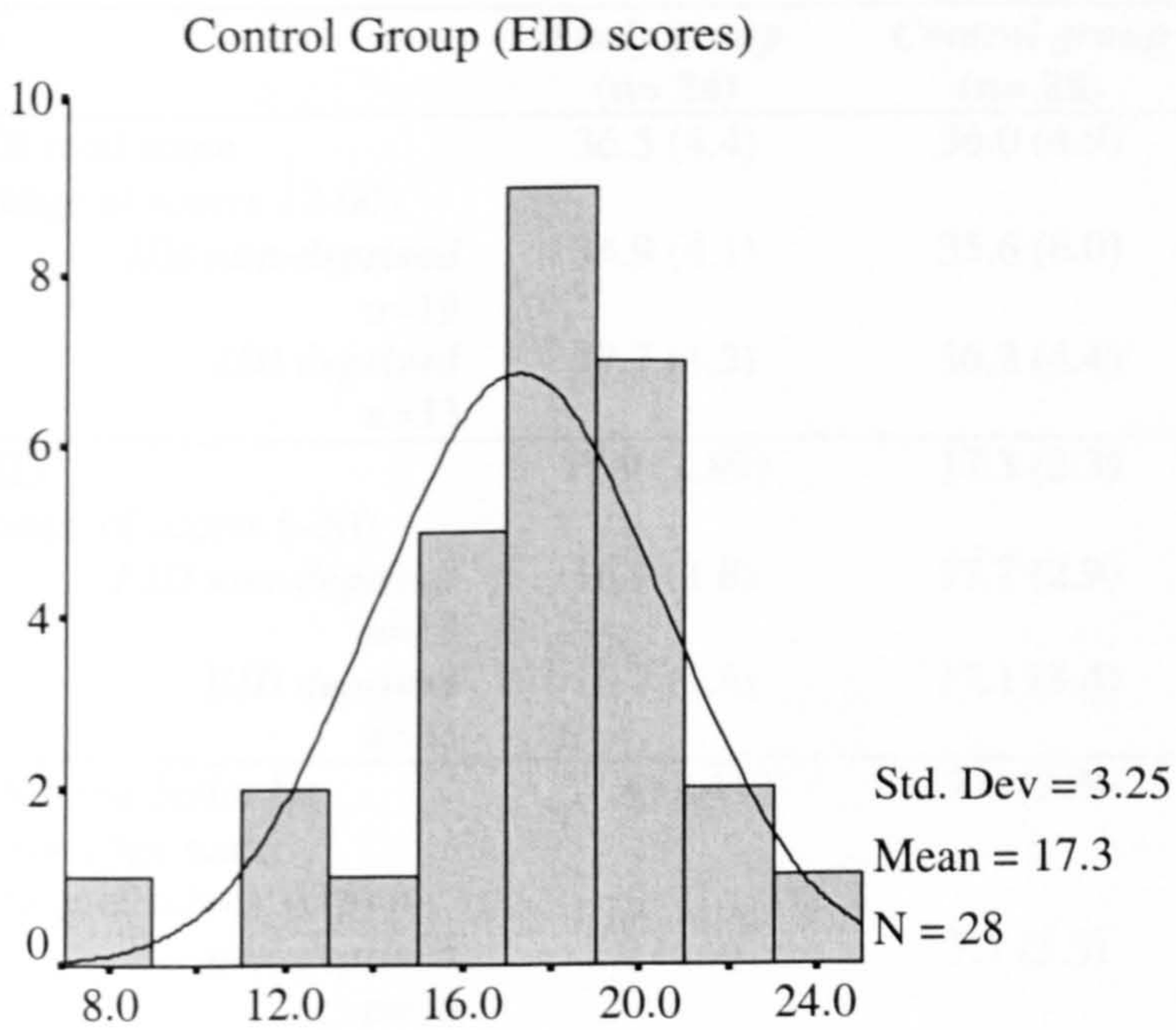


Figure B. Distribution of the EID scores for the study (n=24) and the control (n=28) group after 6 months assessment



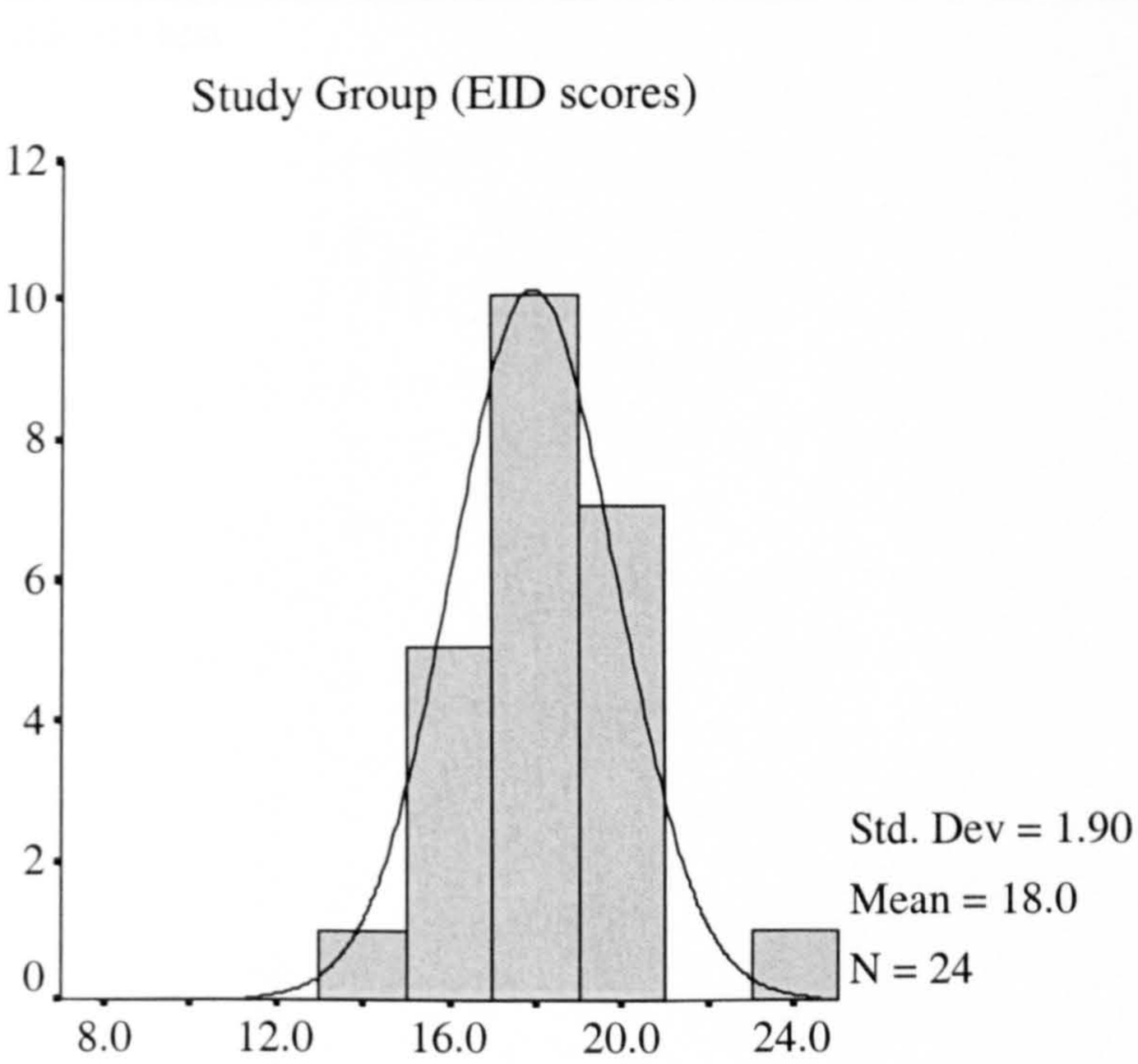


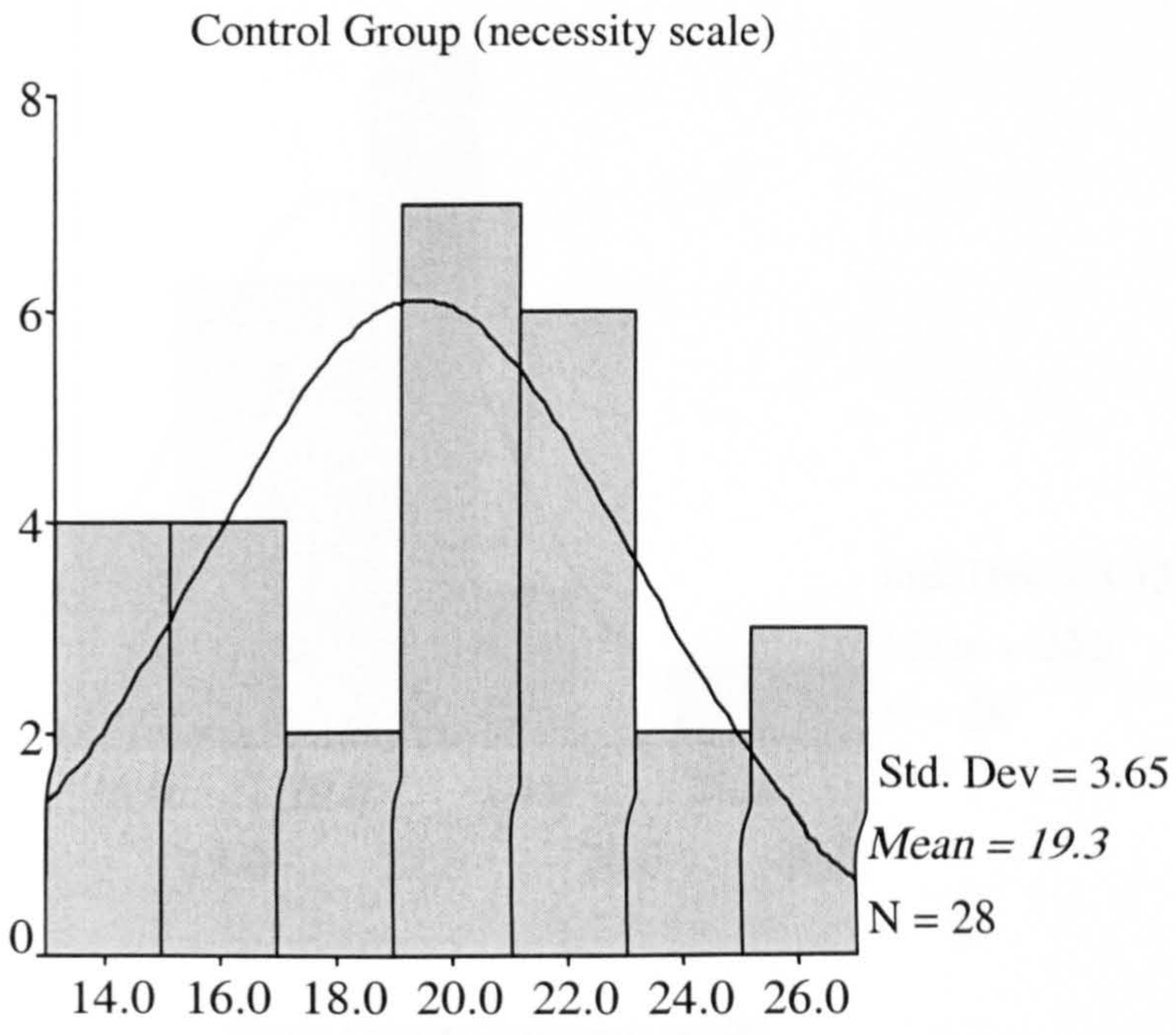
Table A. Summary of results of the Intrinsic Desire for Information Questionnaire after 6 months assessment

	Mean score (standard deviation)			
	Study group (n= 24)	*Control group* (n= 28)	*p value*	*All* (n= 52)
IDI total score (range of scores 12-60)	36.5 (4.4)	36.0 (4.9)	0.69*	36.3 (4.6)
IDI non-deprived n=19	34.9 (4.1)	35.6 (6.0)		35.3 (4.9)
IDI deprived n=33	37.7 (4.3)	36.2 (4.4)		36.8 (4.4)
EID (range of scores 6-30)	17.9 (1.89)	17.3 (3.3)	0.36*	17.6 (2.7)
EID non-deprived n=19	16.9 (1.8)	17.7 (2.9)		17.3 (2.4)
EID deprived n=33	18.7 (1.6)	17.1 (3.4)		17.8 (2.9)
Inhibited desire for knowledge scale (range of scores 3-15)	7.4 (2.4)	7.9 (2.8)	0.50*	7.6 (2.6)
non-deprived n=19	7.2 (1.9)	7.7 (3.5)		7.4 (2.7)
deprived n=33	7.5 (2.7)	7.9 (2.5)		7.8 (2.5)

* Student t test

SPECIFIC BELIEF ABOUT MEDICINE QUESTIONNAIRE

Figure C. Distribution of the 'necessity' scale scores for the control (n=28) and the study (n=24) group after 6 months assessment



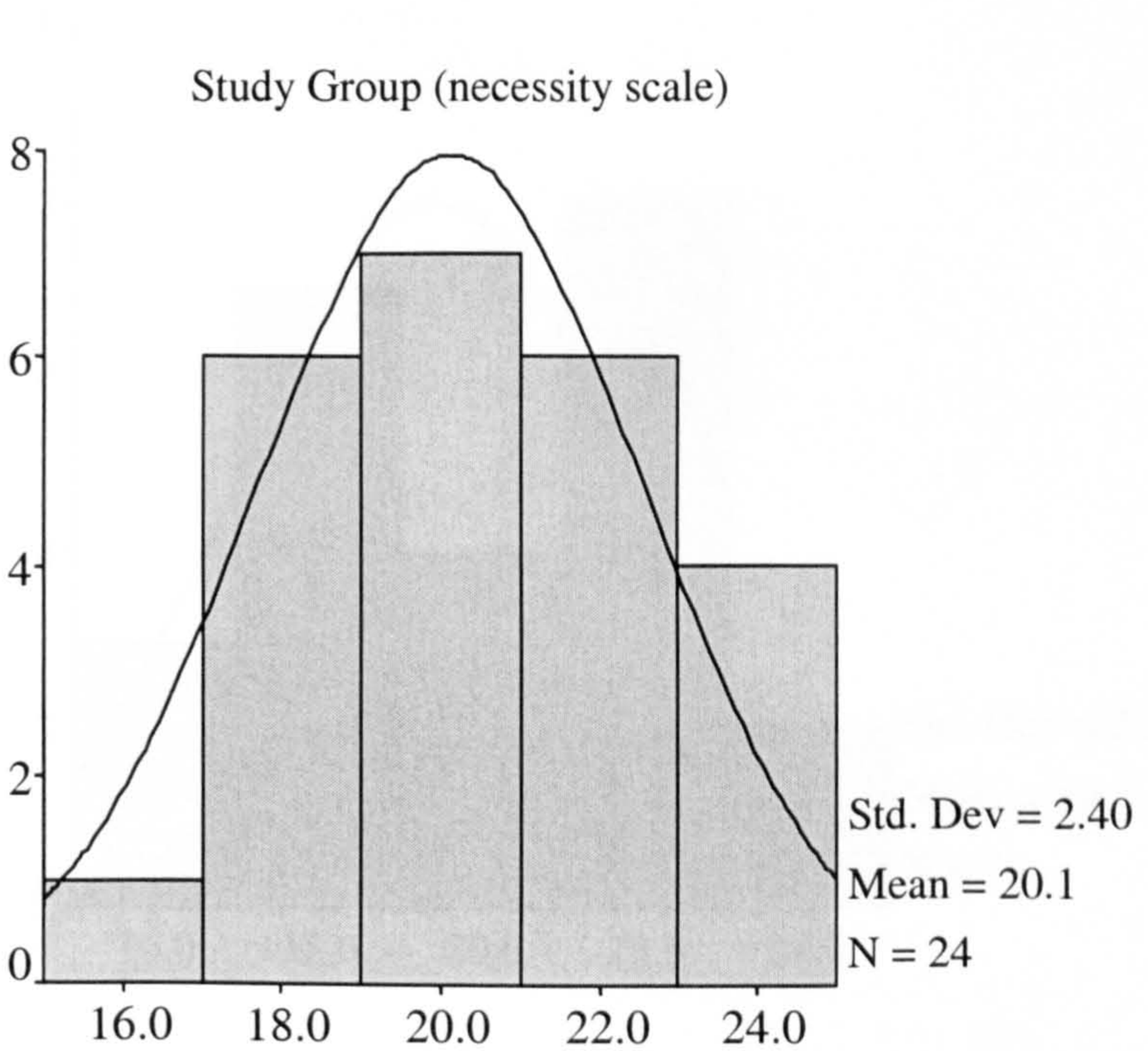
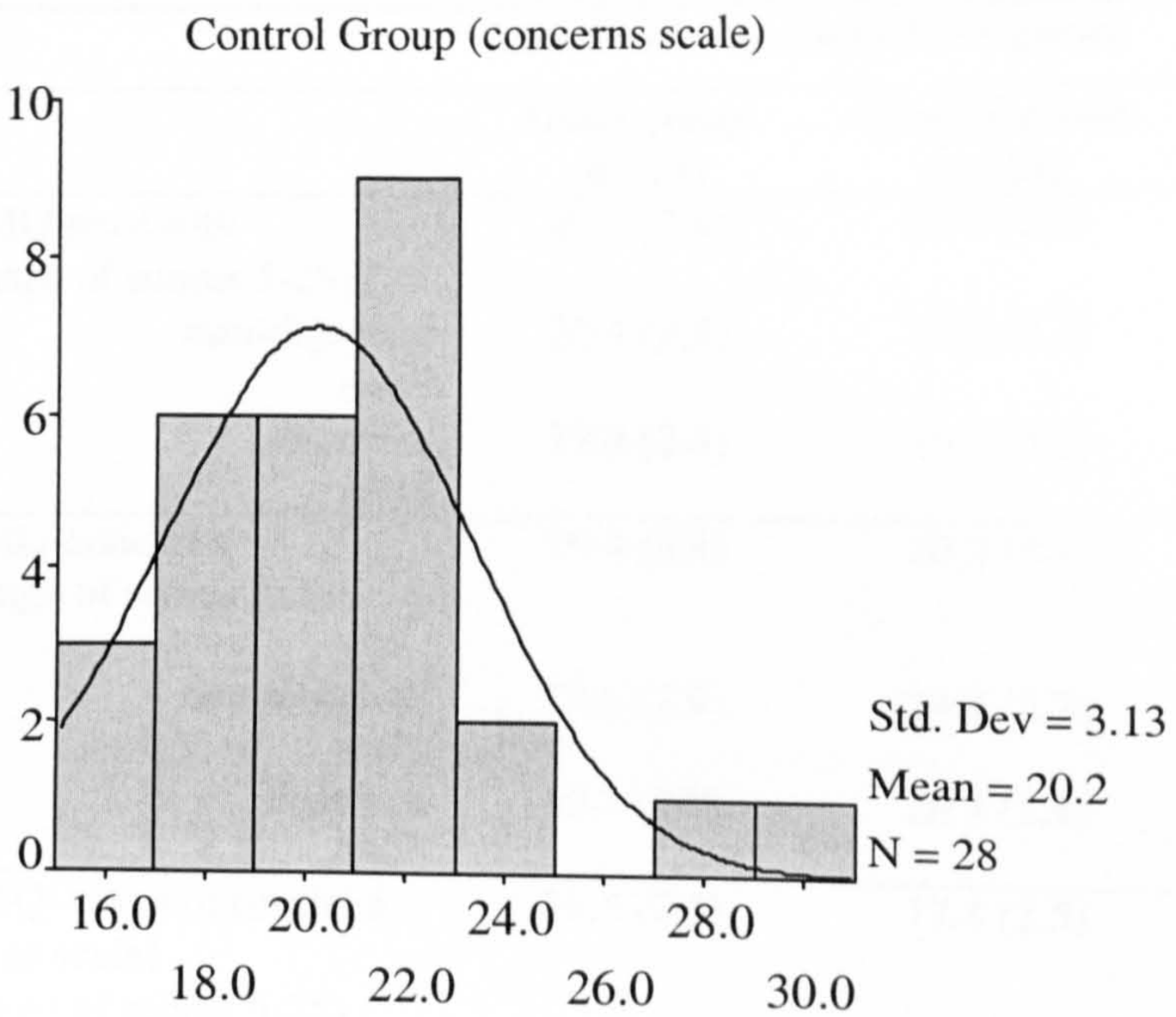


Figure D. Distribution of the 'concerns' scale scores for the control (n=28) and the study (n=24) group after 6 months assessment



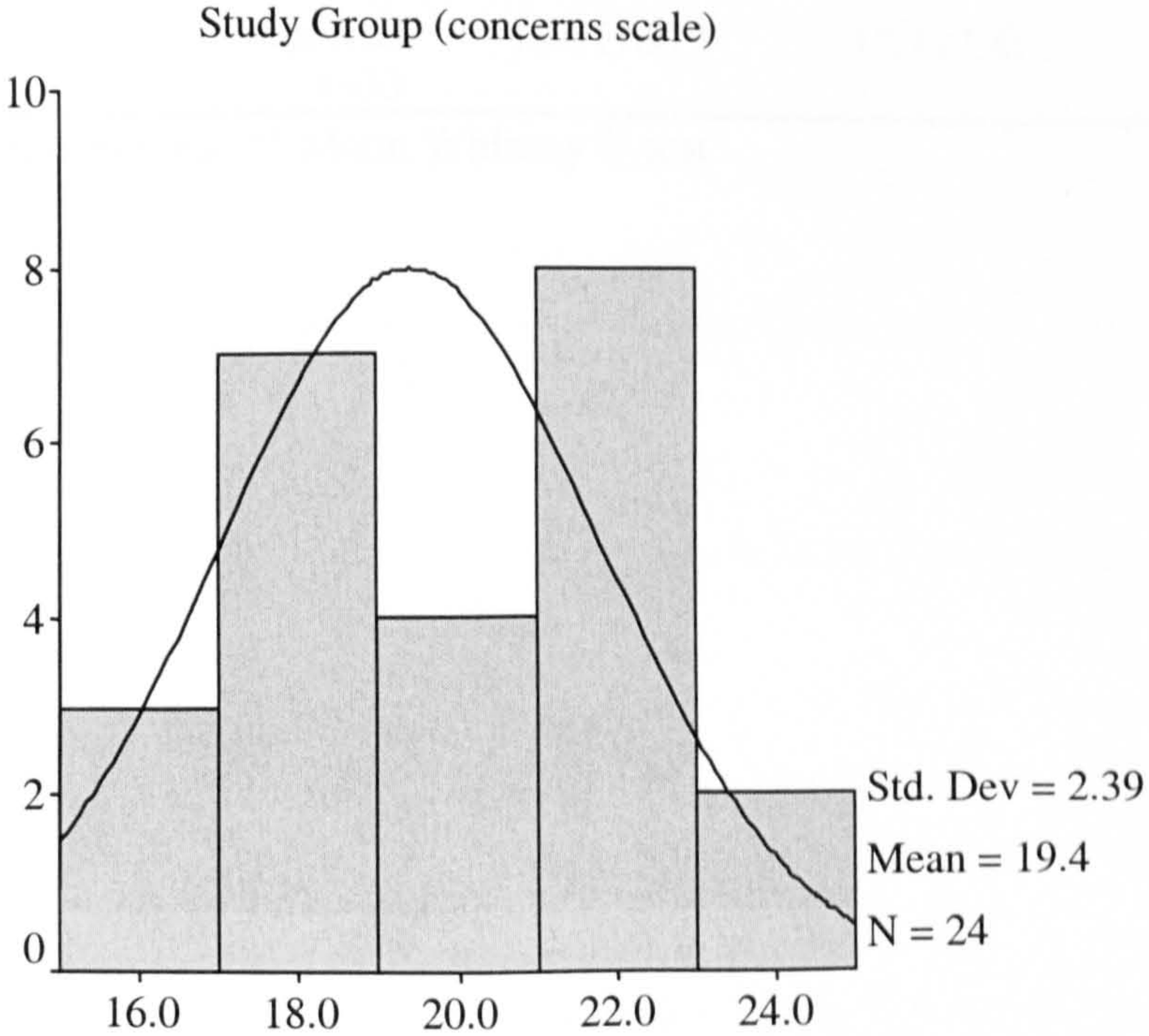


Table B. Summary of results of the specific Beliefs about Medicine Questionnaire after 6 months assessment

	Mean score (standard deviation)			
	Study group **(n= 24)**	***Control group*** **(n= 28)**	***P value***	***All*** **(n=52)**
BMQ-necessity (range of scores 5-25)	20.1 (2.4)	19.3 (3.7)	0.3*	19.7 (3.1)
non-deprived n=19	20.4 (2.5)	19.8 (3.7)		20.1 (3.1)
deprived n=33	19.9 (2.4)	19.1 (3.7)		19.4 (3.2)
BMQ-concerns (range of scores 6-30)	19.4 (2.4)	20.2 (3.1)	0.4** U=293.0	19.8 (2.8)
non-deprived n=19	19.6 (2.9)	19.2 (2.7)		19.4 (2.8)
deprived n=33	19.3 (2.0)	20.7 (3.4)		20.1 (2.7)
BMQ- concern (initial 5 items scale) (range of scores 5-25)	16.5 (2.3)	17.4 (2.5)	0.22*	16.9 (2.4)
non-deprived n=19	16.5 (2.8)	16.6 (2.3)		16.5 (2.5)
deprived n=33	16.6 (1.9)	17.7 (2.5)		17.2 (2.3)

* Student t test ** Mann Whitney U test

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