AN INVESTIGATION OF THE INFLUENCE OF A EUROPEAN FORMULARY ON GENERAL PRACTITIONER PRESCRIBING AS PART OF AN EDUCATIONAL INTERVENTION

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ABSTRACT

This thesis has addressed the issue of primary care prescribing in different European countries. The first hypothesis investigated was: *that the planned implementation of a multinational consensus-based European Formulary in primary care will result in more rational prescribing.* A controlled trial involved 235 GPs from eight European countries with half the GPs participating in an educational intervention. This comprised dissemination of the Formulary and discussion of antibiotic and NSAID prescribing.

Details of **101,544** doctor-patient consultations were collated and prescribing was compared and contrasted, before (Phase I) and after the intervention (Phase II), using performance indicators. This included measurement of the prescribing concordance with drugs recommended in the Formulary which increased by 2.9% (SEM 0.7) between Phases I to II in the intervention group and decreased by 1.3% (SEM 0.6) in the control group. This difference was found to be highly significant ($p < 0.001$). Although some changes in clinical practice occurred, more notable differences were found in prescribing patterns between countries.

A second hypothesis followed: *that identification of the main influences on the participating GPs' prescribing will assist in the explanation of the varying effects of the Formulary in the different countries.* A two-stage Delphi questionnaire study asked the GPs to identify the factors which they perceived to influence their prescribing and to rate their importance. The most important influences were drug related characteristics in six countries, followed by education/information and then patient factors. Pharmaceutical industrial factors were considered the least important influence in six countries, which followed regulatory factors in five countries. More influential factors appeared to be in the GPs' control, rather than ones imposed by national health care systems, regulation and government.

The results show that the extent of Formulary adoption varied in different European countries. There remains a continuing place for the promotion of rational prescribing principally through education and information, including prescribing guidelines. Future initiatives may be more appropriate within countries but require adequate and sustained professional and government support.

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CHAPTER ONE
INTRODUCTION

1.1 BACKGROUND

The concept of a European Formulary was first conceived at an international conference in Bielefeld in former West Germany in 1987 with the theme *Fewer Drugs Better Treatment*. From the surge in interest that followed, a European Formulary Group (EFG) was established to carry forward the pioneering operation to develop the European Formulary. By the end of 1991, a prototype European Formulary was produced with ten members of the EFG forming an Editorial Board. Eighteen months later, a framework European Formulary was developed resembling the version ultimately used for field testing. Up until 1993, the EFG had no success in acquiring independent financial support in order to help pursue the exercise.

At that time opinion was divided among members of the Editorial Board as to what the future held for the European Formulary. Some considered that the ultimate test to prove the validity and worth of the Formulary was to measure its degree of acceptability and use among general practitioners (GPs) in different countries. Only by obtaining feedback from GPs with different views could a future European Formulary be shaped. Other members were not entirely satisfied with what might be perceived by peers as a 'substandard' Formulary for practical use being circulated among clinicians. They preferred the idea of building on the framework Formulary, facilitated by medical literature and discussion with the ultimate aim of compiling a definitive European Formulary. The result of a successful grant proposal for the former idea to determine whether the European Formulary could be successful in improving cost-effective prescribing paved the way for the future direction of the venture. The proposal acquired independent BIOMED (Biomedical and Health Research) funding which became available in the summer of 1994 and I took up the post of junior research associate as the only full-time employee associated with the study at the end of January 1995.

Formulary development needs to be an ongoing process but with the time-lag between applying for funding and getting the project up and running, update of the framework European Formulary had not been sustained. This fact, coupled with the

complication that not all members of the Editorial Board either opted to participate in the BIOMED study or to recruit a colleague to take their place, led to problems in merging the two separate agendas. The compromise reached was that those individuals not participating in the newly funded study would still be invited along to annual meetings where a proportion of time would be allocated to the continued development of the European Formulary but they would receive no financial support from the project grant.

The first of three annual BIOMED project meetings to take place in Newcastle upon Tyne, England was at the end of April 1995. My input for these meetings included discussion of the progress of the study, planning of the content and implementation of the educational intervention, and feedback on the prescribing data. The initial three months prior to the first meeting, since I had taken up the research post, were primarily devoted to constructing diagnoses and drug coding frames. The drug coding frame was initially compiled from drug entities only available in the UK, so it required constant updating as alternative drugs available in other countries were prescribed. In preparation for the co-ordinators' meeting, a sample of data from each of the countries was coded, processed and manipulated in order to provide some basic initial feedback as well as to report on some of the problems encountered in the data analyses. As NSAIDs were one of the areas of prescribing which it was proposed to target, I performed a literature search on NSAIDs in order to contribute to discussion on how the educational intervention was to be formulated and structured.

As my research work progressed, I saw that the European Formulary project and analyses of the data being collated could be utilised into challenging exercises for both continuing education and professional development. Subsequently, I registered for the degree of doctor of philosophy in November 1995, initially on a full-time basis until termination of my research contract in July 1997 and thereafter, self-funding as a part-time student. In the 18 months that followed my higher degree registration until termination of the BIOMED funding, I was able to develop an understanding and vision of how I could carry forward and consolidate the pioneering multidisciplinary collaborative development of the European Formulary and subsequent BIOMED controlled-study into its effect, to culminate in this thesis.

1.2 MAIN HYPOTHESES

Two major hypotheses were investigated in this thesis, these were that:

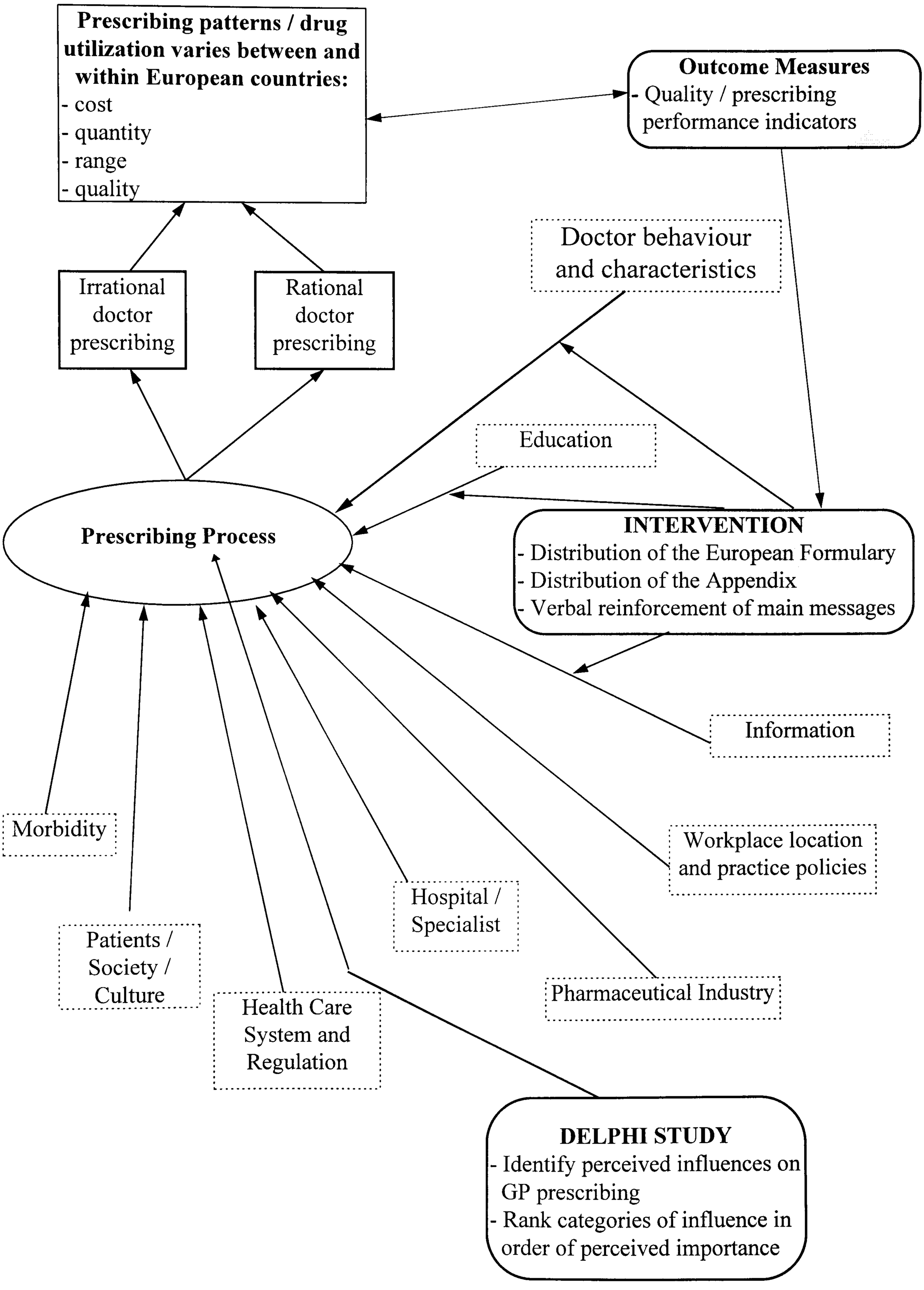
1. the planned implementation of a multinational consensus-based European Formulary in primary care will result in more rational prescribing.

2. identification of the main influences on the participating GPs' prescribing will assist in the explanation of the varying effects of the Formulary in the different countries.

Three areas of literature review are covered at the opening of this thesis and additional literature review was found to be necessary for inclusion at the start of each drug and morbidity results section relating to the investigation of the first hypothesis. A further literature review section comparing the main features of European Health Care Systems with a summary, conclusions and implications for prescribing research is presented in Annex 1. Throughout the thesis tables are located at the end of the Chapters.

A framework of the research conducted in this thesis and how if fits into the wider context can be seen in Figure 1.1. In summary, this thesis has compared and contrasted prescribing patterns between the participating European countries and has assessed the prescribing performance prior to and after the implementation of an educational intervention. The area associated with influences on GP prescribing has also been explored and an attempt has been made to categorise influencing factors and to rank their perceived importance.

Figure 1.1 Framework of the research conducted in this thesis



CHAPTER TWO
REVIEW OF THE LITERATURE

2.1 PRESCRIBING PATTERNS AND FORMULARIES

"I shudder to think of the ceaseless cascade of medicine which is pouring down British throats at the present time". (Aneurin Bevan 1949)

2.1.1 Introduction

In response to a patient's presenting complaint, a problem solving process will begin which may well result in a prescription. A prescription communicates the patient's drug treatment selected by the prescriber to the pharmacist who is responsible for dispensing it. Prescribing is a major clinical responsibility and is one of the core functions of the doctor.[1] Over the past fifteen years though, there has been an increasing amount of published drug utilization research which has questioned aspects of prescribing practice at regional, national and global levels.[2] Some of these problems which are expanded on below include:

1. polypharmacy prescribing
2. drug prescribing not related to diagnosis
3. the prescribing of inappropriate often not therapeutic dosages
4. the prescribing of unnecessary drugs.

Other aspects such as the susceptibility of doctors to pharmaceutical industrial promotion[3] will be discussed in Section 2.2.8.

Polypharmacy prescribing refers to the situation when a patient is being supplied with several drugs which may potentially interact with each other, or when a drug may be being taken to reduce the side-effects of another.[4] Elderly patients with their multiple diseases are particularly susceptible to incremental prescribing which greatly increases the risk of drug interactions as well as other possible adverse reactions which can lead to iatrogenic disease and subsequent hospital admissions.[5] At the end of the 1980s, a study was performed by a multidisciplinary team of researchers to investigate

multiple medication use by over 2,800 elderly patients in Dubbo, New South Wales, Australia. Results of multivariate statistical analyses revealed that polypharmacy was significantly predicted by recent hospitalisation, increasing age, female sex and increasing depression.[5] Widowhood and loneliness may cause or aggravate symptoms of social stress and can sometimes result in the unnecessary and inappropriate prescribing of psychotropic drugs.[6] Young individuals have also been found to be exposed to polypharmacy. A study to investigate the cost burden and extent of medication use by 1,450 outpatients who were up to 16 years of age was conducted by two medical doctors in a Nigerian University Teaching Hospital in the mid 1980s.[7] Five drugs on average were prescribed for each patient and an increasing number of drugs prescribed per patient was found to potentiate poor compliance with drug regimes. Drugs used by elderly patients which have often been found to be associated with polypharmacy include cardiovascular, analgesic[8] and non-steroidal anti-inflammatory drugs (NSAIDs)[9]. In younger patients, polypharmacy predominantly involves anti-asthma drugs, anti-ulcer drugs and psychotropics.[8] Implementing an effective repeat prescribing system could help to identify those patients at risk from polypharmacy prescribing. The issuing of a standard number of days' duration of treatment for items taken regularly, may help to reduce confusion and increase compliance with drug regimes.[10]

The inappropriate prescribing of antibiotics in diarrhoea is a commonly reported example of **drug prescribing not related to diagnosis**, particularly in third world countries.[2] In parts of Indonesia, virtually every patient with simple diarrhoea or common upper respiratory infections is treated with one or more antibiotics.[11] As a result, 60% of the drug cost of treating these common illnesses is due to anti-bacterial agents. In the early 1990s a survey by epidemiologists in Mexico City interviewed housewives of 1,659 households to identify antibiotic misuse in diarrhoea. Patients with diarrhoea who consulted a physician were found to be six times more likely to be treated with an antibiotic than those patients not consulting.[12] Self-medication was also associated with a higher risk of using an inadequate drug or dose and treatment was likely to be taken for less than the recommended duration. As the data was based on information obtained from interviews with housewives about the previous two week

history of family members presenting with diarrhoea, there may have been an element of recall bias in this study.

Prescribing of **inappropriate** dosages has also been found to be a particular problem in a review of published prescribing studies. A multi-disciplinary team of health service researchers in Manchester organised a panel of 10 experts in the field of prescribing to define indicators of prescribing appropriateness in general practice.[13] Nineteen indicators were identified and their prevalence was rated in 62 prescribing studies published between 1980-95, using the then current issue of the British National Formulary (BNF) as the reference standard. 'Inappropriate drug dosages which were outside the advised therapeutic range' was consistently the highest rate indicator recorded. Such dosages were found to be common with respect to thyroid stimulating hormone and narrow therapeutic index drugs such as digoxin, lithium, theophylline and warfarin.

Other drugs have also been found to be prescribed in subtherapeutic doses, for example antidepressants. The pattern of psychotropic drug use by 2,414 residents in 46 nursing homes in Sydney was investigated by researchers in the psychogeriatric services department of a local hospital.[14] Of the 377 patients identified taking regular antidepressants, at least half the antidepressant doses were found to be subtherapeutic. The paper did not discuss the duration of treatment and it is possible that some of these apparently subtherapeutic doses may have been reducing doses which can be prescribed to prevent patient withdrawal.[6] Identifying the type of prescriber may help explain some differences found in the treatment strategies in depression. Analysis of a postal questionnaire circulated throughout England in 1993 compared the management of depression by 89 geriatricians and 72 old age psychiatrists.[15] Although the former might be more up to date with current practice and new drug developments, the survey found that the geriatricians were more likely to suggest antidepressant dosages which were subtherapeutic. The research was performed by a team of psychiatrists and it is possible that they would not wish to publish findings suggesting criticism towards their own specialisation.

In 1994, Glaeske, a pharmacist working for the German Sick Funds and a government prescribing adviser, considered that over 30% of all prescriptions in the

former West Germany in 1992 were **unnecessary**.[16] Forty-four drug groups were identified which he perceived to be of 'doubtful use' amounting to 247.5 million prescriptions, representing almost one third of the total number dispensed in that year. These drug groups included combinations of antitussives, coronary vasodilators and certain migraine drug combinations. Reasons for this poor quality prescribing were considered to be misleading drug information and too many drugs on the market 'blinding' the prescriber. Of the approximately 57,000 drugs on the German market in 1994, only 12,000 were licensed with proof of efficacy, reliability and high pharmaceutical standard in order to fulfil the criteria of the German Drug Act.

A study in Montreal, Canada in 1997 assessed the management by 112 physicians of two clinical cases using standardised elderly patients with NSAIDs.[17] The first case was chronic hip pain due to early osteoarthritis and the second NSAID related gastropathy. Unnecessary prescribing of NSAIDs were found to be written in over 40% of the doctor-patient consultations.

2.1.2 Drug expenditure and prescribing patterns

The availability[18] and cost of drugs on the market varies from country to country.[19] The same drugs may also have different marketing authorisations in different countries.[20] Government and industrial price and profit controls are largely responsible for determining the cost of drugs in different countries.[21] The quality of prescribing is also considered to vary between countries.[22,23] In addition, there are deep rooted variations in medical culture and training between countries.[24,25]

In the epidemiology of disease, cultural factors can be causal, contributory or protective in their relation to ill-health. Some of these cultural factors include: the economic situation, family structure, contraceptive patterns, population policy, diet and religion.[25] Comparing medical culture between four similarly developed Western industrialised nations namely France, Germany, the United Kingdom (UK) and the United States (US) reveals marked variations.[24] The French attribute the origin of many diseases to the liver, even referring to migraines as *'liver crises'*. In contrast, the Germans believe that the source of many medical conditions is the heart and when a

German doctor describes a patient as having *'cardiac insufficiency'*, this may simply mean that the patient is tired. In the US, the human body is generally perceived to function like a machine. Hence in order to *'fix'* the machine, surgical intervention is practised more commonly than in Europe and in the early 1980s American rates for frequency of coronary bypass were 28 times that of some European countries. Unlike the French and Germans, the British have traditionally preferred to place the cause of disease outside their bodies, they disregard the belief in a certain reserve of health that can be drawn upon i.e. *terrain*. Consequently, the British appear to be a fairly conservative race both in paying relatively little attention to their bodies and in tending to favour previously tried and tested treatment strategies rather than the adoption of new ones. The British also have a tradition for being overly concerned about their bowels and regard daily bowel evacuation as almost a religious necessity which has incurred a disproportionately high use of laxatives.[24]

With respect to differences in medical training between countries, between 1986 and 1990, three WHO Working Groups were set up to investigate the spread of clinical pharmacology throughout Europe.[26] Clinical pharmacology was considered to be fundamentally important in many aspects of health care delivery, particularly with respect to influencing rational drug use. In the 21 countries participating in the survey, there were marked differences with the UK leading the way with 29 clinical pharmacology departments compared with Turkey at the other extreme where there was no such formal department. The idea of a clinical pharmacologist running clinics in a general practice in Whickham, Tyne and Wear, UK had been experimented with in the mid 1970s. Their purpose had been to review medication and future patient management and the results of the pilot study appeared positive.[27]

All the factors referred to contribute to drug consumption and drug expenditure being highly irregular from country to country. With growing economic pressures to contain costs, much attention is now focused on analysing prescribing patterns and drug consumption both within and between countries. By 1985, the global drug bill was estimated at US $100 billion annually.[28] In one decade between 1976 and 1985, despite developing countries increasing their share of the world's population from 63% to 75%, their proportion of the global drug bill decreased by 20% to US $15-20 billion.

In 1997, the world pharmaceutical market was $297 billion and 80% of this was consumed by 10% of the world population.

Over the past decade, the primary care prescribing bill in England has more than doubled, increasing from £1.87 billion to £4.37 billion in 1997, representing 10% of all NHS expenditure.[29] Repeat prescribing alone was estimated to amount to £2.5 billion (7%) of all NHS expenditure in 1993.[30,31] In the UK, seven out of ten consultations in primary care with a general practitioner result in a prescription being issued[30] and consequently such acute and repeat prescribing is responsible for the consumption of vast NHS resources. Over the past few years, the annual prescribing bill has been rising at approximately 10% each year gross[32] which represents a real increase against relatively low rates of inflation.

Between European countries, the quantity of prescribing and annual drug costs per head have been found to vary widely and are increasing (Table 2.1). From Table 2.1 it can be seen that doctors in the UK tend to prescribe a low average number of items per patient per anum, although this is slowly increasing with time. Despite the earlier figures indicating the seemingly high cost of prescribing in Britain, doctors there are actually more conservative in what they prescribe compared with most of their European colleagues. At the beginning of this decade, only 50 drugs accounted for 50% of the total NHS drug expenditure and 300 drugs represented 80% of this.[33] Whereas almost one third of Italian drug expenditure during 1991 was on medicines introduced within the previous five years, which compares with 17% of German, 13% of French but only 9% of UK expenditure.[30]

Less affluent European countries such as Greece and Portugal spend much more on pharmaceuticals relative to their total health budgets compared with wealthier countries in the community.[21] Total per capita spending on all medicines in Britain falls well below the average spent in Western European countries; however there is no evidence to suggest that either lower than average expenditure or reduced drug availability is detrimental to the health of the population in the UK. At a global level, the UK market represents only 3% of the world pharmaceutical sales but it carries an international influence that is markedly out of proportion to its volume.[34]

Prescribing has also been found to vary widely within countries. England, for example, is divided into 8 Regions which are further divided into Health Authorities (HAs).[32] The average total cost per patient per annum in 1998-1999 varied between £73.11 in Ealing, Hammersmith & Hounslow HA and £130.40 in North West Anglia HA (national average £98.35). In the same year, the average number of prescriptions dispensed per patient per annum also varied between 6.69 in Kensington, Chelsea and Westminster HA compared to 13.51 in Barnsley HA and Doncaster HA (national average 10.03 items).[32] One of the reasons for these differences is that GPs are treating increasing numbers of elderly patients who tend to be more numerous in certain locations. The average woman over 75 years of age has been found to be prescribed up to twelve times the quantity of medicines of a young man.[35] Many of the factors which have been identified as influencing prescribing and therefore contribute to an explanation of why variations exist are discussed in a later review section (Section 2.2).

Prescribing patterns and drug expenditure are also likely to be influenced by over the counter (OTC) medicine sales. In 1992, OTC sales accounted for nearly a fifth of the total value of medicines on the market in northern countries such as UK, Denmark and Germany.[21] In Portugal, France, Spain and Italy OTC medicines represent only 5 - 10% of sales. Over the last few years the OTC market has expanded all over Europe with a corresponding promotion of self-medication by the governments in the majority of European countries.[18] The main purposes of this has been an attempt to reduce the cost burden on insurance and national health care systems, thereby pushing the cost onto the consumer.

One problem with some of these reported inter-country comparisons is that the information often comes from a variety of independent sources, as a consequence of which drug consumption, cost and associated statistical data may not always be directly comparable. For example, data comparing the average number of prescriptions per head would vary whether this reflected actual drug consumption or the theoretical number of prescribed items written. It has been estimated that between 5 and 10% of prescriptions written are not dispensed.[36]

2.1.3 Rational prescribing

To ensure optimal use of often scarce health system resources, prescribing should be responsible and rational. In 1973 Parish, then a senior medical research fellow in Swansea, considered that responsible prescribing was based on a clear clinical need and that the actions of the prescriber should be defended to both peers and patients.[37] He defined rational prescribing as being appropriate for the patient, effective, safe and economical. This has been an important statement which others have developed. A few years later in 1978, Taylor, an academic general practitioner from Aberdeen, endorsed a similar definition of rational prescribing to that of Parish.[38] More recently, van Zwanenberg emphasised that prescribing should be acceptable to the patient and that the two most important criteria in prescribing were the appropriateness of drug prescribing and the choice of drug / preparation.[39] Patient acceptability can be important; for example, the taste, appearance, dosage schedule and side-effect profile are all features which can effect patient concordance.[40]

In 1995 the definition of rational prescribing was refined by Barber a professor of pharmacy practice at London University School of Pharmacy.[41] He proposed that the main aims of a prescriber should be to: maximise effectiveness; minimise risk; minimise cost (by taking account not only drug costs but also associated costs such as necessary laboratory monitoring) and respect patient choices. He acknowledged that trade-offs may often need to be made between conflicting aims and that, depending on the situation, patient choice may be the most important consideration.

Two pharmacists have more recently performed a qualitative study interviewing 23 GPs from two health authorities in the south of England to analyse why doctors may continue to prescribe in ways which do not fit the ideal of rational prescribing.[42] They revealed that prescribing is often performed in an irrational way as a coping strategy for a variety of reasons including busy workload, to maintain a doctor-patient relationship and to reduce the risk of medico-legal challenge. The following is a quote from a GP who issued a prescription to alleviate a distressing situation.

"A patient came to me...who has cancer and was waiting for chemotherapy. She got a sore throat. I knew that she was terrified that her chemotherapy would be

cancelled...She was convinced she would never get better from the sore throat and it was some other sort of cancer. And I gave her antibiotics more or less without even bothering to look at it. I mean, I did look at it but I was going to give her antibiotics anyway because she had got herself into such a tiz - but they were entirely to calm her down."

The above case does not necessarily mean that the GP disagrees with the criteria of rational prescribing but in certain situations may find prescribing the most rational option. This research left the authors wondering whether it was the definition of rational prescribing which has turned into rigid health policy that was wrong, rather than the doctor.[42]

Health service researchers in Manchester published a review on the appropriateness of prescribing with respect to healthcare in 1997.[43] They differentiated between rational and appropriate prescribing by suggesting that the former could be considered to be a process whereas the latter was an outcome. Appropriate prescribing was thus defined as an outcome of a process of decision-making that maximises net individual health gains within society's available resources.

2.1.3.1 Key political strategies to improve prescribing in the UK

Generic prescribing was advocated as one mechanism of reducing prescribing expenditure back in 1959 by the Hinchcliffe Committee which was set up to investigate the cost of NHS prescribing in Britain.[44] Another of the Hinchcliffe recommendations resulted in the introduction of the Prescribers' Journal.

Current law controlling the production and distribution of medicines in the UK was introduced following The Medicines Act 1968.[45] This ensured that no medicine could be marketed without a product licence (now referred to as marketing authorisation) and that medicines may only be manufactured by the holder of a manufacturer's licence. The Act was particularly relevant to the prescribing of medicines as it was the benchmark for ensuring a comprehensive standard for the efficacy, safety and quality of all medicines.

In 1982, the Greenfield Report concluded that there remained advantages to be gained from generic prescribing and the report went as far as recommending that community pharmacists should substitute generic drugs for proprietary products on prescriptions as hospital pharmacists do. To date this recommendation has not been implemented.[46]

Government concern about the cost of prescribing has resulted in several measures which focus on containing cost. In April 1985, the government introduced the Limited List or Selected List which restricted prescribing of some categories of medicines within the NHS. The intention was to eliminate many heavily prescribed non-advertised pharmacy only (P) and general sales list (GSL) medicines from GP prescriptions and encourage the public to purchase them instead. During the first month after the introduction of the Limited list, two health care professional academics in the Department of General Practice, University of Aberdeen recorded the actions taken by 17 GPs when a recent banned drug would have formerly been prescribed. They found the prevalence of patient contacts affected by the new regulations to be relatively low and of these, approximately half the patients received the same active drug under a different name.[47] This study was only carried out in the short term and the results may not have been an accurate assessment of the impact of the Limited List. In the first year which followed its introduction, the UK government claimed and reported saving over £75 million.[48] The accuracy of this estimate was debatable though and Gilleghan, a GP in Edinburgh and one of the key leaders in the general practice formulary movement in the UK, was of the opinion that the Limited List had not demonstrated an overall reduction in drug costs.[49]

In 1992, the government planned to extend the Selected List. To facilitate this process, the Advisory Committee on Drugs which included extensive professional representation was established.[34] Two years later, the group were only able to recommend that topical NSAIDs which at the time cost more than £7 per 100g should be 'blacklisted'. This resulted in a swift response by manufacturers to reduce their prices and consequently a new Selected List was not produced. The Committee considered that the 'blacklist' focused excessively on drug costs and did nothing to improve prescribing and suggested that a positive ('white') Selected List might be more

successful but to date this has not been adopted. Positive lists are currently more commonly used by other European governments to intervene in the pharmaceutical market rather than negative lists.[18]

Consideration of extending the Selected List was part of the NHS reforms introduced in 1991 to address the problem of escalating NHS costs of which prescribing costs represented a major contributor.[50] Two initiatives were introduced to provide GPs with incentives to reduce prescribing costs. Firstly, GP practices were invited to become 'fundholding' and were given a drugs budget with the power to reinvest any savings that they could make in other services to their patients. Secondly, for non-fundholding practices an indicative prescribing scheme was introduced in the form of an estimated financial target based on previous spending. These budgets and financial targets were set and monitored by Health Authority medical and pharmaceutical prescribing advisers with the aid of PACT data.[51]

In the UK in 1994 the Audit Commission published one of the most in-depth documents to date on prescribing.[30,52] The Commission's strategy for prescribing suggested that £425 million could be potentially saved in general practice prescribing. Those consulted included staff at 54 practices, regional and hospital pharmacists and many professional bodies. Prescribing was evaluated in the 54 practices and a model was developed that could be compared with national averages. The difference between the model and real life formed the basis of its calculations on cost. In order to achieve rational prescribing, the report recommended: less over-prescribing of, for example, ulcer healing drugs; reducing the prescribing of drugs of limited clinical value such as vasodilators; substituting comparable but cheaper drugs, for example, expensive NSAIDs with cheaper ones; more prescribing of generic alternatives to brands and justifiably appropriate use of expensive preparations including modified release formulations. The Commission did accept that in order to achieve this, prescribing behaviour will have to be changed over a period of time.

Following the change in British government in May 1997 Primary Care Groups (PCGs) were proposed in a White Paper published in December of that year.[53] This was the beginning of the phasing out of fundholding for practices and from April 1st 1999 all GPs have had to join PCGs which usually consist of about 50 GPs covering a

population of approximately 100,000 within the same geographical area. In the past, health authority budgets for hospital, general practice medicine, pharmaceutical services and other primary care areas were separate but PCGs now receive a global sum for all these services.[54] This has the advantage of allowing the movement of funds between different budgets, although each PCG will have a ceiling on its prescribing. Should this be breached then other areas of health care expenditure, such as the budget for hospital and community services will have to be curtailed, but savings can be reinvested in the health care of the local community. Each PCG board will have a member who takes a lead on prescribing and it is anticipated that significant change should be visible within the first year of operation.[55]

2.1.3.2 Assessing rational prescribing

In 1977, Mapes, a medical sociologist at Swansea University, attempted to assess the criteria of effectiveness and safety in the definition of rational prescribing by analysing a random sample of approximately 1,000 prescribed items from each of 116 doctors.[56] He found that the writers of large numbers of relatively inexpensive prescriptions tended to display *conservatism* and postulated that with increased workload, *conservative* doctors show a tendency to recall drugs that they learned about in their early training. In contrast, *incaution* was found to be associated with a declared dependence on pharmaceutical industry literature, with the tendency to leave prescription writing to ancillary personnel and with prescriptions having inadequate or no directions. The data demonstrated that prescription analyses can be useful for exposing distinct differences at either end of the spectrum of rationality but also showing that prescribing by some doctors at different times displays both conservatism and incaution. There was some selection bias in the study as all the practitioners were relatively young and had become principals in general practice in 1969.

A multi-disciplinary pharmacist / GP research team in Dundee categorised prescription errors into four classes of severity and investigated the frequency of their occurrence by eight GPs in three practices.[57] Although there were only found to be 504 errors from 15,916 prescriptions, it was estimated that each doctor is still likely to have on average 260 errors which require correction each year. The study also found that

doctors who make minor nuisance and trivial errors are the ones more likely to make major errors and potentially serious mistakes.

In 1987, van Zwanenberg *et al*, academic GPs from the Newcastle Medical School, attempted to study the effectiveness of educational interventions on the prescribing of 12 GPs but acknowledged that there was difficulty in identifying valid measures of Parish's and Taylor's definition of rational prescribing.[58] The results indicated that prescribing habits of GPs can be changed if they are given information and have the opportunity to discuss rational prescribing. They found that measuring the proportion of patients not receiving a prescription, the proportion of items prescribed generically and the proportion of new and repeat prescriptions falling within an agreed local formulary were a useful framework for assessing rational prescribing. There was some selection bias in this study with all the participating doctors aged between 29 and 36 years and therefore not truly representative of the GP population.

One major disadvantage of these various studies is that there is no single methodological approach which can be adopted to assess prescribing competency. The research which has been carried out often has one recurring limitation, for example with respect to the number of GP participants mainly due to the limited resources available. One of the attractions of using the proportion of drugs prescribed generically as a crude indicator of rational prescribing (Section 2.1.3) is that, subsequent to the Newcastle study above[58], this can now be potentially measured on a continuous basis for all GPs in the UK by using systems such as Prescribing Analysis and Cost (PACT) and Scottish Prescribing Analysis (SPA) described below.[59] Generic prescribing is one example of where interventions to improve GP prescribing habits have been successful and maintained compared with the effects of other interventions.[60]

One of the most important factors which has encouraged the assessment of prescribing by GPs is the widespread concern over the rate of increase in drug expenditure across Europe.[61] The introduction of computers has enabled the Central Prescription Pricing Authority in England to produce a revolutionary method of analysing the prescribing patterns of all GPs. Prescription Analysis and Cost (PACT) was introduced to GPs in England and Wales in 1988[40] and in Scotland, a similar

system began in 1990 called Scottish Prescribing Analysis (SPA). PACT and SPA data records every prescription issued and it enables GPs to:

- review their prescribing habits and costs,
- develop and monitor practice formularies and prescribing policies within the practice,
- compare their prescribing with that of their colleagues in the same Health Authority area and also nationally,
- improve the cost effectiveness of prescribing within the practice.

All GPs receive PACT data at quarterly intervals and until 1995 it was available in three levels of increasing complexity and now similar information is available in two formats. The breakdowns of prescribing analysis data are gradually being introduced into other European countries.[62]

Since 1990, each GP in Britain is now given an indicative budget for each year's prescribing based on several factors including the size of the practice and the number of registered patients.[51] Associated with this, Health Authority prescribing advisers have the role of assisting GPs to develop more rational and cost-effective prescribing. With the aid of PACT data, prescribing advisers can monitor the total cost and trends over time for the district and for individual practices. Through the mechanism of an annual review with each practice, the adviser can influence the quality as well as the cost of prescribing. With continuous monitoring and feedback, it is expected that improved prescribing will follow.[63]

Since the introduction of PACT and SPA, prescribing analysis has expanded and diversified in the UK but access to more in-depth sophisticated information is limited. The information contained within PACT is a simple cost listing, not related to morbidity levels or quality of prescribing, and this must be recognised when interpreting the data. There is no information on patient numbers, doses, length of treatment, consultation rates, referrals or treatment outcomes, including failures.[64] In addition, PACT data does not contain any information on prescribing in hospitals and it excludes private prescriptions and drugs that a patient does not have dispensed.[65] Patients are

categorised as prescribing units (PUs) within PACT data but the adjustment for age is not ideal with all patients 65 years and over being classed as three PUs compared with all other patients who are classified as one PU. ASTRO-PUs and STAR-PUs have been derived from the computerised records of general practices which indicate that the simple weightings are inadequate.[35,66] ASTRO-PUs make allowances for age, sex and temporary residents and STAR-PUs are specific therapeutic group age-sex related PUs.

To overcome some of the limitations of PACT, one study in the North East of England attempted to apply professionally derived numeric standards of prescribing performance based on PACT.[67] Eight GPs of different ages and practice environments met on three occasions and by an informal consensus decision-making method selected 13 quality markers which were then applied to all 518 practices in the region. The study proved that realistic indicators to assess prescribing quality can be set but it is debatable whether these standards could be used right across the country.

Using cost as one of the measures of rational prescribing is a particularly complicated aspect to investigate and involves many aspects of pharmacoeconomics. Economic studies should include all costs associated with the treatment or intervention, and those of monitoring and follow-up, as well as the estimated costs of adverse effects and treatment failures. The main four methods of analysis[68] available are:

a) **Cost-minimisation analyses**. These are used in two circumstances: firstly, where it is known for example that different treatment strategies generate exactly the same health care benefits and only the costs differ; secondly, where one option is superior in terms of both clinical effectiveness and costs in terms of hospitalisation for example.

b) **Cost-effectiveness analyses**. These are particularly useful for comparisons of directly competing drugs and therapies when weighing up the price of achieving extra benefit from using one treatment which is superior to another. This can be expressed in units such as cost per infection cured, cost per unit of cholesterol reduction or cost per year of life saved.

c) **Cost-utility analyses.** These can be used to measure the patients' perspective of the various health changes produced by an intervention. Comparative assessments of the net cost per quality-adjusted life year are the most familiar form of cost-utility analysis.

This measure has the advantage in that it can be used to make broad comparisons of the 'health gain' achieved from devoting resources to different health care interventions.

d) **Cost-benefit analyses.** These involve determining health benefits in monetary terms and such analyses are often applied in order to optimise the use of a health care budget. Additionally, they can be used to assess, for example, the benefit achieved from the provision of extra resources to health screening.

All of the above measures differ in the way they handle the benefits of health care. In recent years, there has been a growing trend to widen the criteria upon which drug selection is based by incorporating more emphasis on patient acceptability. If the patient is not satisfied, concordance is likely to be impaired. This is a fairly challenging task on the part of the health care professional - such as in convincing patients that a generic drug is in no way inferior therapeutically to the branded equivalent when the former may appear less glamorous.[69]

In the future, it is likely that prescribing performance will be monitored even more closely because of the importance of patient and financial outcomes.[59] Prescribing assessment in primary care needs to be linked closer to morbidity, health outcomes and hospital admissions and computer software may one day enable this to happen. Meanwhile, GPs should perform regular medical audit to check for example that their system for reviewing patients on long term medication works and continues to do so. In order to optimise rational prescribing and perform medical audit, the use of a drug formulary can prove invaluable.

2.1.4 Formularies and essential drugs

The concept of essential drugs is that in a given situation, there is a list of drugs which are the most needed for the health care of the majority of the population and therefore should be available at all times in adequate amounts and in the proper dosage forms.[70] Similarly, formularies in their most basic form consist of a limited list of drugs with their profiles and they are intended to guide doctors in their prescribing.[71] Formularies may also be more sophisticated by containing additional important prescribing information to help doctors with drug selection.[72]

Essential drugs lists were created in an attempt to extend the accessibility of the most necessary drugs to populations whose basic health needs could not be met by the existing supply system.[71] The World Health Organisation (WHO) Action Programme on Essential Drugs intends firstly to ensure the regular supply of safe and effective drugs and vaccines of acceptable quality at the lowest possible cost and secondly to promote the rational use of drugs.[28]

There are many similarities between a therapeutic formulary and an essential drugs list. Firstly, the basic criteria for drug selection are those based on evidence of efficacy and safety ensuring that the drug has a favourable benefit / risk profile. Where two or more drugs appear to be similar, choice should be made on a cost / benefit ratio and drug availability should also be considered. They should be tailored to local requirements as the range of drugs that must be considered vital to a community will vary both with the actual prevalence of particular disorders and with views of how these can be prevented, diagnosed and treated. Preferably there should be some input into the formulary development from the doctors who will be the users when prescribing and from pharmacists who are able to provide relevant valuable advice and are also affected by the range of drugs likely to be requested. If formularies and essential drug lists are to remain useful, it is crucially important that a mechanism for periodic updating is established.

The main difference between an essential drugs list for use in developing countries and a formulary in a developed country is that the former is often trying to create the best approach to therapy from the limited resources available.[70] In contrast, the latter is attempting to select the most suitable medicines from a wide choice of drugs.

2.1.4.1 Formulary evolution

Formularies containing herbal remedies were recorded by Dioscorides, a surgeon in the Roman army at the time of the Emperor Nero as far back as AD 100.[73] In Britain, herbal formularies have existed for over 500 years.[74]

In 1911, the National Health Insurance (NHI) Act was passed and since then the number of local formularies containing simple medicaments with lists of ingredients

began to increase.[75] This increase was in response to a need for doctors and pharmacists to have access to more practical information about medicines than that limited to pharmacopoeias.

After two years collaboration between the British Medical Association (BMA) and the then Retail Pharmacists Union, a nation-wide formulary was compiled in 1929 for all NHI doctors.[75] The formulary contained 295 monographs and for the first time included 'notes for guidance in prescribing'. Although the NHI Scheme only covered community medical services, most of the larger hospitals also had their own formularies and prescribers were restricted to using drugs listed in the formulary for both in-patients and out-patients.

In 1941, a small committee was appointed to prepare a National War Formulary (NWF).[76] The formulary listed 380 preparations, sufficient in range to meet the ordinary requirements for therapeutics, and it was intended for use by prescribers in both primary and secondary care. As previously, the main titles were in Latin and the doses given in the Apothecary system.

A few years later in 1948, the National Health Service (NHS) was established in the UK. The Pharmaceutical Society and the BMA, the two non-governmental bodies which had been most closely associated with the production of the NWF, continued the publication of a British National Formulary (BNF) for use throughout the NHS.[76] Under the direction of a Joint Formulary Committee new editions of the BNF were produced about every three years until 1976. During this time much detailed discussion took place and the content and style of the formulary changed drastically. English replaced Latin, the metric system replaced the apothecaries' system and monographs on new and important drugs such as antibiotics gradually replaced traditional tonics and mixtures. By the end of the 1960s, there was a flood of new drugs introduced and updating the formulary against the tide of industrial innovation became extremely challenging. Producing a revised BNF once every three years was not enough to maintain widespread acceptance and eventually the BNF was perceived by doctors as being increasingly less relevant.

At this time, the Monthly Index of Medical Specialities (MIMS) was being published under the auspices of the pharmaceutical industry and in 1976 it was estimated that 80% of prescribing was done using the Index and only 20% with the BNF.[75] This led to a demand for a new type of formulary and together with representation on the Joint Formulary Committee of the Department of Health it was agreed that the British National Formulary should:

- no longer be selective
- contain information about all the drugs available for doctors to prescribe
- give information about the price of medicines
- be easy to use
- be handy to fit into a coat pocket
- be kept up to date[76]

Since 1981, the BNF has been published in a new format with six sections. While doctors and pharmacists welcomed the new BNF, the media and pharmaceutical industry were antagonistic. The new BNF format has been published every six months[75] and since 1997, an on-line version of the BNF has been available. This has the added advantages of being easily accessed in the doctor-patient consultation as well as in the pharmacy and it facilitates even more regular update of necessary drug changes.

2.1.4.2 The global perspective

Before the major revision of the BNF took place in the mid 1970s formularies began to proliferate in other parts of the world as can be seen in Table 2.2.

2.1.5 Formulary development with particular reference to the UK

Formularies are designed to offer good quality independent information, with drug recommendations based on efficacy, safety and cost without compromising patient care.[4] Both general practice[77-81] and hospital formularies[82-85] are available which are

tailored to the needs of prescribers depending on the branch of health care in which they practice.

In setting up a local primary care formulary, it is important to establish and agree a number of factors at the outset. Firstly, the aims of the exercise need to be realistic and achievable and they should be ranked in order of priority. For example, is the formulary intended to be simply a list of approved drugs or a more detailed manual providing guidance on prescribing? Secondly, it is necessary to define the intended scope of the formulary as it needs to be representative of the range of its proposed clinical activity.[86] However, it must be sufficiently detailed to allow choice of drug, but not so large that it fails to eliminate excessive duplication.[87] The proposed target of one published formulary, for example, has been to recommend treatment for 90% of patients presenting in primary care.[78] Thirdly, the procedures and funding for ongoing update and review are also best agreed and established at the start. Finally, to ensure deadlines are met, the precise roles and expectations of all those involved in development need to be clearly specified at the outset.

In recent years, there has been steadily increasing political pressure to improve prescribing and one proposal by a former British government has been to encourage GPs to develop their own practice formulary.[46] As GPs in the UK are independent contractors it can be difficult for Health Authorities to enforce the use of formularies. A frequent reservation expressed by some doctors is the fear that formularies devised by other people could be imposed on them so it is better for doctors to be involved and prepare their own formulary based on their experience and needs.[88] The onset of fundholding practices in 1991 inspired many GPs to develop their own practice formularies as it provided them with the financial incentive to control their prescribing budget and the opportunity to reap the rewards of reducing prescribing costs.[89]

2.1.5.1 Preparation of a formulary

Use and acceptance of a formulary is strongly related to a wide network of actively participating GPs.[90] In order to be successful, a practice formulary must reflect the views of its users and provide them with a sense of ownership. This was endorsed by

the Department of Health in 1990.[91] However, the extent of potential users involvement depends upon the amount of time that they are prepared to put into its development.

A different approach is required in hospitals due to the majority of users being junior medical staff, many of whom rotate every six months.[92] Despite no real opportunity for these users to have much input, hospital formularies have been found to be both acceptable to hospital staff and effective in improving the quality of prescribing while effecting cost savings.[93,94] This probably reflects the hierarchical structure of hospitals with prescribing restrictions being placed on junior staff while more senior colleagues in particular specialities may be permitted the use of certain non-formulary drugs. From an educational perspective, the restricted choice of drugs in both general practice and hospital formularies permits prescribers to gain useful experience with a narrower range of drugs.[95,96] If prescribing formularies can help doctors to prescribe from a narrower range of drugs selected for efficacy, safety and economy, this can then lead to more rational prescribing.

Hospital formularies are required to be used by a large number of prescribers in a wide range of specialities and so they tend to have a greater choice of drug preparations than general practice formularies. Hospital multidisciplinary Drug and Therapeutic Committees (DTC) have the responsibility of production, revision and management of formularies in hospitals.[97] Arrangements usually exist for liaison with the different hospital departments so that input can be provided from a wide range of expertise. The DTC has to maximise awareness and co-operation and in so doing smoothly implement established hospital drug policies.

Successful construction of formularies involves multidisciplinary activity to maximise clinical drug usage and cost containment. Pharmacists and GPs have been found to successfully work together in developing formularies and this is one of the many roles of practice pharmacists who are now widely based in GP surgeries.[98-103] Pharmacists, for example, have access to relevant literature and the skills needed to evaluate PACT data and apply the information to the decision making process.[40] They can identify those drugs which are causing high cost prescribing, detect the uptake of

new drugs and monitor prescribing performance indicators. By making recommendations to prescribers, pharmacist can help to develop rational practice prescribing policies.

In two separate studies undertaken in England and Scotland examining GPs' awareness of drug costs, it was found that in both cases GPs tended to overestimate the cost of inexpensive preparations and underestimate the cost of expensive ones.[104-106] A study of Italian GPs' knowledge of prescription costs found them to also overstate the price of cheaper drugs but to be more aware of the expensive ones than GPs in the UK studies.[62] Physicians' perceptions of drug costs have been found to influence their prescribing behaviour so rational prescribing could be enhanced by GPs working with pharmacists and by the provision of better information to GPs about drug costs.[107,108]

Questionnaire surveys involving both the pharmacy and medical professions, by two separate pharmacy practice research departments in the early 1990s, revealed a willingness to collaborate in formulary development.[109-111] One of the surveys analysed responses from 161 GPs and community pharmacists from Enfield and Haringey and North Yorkshire former Family Health Service Authorities and found pharmacists to be more convinced that formularies would improve GPs' prescribing than did the GPs.[109] Positive attitudes are vital if the use of general practice formularies is to be extended in line with, for example, estimates in Northern Ireland predicting that the number of practices actively using formularies would increase from 50% in 1995/96 to 75% by 1997/98.[110] The accuracy of this estimation is uncertain though as a questionnaire in 1993 was sent to all 983 GPs in Northern Ireland to investigate their opinions of the then current edition of the Royal College of General Practitioners Practice Formulary produced in the Province.[112] The responses indicated that 32% of those doctors who received the formulary used it, although 89% considered a formulary useful in general practice.

Traditionally, drug selection criteria in formulary development have focused on efficacy, safety and cost.[93] On producing a formulary, it is important to define and agree criteria. It should be emphasised that formulary preparation is not an agenda with the purpose of giving the patient cheaper and less than optimal medication. Concern

about cost-effective health care should not simply result in a search for the lowest cost solution. In fact, an attempt to rationalise prescribing may not always lead to financial savings if the intention is to optimise the management of conditions such as asthma and depression.[113]

2.1.5.2 Production of a formulary

A formulary must convey a professional image with its users in order to achieve credibility and this will contribute to the effect of the formulary. To optimise its use, the design of the formulary needs to permit quick and easy reference. These factors apply to all formularies and are especially important where potential users have not been involved in the development process.

Decisions will need to be made about the size and presentation of the formulary, for example whether it needs to be carried by doctors around a hospital or whether the intended use is in the GP consulting room.[87] The formulary will need to have good classification and index systems to facilitate cross-referencing. Information on prices should be considered whether in the form of actual prices or treatment courses but will only be relevant at the time of writing, unless updated. Prices fluctuate with time and are inappropriate for international comparisons. Also a formulary is most efficient if it encourages generic prescribing.[95]

In some hospitals a full time formulary pharmacist is employed but in the primary care setting GPs may find it easier to adapt a pre-existing formulary and use it as a model which can be tailored to their local needs. This has the advantage of saving time although the educational benefits might not be quite as great.[90] Alternatively, GPs may attempt to consult a local hospital formulary for reference and guidance which can help maintain continuity in treatment when patients are admitted to hospital or discharged.

Model formularies differ in style, although the range of drugs they contain is usually very similar. In the UK towards the end of the 1980s, there were three main 'model' formularies available at little cost which could be easily adopted. In Newcastle upon Tyne, 'A Basic Formulary for General Practice'[114] was among the first to be published. The first edition discussed treatment for 34 common conditions in general

practice and contained 137 drugs. The Royal College of General Practitioners Practice Formulary in Northern Ireland[115] contained over 200 drugs as well as discussion about good prescribing practice and the potential pitfalls of prescribing. Finally in Scotland, the Lothian Formulary[116] was produced by the Regional Faculty of the Royal College of General Practitioners. This included 330 preparations, many branded, with brief guidance on use and unwanted effects. All three were problem-orientated formularies and contained information about dosage, formulations, cost and notes about treatment. Cross-referencing is made easier with both the Northern Ireland and the Lothian Formularies as they used the BNF classification system. Each of these formularies has undergone revision with the publishing of subsequent editions.

2.1.5.3 Maintaining a formulary

The assessment of formulary performance must always be based on the original aims.[87] The wider the range of conditions a formulary intends to recommend treatment for, the more difficult it will be to achieve higher levels of formulary adherence. Adherence targets must be realistic and repeat prescribing is going to be less amenable to change than new prescribing. In order to assess the success of the formulary, it will therefore need to be monitored. This involves determining the level of non-formulary usage, identifying the drugs concerned and the reasons for them being prescribed. The level of generic prescribing can also be monitored as most formularies give priority to generic names rather than proprietary names.

Formularies can be updated in one of two ways, either in a continual on-going process or in episodes when the current edition becomes dated. Time constraints and limited manpower often determine the likely approach but the frequency of revision needs to be established. Analysis of PACT and SPA can help with monitoring and updating of primary care formularies as well as detecting any areas which will need revising.[117]

One of the most important aspects of formulary maintenance is that there needs to be a procedure for dealing with new drugs on the market.[87] New drugs are often introduced to hospitals first, enabling specialist hospital staff to gain early and sometimes detailed experience with the new product. Use by consultant staff will

usually lead to use in the community and this can have major unplanned cost consequences for primary care as well as conflict between health care professionals. To make allowances for this, health authorities have often 'top sliced' a proportion of the prescribing budget for such products.[118]

In order to balance value for money in the health service with the innovations of the pharmaceutical industry, there have been suggestions for the introduction of an additional step into the drug licensing process between the identification of a new technology and its formal inclusion into main stream use.[119] Both Australia and individual provinces in Canada have taken this approach, requiring economic evaluations on new products prior to making reimbursement decisions.[118] In the future, it is hoped that collaboration between groups such as the National Prescribing centre (NPC)[119], the UK Drug Information Pharmacists Group (UKDIPG)[119] and the National Institute of Clinical Excellence (NICE)[120] will help lead on how to introduce new drugs into a cash limited health service.

- The NPC was established in 1996 to promote high quality, cost-effective prescribing through a co-ordinated programme of activities aimed at all relevant employees within the NHS.
- The UKDIPG was formed over 20 years ago and its remit includes the provision of strategic information on medicines to NHS staff within both primary and secondary care.
- The NICE was set up in 1999 by the government to give guidance to the NHS in England and Wales on the clinical and cost-effectiveness of new and existing clinical interventions.

2.1.5.4 Implementing a formulary

Whether in hospitals or in primary care, managing the on-going development of a formulary is mainly governed by local factors, politics and professional relationships, especially between doctors and pharmacists.[87] It is important to maintain awareness of

the formulary system and to develop a mechanism for introducing the formulary system to new staff.

Ideally, in the first place, the formulary should be appropriately launched and consideration should be given to the timing of this.[86] In the hospital environment for example, there could be an advertising campaign, both internal and external to the hospital, as a form of communication to raise awareness in an attempt to increase its credibility.[121] In primary care, whether there has or has not been multidisciplinary collaboration in formulary development, it promotes good professional relationships if local community pharmacists are informed before its implementation. Local medical and pharmaceutical advisers will also be keen to know of formulary development progress and may well be able to offer support and resources.

2.1.6 The effect of formularies and attitudes to them

In 1984, GPs in Bristol described how their practice used a computerised repeat prescribing system to produce reports of drugs prescribed as a starting point for the compilation of the practice formulary.[122] The authors maintained that this process would allow production of a formulary without restricting drug choice. No data however were given on which to base this conclusion and no patient experiences before and after implementation of the formulary recommendations were described.

Twelve months later, Green, another GP in England described the creation, implementation and monitoring of a general practice formulary.[123] Using the prescribing data of each GP in the practice, the formulary was built up over a period of one year selecting drugs based on current prescribing practice. It aimed to cover 80-90% of common conditions, providing treatment for 70-80% of cases. Prescribing was monitored prior to and following the implementation of the formulary, focusing on antacids, laxatives, hypnotics and sedatives, cough preparations and analgesics. Results indicated that changes in line with the recommendations occurred in all therapeutic areas, with changes persisting for one year after formulary introduction, generating considerable savings. No data relating to patient experiences following formulary introduction were presented.

The model formulary of Grant *et al* described earlier was developed with the help of a select group of 19 GPs, responsible for undergraduate teaching at Newcastle Medical School.[124] The same GPs then recorded prescriptions issued to patients over a two week period, with 10 further GPs acting as controls also performing the same exercise. Results indicated that involvement in formulary development was associated with higher levels of prescribing recommended agents. Formulary adherence was significantly higher for acute rather than repeat prescribing, highlighting the additional difficulties associated with changing established therapies. This study did not however analyse prescribing trends over a period of time.

The same academic GPs in Newcastle assessed the prescribing of a group of 12 young prescribers later on that year, before and after an educational intervention focusing on rational prescribing.[58] No members of the group had previously been involved with formulary development. Analysis of recorded prescribing data for 150 consecutive patient consultations by each of the participants before and after the intervention indicated that there was a significant increase in formulary prescribing. No control group was included in this study but the results indicate that the actual educational aspects of involvement in formulary development may themselves lead to improved prescribing.

In 1987, a multi-disciplinary team of researchers in the Medical School at Dundee reported on similar work.[125] Prescribing data were again used to assess formulary success, with data indicating that the use of formulary medicines increased on introduction and was maintained in the following year. This study also involved regular feedback of performance to prescribers which may well have influenced subsequent prescribing behaviour.

More recently in 1996, a study was performed to investigate influences on prescribing of all non-fundholding practices by health service researchers in the North region of England.[126] It was found that of the 348 (78%) practices that responded, 31% had a written or computerised prescribing policy or formulary but that only 85% of these reported that the practice 'always or usually' used it.

About the same time, pharmacist researchers interviewed practice managers or a GP in 75% of practices in Southampton and south west Hampshire to identify their use of practice formularies.[127] Only 48% of practices had a formulary, the majority of which (63%) only covered drug choice in certain therapeutic areas. The main criteria for drugs included were: efficacy, patient compliance, lack of side effects, prescriber familiarity, generic availability and cost.

None of these aforementioned studies went into any detail about the effectiveness of the formularies in either achieving rational prescribing or patient acceptability.

It has been recognised that adherence to practice formularies may be reduced when patients are discharged from hospital on non-formulary drugs.[30] In addition, adherence to hospital formularies might be reduced with patients admitted to secondary care on non-hospital formulary drugs. The transfer of prescribing from secondary to primary care makes a substantial impact upon the financial framework for primary care prescribing. The transfer of prescribing should be done in the best interest of patients and not be done to ease pressure on drug budgets. As a result, the development and use of joint formularies between primary and secondary care have been widely advocated[46,95,128,129]

One of the first areas to establish a joint drug formulary was in the Grampian region in Scotland.[130] The formulary team consisted of four GPs, three pharmacists and two clinical pharmacologists. Forty-nine randomly selected GPs out of 50 were positive about accepting a copy of the existing hospital formulary upon invitation. Based on this interest, GPs were invited to comment on draft guidelines for each group of drugs to be included. Sixty GPs expressed an interest, resulting in the completion and distribution of the formulary in 1992 and a further revision took place in 1995.[131] Drugs in the formulary were listed in therapeutic category, following BNF classification. Within each section, first choice drugs were highlighted, along with information about recommended drugs. A special indications category was used for those drugs not recommended as first-line, fulfilling the following criteria: used in special situations, specialist supervision required, less favourable side-effect profile and more expensive than first choice agents.

Adherence to the Grampian Joint Formulary as measured by research pharmacists when patients were admitted to hospital was 84%.[132] The study did however have several limitations in that the patients were elderly, being admitted to hospital and mainly receiving repeat prescriptions; hence, they might not be representative of the total patient population nor of comprehensive prescribing in general practice.

2.1.6.1 The effect of formularies on health outcomes

Very little work has measured the effect of implementing drug formularies on health outcomes such as symptom control or health related quality of life.

Field, a medical researcher at the end of the 1980s determined whether the introduction of a formulary was acceptable to doctors and whether any changes implemented as a result would be acceptable to patients.[133] A formulary was developed in one practice, aiming to cover 50% of prescribing, with three neighbouring practices acting as controls. Doctors' attitudes toward formularies were measured prior to and following formulary introduction. Results indicated that those in the active practice were more in favour of the use of a formulary and with its introduction - there was a statistically significant increase in prescriptions from the formulary over the course of the two years. Groups of 90-100 consecutive patients per year for three years receiving repeat prescriptions without consultation in all four practices were selected and interviewed to measure satisfaction with therapy. Those patients in whom therapy had changed (17.7%) were less satisfied than those where no change had occurred; however, the data presented did not demonstrate that those less satisfied belonged to the active practice, nor that the change was actually as a result of implementing formulary recommendations.

More recently other medical researchers in Dundee, measured patient satisfaction upon the introduction of a generic formulary in one practice.[134] Questionnaires were sent to a random sample of 280 patients where therapy had been changed to the formulary recommendation, including substitution of a generic equivalent. A response rate of 60% was obtained, with 46% being either slightly or very unhappy with the change, although this was thought to be associated with inadequate communication relating to the change. Semi-structured interviews conducted with 16 patients, one week

and six months following the change showed that almost all patients were aware that reducing expenditure was at least part of the reason for the change but that none felt that the trial of a cheaper medicine to be unreasonable.

In 1992, Pearce and Begg, health service researchers in the UK, reviewed the literature relating to formularies in primary and secondary care and identified that no research focused on the area of change in health outcomes arising as a result of such developments.[135] Since the beginning of the 1990s though, the importance of patient outcome measures in clinical trials in the US has drastically increased.[136] Drugs have traditionally been marketed on the basis of superior efficacy and/or safety but outcomes research attempts to predict better medium or long term cost-effectiveness compared with competitor products for treatments. Clinical trials increasingly have to measure the criteria which are summarised in Table 2.3.

Outcomes research assesses a new drug's cost effectiveness by examining a range of costs including: direct medical costs, direct non medical costs, indirect costs such as lost earnings due to morbidity, and intangible costs such as those related to pain. In addition, improved patient quality of life, increased functional performance, general health perceptions and satisfaction with care are all considered relevant in lowering health costs. Also important to assess is the degree of improved patient compliance with the dosing regime which may reduce costs by minimising the length of time the patient receives the drug. The better the patient's life quality, the lower the long-term treatment costs will be to the healthcare provider. In the US, one survey of formulary committee members indicated that they would pay an additional 10% or more in drug acquisition prices if the quality of life scores for a new drug were superior to other competitor products.[136]

2.1.7 A European Formulary for General Practice

As discussed earlier in this chapter, the availability, quantity and quality of prescribing varies throughout Europe. However, if it is agreed that drug selection should be made predominantly on the evidence of efficacy and safety, one would expect only relatively minor differences in drug utilization to occur within a homogenous

population. Where large differences are found, it is reasonable to assume that factors external to the influence of clinical pharmacology and pharmacotherapy are prevalent.

One attempt to contain this situation was the development of a European Formulary subsequent to a conference in Bielefeld in 1987 (Section 1.1). Enthusiastic delegates consisting of doctors and pharmacists met on several occasions over the following six years until in 1994, a draft European Formulary with Appendix (providing the reference based justification for drug selection) had been developed.

The aims of the formulary were to;

1. Cover the majority of conditions seen by GPs (minimum of 90%).
2. Provide simple adequate and appropriate treatment for most patients (minimum of 90%) with common conditions requiring the prescription of a drug.
3. Be acceptable and useful to diverse groups of general practitioners throughout Europe and facilitate the free movement of practitioners.
4. Use generic name drugs.
5. Generally exclude drugs introduced within the last 5 years, except where valid trials show strong evidence of advantages over well-tried preparations.
6. Use cost of drugs as an important criterion for their selection.
7. Be compiled by GPs, clinical pharmacologists and pharmacists using best practice and scientifically based evidence from journals of repute.
8. Avoid recommending drug treatment where specialist advice is indicated.
9. Rank order the drugs, but avoid dictating to doctors using the formulary.
10. Be a useful tool for students, doctors, pharmacists to discuss and improve prescribing.[137]

In Britain, detailed prescribing information and advice is provided by the British National Formulary (BNF).[6] Although an extremely valuable reference guide, it does not focus on stepwise approaches to treatment strategies based on evidence. In addition,

although unit prices of drugs are included, the BNF does not really focus on the issue of cost-effective prescribing.

In contrast to the BNF which refers to all the drugs available on prescription in the UK at the time of publication, the European Formulary is specifically aimed at prescribing in General Practice. A study by researchers in the department of general practice in Leicester analysed 6,595 prescription items to investigate the effectiveness of prescribing by comparing those that were hand-written by GPs against computer issued prescriptions to see whether they conformed to BNF guidelines.[138] The results were disappointing with over 40% of the hand-written items not adhering to the guidelines for formulation and strength. Computer generated prescriptions on the other hand were found to be much more accurate but failed to satisfy guidelines on directions and quantity in over 90% of cases. The fact that the European Formulary is focused on prescribing in general practice is important as it has the potential to be more tailored to GPs' needs and requirements

Since the single European market in 1993, implementation of a European Formulary could promote seamless patient care and stability for patients throughout Europe and give confidence to movement of health care professionals between one country and another. For this to happen though there would need to be almost universal agreement on drug selection.

Although both general practice and hospital formularies are known to exist in several countries, there is relatively little published work detailing their development, use and influence on prescribing. The next section reviews the literature on the factors that influence the prescribing process.

2.2 INFLUENCES ON PRESCRIBING

"A desire to take medicines is, perhaps, the greatest feature which distinguishes man from other animals". (Sir William Osler 1891)

2.2.1 Introduction

The writing of a prescription is influenced by a multitude of factors which intertwine causing the prescribing process to become highly complex. An appreciation and understanding of the mechanisms involved in this pathway is very important especially as drug therapy is the most frequently used intervention in general practice medicine. The BNF states that: 'Medicines should be prescribed only when they are essential and in all cases the benefit of administering the medicine should be considered in relation to the risk involved.'[6] This statement complements the main criteria for rational prescribing (Section 2.1.3) which dictate that a drug should be necessary, effective, safe and economic.[37]

The influences on prescribing discussed in this chapter are largely written from a UK perspective, although there has been work published outside the UK on factors influencing drug choice and some of this is referred to. The major factors influencing prescribing will each be reviewed separately; they can be considered under the following headings:

1. Regulatory measures
2. Information
3. Education
4. Pharmaceutical industry
5. Hospital
6. Society
7. Patients
8. Prescriber and workplace

2.2.2 Overview of prescribing influences

In 1975 Hemminiki, a Finnish medical sociologist, was one of the first to review the literature on the factors influencing drug prescribing.[139] She highlighted six main sources of influence, namely: education, advertising, colleagues, control and regulatory measures, demands from society and patients and finally doctors' characteristics. Most of the studies cited were observational and none were large scale controlled-studies. One of the potential limitations with retrospective observational studies which examine prescribing from medical records is that the researcher may not be able to focus on the factors associated with the actual decision to prescribe.[140] Hemminiki's review concluded that the medical and scientific literature lacked data on the factors affecting drug prescribing and their relative importance, but it was recognised that pharmaceutical companies influenced doctors in many ways and other non-medical factors played a substantial part in the influencing process.[139]

Two years later in 1977, Mapes, a British professor of medical sociology at Swansea University, reviewed the literature on the methodological approaches used to investigate prescribing influences.[56] He identified the application of both qualitative methods, such as the measurement of physicians' attitudes, and quantitative methods, such as the measurement of prescribing volume. Mapes carried out a study using prescription data from a cohort of 116 GPs and identified 90 characteristics to help determine the 'prescribing type' of a physician. By factor and discrimination statistical analyses, differences between physicians' prescribing habits could be made on the basis of five characteristics: sex of GP, membership or otherwise of the Royal College of General Practitioners (RCGP), proportion of scripts written by non-medical practice staff, proportion of scripts with inadequate/no directions to the pharmacist and doctor opinion as to the usefulness of different sources of drug information. This study design was limited in that it focused on factors which influenced effective and safe prescribing only and did not explore factors which influence the other criteria for rational prescribing. In addition, the GP sample was neither random nor representative in terms of age and sex.

Cooperstock and Parnell, researchers at the Addiction Research Foundation, Toronto, Canada, published a review in 1982 of studies from the previous fifteen years

on psychotropic drug use in Australia, Canada, Europe and the USA.[141] Their main findings, that females received twice as many psychotropic drug prescriptions as males and that drug use was higher among older age groups, were consistent among the different populations studied. The authors also found that consumption and the associated 'popularity' of some psychotropics had declined while other drugs had evidently replaced them, in part due to stricter regulatory controls of some drug groups in certain countries. The review was restricted to analysing the demographic prevalence and patterns of psychotropics which neither explain the exact reasons for drug use nor the meaning of it. Nevertheless, with the ultimate aim of finding causal relationships, establishing correlations from demographic data is a necessary step in the investigating process. Consensus agreement with definitions of relevant terminology in therapeutic areas such as psychotropic medicine, as well as comparable drug and diagnostic classification systems, would be beneficial in the future evaluation of prescribing influences. To perform a more in-depth investigation, the researchers suggested that future studies should focus on: studies of high-risk populations, health measures, social lifestyles, OTC medicine consumption, frequency of physician visits, comparability of benzodiazepines with alcohol use and the economic cost to health care systems of psychotropic drugs, especially with respect to developing countries.

At the end of the 1980s, McPherson, an academic GP at Oxford University, postulated that the impact of different sources of variation in medical intervention will depend on the level of data collection (Table 2.4).[251] From Table 2.4 in the analysis of variation between GPs (column 4), it might be hypothesised that professional characteristics (row 4), such as clinical style or judgement, are likely to exert a major influence on medical practice variation, other things being equal. At this same level, aspects of the health system (row 3) and characteristics of the population (row 2) are less important since it is assumed that to a degree they will be standardised within a given country. However, they will become much more significant in explaining differences at the level of cross-country comparison (column 1). Patterns of morbidity could be expected to show a certain similarity across countries at a comparable level of social and economic development but to exhibit greater variability at the regional and practitioner level (row 1).

The information in Table 2.4 could have particular relevance for explaining prescribing variation in general practice and a multidisciplinary team of community health researchers from the Auckland Medical School attempted to test it at the GP level.[142] Relevant indicators from New Zealand general practice were used to represent the four sources of variation in Table 2.4 and data were obtained on completed records of nearly 9,500 patient encounters from a representative sample of 115 GPs. Levels of prescribing and the distribution of drug patterns across diagnostic groupings were found to be broadly comparable to results drawn from international benchmark data. Information was also gathered on seven measures of prescribing activity in the areas of volume, script detail and therapeutic choice and these were subjected to multivariate statistical analyses. From this, the overall analysis indicated that the main influences were diagnosis followed by practitioner identity. The prescribing task could be considered as a process of decision-making in which 'core' judgements such as the decision to prescribe and the choice of drug are highly predictable and influenced by diagnosis. The prescribing of antibiotics and psychotropics in the study followed this predictable pattern, but the prescribing of analgesics was less predictable, possibly because of their less precise therapeutic action. In contrast, peripheral features of the task, for example choosing a combination drug or prescribing generically, are less determinate and more subject to clinical discretion. Limitations of the study are firstly that this was a single sample study restricted in time and place and secondly the status of diagnosis as a measure of morbidity data is problematic. Therefore, the data have to be interpreted with a degree of caution. Finally, some important indicators of health system variation were not investigated, such as pharmacoeconomic factors and OTC drug use and availability, although these are fairly constant within a country.

The influence of prison inmates' clinical (diagnosis, impairment level and hospitalisation history) and social (gender, race and social class) characteristics as well as prison setting factors on the appropriateness of psychiatric prescribing have been examined in a New York prison.[140] The study examined which of these characteristics predominate by investigating two perspectives: a psychiatric perspective which argues that patient clinical characteristics are found to account for the prescription of psychiatric medicines and a social control perspective which argues that non-clinical factors predominate in drug prescribing decisions. Measures were taken on a twelve per

cent random sample of 36,144 inmates in New York State and the relative influence of the different variables were examined by multivariate analysis. Overall, the results indicated that psychiatric impairments, measured in terms of levels of depression, manifest symptomatology, agitation and prior psychiatric hospitalisation, were found to be highly significant predictors of drug prescription. These findings suggest that patient clinical characteristics predominated in the psychiatric medication prescription process. Social factors were found to influence the decision to prescribe medication for mildly impaired inmates. The study was limited in that prescribing was examined retrospectively and did not focus on factors associated with the actual decision to prescribe. The study is an investigation of patient characteristics in high security psychiatric units and the findings may not apply to patient populations in the wider community.

In 1995, Denig, a pharmacist, and Professor Haaijer-Ruskamp, a medical sociologist from the Netherlands, published a review of the influence of cost on prescribing decisions.[107] They summarised studies which involved groups of prescribers, rating criteria for drug selection. To facilitate the comparison, all studies were converted to the same ten point scale. The results showed cost to be a reasonably important criterion but always considerably less so than considerations of efficacy, adverse drug reactions and the prescribers' experience of particular drugs.

Opinion is divided as to how significant a part cost should play in the prescribing process. On the one hand, GPs should morally prescribe cost-effectively and the prescribing of expensive drugs should be critically justified. On the other hand, prescribers might feel that they should have the right to prescribe freely within the therapeutic spectrum and that cost reductions can have a negative impact on the quality of health care.

Until recently, doctors have generally been unaware of the costs of drugs and could claim with confidence that cost was not a major consideration in their prescribing decisions.[108] With an increasing number of GPs now believing that prescribing costs should be taken into account when deciding on the best treatment for an individual patient, possibly an increased emphasis should be made at the undergraduate level.[108] Prescribing costs are not constant however and fluctuate with time.

2.2.3 Factors influencing the decision whether to prescribe or not

At the beginning of this decade, Bradley, an academic GP, observed that attempts to establish influences on prescribing practice have tended to concentrate on which drug should be prescribed rather than on whether to prescribe a drug at all.[143] Prior to the drug selection process, the prescriber must initially decide whether or not to even issue a prescription. The decision by a physician not to prescribe is not an easy one although it may appear perfectly logical on pharmacological grounds alone. If a patient is not satisfied, the doctor-patient relationship becomes threatened which may result in either a formal complaint, a decision to change the GP or in extreme cases pursuit of medico-legal action. Consequently many physicians feel pressurised to 'play safe' and would rather over-prescribe than prescribe too little.[144]

One of the commonest areas of dilemma for GPs is in the prescribing of antibiotics for acute respiratory tract infections. Most infections of the respiratory tract are self limiting and often viral in origin with antibiotic treatment not being indicated. The results of bacteriological investigations which may indicate the need for antibiotic treatment often take several days to occur and so treatment has to be started on a best guess basis. Either type of diagnosis is therefore based on probability rather than certainty. Placebo-controlled studies have even shown that there is little or no benefit in treating respiratory symptoms in previously well patients.[145] If a decision is made not to issue a prescription, the consequence can be that more of the GPs' time will be required to explain adequately to the patient the reasons why. Some GPs believe that prescribing a relatively cheap antibiotic, for example amoxycillin, with few potential side-effects is the simplest solution. However, the inappropriate use of antibiotics helps to build up resistance to the drug and should the prescriber not be cost-conscious, then newer expensive antibiotics may be prescribed contributing to the wasted millions of pounds estimated to be spent on this group of drugs in the UK alone.[30]

In 1976, Howie, an academic GP in Scotland, hypothesised that clinical and social considerations interact in the decision-making process of doctors to determine whether or not a prescription is issued.[146] He tested this hypothesis by studying the clinical judgement and antibiotic prescription use of GPs. Booklets were posted to 1,000 GPs containing transparencies showing varying degrees of redness of throat relating to 16

patients but with variable social and psychological information. From an approximately 60% response rate, he found that the variations in social and psychological history presented had resulted in significantly different prescribing practices among the doctors.

A study by academic physicians in Nottingham published in 1997 investigated factors influencing patient reconsultation in the month following initial management of lower respiratory tract infections (LRTIs) in general practice.[147] The commonly perceived belief that the prescribing of antibiotics reduces reconsultation was the main stimuli for this research. Contrary to this belief though, the research revealed that reconsultation appeared not to be influenced by the prescribing of antibiotics. Reconsultation was found to be common in acute LRTI which supports the findings of other studies[148,149] and this was associated with the presence of previous ill health, dyspnoea and a heightened consulting habit.

To explore the dilemmas surrounding decisions taken about whether or not to prescribe, Bradley interviewed 51% of the general practice principals in one English region.[150,151] Drug groups which most often led to uncomfortable feelings included antibiotics, cardiovascular drugs, NSAIDs and psychotropics. Patient expectations, their ethnicity and social class, clinical appropriateness, and preserving the doctor-patient relationship were found to be the important reasons given for influencing decisions. The main reasons for feeling discomfort included concerns about drugs, personal expectations, peer influences, appropriateness of treatment and uncertainty.

2.2.4 Factors influencing the uptake of a drug

Miller, an academic pharmacist from the US, summarised the stages in the uptake or adoption of a new drug by a prescriber in Figure 2.1 [152] The most important step to have been identified in drug adoption is that between the first awareness of a drug and the decision to use it. These findings suggest that there is a considerable difference between communication mechanisms that inform physicians of up to date developments and those that persuade physicians to take them on board.

Evidence suggests that new practices may be adopted by physicians more rapidly than old practices are discarded. Winkler *et al*, non-medical researchers in Los Angeles,

concluded that whereas various factors may heighten physicians' awareness of assessment information, a restricted set of influences may actually lead them to alter their practices.[153] Educating prescribers face-to-face has been reported to be the single most effective method for influencing their decisions,[154] especially when it involves a regular re-enforcement component.

Williamson, a non-medical academic in Liverpool, had earlier suggested that where the adoption of a drug represents little risk, the prescribing doctor is often willing to prescribe on the basis of information provided by the pharmaceutical manufacturer, thereby initially relinquishing his personal independent evaluation.[155]

Twenty years ago, Strickland-Hodge, a research pharmacist in the West Midlands, found that 'commercial' information was used more at the awareness stage in drug adoption, providing the first information about a new drug.[156] Commercial information seemed to be preferred by older doctors who had a minimum first degree qualification who did not specialise and who had no immediate contact with colleagues as they were practising alone. 'Professional' sources of information such as medical journals were used more to evaluate a new drug when the prescriber was actively considering prescribing one.

In the early 1980s, Peay and Peay, two Australian academic psychologists, found similar results from studying the preference for information sources in the adoption of new drugs by 124 doctors.[157] At the stage when doctors are acquiring the information needed to prescribe, younger doctors were found to more frequently seek out the 'active' source of journals, while the older doctors tended to continually rely on the 'passive' source of drug representatives otherwise known as detailmen. In this study, doctors practising alone were not found to rely on drug representatives any more than doctors working in group practices, although they were reported to have a wider range of literature based sources.

In 1988, Denig *et al* hypothesised that physicians select drugs by a process of reasoned action i.e. weighing up the pros and cons before a drug choice is made.[144] This is difficult to prove when 'directly' asking physicians about their decision criteria as much of the prescribing process occurs subconsciously. The researchers therefore

investigated this hypothesis by testing a drug choice model for the treatment of irritable bowel syndrome (IBS) and renal colic on 169 physicians. Medication was the only treatment option analysed and so the influence of patient demand on the decision whether or not to prescribe was not considered. Prescribing decisions seemed to be particularly influenced by the professional environment of the GP and by prescribers' past experience. The authors concluded that their findings may be useful when trying to change prescribing behaviour as the importance of the professional environment suggests that educational programmes in groups might be more effective than targeting individuals alone.

In a separate paper, the same authors described the approach of providing physicians with hypothetical patients for whom relevant and irrelevant information is varied systematically as 'clinical judgement analysis'.[154] Bradley, when looking at uncomfortable prescribing decisions, used a similar term by describing GPs as using 'reasoned thought' in arriving at a decision.[150] He found that many GPs were attempting to balance out several disparate considerations and in so doing worked out what to do for the best, following a rationale that was not just purely pharmacological but could be described as a combination of rational behaviour and habit.

2.2.5 Drug regulation

In the UK, the influence from drug regulation is largely punitive and has been centred on the Medicines Act 1968.[45] The Act is primarily concerned with the safety, quality and efficacy of medicinal products and covers the licensing of manufacturers, of products and of wholesalers. Medicinal products are pharmacy only (P) unless the licensing authority has taken statutory measures to classify them on the general sales list (GSL), if considered to be sufficiently safe. Medicines inappropriate for self-medication may be restricted and classified as prescription only medicines (POMs). Classification has an influence on prescribing as patients are increasingly encouraged to purchase medicines which do not require a prescription.

2.2.5.1 NHS Drug Tariff and the Limited List

Historically, doctors' freedom to prescribe medicinal products for their patients has in general been respected and left unchallenged in the UK until recent time. As mentioned previously (Section 2.1.4.1), in 1911 a National Formulary was developed which limited and restricted prescriptions for low paid workers entitled to NHI. Within the context of the British NHS, a GP's prescribing of dressings, appliances, and reagents has been restricted to those approved items listed in the Drug Tariff.[158] Items in the grey area of 'borderline substances', which includes some special foods and cosmetics, could be prescribed but might be subject to justification by the prescriber depending on the detailed guidelines on 'borderline substances'.

The selected 'Limited List' imposed in April 1985 by the Secretary of State for Health was of much significance as it created control of a kind not previously applied in the NHS. The intention was to eliminate many heavily prescribed OTC medicines from GP prescriptions and encourage the public to purchase them instead.[48]

2.2.5.2 Prescription charges

NHS prescription charges have also been used to contain prescribing. In 1952 when the NHS was four years old, a modest charge of 5p per form was introduced and was intended to make a contribution towards health services costs, encourage people to value more what was supplied and also to inhibit, unofficially, surgery malingerers. Currently the charge per item has risen to £6.00, although 85% of prescriptions dispensed are exempt from charges.[29] Many medicines available for self-medication are noticeably priced somewhat below the prescription charge.

The charges should act as a disincentive to prescribe medicines which can be bought without a prescription and which may well cost the patient less than the NHS charge. As a counter influence on prescribing, prescription charges can encourage larger quantities to be both prescribed and expected by the patient.

2.2.5.3 Generic prescribing

Generic name prescribing, which has been encouraged by successive governments, is economically motivated in order to effect financial savings. The Government's position is complicated by the nation's need to maintain its high profiled, very successful pharmaceutical industry which contributes greatly to the UK balance of payments. Generic drug name products have almost no supportive advertising other than the indirect promotion through independently evaluated sources of information like the BNF, Drug and Therapeutics Bulletin and Prescribers' Journal.

A generically written prescription is one that has been written using the British Approved Names (BAN). These drug names have syllables characteristic of the particular class of drug but the names are invariably longer and not as easily remembered as many proprietary names.[29]

In the UK, encouragement to prescribe generically has resulted in an increase in the number of NHS generic prescriptions dispensed. In England, items prescribed generically have risen from 39% in 1987 to 60% in 1997 and items dispensed generically have risen from 34% to 49%.[29] This mismatch is primarily due to GPs using generic names for medicines still under patent.

The extent to which financial savings can be made from generic prescribing is often poorly understood by GPs. Issues of the MeReC Bulletin[159], the centre pages of PACT reports[32] and more recently Bandolier[160] provide useful practical information in this respect. Pharmacists can also advise GPs with regard to drugs where significant savings can be made and advise about the significance or otherwise of bio-inequivalence. At present, generic substitution is not allowed on NHS prescriptions in primary care but is well established in secondary care.

2.2.5.4 Prescribing advisers

Health Authorities (HAs) have a legitimate interest in the question of cost and quality which arise from the prescribing of drugs. In order to increase the professional advice available to GPs, pharmacists and to the HAs, medical and pharmaceutical advisers have been appointed by the HAs.[51,91] The HA advisers are expected to visit

GP practices, particularly those where over-prescribing is said to occur, to discuss prescribing habits as part of the indicative prescribing scheme. For an assessment of practice demography and factors such as the number of patients with medical disorders requiring expensive medication, both the practice and the HA will be advised on indicative prescribing amounts.

The pharmaceutical adviser's role also includes acting as a facilitator, to bring about greater co-operation between pharmacists and their local GPs. Other areas which are recognised as benefiting from pharmaceutical advice include formulary development at a practice level, reinforcing confidence in generic products, advising on individual prescribing problems, offering advice to GPs on product choice and maintaining links with drug usage and prescribing policies in hospitals and at a regional level.[91]

2.2.6 Information sources

In 1977, Dingwall, a GP in Scotland, stated that GPs needed easily accessible, reliable, unbiased information about new drug trials presented to them by an independent authority.[161] Over the past two decades this has been achieved in part by the following developments: formularies have become more widely established; consensus and/or evidence-based guidelines have been drawn up in many areas of practice; hospital pharmacies provide drug information services for both primary and secondary care; prescribing analysis data is routinely distributed to every GP in the UK; many practice pharmacists are now located in GP practices to review patient medication and run clinics, and computer technology as a medium for information provision and transfer continues to gather momentum. In addition, independent evaluated information is regularly published and is widely available and HAs also distribute free drug information bulletins including relevant topical issues. In the UK, the Drug and Therapeutics Bulletin is now provided free of charge to medical students in the latter part of their studies. However getting the most out of information sources within a limited time period still remains very challenging for many doctors. GPs are often saturated with material and the difficulty lies in information selection rather than access. With the ever increasing mass of conflicting claims and counter-claims about the relative effectiveness of competing drugs, not many GPs have the time to adequately analyse published drug trials.

Different types of information source appear to generate different levels of success with respect to changing prescribing practice. Haaijer-Ruskamp found that printed information has limited success in isolation and that there is a need to reinforce this with other methods of education and communication such as by face-to-face interaction.[154]

In 1983, Avorn and Soumerai, researchers at the Department of Social Medicine and Health Policy, Harvard Medical School published a study which investigated whether physician background characteristics and the quality of a number of educational exposures influenced a reduction in the excessive use of three drug groups.[162] They recruited a four State sample of 435 doctors randomised to control and intervention groups, interventions consisted of printed educational materials and face-to-face visits by clinical pharmacists. Results showed that the rate of prescribing change was independent of most of the physicians' background characteristics including age, locality, where qualified, previous level of prescribing and practice size. A follow-up reinforcement visit was a strong independent predictor of prescribing change and an increase from one to two visits was associated with an approximate doubling in the effect of the program.

The same researchers used the aforementioned study to establish the principles of educational outreach or 'academic detailing' in order to improve physicians' clinical decision-making and enhance the quality and cost-effectiveness of care.[163] They analysed the techniques of pharmaceutical industrial marketing and expertise in targeting physician communication and behaviour. The authors identified the following as the most important techniques to carry out academic detailing:

- interviews to investigate knowledge and current prescribing patterns
- focusing programmes on certain groups of GPs and their opinion leaders
- defining clear educational and behavioural objectives
- presenting arguments for and against issues, citing key clinical trials and establishing credibility
- stimulating active physician participation in educational interactions
- using concise graphic educational materials

- highlighting and repeating the essential messages
- providing positive reinforcement of improved practices in follow up visits.

Prescribers in the UK have also been shown to be influenced by short professionally produced presentations of information delivered by an academic pharmacist 'representative'. In Leeds, a project was designed to encourage a rational approach to NSAID prescribing in an intervention group of 101 randomly selected GPs.[164] The average prescribing cost of the intervention group doctors decreased compared with the control group and there was a significant increase in the prescribing of the recommended agents in the intervention group.

Two fundholding GP practices in the Midlands participated in a study published in 1997 to see whether a therapeutics advisory service provided by a consultant clinical pharmacologist and a clinical pharmacist could facilitate cost-effective prescribing.[165] A range of techniques were used to bring about change including: audit, peer review, feedback, guidelines, target-setting and small group teaching. Although the standard of prescribing dramatically improved, a saving in prescribing costs did not always follow. For example, the changes in prescribing for hypertension resulted in improved control of blood pressure but the overall treatment costs increased from 12-15%. Initial cost savings may be sustained but more appropriate prescribing and improved patient care should and must be recognised as being of paramount importance. In this case, the GPs found it so useful to have outside experts objectively assessing their prescribing that for at least a further twelve months period they opted to continue to purchase this educational facility and advice. This study did not include a control group so some degree of caution has to be made when interpreting the impact of the intervention.

This study also found that progress in therapeutics relied on a combination of willingness to explain to patients the need for change, familiarity within agreed guidelines and appropriate outcomes for the treatment at the time of the consultation.[165] To help implement this strategy, copies of flow charts were incorporated into patient records. Since 1995, an NHS Executive funded campaign called PRODIGY (Prescribing Rationally with Decision Support in General Practice) has been testing information like this with patient specific decision support incorporated into computer software accessible at the time of consultation.[166] As computer

technology has diversified in recent years, several studies[167-170] have indicated the potential benefits of computer decision support systems which use an underlying knowledge base of clinical information to present the GP with advice relevant to specific clinical decisions.

PRODIGY is a combination of active and passive systems helping doctors to make prescribing choices, predominantly based on drug efficacy.[171] Interim results published in the autumn of 1996 looked positive with 94% of GPs in 137 voluntary practices rating the scheme worthwhile.[172] Despite receiving a very mixed reception throughout the medical profession and by the pharmaceutical industry[173], by the autumn of 1998, PRODIGY had achieved one of its early aims by being given DoH support for extension throughout the UK. PRODIGY is actually based on a similar system which was developed in the Netherlands but was abandoned there after initial experimentation.[174]

In 1990, a study in Derbyshire surveyed 463 GPs' perceived use of drug information.[175] Similar results were found to a study discussed earlier by Peay and Peay which looked at differences in the preference for information sources among doctors in the USA.[157] In this case, the BNF and MIMS (printed sources) and fellow GP colleagues (personal source) were predominantly the most frequently used sources. Drug firm mailings, drug advertisements and non-professional journals were all ranked above professional journals indicating the potentially powerful influence of the pharmaceutical industry, although this study only looked at perceived use and not at how plausible GPs thought the information sources to be. One limitation to this and similar studies is that the researchers often compile their own list of possible influences, thereby introducing an inevitable element of bias.

2.2.7 Education

2.2.7.1 Undergraduate

With modern advances in research and development, there is constant production of new drugs and a large growth in the range of formulated products. Consequently, doctors throughout their working life will experience many dramatic changes in the availability of drugs within their country.

A study previously referred to which investigated the establishment of clinical pharmacology departments across 21 European countries revealed marked differences suggesting that more attention needs to be focused on establishing a sounder education base during the training of medical students.[26]

A paper on prescribing in general practice in the UK from the early 1980s by Brodie *et al* (backgrounds in clinical pharmacology and pharmacy), criticised undergraduate medical education for placing too little emphasis on clinical pharmacology and the critical evaluation of scientific papers and advertising material.[176]

In the USA, aspects of medical education have also been questioned. Meyer, an academic doctor in Pennsylvania, suggested that an early essential training in pharmacology should be followed in clinical medicine with greater attention paid to emphasising the basic principles and important facts necessary for rational prescribing.[177]

An international randomised control trial assessed the impact of a short course in pharmacotherapy by 219 medical students from five continents.[178] The intervention students received a short problem-based training course and a WHO manual on the principles of rational prescribing whereas the controls received neither. Both groups were tested before training, immediately after and six months later. The study group performed better than controls in all patient problems and importantly the effect was maintained at least six months later.

A few years ago, twenty seven medical schools in the UK were questioned about current and future teaching of undergraduate clinical pharmacology and therapeutics.[179,180] Opinions were divided with respect to whether there was a role for a national core curriculum in the UK. The most important items of core knowledge were considered to be prescribing for the elderly, management of overdose and adverse drug reactions; these were taught in the majority of institutions.

In the UK in recent years, there has been a number of reports increasingly recognising that the delivery of optimum healthcare to patients requires a multidisciplinary approach.[4,30,46,91] There could be considerable benefit from increasing the integration between the undergraduate medical curriculum and those of other vocational health care disciplines. Currently, only medical and dental students benefit from a widely implemented joint education in the UK. However at Kings College London, inter-professional clinical education of medical and pharmacy students has been tried and found to be a successful method of clinical teaching with nearly all the students finding the interaction beneficial.[181] In some countries, for example in India and Thailand, students have a core curriculum in medico-pharmaceutical sciences and then specialise into pharmacy or medicine later in their programmes.

Although no undergraduate course can be considered responsible for the future prescribing practices of qualified doctors, one of the main purposes of undergraduate medical training should be to educate students to keep abreast of changes in their field and equip them with the necessary skills to adapt to change.

2.2.7.2 Postgraduate

Continuing education is vital for physicians in order to maximise their knowledge, keep up-to-date and deliver quality care to the patient. Terms such as life-long learning and continuing professional development (CPD) are now established and recognised. Different countries place different emphases on continuing education; in the UK for example, it is a mandatory requirement, whereas in other countries such as Finland, it is left to the discretion of the physician. In 1980, Evered, a doctor, and Williams, a librarian both based in London, published a review of papers from the previous twenty years in an attempt to measure the success of postgraduate education.[182] From 51

papers, objective data were found in only eleven and just four included adequate control data. The authors concluded overall that knowledge acquired from postgraduate courses was only likely to be retained if subjected to periodic reinforcement.

In the Netherlands, Haaijer-Ruskamp and Denig found marked differences in their success after experimenting with different educational approaches: printed material only, one-to-one education, targeted lectures, feedback without comment, and feedback with group discussion.[154] Of these, the most successful individual method was either one-to-one education with an academic detailer/education modifier or group discussion with feedback, but the authors found that no single approach was as effective as a combination of techniques.

Attitudes towards postgraduate education seem to be very mixed among physicians. While it has been reported that many doctors find continuous education beneficial[157], a survey of 1,161 practitioners in Scotland showed that if the financial incentive for participation in continuing education was removed, the attendance at meetings would be noticeably reduced.[183] The same survey also revealed that doctors found the topics covered at meetings provided by pharmaceutical companies to be more interesting than non-commercial postgraduate meetings.

Regarding the method and style of teaching, Brigley *et al,* medics involved in teaching public health in London, have recently criticised the emphasis of formal didactic teaching and academic knowledge in continuing education because of its low educational value and failure to change professional practice.[184] Their opinion is that a more systematic and coherent approach is required - learning by reflective practice thus improving self-development.

In Germany and the Netherlands, continuing education is taking place in the style of pharmacotherapy circles for GPs.[185,186] The concept is based on quality assurance in medical care and consists of: assessment, problem selection, problem analysis, formulation of guidelines and repeated evaluation stages with the goal of optimising prescribing behaviour and reducing costs. Participating groups consisting of seven to ten GPs and a pharmacist meet about four times a year.

Bradley has argued that doctors need additional knowledge and skills to those usually taught under the traditional headings of clinical pharmacology and therapeutics.[187] However, a randomised control trial of continuing medical education in the US back in the early 1980s found that better knowledge does not guarantee better prescribing behaviour.[188] Physicians know that prescribing antibiotics for acute viral RTIs is irrational, but pharmacology alone will not change these prescribing habits. Education in how to avoid prescribing when it is not clinically indicated is needed, so that skills must be acquired to deal with pressures from patients, colleagues, industry and from funders of health care.[187]

2.2.8 Pharmaceutical industry

The potential influences on a doctor's prescribing start during medical undergraduate education and throughout this period, they may be exposed to many pharmaceutical industrial sponsored events. Recent Governments in the UK and USA have encouraged universities to attract an ever larger proportion of their annual funding, especially for research, from industrial and commercial sponsorship which may inevitably lead to some compromise and a reduction in objective independence. In addition, difficulties and shortage of funding for continuing education have led to the wider use and attraction of pharmaceutical industry sponsorship. Sponsorship can be in a variety of forms, including:

- unrestricted donations to providers;
- specialised programmes for lectures, meetings and symposia;
- specialised programmes combined with non-educational gifts.[189]

In the UK, the Government through the Voluntary Price Regulation Scheme (VPRS) contains the prices of ethical prescription products purchased by the NHS and also restricts manufacturers' spending on drug promotion to a maximum of 17% of sales. Nevertheless, with the pharmaceutical industry probably being the most successful manufacturing industry in the UK, for those companies whose annual sales are in excess of £400 million such as Glaxo[190], this figure of seventeen per cent can represent a very large sum of money.

In the UK, it has been reported that the pharmaceutical industry has a network of 6,000 drug representatives and spends £570m per anum on drug promotion which is equal to approximately £12,000 per GP and yet prescribing is still considered to be conservative compared with other countries.[4] These figures compare with an estimate of less than 200 HA prescribing advisers in post, mid 1998 and in the region of £4m per anum spent by the DoH on educating doctors. Drug representatives target prescribers in a direct manner relying on good communication techniques and sophisticated salesman-like strategies.[152]

Like all public companies, pharmaceutical companies have share-holders to satisfy and therefore need to be successful in promoting and selling their products, whereas the purchasers of these products have to satisfy patients who ultimately require value for money. Prescribers are often dependent on drug companies when they require information about a new drug and there is thus a great need for careful regulation of the advice and information given to GPs by the pharmaceutical industry. This is particularly so in countries where there is no mandatory postgraduate education. Consequently, this can present a potential conflict of interest between purchasers, providers and patients. Governments are conscious that changes in the balance between these interests can dramatically influence their popularity as well as affecting the exchequer balance of payment.

A study carried out by a multidisciplinary research team from the Harvard Medical School in the 1970s investigated the relative influence on prescribing influences of scientific versus commercial sources in the USA.[162] A random sample of GPs were interviewed about their beliefs about vasodilator drugs and propoxyphene where results of clinical trials suggested that they both had limited proven clinical value but were heavily advertised as being effective. Denial of industrial influence and yet believing that a drug of limited proven clinical value is effective is contradictory, suggesting that scientific literature was not the source of such views. The results found that physicians were generally unaware that they were strongly influenced by commercial information sources. For vasodilators, there was a significant tendency for those who believed in these drugs to report greater reliance on commercial sources. Nonetheless 48% of those

who believed vasodilators to be effective treatment for senile dementia also stated that they were influenced more by scientific sources than commercial sources.

Another study performed by Orlowski, a paediatrician, and Wateska, a hospital pharmacist, in Cleveland, USA looked at the effects of pharmaceutical company all expenses paid trips to attend symposia at popular sunbelt vacation sites.[3] The two drug promotions investigated concerned an intravenous antibiotic and an intravenous cardiovascular drug, both for use in hospitals only. By tracking the pharmacy inventory usage reports before and after the symposia against two control drugs intended to be replaced by them, the usage of the two promotional drugs was found to significantly increase after the symposium and this was also significantly different from their impact nationally. These alterations in prescribing patterns occurred even though the majority of physicians who attended the symposia believed that such enticements would not alter their prescribing patterns. The nature of advertising is such that physicians often deny the relative importance of commercial sources either because they believe they are unaware of them or because they are reluctant to admit to being influenced by non-scientific sources.

One of the criteria in the 1968 Medicines Act[45] requires manufacturers to supply an official data sheet on a product sometime within the 15 months preceding any form of marketing promotion to doctors and pharmacists. Most promotional mailings include a copy of relevant data sheet(s) to ensure legal compliance. The Data Sheet Compendium (DSC) which contains most major manufacturers products is a useful source of drug information and is supplied free of charge to all general practitioners, dentists and pharmacies and is updated annually.[191] Physicians who prescribe for an indication outside the product licence do so entirely on their own responsibility and liability.

As part of an ethical defence and standards established by pharmaceutical companies, the Association of the British Pharmaceutical Industry (ABPI) of which the vast majority of pharmaceutical companies are members, also has its own 'code of practice' which is published in the DSC. The code of practice was first drawn up in 1958 and is revised in consultation with medical and pharmaceutical professional bodies, the Medicines Control Agency (MCA) and the DoH. Its aim is to ensure that

the promotion of medicines to members of health professions is carried out in a responsible, ethical and professional manner. The code of practice is very detailed in all aspects of advertising, claims, definitions of appropriate terminology, for example it states that '*an "inexpensive" gift means one that has cost the donor company no more than £5 excluding VAT and gifts must be inexpensive and relevant to the recipients work'*.[191]

A successful research based pharmaceutical industry has become essential to ensure major advances and innovations in drug research and development. Heavy research investment in the UK has resulted in the discovery and development of five of the current top twenty medicines world-wide. No Government has been willing to invest on the same scale. Satisfying shareholders on the one hand and providing value for money in a competitive market, whilst making financial savings to cover the cost of research and development for future innovative drugs is a fine line and one needs to bear in mind that the ethical and moral standards of global business and professional health care practice may well be different.[192]

2.2.9 Hospital

The Greenfield Report of 1982 and the Audit Commission Report of 1994 have both stated that the influence and events that take place in hospitals strongly influence GP prescribing.[30,46] Estimates range from as low as ten per cent to as much as forty per cent of general practice prescribing being influenced but precisely how and to what degree remain unclear.[30,193]

It seems logical that hospital prescribing has some influence on prescribing in primary care as all medical students traditionally spend a major part of their training in the secondary care environment. Also, when patients are discharged into the community, GPs are generally unwilling to change any hospital initiated prescribing without reference back to the hospital.[194] Some GPs may also decide to adopt some of the prescribing strategies of hospital physicians, especially the prescribing by consultants who might be perceived as the 'gold standard' as they are 'specialists' in a particular field of medicine. The resulting economic effect on the primary care budget can be profound, especially when the medicines are required for the long term treatment

of a chronic condition.[118,119] This effect can be further potentiated as many drug companies disguise the cost of their drugs, making some of them market loss leaders by offering major discounts to hospital pharmacies compared with the wholesale costs to pharmacies in primary care.

A study carried out by academic pharmacists in Brighton looking at how hospital doctors and GPs rated the different factors involved in choosing an NSAID for a formulary revealed subtle differences in their approaches to drug selection.[195] Hospital doctors were primarily concerned with drug efficacy compared with their GP colleagues who were relatively more concerned with possible side-effects than the potential benefits of a drug and tended to rate past experience more highly. The study only involved a total of 44 doctors and the hospital cohort studied were of younger age than their GP counterparts. The study also revealed that dispensing doctors were equally influenced by hospital pharmacists as by community pharmacists which may reflect the promotion and availability of hospital-based drug information services directly to GPs.

2.2.10 Society

The two main aspects of society which have the potential to influence prescribing are culture (Section 2.1.2) and the mass media. Media can influence prescribing in two ways: either through negative publicity causing downward prescribing trends or product advertising having the reverse effects. Research at the Prescription Pricing Authority (PPA) in Newcastle upon Tyne focusing on downward prescribing trends in the early to mid 1990s, found that television and newspapers seemed to have the greatest influence on this outcome.[196]

One of the most damaging media reports with detrimental consequences was the 'pill scare' in the UK towards the end of 1995. The UK Committee on Safety of Medicines (CSM), anticipated that publication was about to take place of three studies which were likely to cause public alarm, held a press conference announcing that 'combined oral contraceptives' (COCs) containing gestodene or desogestrel (third generation) should only be used by women who are intolerant of other COCs and prepared to accept an increased risk of thromboembolism'.[197] Unfortunately, such was the media hype that considerable public anxiety resulted and a substantial number of

women, both in the UK and abroad, stopped taking the pill with the inevitable consequence of increases in pregnancies and abortions throughout Europe and the rest of the world.[198] Despite the adverse effect of venous thromboembolism (VTE) appearing to be statistically significant, there was doubt as to whether this was clinically significant.[199] VTE is so rare that the population to demonstrate that the third generation OCs double the risk of death from VTE compared with second generation OCs would be greater than the total number of women using OCs in the UK and Netherlands combined.

The media is a powerful means of communication and there have been other drug-related reports that have done nothing to instil confidence into the public.[200] Unfortunately, media reports are often misleading and are largely written to attract attention - this may counteract and complicate the work of many health professionals. Perhaps more effort should be made into forging links between health care professional bodies and the media to educate the public so that issues can be handled more evenly and accurately.

2.2.11 Patients

A number of patient factors are known to influence prescribing such as their age, socio-economic status and how informed they are. These, along with patient demand, have been discussed earlier as being important determinants of varying drug consumption.[139] Bradley found expectations of patients to be the commonest reason cited by GPs for issuing a prescription.[150]

In 1991, medical sociologists at the University of London published the findings of a questionnaire study which measured patients' attitudes towards the issue of a prescription in general practice and recorded whether or not a prescription was issued.[201] The results were not entirely conclusive but they indicated that the attitude of the patient influenced the outcome. Patients presenting without appointments were associated with a greater tendency to receive a prescription. The proportion of patients receiving a prescription (61%) was found to exceed the proportion of patients expecting

a prescription. The researchers also found that doctors were more aware of the pressure to prescribe than of the preference for self-care.

This research was followed three years later by semi-structured interviews with 30 adult patients from two general practices to describe their ideas and expectations about prescribing and their self-reported behaviour in cashing prescriptions.[202,203] Interviews revealed that the desire for a prescription can be related to the stage of the illness at which a patient consults their doctor but that it is impossible to satisfy all patients' expectations. Also, it was found that not all patients either wanted a prescription or collected it if they received one. Britten concluded that the appropriateness of the outcome of the consultation could beneficially include confronting the patient about their expectations in receiving a prescription.

For those patients receiving an unexpected prescription, it could be that either they are disinclined to use their medication or that they are non-concorders with prescribed medication. The latter could be as a result of not having the prescription dispensed or by not taking the prescribed items as directed. In 1984, Begg carried out an audit of patients who received prescriptions in one GP practice and suggested that the number of prescriptions not dispensed could be a measure of the quality of doctor-patient communication.[204] A study to determine the rate of patients not redeeming their prescriptions in primary care was performed by Beardon *et al*, from the Department of Pharmacology and Clinical Pharmacology, Dundee Medical School.[36] Over a three month period in one Health Centre in Tayside, 4,854 patients received a total of 20,921 prescription items and overall 702 (15%) patients failed to have 1072 (5.2%) prescriptions dispensed.[36] The authors suggested that prescribing levels may have exceeded patients' expectations. Of those who redeemed prescriptions, seventeen per cent were not exempt from prescription charges compared with 33% of patients who failed to redeem them.

Other research from the patient perspective has also been carried out on 1,068 randomly selected Chinese in Hong Kong using telephone interview and questionnaire techniques.[205] The study investigated whether the Chinese expect prescribed medication when they are ill because doctors are known to prescribe in nearly 100% of consultations. A much higher proportion of patients admitted to always expecting a

prescription (76%) than reported in the UK[201] and half this number thought medicine was always necessary. With respect to the medication last prescribed to them, only 48% had completed the prescribed course with a significantly higher proportion (72%) of those who thought too many drugs had been prescribed not finishing the course. Younger patients who had received more education, were less convinced that illnesses always needed drug treatment and were less likely to expect a prescription for every consultation.

In Australia in 1997, two behavioural scientists investigated expectations of 336 patients' and their GPs perceptions of these patients' expectations.[206] Patients who expected medication were nearly three times more likely to receive medication and ten times more likely to receive medication when the GP thought the patient expected it. Overall patients were more likely to receive medication when the practitioner judged the patient to want medication than when the practitioner ascribed no medication to the patient.

A similar study by Britten and Ukoumunne a statistician, involved 544 patients who had consulted 15 GPs in four practices.[207] These researchers also found that the decision to prescribe was closely related to actual and perceived expectations but that the latter (doctors' perceptions of patients' expectations) was the more significant influence.

However, the findings of research involving 371 patients in five Oxford general practices conducted by three senior house officers[208] slightly contradicted the previous study by Britten.[207] Ramsden *et al* found no relation between GPs confidence in the pharmacological efficacy of their prescriptions and the patients' expectations for prescriptions, concluding that doctors are not pressurised into giving prescriptions they do not believe are of benefit. Britten's study directly measured both patients' expectations and doctors' perceptions of patients' expectations along with their decision to prescribe, whereas the study by Ramsden *et al* was limited to using the patients' expectations as a proxy for doctors feeling pressurised.

2.2.12 Prescriber and working environment

In 1992, researchers from the Department of Primary Health Care, University College London found that the decision making by GPs in the diagnosis and management of lower urinary tract symptoms in women revealed extensive differences between patients.[209] Of 61 subjects from two group general practices in suburban London presenting with symptoms of frequency or dysuria, GPs who knew the patients well were found to be four times more likely to make a correct prediction of the test result and twelve times less likely to prescribe antibiotics. The GPs were five times more likely to make more accurate predictions in patients from social class one and two and were six times more likely to prescribe antibiotics for older women in the sample. This study was limited in sample size and may not be representative of general practice consultations. It might be inferred from this study that in addition to patient factors, there are probably a variety of physician characteristics which must be associated with the outcome of the consultation.

In the same year as previously, a paper published by researchers from the Drug Utilization Research Unit in Northern Ireland analysed the prescribing of 362 GPs from 132 practices to establish the relationship between the number of partners and the number of drugs prescribed.[210] Not surprisingly, there was found to be a significant correlation between the number of different preparations prescribed and the number of GPs working in the practice; however, this was the first study to establish this. No correlation was found between the number of different drugs prescribed and the mean prescribing cost per patient or the mean list size of the doctors in each practice. Of some concern was the finding that the number of different drugs prescribed by practices claiming to have a practice policy or operate a formulary was not significantly different from that among practices with no such formulary. These findings are of importance as the greater the number of different drugs prescribed, the greater will be the risk of side effects and possibly dangerous interactions.

Researchers in the Department of General Practice in Edinburgh investigated the duration of patient-doctor consultation of 86 GPs to see whether this affected patient care.[211] Despite the patient case mixes of the GPs appearing to be similar, the results varied greatly. Patients reported greater satisfaction with longer consultations which

were associated with dealing: with more of the patients' psychological problems; with more long term relevant health problems and with health promotion. With respect to prescribing, longer consultations involving a more thorough patient examination could reveal problems requiring a prescription and yet the provision of a prescription has also been long associated with a method of terminating short consultations.

In Section 2.2.7.2 the importance of postgraduate education to maintain up-to-date drug knowledge for prescribers was discussed. Murray *et al*, academic GPs from the Department of Postgraduate Medicine, University of Glasgow published two studies in the early 1990s which analysed the characteristics of GPs attending educational meetings[212] and a follow up study[213] looking at their demographic characteristics. In the first study, of 171 GPs who had attended more than 35 half day sessions of accredited education, the high attenders were more likely to be women, to be members of the Royal College of General Practitioners and to work in a training practice.[212] The majority of doctors had been qualified for between 10 and 30 years and worked in group practices of three or more doctors. The second study involved sending a questionnaire to identify the demographic characteristics of 1,672 doctors who had attended sufficient sessions to claim their postgraduate education allowance.[213] A 93% response rate was achieved and there were found to be particular differences in the attendance at different styles of meetings, namely, disease management, service management and health promotion. GPs older than 55 years attended the highest mean number of educational sessions on disease management and the lowest number of the other two styles of meeting. GPs in rural areas attended fewer meetings than those in urban areas, particularly with respect to disease management. Doctors from smaller practices attended significantly fewer sessions on service management than those from larger practices and full-time doctors attended more service management sessions than part-time doctors. The only difference between sexes was that men attended significantly more sessions on service management and women attended more on health promotion.

Earlier in the 1990s, a number of studies in the UK investigated the differences in prescribing between fundholding and non-fundholding practices. Health service researchers at the University of Oxford used PACT data to measure various aspects of prescribing in a variety of dispensing, non-dispensing, fundholding and non-

fundholding practices.[214] In the six months after the NHS reforms, prescribing costs increased most among non-fundholders and the increase in average cost per item was greatest among this group too. The number of items prescribed increased most in the non-dispensing fundholders group but the level of generic prescribing in the dispensing fundholders at 34% was nearly 15% below that of the other two groups. Overall, five of the eight fundholding practices made savings in their drugs budget at the end of their first year compared with none of the seven non-fundholding practices.

A multi-disciplinary team of researchers from the Department of General Practice, Edinburgh compared prescribing patterns between six fundholding practices and six non-fundholding practices using the more accurate 'defined daily dose' measure.[215] Over a two year period the costs rose least in the fundholding practices.

Pharmacists and clinical pharmacologists in Newcastle upon Tyne examined the effects of a financial incentive scheme on prescribing in non-fundholding general practices.[89] Of 442 practices, 102 achieved their target savings indicating that the prescribing behaviour of non-fundholding general practitioners responded to financial incentives in a similar way to that of fundholding practitioners.

At about the same time health service researchers in Oxford investigated the changes in prescribing practice between eight fundholding practices and five non-fundholding practices which had similar practice characteristics.[216] The results indicated that prescribing costs rose by a third or more in all practices irrespective of their type. The period of prescribing data investigated was over three years which was greater than in the previous two studies and in this study the effectiveness of fundholding in curbing prescribing costs was not proven.

Researchers from the Department of Pharmacology and Therapeutics at the University of Liverpool published a study in 1996 which investigated the influence of practice characteristics on prescribing in GP practices.[217] With the exception of variation in total prescribing costs which was largely accounted for by fundholding, differences in prescribing behaviour were better explained by deprivation, training status and partnership status.

2.2.13 Summary

This review section has indicated that GPs are exposed to a wide range of factors that can potentially influence their prescribing. Many influences are independent of national boundaries, others may be peculiarly related to local or national health care practice and professional organisations. Although the volume of literature associated with prescribing influences is substantial, there appears to be relatively little which either investigates the impact of different influences or how GPs perceive their relative importance. The next key area of the literature review explores, aspects of quality prescribing.

2.3 QUALITY PRESCRIBING

"I do not want two diseases: one made by nature and one made by the doctor". (Napoleon Bonaparte 1820)

2.3.1 What is quality?

Quality of care is an increasingly important criterion in the provision of health-related services. Quality assurance covers a wide range of factors incorporating how to develop, ensure, improve and manage the quality of patient care[218]. At the beginning of the 1990s, the WONCA European Working Party on Quality in Family Practice (EQuiP), a collaboration between professional organisations for family doctors in 17 European countries carried out a cross-country investigation of quality assurance.[219] The purpose of this exercise was to exchange experience of activities and offer support where necessary in order to speed up developments in different countries. These activities include the setting of guidelines for practice through structured methods, application of feasible methods for quality assessment and use of new methodologies for changing practice performance in order to improve future quality of care as well as cost containment. From the findings it appeared that countries where the health care system favoured a strong and central position for the GP were more advanced in developing quality assurance in general practice. However in all countries, the resources available to GPs and practices in order to set up quality activities in their work setting were limited.

Although prescribing is just one aspect of patient care, it is nevertheless an essential component representing one of the core functions of the doctor. In the UK, The Royal College of General Practitioners began to address quality in general practice in 1983 with the underlying belief that quality was measurable through such activities as audit and hence GP practices were encouraged in this respect.[220] The process continues to this day with attempts to link 'better' general practice to 'better' hospital and community services in order to offer seamless care to patients.[218] Quality in general practice has been described as the relationship between actual care and the expectations of the various parties involved.[61]

Since the late 1980s, quality improvement has become a government strategy for reforming the management and organisation of public services.[221] The current British Government produced a white paper in December 1997 entitled 'The New NHS: Modern and Dependable'[53] which introduced the term clinical governance, defined as *'a framework through which NHS organisations are accountable for continuously improving the quality of their services and safeguarding high standards of care by creating an environment in which excellence in clinical care will flourish.'* A subsequent white paper 'A first class service: quality in the new NHS'[222] published in July 1998 announced that quality health care would be tackled in three ways: by setting, delivering and monitoring standards.

2.3.2 Quality indicators

In general, the quality of prescribing cannot be assessed directly as there are no routine data available which directly link morbidity to drugs. Even if this were possible, the medical history of the patient would ideally also need to be known. Furthermore, there are anomalies in that many traditional and generally accepted treatments do not entirely follow the principles of evidence-based medicine.[223] Consequently performance or quality indicators are proxy tools used to monitor and evaluate prescribing by measuring aspects of drug utilization. The EQuiP Working Party has defined an indicator as: *'a measurable element of practice performance for which there is evidence or consensus that it can be used to assess the quality and hence change the quality of care provided'.*[224] They can be used for three overlapping purposes: to raise awareness, to target interventions and to facilitate audit.[225] Medical audit has been defined by the NHS executive as the systematic, critical analysis of the quality of medical care including the procedures used for diagnosis and treatment, the use of resources and the resulting outcome and quality of life for the patient.[218]

A number of principles underlie prescribing indicators[226] and include:

- risk benefit - the use of more potent but toxic drugs within a group should be restricted to patients with an appropriate risk benefit ratio
- doctor's knowledge - drugs should be consistently prescribed from a familiar

range of drugs which is recognised as good medical practice

- monitoring and management of care - patients with long term pathology particularly those receiving active treatment should have their condition and treatment (ideally the most cost-effective available) regularly reviewed
- patients' clinical needs - the appropriate quantities of drugs for patients' needs should be provided as economically as possible in order to free resources for other health needs

Houghton, an associate advisor in general practice and GP in the West Midlands, has proposed that if prescribing performance indicators can identify substandard medical performance then they could help form a relatively inexpensive and simple system of reaccreditation for doctors, especially GPs.[227]

2.3.3 Measuring quality prescribing

In this context, quality is not only difficult to define but it is even more difficult to measure adequately and satisfactory. In England, prescribing is commonly measured by three rates: the number of items prescribed, the cost per item and the cost per patient. The rates can be applied both to prescribing overall and to prescribing in specific therapeutic groups. Measurement of prescribing is facilitated by the use of prescribing analysis and cost (PACT) data which has traditionally been used to set and monitor prescribing budgets and is now increasingly used for the purposes of developing prescribing indicators.[65] Practices' prescribing rates are compared with the local health authority averages (weighted with respect to prescribing units based on the number of patients over 65 years of age and those under 65 years) and with national averages. None of these measures is entirely meaningful and using health authority averages as the standard for comparison is questionable.[223] However, when they are used to compare health authorities with each other, some patterns have been found to emerge. In poorer, more industrialised areas, the items-per-patient rate tends to be relatively high and the cost-per-item relatively low. In more affluent areas, items-per-patient tends to be lower and cost-per-item higher. The cost-per-patient in both cases is determined more by the number of items than the cost of each item. Reasons for these trends are considered to be in part due to higher unemployment levels in poorer. more

industrialised areas with a corresponding higher proportion of people exempt from prescription charges being prescribed items which would tend to be purchased over the counter in more affluent areas.[228]

2.3.3.1 Units of measurement

2.3.3.1.1 Volume

Quantifying drug consumption can be related to simple physical units, such as the number of packages or tablets, grams of ointment and the number of prescription items.[229] The number of units depends to a considerable extent on the intended duration of the prescriptions and thus the number of tablets for the same drug will vary from prescription to prescription. However, the number of units is of value in evaluating the clinical use of drugs as well as measuring the frequency of prescriptions.

Simple counting of tablet numbers ignores variations in tablet strengths resulting in low strength preparations disproportionately influencing numbers more than high strength preparations. Similarly short-acting preparations will tend to contribute more than long-acting preparations.

If consumption is given in terms of grams or active ingredients, drugs with a low potency will have a larger fraction of the total than drugs with high potency. Combined products may also contain different amounts of active ingredients from single drug products which will not be reflected in the figures.

2.3.3.1.2 Defined daily dose (DDD)

The basic definition of the defined daily dose (DDD) unit is that it is: *the assumed average maintenance dose per day for a drug used on its main indication in adults.*[229] DDDs are a much more meaningful way of measuring volume as they are independent of prescription duration though they may not necessarily reflect the recommended or actual dose prescribed. The individual dosages used will often differ from the DDD because of individual patient characteristics such as age and weight, severity of clinical condition and pharmacokinetic considerations.

Since many drugs are used at different dosage levels for different indications, this needs to be taken into consideration when evaluating drug consumption figures. For drugs used in short courses, for example antibiotics, the duration of treatment may differ from one drug to another and this is important when comparing the use of the different drugs. DDDs have not been established for some types of drugs, for example skin preparations and a recommended dosage of a drug may vary between countries, making national comparisons difficult. Sales or prescription data monitored and presented in DDDs will thus give only a qualified estimate of consumption and not an exact picture of actual use.

Despite its limitations, the defined daily dose is a much improved unit of measuring prescribing comparisons which is independent of price differences and different preparations. Both national and international long term studies have been carried out using DDDs and comparisons between countries have also been made, notably in Scandinavia.[230-234]

2.3.3.1.3 Prescribed daily dose

The prescribed daily dose (PDD) can be determined from prescription records and patient interviews but it is important to relate it to the diagnosis on which the dosage was based.[229] The PDD will give the average daily amount of a drug that is currently prescribed. There are occasionally substantial discrepancies between the PDD and the DDD for example with antibiotics, PDDs vary according to the severity of the infection whereas the DDD for most antibiotics are based on treatment of moderately severe infections. In hospital care, much higher doses are frequently used and this must be considered when using the DDD as a unit of measurement. Therefore, it is important to take this into consideration when evaluating and interpreting drug consumption figures. PDDs may well differ from one country to another and so there should be an element of caution when international comparisons are made and considered. The PDD can vary according to both illness treated and national therapy traditions.

For drugs where the recommended dosage differs from one indication to another, for example antipsychotics, it is important that diagnosis is linked to the prescribed

daily dose given. Pharmacoepidemiological information, for example sex, age and single/combination therapy is also important in order to interpret a PDD.

2.3.3.1.4 Cost

Local cost analysis of drug expenditure is satisfactory provided comparisons are being made in the same sector of health care at a similar point in time. However, national and international comparisons based on cost parameters are often misleading and of limited value in the evaluation of drug use. Price differences between alternative preparations and different national cost levels make the evaluation difficult. Long-term studies are also difficult due to fluctuations in currency and changes in prices. When cost data are used, an increase in the use of cheaper drugs may have little influence on the total level, while a shift to more expensive drugs is more readily noticed.

Cost analyses are applicable for prescription studies of a single substance. As with the number of prescription items though, cost is also partly determined by the intended duration of the prescription, not just the basic cost of the drug.

2.3.3.1.5 Patients and population

Prescribing levels are effected by the level of morbidity in a practice population in general practice but currently there is no way of measuring it.[223] The age and sex structure of the population also influence prescribing patterns. Different patients require different numbers of prescriptions and before reasonable comparisons can be made, a practice population needs to be standardised as far as possible. In England, the prescribing unit gives some allowance for this by weighting patients of 65 years and over three times as heavily as younger patients but the system is crude and inaccurate. In an attempt to improve this measurement, a system was developed in 1993 of ASTRO-Pus (age, sex and temporary resident originated prescribing units) that weights for nine age bands in both sexes and for temporary residents and this is now used in determining prescribing budgets.[35] More recently for specific therapeutic groups, similar cost weightings called STAR-PUs (specific therapeutic group age/sex related prescribing units) have been established which make possible much fairer comparators for a practice's prescribing than the system of PUs.[66] The rationale behind their

development is because each therapeutic group has a different age/sex distribution of use, for example cardiovascular and gastrointestinal drug costs are particularly high in older patients and endocrine drug costs are higher for women than for men.

2.3.4 Development of quality indicators

The Delphi approach has often been used in the development of quality indicators or markers in an attempt to obtain a consensus opinion. In 1993, Schrijver and Crede, two pharmacists working for Barking and Havering Health Authority, drew up a list of five prescribing quality statements following wide consultation with experts and GPs.[235] These were with respect to the:

- percentage cost of inhaled prophylaxis to total costs of asthma treatment,
- level of generic prescribing,
- percentage of total NSAIDs prescribed from the five most commonly used,
- appropriate upper benzodiazepine prescribing level (items per 1000 patients),
- appropriate percentage of cephalosporin relative to penicillin prescriptions.[235]

After presentation at two postgraduate meetings, GPs were asked to attach a value to each statement and this process was repeated twice. The first three statements were generally considered to be fairly valuable quality markers but there was a low opinion of the usefulness of the final two statements. Despite the recognition by the GPs of certain quality markers, their prescribing behaviour based on the three accepted statements was found to significantly fall short of their rating.

Academic health service researchers at the University of Manchester published a study in 1998 which attempted to develop indicators of appropriateness of long term prescribing in general practice.[236] A nominal group composed of nine national key personnel in the field of prescribing identified potential prescribing indicators. Of 34 statements, 13 prescribing indicators suitable for application were identified and rated in a two round Delphi study by 100 GPs and 100 community pharmacists. Subsequently nine indicators of appropriateness of prescribing were produced suitable for application to the medical record of any patient on long-term medication in UK general practice.

Roland *et al* from the National Primary Care Research and Development Centre in Manchester, recently undertook a large study into the agreement between GPs and health authority managers on what should be counted as a good performance indicator for use by health authorities in monitoring general practice.[221] In an initial survey of all health authorities in England, they identified a total of 240 relevant indicators that were in use for assessing performance. Again the Delphi approach was used, this time among 57 GP course organisers and 47 health authority managers. Agreement on what is an acceptable indicator of quality was achieved for only a tiny minority of conditions, and for many of these, performance data were not routinely available. In the area of prescribing, there was a low level of support for prescribing indicators. The most highly rated indicators were associated with the organisation of care and training within the practice such as prescribing audit and regular prescribing meetings. The most highly rated indicator relating to individual drug details was the ratio of co-trimoxazole to trimethoprim prescribed.

Consensus methods such as the Delphi technique have been criticised for the lack of a formal decision making structure and for having their outcome influenced by their panel composition.[237] Clinical pharmacology and pharmacy researchers in Newcastle upon Tyne managed to avoid these issues when developing a range of criteria of prescribing quality.[67] This was dealt with firstly by requiring unanimity on the choice of criteria and standards within the group which consisted of eight GPs. Secondly, by convening a group of practising GPs, decisions on general practice prescribing were made by a peer group. In contrast to the former studies discussed, it remains questionable whether unanimity with eight GPs would be more meaningful than general consensus by larger numbers of practitioners.

Where some quality indicators have been developed though, other groups have found them unacceptable, which makes it difficult for standards to be confidently established. For example the ratio of inhaled steroids to bronchodilators in the management of asthma has been used as a quality indicator by many health authorities in the UK, mainly since its reference in the Audit Commission Report in 1994[30] and it has subsequently been endorsed by others.[238] However, when attempting to develop consensus indicators, others have found that there is no agreement about how much

prescribing meets the needs of asthmatics.[67] Also bronchodilators are of symptomatic benefit for many patients with chronic bronchitis or emphysema where steroids are less often of value. Thus it may be argued that a high steroid:bronchodilator ratio represents poor prescribing in the context of non-asthmatic disease and as an indicator it is inappropriate unless there is a link of drug use to morbidity. A study attempting to determine appropriateness of this co-prescribing from PACT data alone even concluded that a more sophisticated approach was required to assess and improve prescribing quality taking into account the many factors which influence prescribing decisions[239] and yet the ratio continues to be used as a prescribing indicator.

2.3.5 Quality indicators in use

There have been many types of performance indicators used to assess prescribing including the:

- appropriateness of drug use[240]
- appropriate monitoring of drugs[236]
- prevalence of fixed combination drugs use of three or more ingredients[241]
- prevalence of polypharmacy prescribing[8]
- generic prescribing rate[30]
- adherence to prescribing guidelines / formularies[132]
- prescribing of drugs from a limited range[242]
- frequency of prescribing i.e. rates and ratios of prescribing[243]
- quality of life outcomes[244]

With larger numbers of people living into old age, there has been an increase in the number of nursing homes, particularly throughout the 1980s. The availability of nursing staff to administer drugs and initial prescription charts has meant that monitoring an elderly person's regular pattern of drug consumption is considerably more accurate than it would have been in the domestic setting. Associated with this, assessment of the quality of prescribing in nursing home residents is one example of

where a number of investigations have been performed. In 1987, benzodiazepines were described as drugs to avoid in the elderly.[245] Shortly afterwards, a study was carried out in 15 Oxfordshire nursing homes by two community health researchers to examine how widely these drugs were prescribed by GPs to patients.[246] In this study, despite the limited numbers and similarity of the subjects, there was a forty-fold difference found in the average number of benzodiazepine prescriptions per resident. Whilst no attempt was made to identify what the cut-off point should be for good and poor quality prescribing of benzodiazepines, monitoring their use appeared to be an effective tool for highlighting the range of variation in prescribing between nursing homes.

In 1993, a team of medical and non-medical researchers from the medical school, University of California published a study in which they attempted to relate the quality of prescribing in 12 nursing homes in the greater Los Angeles area to the characteristics of the physicians who served them.[247] The definitions used to assess quality of prescribing were the overall number of prescription drugs per resident and the use of medications deemed inappropriate by a panel of experts. The characteristics of the doctors having the most inappropriate prescribing included older age, having infrequent consultation with psychiatrists and those who worked in smaller practices. The doctors associated with the best prescribing were those who held certificates of added qualification in geriatrics, those who frequently consulted psychiatrists and female doctors. As relatively few doctors were found to have relevant postgraduate qualifications and as only 6% of the 221 participants were female, these results must be interpreted with caution. Such was the belief that there was a link between qualifications and better quality of care by doctors that in 1991, two years prior to this study the Medical Insurance Agency in the UK decided to offer annual indemnity arrangements at considerably lower rates to doctors who had passed the membership examinations of The Royal College of General Practitioners.[248]

A research team from the School of Pharmacy, University of Stockholm investigated the influence on the quality of psychotropic prescribing from the resident and organisational perspective in 33 Swedish nursing homes.[240] A list of 13 drug criteria based on published guidelines and recommendations were developed to measure appropriateness, in terms of excessive use of psychotropic drugs. Residents diagnosed

with a psychiatric disorder and younger residents had more deviations from the criteria although resident's clinical and demographic characteristics did not account for variations in appropriateness of drug use from one home to another. Facilities with better nurse staffing and drug intervention teams had fewer deviations from the criteria but only 15-20% of the variation in drug prescribing was explained by these predictors. Drawbacks to this study included the documented diagnostic reports which were thought to be limited and their accuracy was uncertain. Like most of the aforementioned studies, the criteria for measuring quality in this study in terms of appropriateness do not take into consideration the clinical condition of individual patients. The use of some drugs classed as inappropriate may in fact be appropriate, especially where no alternative treatment is available in those cases where some residents experience serious psychiatric symptoms.

2.3.6 Implications for research

There is no current system which is entirely adequate to evaluate the quality of GP prescribing. As systems are developed in the future, they may only be relevant on an international level where there are standard accepted guidelines between countries in the treatment management of conditions. Currently over- or under- prescribing is often selected as a marker, but neither are necessarily accurate indicators of appropriate prescribing.[51] Improving some aspects of the quality of prescribing may lead to short-term cost savings due to initiatives such as generic prescribing. In other areas, increased drug costs may be forecast but with potential reductions in the overall health care bill and social consequences especially including the return to work. For example, in asthma the use of expensive prophylactic inhaled corticosteroids may reduce emergency hospital admissions.[30] Thus, the standardised measures being developed already reveal that an apparently high cost practice may in fact be more economical than an apparently low cost practice. Drugs that seem initially expensive in general practice may save money long term. This is a very under-researched area.[223]

Nevertheless, by indirectly measuring quality, prescribing indicators can alert prescribers and point to potential performance issues that may require more intense

review within a practice.[249] Quality is a very difficult concept to pursue and educational use of performance indicators may be one realistic way forward.

Table 2.1 Prescription items and cost of prescribed medicines per head per year in EC countries[33,250]

Country	Rxs per head 1980	Rxs per head 1990	Annual drug costs per head (£) 1991	Annual drug costs per head (£) 1995
France	27.6	38.0	112	202
Italy	19.9	38.0	107	106
Spain	14.4	20.1	64	112
Germany	14.3	14.8	91	154
UK	6.6	7.6	64	88
Netherlands	3.9	4.2	53	110

Table 2.2 A brief history of therapeutic formularies and essential drug lists[71]

1970 to 1975	Development and evaluation of hospital formularies in Italy and the US; Systematization of the national drugs lists with guidelines in Scandinavia; First essential drugs lists in developing countries such as Mozambique and Peru
1977	Publication of WHO Technical Report Series No. 615 (*The selection of essential drugs:* report of a WHO Expert Committee)
1978	WHO Declaration of Alma-Ata on Primary Health Care Publication of WHO; Regional Office for Europe's first book on drug utilization studies (WHO Regional Publications, European Series, No. 8); A formulary tailored for general practice Creation of WHO Action Programme on Essential Drugs
1981	Creation of periodic British National Formulary
1985	After long debate, approval of limited lists of drugs in the UK for use by GPs; In the first half of the 1980s, publication of various problem-solving or drug-orientated therapeutic formularies for general practice, in for example Belgium, Nicaragua, Scandinavia, Spain (starting from Catalonia)
1988	Fifth edition of the List of Essential Drugs (WHO); Clear and growing acceptance of general practice formularies in most developed countries; Availability of formularies with prescribing guidelines in many of the least developed countries such as Burkina Faso, Ghana and Zimbabwe

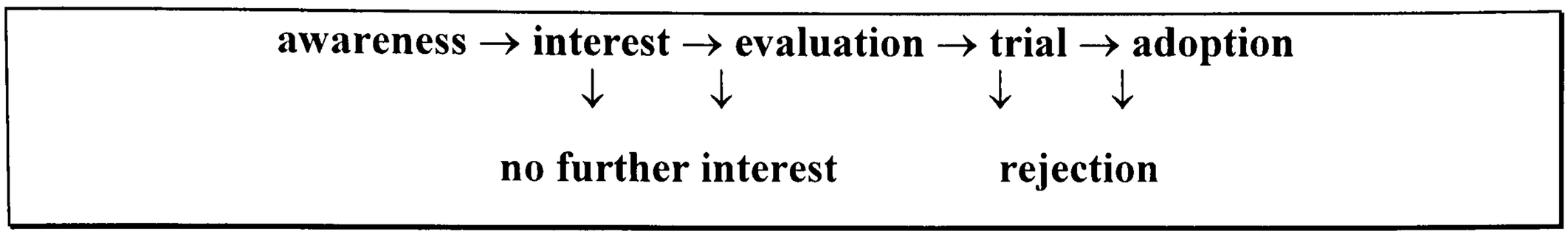
Table 2.3 The types of outcomes that can be measured by clinical trials

Clinical outcomes	Patient outcomes	Economic outcomes
Clinical endpoints Signs and symptoms Laboratory values Rate of mortality	Quality of life Functional status General health perception Satisfaction with care	Cost minimisation Cost effectiveness Cost-benefit analysis Cost-utility analysis

Table 2.4 Model specification: source of variation by level of data collection[251]

Sources of variation	Level of collection		
	Countries	Regions	GPs
Morbidity	Small	Medium	Medium
Population	Large	Small	Small
Health system	Large	Medium	Small
Professional	Small	Medium	Large

Figure 2.1 The stages in the uptake of a new drug by a prescriber[152]



CHAPTER THREE
METHODS

The research presented in this thesis consists of two distinct parts of the study, namely the main prescribing study and the two-stage Delphi prescribing influences questionnaire study. The methodology employed is presented separately.

3.1 INTRODUCTION TO THE PRESCRIBING STUDY

One outcome of the Bielefeld conference (Section 1.1) was agreement by delegates that the development and implementation of a European Formulary for general practice might improve the standard of prescribing with the provision of more rational, appropriate and safer prescriptions for patients of all European countries. Subsequently, a multidisciplinary group of approximately 50 delegates from 17 East and West European countries established a European Formulary Group with ten members forming the editorial board. Work then began on producing a European Formulary, based on the sound principles of clinical pharmacology and therapeutics, selecting drugs with proven efficacy, relative safety and where possible which were economic in use. It was agreed that the European Formulary should be designed to be presented in two sections: firstly, as a rapid consultation Formulary document, listing conditions and appropriate drug recommendations together with contra-indications, interactions, dosages, duration of action and side effects; and secondly, in the form of a more comprehensive Appendix providing referenced justification for the selected drugs. The European Formulary was also to include general guidelines on rational prescribing.

In 1994, after 16 meetings, a draft European Formulary with Appendix had been developed. A trial to evaluate the combined effectiveness of the European Formulary in association with an educational intervention upon European general practice prescribing was granted three years BIOMED funding between May 1994 and May 1997. The study was planned to involve 11 European countries, namely Belgium, England, France, Ireland, Italy, the Netherlands, Northern Ireland, Norway, Portugal, Scotland and Spain and to be centrally co-ordinated from Newcastle upon Tyne. Those individuals who were actively involved with the development of the European Formulary agreed to act

as national co-ordinators in each of the eleven European countries. Their role included the recruitment of local GPs to the study, the collection and translation of data and the delivery of the educational intervention. Centres in other European countries originally considering participation in the study included Gottingen and Wuppertal in Germany but withdrew due to insufficient finance as it was considered that GPs would only participate in research if they received adequate remuneration. Nevertheless, German representation on the Editorial Board of the European Formulary continued to play an active role in its on-going development. Annual weekend meetings for the co-ordinators and a research team were planned to take place in the spring each year in Newcastle upon Tyne, until termination of the funding in 1997. My input for these meetings included discussion of the progress of the study; planning of the content and implementation of the educational intervention and feedback on the prescribing data. At the meetings, time was set aside for discussing the update of the European Formulary.

3.1.1 Aims

3.1.1.1 Main aim

- To determine the effect of a consensus-based European Formulary as part of an educational intervention on the prescribing practices of GPs.

3.1.1.2 Subsidiary aims

- To record and evaluate prescribing in the different European countries and to compare and contrast differences in diagnoses and use of drugs with regard to the number of prescribed items and types of medication prescribed.
- To investigate the extent to which the drugs prescribed in the different European countries are in agreement with those recommended in the Formulary and the extent to which the proportion of presenting patient diagnoses are covered by the Formulary.

- To assess the prescribing patterns using performance indicators after implementation of the educational intervention, in order to see in which countries prescribing patterns changed in line with the recommendations of the European Formulary.

3.1.2 Prescribing performance Indicators

Generic indicators measured were whether:

- the proportion of total new drugs prescribed for a given condition as recommended in the European Formulary increased.
- the range of different drugs being prescribed was reduced.
- the number of consultations resulting in a prescription reduced where diagnosis associated with no prescription reflected European Formulary and educational intervention advice.

More specific indicators measured were whether:

- prescribing performance improved by investigating the uptake of the European Formulary Group's recommendations, in certain therapeutic areas.
- additional markers identified from reviewing the relevant prescribing literature, could also be explored in order to assess the prescribing performance of the GPs in the different countries.

3.1.3 Methods

3.1.3.1 Design

The study design was a multi-centre controlled trial involving up to 40 participating GPs recruited by a co-ordinator in each of the eleven countries listed previously (Section 3.1). Within each country, the participating GPs were randomised into two groups; one was to receive the European Formulary and educational intervention (the study group) while the second (the control group) received neither the Formulary nor the intervention. In countries where GPs operate in group practices, randomisation was conducted at the practice level to avoid contamination between control and study groups which could otherwise have occurred within practices (i.e. no two doctors in the same practice were randomised to different groups).

3.1.3.2 Subject sample

No finances were available from the research grant to reimburse the GPs' time for participation in the trial and so the only incentives were the availability of feedback from the project analyses three years later and access to the educational intervention, which only half the GPs were programmed to receive within the study period. With this in mind, each co-ordinator attempted to recruit 40 GPs to participate in the trial, half of whom would form the study group and the other half the control group. For GP confidentiality and data management purposes, the co-ordinators numbered each control group 1 to 20 and each intervention group 21 to 40.

3.1.3.3 Ethical considerations

Ethical permission for this study was not required since patients' medical care was not being adversely affected and the intervention only involved the doctors concerned. In addition the information recorded by the GPs was anonymous as each patient was identified only by a number.

3.1.3.4 Information to GPs

All the GPs who were recruited to the trial received project guidelines together with standardised data recording forms and illustrated examples of completed ones (Annex 2 and 3). The guidelines were translated into the appropriate language by each national co-ordinator and they explained clearly and concisely how the data record forms were to be completed.

3.1.3.4.1 Pilot study

The data recording forms issued to the GPs and the information provided was based on a relatively small scale pilot performed by the co-ordinators who also worked as GPs part-time. Co-ordinators kept a record of all patients seen over a two week period and the information recorded included the patient's name, age, diagnosis and treatment given.

3.1.3.5 Data recording

3.1.3.5.1 Phase I

Each participating GP recorded two sets of data, the first time period (Phase I) of data recording being in the autumn of 1994. The GPs were asked to record information from consecutive face-to-face consultations until a total of 200 different patient drug prescriptions had been written. Where a drug was prescribed, the doctor recorded the name of the drug, whether the drug was a single active entity or part of a combination preparation. Also recorded was one of four possible factors which influenced the prescribing of that particular drug preparation, identified by a code letter, as follows:

R where a drug was prescribed as a regular repeated prescription item.

H where a drug was prescribed as directed by a hospital or specialist.

A where a drug was prescribed and requested by the patient, as a result of having been prescribed the drug by another doctor previously.

N where a drug was prescribed for a patient's new problem uninfluenced by any previous prescription the patient had received.

Other recorded details included the patient's age (to the nearest whole number), sex and diagnosis(es) where appropriate. The GPs were asked to record a diagnosis for every drug prescribed, even if there was more than one drug for the same diagnosis and in addition they were asked to clearly indicate which drug was associated with which diagnosis. Finally, the GPs were also asked to record details of any intervening consultations where a prescription had not been issued.

The diagnostic data were translated into English as necessary by the national co-ordinators. Completed data sets were then sent to Newcastle upon Tyne for manual coding and computer data entry by the author GJ. Specific drug and diagnosis coding frames were developed, which were diverse enough to allow for the variety of prescribing practices across Europe and to facilitate the data coding process (Section 3.1.3.6)

3.1.3.5.2 Phase II

To measure the effects of the educational intervention, the second time period (Phase II) of data collection by the participating GPs was in the autumn of 1995, twelve months after the first period. Prior to Phase II, the GPs who were part of the study group received the educational intervention at the beginning of the autumn. The same fields of data were required to be recorded in Phase II, as described above in time Phase I (Section 3.1.3.5.1).

3.1.3.6 Coding Frames

Both the drug and diagnosis coding systems were specifically developed (by GJ) for the study as outlined in detail below.

3.1.3.6.1 Diagnosis codes

The diagnosis coding frame consisted of two types of codes: two digit codes for those diagnoses covered by the European Formulary and three digit codes for any others. Of the latter, several diagnoses were not explicitly mentioned in the European Formulary but could be considered to be implicitly referred to in the European Formulary. Two examples of these 'half-way house' type diagnoses included;

ischaemic heart disease (IHD) and *bronchitis*. IHD can mean that the patient is being treated for either *angina pectoris* or treatment following a *myocardial infarction*, or possibly both, and many GPs used the label IHD when recording the patient's diagnosis. The treatment strategy for both these conditions was discussed separately in the European Formulary but as the term IHD was not explicitly stated, it was decided to use an additional code where this was recorded. With the second example *bronchitis*, many GPs recorded this only as the patient diagnosis, without specifying whether it was either *acute* or *chronic*. The European Formulary discusses lower respiratory tract infections which includes *acute bronchitis* only so it was decided to give both *bronchitis* and *chronic bronchitis* two additional separate diagnoses codes. In total, 173 diagnoses codes were utilised, 66 (Annex 4) representing areas covered by the Formulary and 103 (Annex 5) further codes representing conditions outside the scope of the European Formulary. The non-Formulary diagnoses codes were added after referring to the ninth version of the International Classification of Diseases.[252]

The layout of the European Formulary was broadly based on the British National Formulary (BNF)[6] classification system but some therapeutic sections were further subdivided; for example, *allergy* formed a section heading of its own in the European Formulary whereas in the BNF, *allergy* is included within the Respiratory System Chapter. Overall, the European Formulary consisted of eighteen clinical therapeutic section headings which as previously mentioned differed from the BNF in that its focus was specifically concerned with use in primary care only and therefore also included a section on drugs held in the 'doctor's bag'.

3.1.3.6.2 Drug codes

The drug coding frame was based on the British Read Codes Classification system.[253] An up-to-date list of alpha-numeric Read Codes was obtained in February 1995 and converted into four digit numeric codes falling between 0001 and 9999 as this was considered to be the optimum format for manual coding purposes.[254] For ease of reading, the list was sorted into lower case alphabetical generic drug names in clinical therapeutic chapters equivalent to the BNF. The drug database had to be diverse enough to allow for the wide range of active drug entities prescribed in the participating countries and yet practical to use. To make this list more manageable, certain drugs

were deleted which would not be expected to be routinely prescribed in primary care for example many cytotoxic drugs. Adequate space was left between each of the therapeutic chapters to enable additional drug entities to be added as the coding of data from the different countries progressed. The European Formulary listed 126 drugs, their selection having been based on efficacy, safety, cost and availability in the participating countries. As a result, all the recommended drugs were already included within the Read Codes Classification. Overall, 1,616 drug codes classified into eighteen therapeutic chapters were cited in the study. Chapters 1 to 15 were synonymous with the corresponding BNF chapters. Chapter 16 consisted of miscellaneous supplementary drugs, Chapter 17 included appliances, dressings, reagents and borderline substances and Chapter 18 included unknown and unidentifiable drugs. In Chapters 16 to 18, single codes were given to groups of drugs, for example 9501 represented appliances, dressings and reagents. Unknown drugs were ones where the writing was illegible, whereas unidentifiable drugs were ones which could not be traced from the information sources utilised. This could have been because, firstly, they were herbal or homoeopathic derivatives and possibly excluded from more pharmacologically based drug manuals; secondly, they may have been recently granted a licence in a country; or thirdly, they may have been spelt incorrectly hindering their identification. Unknown and unidentifiable drugs represented less than 1% of the total number of drugs recorded in this study.

3.1.3.7 Diagnosis and drug coding procedure

The process began with (GJ) coding the data from non-English speaking countries as it was anticipated that this would present the biggest task which should be tackled at an early stage. The data collated in the project were of varying quality both within and between countries. Original copies of translated data sets with adequate space left for coding purposes, which had either been computer generated, typed or neatly printed, were considerably more acceptable than photocopied, untranslated forms written in an illegible cramped up style at the other extreme. Examples of where slight variations in hand writing caused problems with identification, included adoption of the following abbreviated diagnoses terminology by participating GPs:

PUO	pyrexia of unknown origin
PUD	peptic ulcer disease
PVD	prolapsed vertebral disc
PVD	peripheral vascular disease
PID	pelvic inflammatory disease

Patient symptoms were frequently recorded by the GPs, rather than specific diagnoses, so the coding frame had to be developed to be sufficiently versatile but still capable of enabling rapid reference. Where combination drugs were prescribed, additional diagnosis codes were matched with each separate active drug entity ingredient. Although the GPs were asked to record a diagnosis for every drug prescribed, even where there was more than one drug for the same diagnosis this was sometimes inadequately done. As a result, clustering of diagnoses and drugs was sometimes a problem, leaving one to interpret which drug had been prescribed for which diagnosis. In these situations, links between diagnosis and drug were only made where this was considered unambiguous.

Generic prescribing is not widely used around Europe and even in countries where it is practicable and encouraged for example in the UK, prescribers may still use proprietary drug names. Often co-ordinators translated the commonly occurring proprietary drugs on the recording sheets but left the remainder to be identified. All the generically named active drug entity ingredients present in combination drugs had to be identified and coded, which resulted in a complex investigative exercise to reveal the ingredients of unusual proprietary drug compound formulations which are especially common in Belgium and the southern European regions. Also generic drugs with added proprietary names, for example Salamol (salbutamol) appeared to be particularly common in the Republic of Ireland. For this process, a variety of reference documents were used to identify the unknown and untranslated drugs as follows:

a) Martindale Extra Pharmacopoeia, the 30th and 31st editions[20,255], which describe many proprietary preparations available in a wide range of countries, all their ingredients (the majority of which have separate entries as monographs) and their indications for use;

b) the World Health Organisation (WHO) Anatomical Therapeutic Chemical (ATC) classification indexes (1995 and 1996),[256]

c) a variety of sources including regional and national formularies available in the different countries.[257-259]

The use of these reference documents was essential, not only for identification purposes, but also when deciding in which relevant section to classify and code additional drugs on the same prescription as some drugs, for example aspirin and propranolol, can be used for a variety of indications. For the coding of oral contraceptives and hormone replacement therapy (HRT), it was decided to give the preparations one standard code each, instead of coding all the separate drug entities as follows:

3617 oestrogen and progestogen combined oral contraception

3625 progestogen only oral contraception

3003 conjugated oestrogens with progestogen for HRT

3083 oestrogens only for HRT

3059 progestogens only for HRT

3632 ethinyloestradiol (when combined with 7229 below)

7229 cyproterone acetate where recorded for the treatment of acne.

The active ingredients cyproterone acetate combined with ethinyloestradiol which when combined together are indicated for the hormonal treatment of acne as well as for contraception were separately coded.

Problems encountered in the coding procedure were successfully dealt with as they presented but were instrumental in prolonging the coding procedure. Once all the data from Phase I had been coded, a month was devoted to cleaning up the data and editing codes where necessary. This cleaning and editing exercise was again repeated on completion of the coding from Phase II.

3.1.3.8 Data Processing Management

The data management was split into three distinct parts. In order to manage the data, various computer programs were written in FONTRM 77 and compiled to run on Newcastle University's UNIX machines.

3.1.3.8.1 Data entry systems

A menu-driven data entry system was developed by a computer/medical statistician advisor and installed on the project computers. The system managed eleven fields of information: country; data period Phase I/Phase II; study/control group GP; GP number; patient number; patient age; sex; diagnosis code; drug code; combination drug/non-combination drug; and category of prescription.

3.1.3.8.2 Data analysis systems

After data entry, data analysis systems were run on Newcastle University's UNIX machines. Access to these was through terminal software running on computers linked to the University Main Frame. These analytical systems linked the drug, diagnoses, and survey data to allow analysis by country, GP, patient category, drug category and/or diagnosis category.

3.1.3.8.3 Data processing

Using purpose-written software, a menu-driven data processing program was created by the computer/medical statistician advisor. This complemented the data entry system and facilitated extraction of selected data to be investigated further.

3.1.3.9 Statistical analysis

Statistical analysis was done using the SPSS 7.0 statistical analysis package. For the primary response variables (the percentage of drugs used, the range of items prescribed and the percentage of patient-doctor consultations for a condition), paired differences were calculated for each participating GP and analysed using analysis of variance (ANOVA). Results are expressed as means and standard errors of the mean (mean ± SEM) where measuring differences between populations and standard

deviations are stated where describing the spread within a population. Use of the term 'study group GPs' in this thesis is synonymous with 'intervention group GPs'.

When performing the necessary searches in the database before conducting the statistical analyses, all the searches involved linking/matching drugs prescribed to their diagnosis, except where stated. This matching ensured that additional drugs a patient may be receiving for other presenting conditions were excluded from the analysis. A search involving no matching of drugs to diagnosis identified all the consultations for a condition (whether or not they resulted in a prescription), in order to establish the proportion of GP consultations for that condition. On investigating the levels of concordance with drugs prescribed in the European Formulary and the range of drug items prescribed, the analyses were performed considering those recorded as 'N' drugs only (Section 3.1.3.5.1) unless where explained otherwise. It was considered that newly prescribed drugs would be a more realistic measurement of the GPs' prescribing practice, uninfluenced by hospitals or previous prescriptions as other researchers have suggested.[260] In order to assess whether the range of items prescribed would be reduced by the educational intervention in certain situations, the absolute range of items prescribed was quoted.

3.1.3.10 Content, development and dissemination of the educational intervention

The trial sought to evaluate the effect of the European Formulary and the intervention exercise in the areas of antibiotics; non-steroidal anti-inflammatory drugs (NSAIDs); and the prescribing of drugs of limited proven clinical value. Rational prescribing of these three groups of drugs was thus to form the basis of the educational intervention and to be delivered to the study group GP participants prior to the data recording of Phase II.

In 1995, at the annual weekend meeting of the co-ordinators (Section 3.1), time was spent finalising the plans for the dissemination of the European Formulary to the GPs and discussion also took place on what advice and instruction should be given by co-ordinators to the GPs. It was agreed that the co-ordinator in each country would be responsible for delivering this educational package and it was recognised that the intervention protocol needed to be standardised so that the procedure could be carried

out as consistently as possible in each country. Although the content of the educational intervention was standardised, the style of its administration would obviously vary from co-ordinator to co-ordinator in each country and this could not be controlled.

It was decided that the European Formulary along with appropriate sections of the more detailed Appendix would be disseminated to the doctors in the intervention group at the beginning of the autumn of 1995, approximately two weeks before the date of a predetermined meeting. The GPs would receive their copies together with some clear and concise messages offering guidance on rational prescribing in each of the three therapeutic areas being targeted. It was anticipated that the GPs would consider these messages and discuss them at the scheduled meeting. It was also felt that this approach would increase the doctors' commitment to attend.

3.1.3.10.1 NSAIDs - main messages[261,262]

- Critical assessment of the use of NSAIDs is needed particularly where minor or self-limiting ailments present, for example sprains and strains. If drug intervention is required, simple analgesics should initially be used.
- NSAID use in elderly patients with osteoarthritis should be minimised.
- The duration of NSAID therapy should be limited when possible.
- Particular attention should be made to the effects of NSAIDs on elderly patients and the lowest effective dose used.
- NSAIDs with a long half-life, for example the oxicams, tend to be associated with more severe side effects and consequently their use should be discouraged, especially in the elderly.
- Special caution is required in prescribing NSAIDs for patients with a history of asthma, gastro-intestinal complications especially ulcers, renal problems, inflammatory bowel or diverticular disease and with concomitant intake of aspirin, diuretics, ACE inhibitors and steroids.
- Where a topical formulation is required a rubefacient should be used as evidence implies that topical NSAIDs are not cost-effective.

- GPs should prescribe from a small range of NSAIDs.
- The European Formulary Group (EFG) recommends that simple analgesics should be used where possible before NSAIDs. Where NSAIDs are indicated the EFG recommends:

  first-line - ibuprofen

  second-line - diclofenac or naproxen

  third-line - indomethacin

  These drugs are predominantly the most effective, safe and economical NSAIDs as supported by evidence from the Committee of Safety of Medicines (CSM) in the UK.[263]

3.1.3.10.2 Antibiotics - main messages[261,262]

Antibiotic prescribing covers the treatment of a vast range of infections and so it was decided to target the management of urinary tract infections (UTIs) and infections associated with the respiratory tract. In all common infections, first line use of third generation broad spectrum cephalosporins, fluoroquinolones and the new macrolides should be avoided or strictly limited. They are relatively expensive and unjustified use increases the likelihood of microbial resistance.

<u>Urinary tract infections</u>

- UTIs are more common in women and present as either lower or upper types.
- Urine cultures should always be taken in men with lower UTIs because of possible complications and treatment duration should be 7-10 days.
- In women with single cases of uncomplicated lower UTIs, culture is not usually necessary but care needs to be taken such as urinating after sexual intercourse to prevent the ascent of the infection.
- Upper UTIs may coexist with lower UTIs and if a 3 day antibiotic course is ineffective then a renal infection should be suspected.
- In case of the latter, an early start of effective drug therapy is important,

especially in children. Hospitalisation and parenteral therapy may be needed.

- Asymptomatic bacteriuria should be treated in pregnant women and children.
- The EFG recommends UTI treatment with: trimethoprim or amoxycillin. Where these drugs fail or are contraindicated then norfloxacin or consistent prescribing of an alternative quinolone depending on availability and comparative cost per country is recommended.

Upper respiratory tract related infections

The upper respiratory tract related conditions covered by the Formulary include acute otitis media, acute pharyngitis / tonsillitis and acute sinusitis. For the purposes of this thesis we only investigated prescribing for acute pharyngitis / tonsillitis.

Acute pharyngitis / tonsillitis

- These conditions are very common, usually viral in origin and can therefore normally be treated adequately with paracetamol.
- Delaying treatment to await the results of culture samples does not increase the risk of complications.
- When a swab confirms a bacterial infection, phenoxymethylpenicillin (penicillin V) is the drug of choice or alternatively erythromycin (beware of interactions) for patients allergic to penicillin.
- The drugs recommended by the EFG are phenoxymethylpenicillin, erythromycin and paracetamol.

Lower respiratory tract infections

- Prescribing of antibiotics for acute bronchitis is almost always irrational.
- Prescribing of antibiotics to treat acute exacerbations of chronic bronchitis is more acceptable although still controversial.
- Previously well children and adults with pneumonia usually recover well with a prescription for a penicillin or erythromycin but beware of interactions with

the latter.

- Rare pathogens should be suspected in patients at risk from pre-existing conditions and hospitalisation may have to be considered.
- GPs should prescribe from a small range of antibiotics.
- The four drugs recommended by the EFG are:

amoxycillin, benzylpenicillin, doxycycline and erythromycin.

3.1.3.10.3 Limited perceived clinical value drugs - main messages

This group could potentially include many different drugs; however, this area of prescribing is controversial and there are also legal implications of labelling drugs as of 'little value'. Consequently, for the purposes of the intervention it was agreed that: cerebro-active drugs; vitamins; tonics and appetite suppressants would be the drugs targeted and discouraged from prescribing. This area of prescribing is not presented or discussed in this thesis.

3.1.3.11 Selection of the prescribing data analysed in the thesis

The data analysed from the main prescribing study in this thesis are divided into three sections. The first section compares general features of the data in terms of the numbers of participating GPs in the different countries, patient characteristics, prescription details, overall concordance with the European Formulary and the most commonly presenting diagnoses and drugs used. The second one investigates the main areas of prescribing targeted in the educational intervention namely antibiotics and NSAIDs but excludes drugs of limited clinical value. The third section considers prescribing patterns for hypertension and asthma, two areas covered by the European Formulary but not targeted in the educational intervention.

Of the drug groups targeted in the educational intervention, the BIOMED study analyses fundamentally focused on whether overall prescribing patterns in these areas showed changes towards the drugs recommended in the European Formulary. These analyses were limited in that there was no linking or matching of drugs prescribed to diagnoses and therefore as well as not revealing which drugs were being prescribed for which conditions, it could not be inferred whether prescribing of the recommended

drugs was appropriate or even necessary. For example, prescribing of broad spectrum antibiotics such as tetracyclines were discouraged when acute pharyngitis or tonsillitis presents but as a result of tetracyclines being recommended in the European Formulary for other conditions, their inappropriate use could artificially bias concordance levels unless analyses were performed linking drugs to diagnoses. By extracting the prescribing data, linking drugs to their appropriate indications in the European Formulary, the results presented in this thesis give a more detailed accurate and meaningful comparison and evaluation of prescribing patterns.

Exploring prescribing patterns for conditions included in the European Formulary but not targeted by the educational intervention enabled one to determine how successful the dissemination of written prescribing recommendations alone were in improving prescribing. Hypertension and asthma therefore were primarily selected because of their common occurrence in the study; they were the first and sixth most frequently occurring diagnoses respectively. As well as it being logical to analyse areas where data would be most abundant, hypertension and asthma are distinct diagnoses as opposed to those symptoms, although both present with different levels of severity which could not be reliably investigated. The results are presented in Chapters 4, 5 and 6.

3.2 INTRODUCTION TO THE PRESCRIBING INFLUENCES STUDY

The prescribing data from the European Formulary project presented in Chapters 3, 4 and 5 have indicated that there are wide variations in drug utilization by GPs between the participating countries. It was postulated that additional knowledge of the factors influencing the GP participants prescribing could contribute to a more rigorous interpretation of these data. From reviewing the literature of the factors influencing prescribing (Section 2.2), no previous study appears to have attempted to ask a pan European group of GPs to rate the importance of what they perceive to have influenced their individual prescribing.

3.2.1 AIMS

3.2.1.1 Main aims

- To identify what the main factors are that GPs perceive to influence their prescribing in the different countries.
- To compare the demographic profiles and working environment of the sample of GPs from the eight European countries.

3.2.1.2 Subsidiary aims

- To enable separation of the reported influences into different categories.
- To obtain a consensus-based list of influences ranked in order of perceived importance.
- To consider how environmental and personal characteristics could contribute to variations in prescribing behaviour.

3.2.2 Pilot study

The questionnaire evolved from one initially designed and piloted in the summer of 1996 among twenty members of the Department of Primary Health Care in Newcastle upon Tyne. The twenty participants had a variety of medical and non-medical backgrounds and all were engaged in research at the time. Shortly afterwards in November 1996 a revised questionnaire was further piloted among 27 GPs from the Newcastle area who had participated in the European Formulary Project. Of the Newcastle GPs, 26 responded and feedback from this exercise resulted in further amendments being made to the questionnaire.

No ethical committee approval was felt to be required for this study to proceed.

3.2.3 Subject sample

The questionnaires were circulated to 241 GP participants from eight countries who had participated in the main controlled trial investigating the effect of a European Formulary as part of an educational intervention. This sample differed slightly from the 236 GPs whose data was utilised in the main prescribing study in that seven additional GPs from Belgium (five Flemish speaking and two French speaking) whose earlier prescribing data could not be analysed were also included. One English and one Spanish GP who dropped out of the study between Phases I and II were excluded as they changed locations and were not traced.

3.2.4 Questionnaire number one

A short questionnaire was developed consisting of 13 questions (Annex 6). Twelve were simple 'tick box' or 'one word answer' style questions on demographic details and the working environment of the doctor. Question number 13 was in the form of an 'open' style question. The length of the questionnaire was limited to fit one side of A4 paper in order to optimise the response rate. The final question was formed to generate a staged Delphi study.[264] The Delphi design technique is an approach in which participants respond to open question(s) by generating ideas that are subsequently used to form the basis of the questions for later qualitative rounds.

Translations of questionnaire stage one into the appropriate languages, namely Dutch, French, Italian, Spanish, and Portuguese, were performed by pharmacists or doctors independent of the project from each of the non-English speaking countries. In addition, a standard letter for distribution with the questionnaire to each of the participating GPs (Annex 7) was translated by each of the countries' co-ordinators.

3.2.5 Questionnaire number two

After distribution and return of the completed stage one questionnaires, perceived influences generated by the GPs in response to question 13, the 'open' style question, formed the basis of the second questionnaire (stage two). Prior to the dissemination of the second questionnaire (Annex 8), all the responses received from the open ended question 13 were separated into different categories or themes of likely influences (Annex 9). In this second round, the GPs were presented with a list of all the perceived influences of the GP participants under category headings and asked to rank the categories in order of decreasing importance which he/she believed to have acted on their personal prescribing since the autumn of 1994. As previously, with the help of the co-ordinators the necessary translations were obtained as appropriate, including a standard letter for distribution with the questionnaire to each of the participating GPs (Annex 10).

3.2.6 Validation process

In order to validate the questionnaires as part of a quality control procedure, each co-ordinator was sent the translation of Questionnaire number one (independently obtained) sealed in an envelope with a copy of an English version in a separate envelope. Each co-ordinator was asked to back translate the translated questionnaire, before comparing this with the English version. The co-ordinators were asked to translate the stage two questionnaire which was much simpler; consequently, from the experience gained, it was considered that no back-translation was necessary.

3.2.7 Mailing schedule

The addresses of the GP participants in the different countries were requested and obtained from the co-ordinators which enabled control of the distribution of the questionnaires from Newcastle upon Tyne. This was necessary so that by mailing questionnaires to GP participants furthest away from Newcastle in a staggered process, this would facilitate their arrival at all destinations on a similar time scale.

Both Questionnaires numbers one and two were mailed with an International Reply Paid Coupon to GPs outside the UK and with Reply Paid Envelopes enclosed to GPs within the UK. At the bottom of each questionnaire there was a GP identity number which was used to identify the original questionnaire upon its return. With the Delphi approach, it is recommended that subsequent rounds of questionnaires need to be sent out at fairly precise six weekly intervals.[264] However, due to the geographical distance over which the exercise was taking place, extra time had to be allocated for both the outward and return postage time as well as for the follow-up reminder questionnaires. In order to attempt to achieve a response rate in excess of 60%, one follow-up reminder questionnaire to all non-responders was distributed in the first round which resulted in an interval of approximately five months between staged Questionnaire number one and Questionnaire number two being sent out. In the second round two follow-ups were necessary and non-responders to Questionnaire number one were sent both questionnaires.

As an added incentive for the GPs to respond, a six page summary was included with Questionnaire number one, based on the final report sent to the BIOMED sponsors upon termination of the funding for the European Formulary project. In addition, the GPs were offered feedback from the final results of the two-stage Delphi questionnaire study upon completion of the research. Finally, it was stressed to all the GPs that the contents of their questionnaires would remain anonymous.

3.2.8 Data entry and analysis

The data in this questionnaire study was managed in Access for Windows 95 Version 7.0. Tables called QUESTIONNAIRE 1 DATA and QUESTIONNAIRE 2 DATA were created to hold all the information from Questionnaires number one and

two upon their return in various fields. All information collected from each returned questionnaire was coded prior to entry into the database tables as necessary. All the codes were numerical; for example, 'yes' and 'no' were substituted with '1' and '2' respectively. The Access program also enabled address labels to be prepared and by creating a 'Returned Questionnaire' field in the database, non-respondents could be easily identified in order to send out reminder questionnaires.

The data, once entered into the database tables were analysed using a series of queries (questions about data stored in tables). Once the data were entered into the database, 'queries' were designed and run to retrieve certain information for the necessary comparisons to be made, for example all GPs from a certain country.

For Questionnaire number two, each response was weighted such that a category of influence positioned in first place (i.e. representing the most influence), received a score of seven, a category in second place received a score of six and so on until the category of least importance received a score of one.[265] All categories were scored as it is assumed that they all have some degree of influence irrespective of whether acknowledged by the GP participants from each country. The results are presented in Chapter 7.

CHAPTER FOUR
PRESCRIBING STUDY
GENERAL COMPARATIVE RESULTS

4.1 NUMBERS OF PARTICIPATING GPs

In total there were 236 doctors who participated in the prescribing study with 217 valid matching pairs of GP data sets from Phase I and Phase II (Table 4.1). Of these, there were 116 study and 101 control GP pairs. The target of recruiting 40 GPs was only achieved in Italy and Scotland in Phase I.

4.2 PATIENT CHARACTERISTICS

4.2.1 Numbers of patients consulting

Data were recorded on **101,544** doctor-patient consultations in this study. Statistically significant differences were found between the countries ($p < 0.001$) in the number of patients consulting but not between the control and study groups within countries ($p = 0.80$) (Table 4.2). There were found to be no statistically significant differences ($p = 0.08$) between Phases I and II in the number of patients who consulted. Overall there was an average increase of 6 patients per GP (3.34). After the educational intervention, the differences between the control and study groups were not significant either ($p = 0.67$).

In Belgium, data was not provided on patients who consulted without receiving a prescription, therefore only approximately 200 patients were seen on average (Table 4.2). There were slight variations in the numbers within each of the subgroups (Phase I/II control/intervention groups) though, which was due to factors such as the prescription data including patients receiving vaccines during consultations. Many of the GP participants recorded patients receiving vaccines as a form of treatment but for the purposes of this study they were not included in the coding of the drug data.

The Portuguese GPs did provide data on patients who consulted without receiving a prescription but most GPs there, failed to reach the target of 200 patients who received prescriptions.

The data from England, Northern Ireland and Scotland showed a similar trend with the highest numbers of patients being recorded in these regions. This is indicative of a lower prescribing rate in the UK than in the other participating countries.

4.2.2 Gender profiles of patient consultations

The differences in the proportion of consultations for male patients between countries were found to be highly significant ($p < 0.001$) in both Phase I and II but there were no significant differences within countries or between Phases (Table 4.3). Differences in the proportion of male consultations between the control and study groups after the intervention were also not statistically significant ($p = 0.66$). There were highly significant differences in gender between countries ($p < 0.001$) but not between control and study groups ($p = 0.08$).

In all of the countries, the proportions of males consulting were below the 50% level, indicating that the majority of consultations were for females. In Belgium, the proportion of consultations for males was much closer to females compared with any other country.

4.2.3 Age profiles of patient consultations

The average patient age in Phase I was 45.9 years (0.09) compared with 45.1 years in Phase II (0.11). Although this difference in age only represents approximately 10 months, this was statistically significant ($p = 0.02$). The average age of patient in the study group overall was 44.9 years (0.1) compared with 46.2 years (0.1) in the control group. This difference in age was of borderline statistical significance ($p = 0.04$).

4.3 PRESCRIPTION DETAILS

4.3.1 Proportion of consultations resulting in a prescription

Highly significant differences were found between the countries ($p < 0.001$) but not within countries in the proportion of consultations resulting in a prescription (Table 4.4). Between Phases I and II, there were found to be statistically significant differences ($p = 0.03$) in the proportion of patients consulting who received prescriptions with an

average decrease of 2% (0.8) per GP. Differences between the control and study groups after the intervention were not significant ($p = 0.45$).

A higher proportion of patients received prescriptions in all the southern European countries compared with the English speaking countries. England was the only country where there was a notable increase in the number of consultations resulting in prescriptions within the study group after the intervention. Although this was contrary to one of the objectives of the intervention exercise, this difference was not statistically significant ($p = 0.71$).

4.3.2 Categories of prescriptions

Overall 42% (1) and 41% (1.1) of prescribing were N drugs in Phase I and Phase II respectively (Table 4.5). Category A prescriptions accounted for 11% (0.7) and 10% (0.6) of drug items in Phase I and Phase II respectively. Drugs prescribed by repeat prescription accounted for 37% (1) and 38% (1) of items and hospital/specialist prescribed drugs accounted for 9.1% (0.7) and 9.2 % (0.6) of all drugs prescribed for in Phase I and Phase II respectively.

There was a high level of consistency in prescribing patterns within the countries from Phases I to II. For category A drugs, the lowest levels were found in the control and study groups of Italy and the highest levels were found in England and Scotland for both Phases. England, Scotland and Northern Ireland had similarly low patterns of hospital/specialist initiated prescribing, in contrast to approximately one in four prescriptions in Spain fitting into this category. For newly prescribed items, the highest levels were found in Northern Ireland for both Phases and these were double those of Spain which consistently had the lowest levels of new prescriptions. Relatively high levels of repeat scripts were found in all countries

4.3.3 Number and range of drug entities prescribed

There were highly significant differences between countries in both the number and the range of drugs prescribed ($p < 0.001$) excluding the Spanish data from the analyses (Table 4.6 and Table 4.7). There were also highly significant differences ($p < 0.001$) between Phases with respect to both the number and the range of drugs used. Exclusion

of the Portuguese data from this analysis removed these statistical differences. After the intervention there was an average decrease of 29 drugs in the study group overall compared with a decrease of 21 drugs in the control group and this difference was statistically significant ($p < 0.001$). With respect to the range, there was an average decrease in 12 drugs prescribed by the study group overall compared with only a fraction of a decrease by the control group after the intervention and this difference was also highly significant ($p < 0.001$).

The lowest number of drugs were prescribed in England, Scotland and Portugal but in the latter there was a lower volume of doctor-patient consultation data recorded and so one would expect a lower average number of drug entities prescribed there. The smallest ranges of drug entities prescribed were in England, Northern Ireland and Scotland. The largest range of drugs were found to be prescribed in Spain and despite only half the number of patient consultations being recorded by the Spanish GPs in Phase II, the average range of drugs remained relatively high.

4.4 FORMULARY CONCORDANCE

4.4.1 Drug concordance with the European Formulary

Highly significant ($p < 0.001$) differences were found between countries in the variation in percentage of drug concordance with the European Formulary (Table 4.8). Overall in Phase I the level of concordance was 47.8% compared with 46.5% in Phase II and this difference was of borderline statistical significance ($p = 0.06$).

For all data combined, there was a 2.9% (0.7) increase in the proportion of prescribed drugs which were listed in the European Formulary for the study group compared to a reduction of 1.3% (0.6) in the control group. This difference was highly significant ($p < 0.001$). There appeared to be notable increases in the prescribing of Formulary recommended drugs after the intervention in the study groups of Belgium, Italy, Northern Ireland and Portugal compared with their corresponding control groups. These differences were highly significant ($p < 0.001$) in Italy and Portugal. In general the highest levels of Formulary concordance were found in England averaging about 60% in each of the subsets, followed by Scotland. The lowest level of Formulary

concordance was found in Portugal, where approximately one in three drugs prescribed was listed within the Formulary.

4.4.2 Diagnosis concordance with the European Formulary

Highly significant differences ($p < 0.001$) were found between countries in the proportions of diagnosis presentations covered by the European Formulary (Table 4.9). No statistically significant differences were found between Phase I and II ($p = 0.37$).

Overall, the difference between the slightly higher proportion of diagnoses being covered by the Formulary in the study group compared with the control group after the intervention was not statistically significant ($p = 0.26$). The greatest increase in presenting diagnoses covered by the Formulary in the study group compared with the control group was in Belgium but this difference was not statistically significant ($p = 0.17$). In general, the management of presenting patient diagnoses in the Mediterranean countries, especially in Portugal, appeared to be covered to a greater extent by the European Formulary than in the other countries.

4.5 MOST COMMON PRESENTING DIAGNOSES AND DRUGS USED

4.5.1 Top ten Formulary and non-Formulary drugs

Amoxycillin was the single most commonly prescribed drug overall from the prescribing data and the only antibiotic to feature in the top ten Formulary listed drugs (Table 4.10). Paracetamol was the second most commonly prescribed single component drug but its use in both combination and non-combination form combined would have made it the most commonly prescribed drug overall. Of the top ten most commonly prescribed Formulary drugs, four were indicated for cardiovascular related conditions and three represented pain/anti-inflammatory use.

Co-amoxiclav was the most commonly prescribed non-Formulary recommended drug and one of two antibiotics to feature in the list of the top ten of these. When comparing co-amoxiclav and amoxycillin use it can be seen that the latter was consistently the antibiotic of choice compared with co-amoxiclav in all the countries.

Three of the top ten non-Formulary recommended agents were combination drugs, generally discouraged by the European Formulary.

Overall the volume in terms of number of prescribed items that the top ten Formulary recommended drugs represented was approximately three times the use of the top ten non-Formulary agents

4.5.2 Top ten Formulary and non-Formulary diagnoses

Hypertension, whose management was covered by the European Formulary was the most commonly occurring diagnosis overall and the number one condition in all the countries except for England and Northern Ireland (Table 4.11). The top ten most commonly presenting diagnoses covered by the Formulary accounted for almost one third of the total patient diagnoses. In contrast the top ten most commonly presenting patient diagnoses not covered by the Formulary represented approximately 13% of conditions. The most commonly presenting non-Formulary diagnosis was low back pain.

4.6 DISCUSSION

Of the GPs participating in the study, dropouts were only a slight problem in the control group of Phase II. The main reason for this was probably due to the fact that these GPs did not have the added incentive of receiving the European Formulary and participating in the educational intervention.

All the data collected from the different countries were comparable with two exceptions. Firstly the Belgian GPs did not provide details of consultations not resulting in a prescription and the Spanish GPs only agreed to participate in Phase II if they recorded approximately 50% the number of consultations recorded in Phase I. Therefore where appropriate these two data sets were excluded from certain analyses.

For the patient characteristics, there was found to be a highly significant difference in age between Phases. Whilst this may appear to be problematic with respect to potentially interfering with the results in this study, there is no clinically significant difference in prescribing for an age of 45.9 years compared with 45.1 years. Statistically significant differences are more likely to occur with larger sample sizes

associated with large denominators, for example in this analysis there were 52,389 patients in Phase I and 45,481 patients in Phase II. Therefore these statistically significant differences neither affected the analyses nor the conclusions.

Comparing the prescribing patterns between countries, it was found that a higher proportion of patients received prescriptions in all the southern European countries compared with the UK. The proportion of patients receiving prescriptions in Ireland fell in the middle. This compares fairly well with international health statistics data which found that of the countries participating in this study, that the UK had the lowest number of prescription items per person followed by (Belgium), Ireland, Spain, Portugal and then Italy.[250]

Category of prescription (N, A, R or H) is problematic in interpretation. While 'N' drugs are clearly defined, many drugs which were recorded as repeats would have originally been initiated by hospital doctors, for example insulin. Therefore the results recorded in this study for hospital/specialist prescriptions do not reflect all hospital initiated prescribing and are generally lower than others have reported.[30] Spain recorded the highest 'H' prescription rates which may be as a result of the combination of short consultations and high referral rates seen in primary care in that country.[266] However this is conjecture. Also the study recorded lower numbers of 'R' prescriptions than others have found[30] but this is a reflection of the fact that data were recorded of prescriptions issued from face-to-face doctor-patient consultations only.

The study showed that there was a significant reduction in the range of drugs prescribed after the educational intervention. Spain recorded the highest average range followed by the other southern European countries and Belgium. This could be due to a higher number of drugs available on the market in these regions compared with the UK and Ireland, thus allowing more choice.[16]

Drug concordance with the European Formulary was between 33 and 60% which was considerably lower than the aim to cover 90% of the treatment. The drug concordance levels are also likely to be artificially high as the analysis did not take into account whether the listed drugs were being prescribed appropriately for their recommended indications. The proportions of diagnoses presentations covered by the

European Formulary were also considerably lower than its aim to cover 90% of the conditions seen by GPs. Despite this their levels were notably higher than the drug concordance levels.

A comparison of the top ten Formulary and non-Formulary recommended drugs indicated that the bulk of prescribing is represented by a small number of drugs and the most commonly used drugs were those listed in the European Formulary. Of the top ten non-Formulary drugs, a future European Formulary would need to consider whether to include the likes of ranitidine, bendrofluazide, flucloxacillin and betamethasone. Although the list of top 10 non-Formulary drugs did include what could be perceived as unnecessarily high use of certain ones such as co-proxamol, lorazepam and piroxicam..

For the top ten Formulary diagnoses, it can be seen that they represented the majority of diagnosis presentations. Of the top ten non-Formulary diagnoses, six of these conditions (low back pain, URTI, ischaemic heart disease, bronchitis, chronic bronchitis, and respiratory tract infection) could be described as 'half way house' diagnoses (Section 3.1.3.6). These 'half way house' diagnoses were not explicitly listed in the Formulary but ones which could be interpreted as implicitly being included under the management of related conditions. This also highlights that there were problems in the way this information was recorded. For example, the European Formulary discusses lower respiratory tract infections which includes acute bronchitis but many GPs just recorded a diagnosis of bronchitis without specifying whether this was acute or chronic. Inclusion of these half-way house diagnoses to the list of Formulary conditions may have increased the proportions of presenting diagnoses covered by the Formulary levels to around the 75% mark.

Table 4.1 Number of participating doctors by country in Phases I and II

Country	Phase I	Phase II	Completed data sets (study, control)
Belgium	10	10	10 (5, 5)
England	27	26	26 (13, 13)
Ireland	35	32	32 (18, 14)
Italy	40	35	35 (18, 17)
N. Ireland	13	12	12 (7, 5)
Portugal	39	39	38 * (19, 19)
Scotland	40	34	34 (22, 12)
Spain	31	30	30 (14, 16)

* Portugal recruited an additional GP for Phase II, while there was one dropout from Phase I

Table 4.2 Average number (SEM) of patient consultations recorded for each control and study group in Phases I & II

Country	Phase I		Phase II		Phase II - Phase I	
	Study	Control	Study	Control	Study	Control
Belgium	193 (7.5)	199 (0.5)	174 (16)	200 (1.4)	**-19 (14)**	-0.8 (1.5)
England	279 (22)	263 (22)	287 (17)	277 (15)	**+8.2 (15)**	-9.9 (18)
Ireland	239 (8)	246 (9.2)	254 (12)	248 (8.8)	**+14 (10)**	+1.7 (7.9)
Italy	226 (5.3)	242 (8.3)	232 (5.2)	247 (11)	**+5.7 (5.8)**	+4.5 (11)
N. Ireland	259 (16)	280 (7)	276 (21)	285 (7.6)	**+17 (18)**	+5 (11)
Portugal	120 (7.8)	141 (8)	135 (9.3)	155 (11)	**+15 (10)**	+14 (9.6)
Scotland	292 (19)	278 (15)	293 (15)	265 (11)	**+0.7 (15)**	-13 (8.4)
Spain *	226 (5.1)	217 (5.6)	123 (2.8)	110 (2.4)	**-103 (5.8)**	-107 (4.8)
Total	230 (8)	229 (7.4)	238 (7.5)	233 (6.7)	**+7.7 (4.9)**	+3.7 (4.5)

* The Spanish data was excluded from this analysis as the number of prescriptions recorded by GPs was halved in Phase II

Table 4.3 Average percentage (SEM) of male patients per GP for each control and study group in Phases I and II

Country	Phase I		Phase II		Phase II - Phase I	
	Study	Control	Study	Control	Study	Control
Belgium	44 (2.2)	41 (2.4)	47 (1.5)	44 (2.7)	**+3.3 (2)**	+2.4 (1.5)
England	40 (3.1)	34 (2.9)	40 (2.6)	37 (3.1)	**-0.5 (1.2)**	+2.4 (1)
Ireland	38 (1.3)	40 (0.9)	40 (1.6)	42 (0.9)	**+1.9 (0.9)**	+2.2 (1.1)
Italy	39 (1.1)	40 (1.3)	38 (0.7)	40 (1.6)	**-0.6 (1.3)**	0.2 (1.5)
N. Ireland	41 (2.7)	37 (4.6)	42 (3.1)	41 (4.5)	**+1 (1.4)**	+3.9 (1.1)
Portugal	32 (1.2)	39 (1.3)	33 (1.2)	39 (1)	**+1.3 (1.5)**	-0.05 (1.8)
Scotland	37 (2.7)	40 (1.9)	38 (2.6)	40 (2.3)	**+1.2 (2.2)**	-0.1 (1.3)
Spain	42 (1.1)	41 (1.1)	43 (0.8)	40 (0.9)	**+0.7 (1.7)**	-0.3 (1.2)
Total	**38 (0.8)**	**39 (0.7)**	**39 (0.8)**	**40 (0.7)**	**+0.8 (0.6)**	**+0.5 (5.3)**

Table 4.4 Average percentage (SEM) of consultations resulting in a prescription for each control and study group in Phases I & II

Country	Phase I		Phase II		Phase II - Phase I	
	Study	Control	Study	Control	Study	Control
Belgium *	99 (0.6)	97 (1.6)	100 (0.1)	97 (2)	**+0.7 (0.8)**	-0.03 (0.7)
England	69 (4.2)	69 (3.6)	72 (4.3)	66 (1.4)	**+2.2 (3.3)**	-3 (3.9)
Ireland	83 (2.8)	81 (2.6)	79 (3.2)	81 (2.8)	**-4.5 (2.9)**	-0.4 (2.3)
Italy	88 (2)	82 (3.1)	85 (1.9)	83 (3.4)	**-3.2 (2.3)**	+1.5 (3.4)
N. Ireland	78 (4.7)	71 (1.7)	72 (4.2)	70 (1.7)	**-6.4 (5.1)**	-1.4 (2.5)
Portugal	86 (2.3)	95 (1.7)	86 (2.9)	88 (2.6)	**-0.1 (2.3)**	-7.2 (3)
Scotland	68 (3.1)	73 (3.6)	68 (3.1)	75 (2.9)	**+0.6 (3.1)**	+2.1 (1.5)
Spain	88 (2.1)	91 (2)	81 (1.8)	91 (2)	**-6.3 (2.6)**	-0.1 (2.2)
Total	80 (1.3)	82 (1.4)	78 (1.3)	81 (1.3)	**-2.1 (1.1)**	-1.4 (1.1)

* The Belgian data was excluded from this analysis as patient consultations that did not result in a prescription were not recorded

Table 4.5 Average percentage (SEM) of all prescriptions by category

Phase I					
Region	Group	**Category of Prescription**			
		A	**H**	**R**	**N**
Belgium	Study	10 (4.4)	8 (2.2)	43 (5.3)	39 (3.8)
	Control	6 (3.8)	5 (3.4)	39 (6.6)	50 (7.4)
England	Study	20 (2.3)	3 (0.9)	26 (3.2)	51 (2.7)
	Control	20 (4.7)	2 (0.8)	34 (4.9)	44 (4.7)
Ireland	Study	10 (2.9)	5 (1.3)	34 (3.4)	52 (3.3)
	Control	11 (1.6)	7 (2)	42 (2)	40 (2.1)
Italy	Study	4 (1.1)	9 (1.3)	45 (2.8)	42 (2.2)
	Control	5 (1.4)	11 (1.1)	50 (2.7)	35 (2.5)
N. Ireland	Study	10 (2.2)	3 (1.2)	27 (2.6)	59 (3.1)
	Control	14 (5.7)	5 (1.3)	31 (6.8)	50 (2.4)
Portugal	Study	6 (1.1)	16 (2.5)	48 (2.6)	30 (2.8)
	Control	6 (2)	9 (1.5)	37 (3.8)	49 (4.8)
Scotland	Study	20 (2.4)	3 (0.5)	28 (3.3)	49 (2.6)
	Control	16 (3.3)	2 (0.6)	33 (3.8)	50 (2.2)
Spain	Study	6 (1.1)	31 (2.1)	38 (2)	25 (1.6)
	Control	12 (1.6)	21 (3.2)	38 (4.1)	29 (1.9)
Phase II					
Region	Group	**Category of Prescription**			
		A	**H**	**R**	**N**
Belgium	Study	10 (4.8)	10 (3.8)	41 (5.6)	39 (2.2)
	Control	9 (4.1)	6 (3.9)	37 (6)	48 (6.5)
England	Study	18 (2.3)	5 (1.2)	27 (2.4)	50 (1.9)
	Control	12 (3)	4 (1.1)	39 (4)	45 (3.5)
Ireland	Study	9 (2.3)	6 (1)	29 (3.2)	57 (2.9)
	Control	9 (1.5)	10 (2)	36 (2.1)	46 (2.3)
Italy	Study	5 (1.2)	8 (1.3)	49 (3.3)	37 (2.7)
	Control	5 (1.6)	11 (1.2)	49 (2.9)	34 (3.8)
N. Ireland	Study	13 (2.9)	3 (1.5)	27 (2.1)	57 (4.4)
	Control	12 (3.9)	4 (1.4)	30 (4.1)	53 (4.6)
Portugal	Study	8 (1.7)	17 (2.7)	45 (2.5)	30 (3.2)
	Control	6 (1.8)	8 (1.4)	41 (2.6)	45 (3)
Scotland	Study	16 (2.5)	4 (0.8)	31 (3.3)	49 (2.5)
	Control	15 (3.3)	1 (0.3)	32 (3.8)	52 (2.4)
Spain	Study	7 (1.9)	26 (2.8)	44 (3.6)	23 (2.2)
	Control	8 (2.3)	20 (3)	49 (4.6)	24 (2)

Table 4.6 Average number (SEM) of drug entities prescribed by country

Country	Phase I		Phase II		Phase II - Phase I	
	Study	Control	Study	Control	Study	Control
Belgium	425 (19)	353 (20)	357 (53)	320 (9.4)	**-67 (35)**	-33 (13)
England	288 (9.2)	291 (21)	310 (9.2)	293 (22)	**+23 (13)**	+2.5 (22)
Ireland	319 (10)	345 (15)	294 (14)	313 (17)	**-24 (13)**	-33 (12)
Italy	320 (16)	315 (14)	318 (12)	327 (12)	**-1.9 (11)**	+12 (17)
N. Ireland	305 (29)	299 (17)	314 (27)	315 (14)	**+9.3 (18)**	+16 (11)
Portugal	286 (22)	263 (14)	265 (13)	315 (19)	**-22 (26)**	+53 (23)
Scotland	280 (14)	308 (13)	289 (10)	317 (18)	**+9.1 (8.1)**	+8.8 (12)
Spain *	420 (16)	398 (16)	227 (8.3)	213 (7.8)	**-193 (18)**	-185 (13)
Total	319 (7.4)	320 (7.2)	290 (5.7)	298 (6.9)	**-29 (8.4)**	-21 (10)

* The number of prescriptions recorded by the Spanish doctors was halved in Phase II

Table 4.7 Average range (SEM) of drug entities prescribed by country

Country	Phase I		Phase II		Phase II - Phase I	
	Study	Control	Study	Control	Study	Control
Belgium	160 (5.5)	135 (7)	138 (15)	134 (5.4)	**-22 (15)**	-0.8 (5.3)
England	109 (2.9)	108 (5.8)	114 (3.1)	108 (5.3)	**+5.9 (3)**	+0.2 (7.1)
Ireland	121 (4)	129 (5.1)	111 (5.8)	124 (4.2)	**-10 (5.3)**	-5.2 (4.6)
Italy	143 (7.3)	137 (5.1)	132 (6.5)	133 (5.4)	**-11 (5.1)**	-3.1 (7.6)
N. Ireland	118 (8)	118 (3.9)	119 (9.7)	118 (6.5)	**+0.4 (9.5)**	+0.6 (6.6)
Portugal	140 (5)	94 (12.4)	123 (6.3)	139 (6.3)	**-17 (7.5)**	+45 (13)
Scotland	106 (4.5)	115 (4.5)	109 (2.9)	115 (3.9)	**+2.7 (3.4)**	+0.1 (5.5)
Spain *	168 (7.1)	158 (5.1)	119 (3.6)	112 (4.2)	**-49 (7.3)**	-46 (5.1)
Total	131 (2.8)	124 (3.5)	119 (2.1)	124 (2.2)	**-12 (2.6)**	-0.09 (4.1)

* The number of prescriptions recorded by the Spanish doctors was halved in Phase II

Table 4.8: Average percentage (SEM) of drugs prescribed contained within the European Formulary within each country

Country	Phase I				Phase II				Phase II - Phase I	
n = total N^0 drug entities	Study *n*	Study % (SEM)	Control *n*	Control % (SEM)	Study *n*	Study % (SEM)	Control *n*	Control % (SEM)	STUDY % (SEM)	CONTROL % (SEM)
Belgium	2,127	37 (1)	1,766	40 (1.5)	1,784	46 (9.2)	1,601	39 (3.6)	**+9.1 (8.6)**	-1.2 (3.1)
England	3,738	59 (1.7)	3,781	60 (1.4)	4,034	60 (1.3)	3,813	59 (1.1)	**+0.7 (1.7)**	-1.3 (1.8)
Ireland	5,742	51 (1.5)	4,834	53 (1.5)	5,299	52 (1.7)	4,375	54 (1.3)	**+1 (1.2)**	+1.6 (1.2)
Italy	5,761	40 (1.2)	5,354	45 (1.8)	5,726	46 (1.5)	5,556	43 (1.5)	**+6.4 (1.3)**	-1.7 (1.1)
N Ireland	2,136	51 (2.6)	1,494	49 (1.9)	2,201	56 (2.6)	1,576	49 (2.1)	**+4.8 (2.5)**	-0.2 (1)
Portugal	5,441	33 (1)	4,994	38 (1.9)	5,026	39 (2.5)	5,994	35 (0.9)	**+6.2 (2.4)**	-3.6 (1.6)
Scotland	6,161	54 (1.6)	3,698	54 (1.2)	6,360	55 (1.1)	3,804	54 (1.8)	**+0.5 (1.3)**	-0.04 (1.7)
Spain	5,876	43 (1.2)	6,367	46 (1.5)	3,172	43 (1.1)	3,412	44 (1.4)	**-0.7 (1.1)**	-2.3 (1.3)
Total	36,982	46 (1)	32,288	48 (0.9)	33,602	49 (0.9)	30,131	46 (1)	**+2.9 (0.7)**	**-1.3 (0.6)**

Table 4.9: Average percentage (SEM) of presenting diagnoses in each country covered by the European Formulary

Country	Phase I				Phase II				Phase II - Phase I	
n = total N^0 diagnoses	Study *n*	Study % (SEM)	Control *n*	Control % (SEM)	Study *n*	Study % (SEM)	Control *n*	Control % (SEM)	STUDY % (SEM)	CONTROL % (SEM)
Belgium	1,310	61 (2.3)	1,232	55 (2.5)	1,149	67 (5.3)	1,187	54 (2.2)	**+5.1 (4.2)**	-1.5 (1.2)
England	4,386	58 (1.3)	4,317	59 (1.5)	4,524	60 (1.5)	4,552	59 (1.1)	**+2.2 (1.6)**	-0.4 (1.7)
Ireland	5,320	60 (2.3)	4,638	62 (2.2)	5,398	58 (1.7)	4,268	59 (1.6)	**-2.1 (1.6)**	-2.4 (1.6)
Italy	5,055	65 (1.6)	5,093	65 (1.2)	5,227	64 (1.4)	5,260	65 (1.7)	**-0.8 (2)**	+0.3 (1.8)
N Ireland	2,078	64 (2.3)	1,523	62 (2.6)	2,513	58 (3.6)	1,756	55 (3.2)	**-5.5 (2.6)**	-7 (1.3)
Portugal	3,981	64 (2)	3,696	63 (1.3)	4,127	68 (2.1)	4,358	66 (2)	**+4.5 (1.9)**	+2.3 (2.2)
Scotland	7,670	55 (1.2)	4,034	59 (1.4)	7,773	56 (1.3)	3,867	59 (2.6)	**+0.5 (1.5)**	+0.2 (1.8)
Spain	4,631	63 (1.6)	4,849	61 (0.9)	2,629	64 (1.4)	2,724	65 (1.4)	**+1 (1.4)**	+3.4 (1.4)
Total	34,431	61 (0.7)	29,427	62 (0.6)	33,340	61 (0.8)	27,972	62 (0.8)	**+0.6 (0.7)**	**+0.2 (0.7)**

Table 4.10: Percentage use of top 10 Formulary and non-Formulary drugs overall from Phases I and II combined

Drug	Belgium	England	Ireland	Italy	N. Ireland	Portugal	Scotland	Spain	Overall
Formulary drugs n =	**7,278**	**15,589**	**21,159**	**23,781**	**7,684**	**21,932**	**21,915**	**19,277**	**138,615**
amoxycillin %	2.5	5.7	6.2	1.9	6.7	1.5	6.4	1.4	3.8
paracetamol %	4.2	3.7	1.4	2	3.7	1.8	2.5	8.3	3.2
diclofenac %	1.6	1	3	2	1.6	3.2	1.6	2.9	2.3
combined oral contraceptive %	1.4	3.1	2.9	1.9	1.8	1.2	3.3	0	2
salbutamol %	0.8	3.1	3.2	0.8	2.3	0.9	2	1.9	1.9
ibuprofen %	0.4	1.8	1.7	0.7	2.6	1	1.8	0.4	1.2
atenolol %	1.8	1.7	1.1	1.4	1.1	0.7	1.7	0.7	1.2
aspirin (antiplatelet only) %	1	1.3	1.3	1.9	1.1	0.5	0.7	1.4	1.2
nifedipine %	0.9	1	0.7	1.7	1	1.5	0.7	1.3	1.1
enalapril %	0.6	0.5	0.1	2.5	0.2	0.8	0.6	1.8	1
Non-Formulary drugs									
co-amoxiclav %	1.4	0.6	2	0.4	1.3	0.9	2.4	0.8	1.2
co-codamol %	0.3	2	0.7	0.2	2.7	0	1.3	2.2	1
ranitidine %	0.3	0.4	0.3	1.5	1	0.7	0.8	1.9	0.9
nimesulide %	0	0	0	2	0	2	0	0	0.7
piroxicam %	0.4	0.2	0.1	1.6	0.3	1.1	0.1	0.5	0.6
lorazepam %	1.4	0	0	1.4	0.1	1	0	0.9	0.6
bendrofluazide %	0	1.5	1.2	0	1	0	1.2	0	0.6
betamethasone (skin use only) %	0.3	1	0.7	0.4	0.4	0.3	1.1	0.4	0.6
flucloxacillin %	0.2	1.2	1	0	0.7	0.5	1	0	0.6
co-proxamol %	0	1.5	0.7	0	0.3	0	1.7	0	0.6

Table 4.11: Percentage of to 10 Formulary and non-Formulary diagnoses in all patients from Phases I and II combined

Drug	Belgium	England	Ireland	Italy	N. Ireland	Portugal	Scotland	Spain	Overall
Formulary diagnoses n =	**4,878**	**18,041**	**20,541**	**22,023**	**8,124**	**16,560**	**25,271**	**15,219**	**130,657**
hypertension %	8.3	3.6	4.7	13	4.1	10	4	11	7.3
arthropathies %	3.8	3.5	2.5	3.4	3.1	7.3	2.9	5.6	3.9
pain %	1.8	4	2.8	3.8	4.5	2.2	3.5	5.1	3.5
depression %	2.9	4.9	2.6	1.4	3.9	2.7	3.7	2.8	3.1
asthma %	1.8	3.4	4.7	1.5	4.3	1.2	3.2	1.5	2.8
anxiety %	1.7	1.7	2.3	3.1	1.9	4.4	1.7	2.3	2.4
contraception %	2.1	3.2	3.1	1.9	2	1.6	3.1	0.1	2.3
acute pharyngitis / tonsillitis %	3.2	1.3	2.5	3	2.4	2.3	1.7	1.4	2.1
eczema / dry skin %	1.1	2.6	1.6	1.2	2.3	0.8	2.8	1.5	1.8
LRTI %	0.2	2	3	0.5	3	0.4	2.2	0.7	1.6
Non-Formulary diagnoses									
low back pain %	1.1	2.8	2.4	2.3	2.2	1.9	2.1	1.9	2.2
URTI %	1.8	2.7	3	0.2	3	0.3	2.8	2.3	2
other skin infections %	1.3	1.6	1.7	0.5	1.5	0.8	1.9	0.7	1.3
ischaemic heart disease %	1.8	0.5	0.6	2.4	0.5	2	0.7	1.3	1.2
bronchitis %	4	1	0.9	1.6	1.2	0.6	1.2	0.5	1.1
chronic bronchitis (COPD) %	2.9	0.9	0.9	1	0.9	0.6	0.6	2.7	1.1
respiratory tract infection %	1.9	0.2	2.2	0.5	1.6	1	1.1	0.7	1
pregnancy / antenatal %	0.5	0.9	1.6	0.4	1.5	0.6	1.9	0.1	1
HRT %	0.4	1.7	1.1	0.8	0.8	0.4	1.6	0.3	1
Other women's problems %	0.6	1.9	0.8	0.5	1	0.5	1.5	0.4	1

CHAPTER FIVE
PRESCRIBING STUDY RESULTS
EFFECT OF THE EUROPEAN FORMULARY AND EDUCATIONAL INTERVENTION

5.1 NON-STEROIDAL ANTI-INFLAMMATORY DRUGS

5.1.1 Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are used by people with both acute and chronic musculoskeletal disorders to relieve pain, particularly where inflammation is a factor. In the UK, there are currently 25 NSAIDs available in the BNF[6] in over 90 different formulations indicating a great deal of choice. In Martindale's Extra Pharmacopoeia (31st ed)[20], 124 different NSAIDs are discussed. NSAIDs are one of the most frequently prescribed groups of drugs in general practice but treatment with them can be associated with a variety of serious side-effects (SEs), particularly in the elderly.[263] As a drug class, NSAIDs have been shown to be the most frequent cause of reported adverse drug reactions ADRs in various countries,[267] with up to 25% in the UK. In England in 1997, almost 20 million prescriptions for NSAIDs were dispensed with a net ingredient cost of approximately 160 million pounds[29] and world-wide it is estimated that in excess of 30 million people take NSAIDs daily[268], 40% of whom are older than 60 years of age[269].

5.1.2 Rational prescribing of NSAIDs

When prescribing for patients with musculoskeletal and joint diseases, many factors have to be taken into consideration before deciding which drug to prescribe. Initially, the prescriber will have to decide whether an NSAID is really needed as the majority of musculoskeletal conditions will respond to simple analgesics or a topical rubefacient may suffice. It has been found that up to 50% patients with osteoarthritis can be managed by paracetamol alone.[270] Taking single one-off doses of an NSAID will only combat pain, which may be appropriate in osteoarthritis, but if a full anti-inflammatory effect is required, such as in rheumatoid arthritis, regular dosing is essential.[270] Once

an NSAID is considered necessary, awareness of the marketing authorisations for different NSAIDs is important before selection for a condition.[191]

The balance between the benefits and risks of NSAIDs requires careful consideration, particularly in the elderly.[6] The majority of NSAIDs appear to have similar efficacy but variations exist in patient response to NSAIDs which may be related to drug pharmacokinetics associated with differences in chemical structure. Safety profiles of NSAIDs appear to differ considerably and so this should play a large part in drug selection for a particular indication. Dosages for the elderly should be tailored to the individual because with increasing age there is a reduction of renal clearance as well as drug distribution and metabolism being significantly altered. Consequently the clearance of some NSAIDs, including naproxen, ketoprofen and ibuprofen, has been found to be reduced in the elderly.[271]

The severity of side-effects is thought to be linked to drug plasma half-lives.[272] NSAIDs are generally divided into two groups, those with short half-lives (less than six hours) including ibuprofen, flurbiprofen, ketoprofen and diclofenac and those with long half-lives (more than twelve hours) including piroxicam, tenoxicam and fenbufen. Drugs with longer half-lives take longer to achieve maximal clinical effects.[273] The Committee on Safety of Medicines (CSM) data[263] in the UK have supported evidence that long half-lives are associated with a greater number of side-effects and have attempted to rank NSAIDs in terms of their relative safety.

Side-effects of NSAIDs include gastro-intestinal (GI) complications, hypersensitivity reactions and nephrotoxicity.[6] The majority of the intestinal problems occurring in patients with arthritis are the result of NSAIDs. The elderly are particularly at risk of NSAID-induced peptic ulcer disease which can lead to perforation, bleeding and ultimately to death. For elderly people with a previous history of peptic ulcer disease where no other pharmacological or non-pharmacological methods other than treatment with an NSAID is possible, co-prescribing of misoprostol or an H_2 antagonist prophylactically with an NSAID should be considered. However, if all prescriptions for NSAIDs in England, for example, were prescribed with misoprostol or ranitidine then

the annual additional cost of co-prescribing based on 1995 data would be approximately £200m and £600m respectively.[274]

The criteria upon which rational prescribing of NSAIDs should be based include that:

1. they should be used when licensed and necessary for the presenting diagnosis,
2. patient history should be checked for concomitant diseases, e.g. GI disorders,
3. concomitant prescribed and OTC drugs should be checked for interactions,
4. the use should be avoided in the elderly where possible,
5. those with the lowest risk of side-effects (shortest half-life) are preferential,
6. treatment should begin with lowest recommended dose and increased against symptom relief,
7. a small range should be used (60% of patients will respond to any NSAID),
8. no patient should be co-prescribed more than one NSAID at a time,
9. topical NSAIDs have limited proven clinical value.

5.1.2.1 NSAIDs by injection, suppository or topical application

NSAID administration by injection is seldom the preferred route, although diclofenac for example is often given by injection formulation for the relief of pain when ureteric colic presents. Some NSAIDs such as diclofenac and indomethacin have been formulated as suppositories, which can be used to relieve night pain and early morning stiffness. Drugs are generally absorbed more slowly through the rectal mucosa than after oral administration but prescription of a longer acting oral NSAID can achieve the same benefit.[272] An advantage of NSAID suppositories is that they avoid the GI complications but one negative aspect of them is that they have the potential to cause rectal irritation or proctitis.

Topical NSAIDs are widely prescribed and purchased over the counter for soft tissue, musculoskeletal and joint conditions. There is little or no published evidence on topical NSAIDs either in comparison to, or in combination with, standard treatments such as paracetamol, rubefacients or oral NSAIDs.[275] The efficacy of topical NSAIDs has been discussed in a few clinical papers with different outcomes. One systematic review has found that the majority indicate a large placebo effect but others reveal that topical NSAIDs are significantly more effective than placebo in terms of pain reduction.[276] It is generally considered that the warmth and rubbing sensation associated with the application of topical NSAIDs might be equal to that of conventional rubefacients or embrocations which are much cheaper and do not require a prescription.[277] Many topical NSAIDs have been marketed in the hope that their local application will overcome the adverse effects associated with oral NSAIDs and at the same time have an enhanced therapeutic action. Following the application of topical NSAIDs, the drug plasma levels are many times lower than after dosing with equivalent oral NSAIDs[272] and so they are well tolerated and seem relatively safe. However, topical NSAIDs do have a degree of systemic absorption and therefore it is possible for side-effects to occur in the same way as with oral NSAIDs.

In general, topical NSAIDs are relatively expensive compared with oral NSAIDs and there is insufficient evidence available to allow ranking of these preparations in terms of efficacy and relative systemic safety. Clinical trials to date only offer some support in the use of these preparations for acute, self-limiting, soft tissue injuries.[278]

5.1.2.2 European Formulary recommendations

Four NSAIDs were recommended in the European Formulary, namely ibuprofen, diclofenac, naproxen and indomethacin and all were selected on the basis of efficacy, safety and cost. Although aspirin is chemically classed as a salicylate NSAID[20,256], it is important to note that aspirin is recommended for use as a simple analgesic in the Formulary rather than for its anti-inflammatory effect. Of the disorders covered by the European Formulary, NSAIDs were included in the symptomatic drug management of the following conditions:

- pain
- migraine
- cholecystitis/gallstones
- renal colic/calcinosis
- pre-menstrual syndrome/dysmenorrhoea
- arthropathies
- gout and hyperuricaemia
- terminal care

The European Formulary Group (EFG) recommendations associated with NSAID prescribing included that:

- aspirin (salicylates) should not be given to children under the age of 12 years because of the risk of Reye's syndrome,
- simple analgesics should be tried first-line, before NSAIDs
- NSAIDs are appropriate for bone pain and where an anti-inflammatory action is required,
- NSAID use should be minimised in elderly patients (particularly those with osteoarthritis which is a degenerative condition, not anti-inflammatory), because of the risk of GI problems,
- routine prophylactic prescription of misoprostol to counteract possible GI ulceration should be considered only in the frail elderly and in those with previously documented chronic peptic ulcer,
- the duration of NSAID treatment should be limited where possible,
- the lowest effective NSAID dose should be used, particularly in the elderly,
- prescribing of NSAIDs needs special caution in patients with a history of asthma, inflammatory bowel, diverticular or renal disease, and with concomitant intake of aspirin, diuretics, ACE inhibitors and steroids.

5.1.2.3 Proposed prescribing performance indicators

There are many criteria which can be used in the assessment of rational prescribing of NSAIDs, several of these were referred to in Sections 5.1.2, 5.1.2.1 and 5.1.2.2. Due to the method of data collation in this study, some criteria, including the drug formulation and prescribed dosage cannot be investigated in this results section. Consequently, the following hypotheses were drawn up based on quality indicators which could be adapted to critically explore the NSAID prescribing data in the different countries. The hypotheses were that:

- the proportion of newly prescribed NSAIDs which were listed within the European Formulary increased following the educational intervention and distribution of the Formulary,
- over 90% of patients in whom NSAIDs are indicated should be adequately treated with the four Formulary recommended NSAIDs,
- the NSAID of choice in each country was used in approximately 60% of cases as 60% of people respond to any NSAID,
- the range of newly prescribed NSAIDs would be reduced following the educational intervention and distribution of the Formulary,
- the proportion of new prescriptions for simple analgesics (recommended in the European Formulary) which were prescribed for the conditions listed in Section 5.1.2.2 increased following the educational intervention,
- the proportion of consultations for conditions listed in Section 5.1.2.2 resulting in a new analgesic prescription increased following the educational intervention and distribution of the European Formulary.

5.1.2.4 Data manipulation/methodology

For the purposes of the NSAID analyses in this thesis, it has been assumed that aspirin is predominantly prescribed for either its analgesic or for its antiplatelet effect and therefore it has not been classed as an NSAID. To produce an anti-inflammatory effect, high regular dosage of aspirin is required but no dosage information was

recorded in the prescribing data obtained, which would be essential in order to establish this use. In order to critically evaluate the NSAID prescribing by the GP participants in the different countries, all the searches except where specified involved drugs matched to diagnoses. The following searches were performed within the database:

- all Phase I prescribing of new NSAIDs,
- all Phase II prescribing of new NSAIDs,
- all Phase I study group prescribing of new NSAIDs,
- all Phase II study group prescribing of new NSAIDs,
- prescribing of new NSAIDs for both Phases combined,
- all Phase I prescribing of new NSAIDs and simple analgesics for conditions listed in Section 5.1.2.2 , no matching of drugs to diagnoses,
- all Phase II prescribing of new NSAIDs and simple analgesics for conditions listed in Section 5.1.2.2, no matching of drugs to diagnoses,
- NSAID prescribing for both Phases combined,
- NSAID prescribing for both Phases combined in patients under 60 years,
- all NSAID prescribing for both Phases combined in patients over 60 years.

For the country by country comparative prescribing results section, it was decided to combine the data from Phase I and Phase II which is likely to provide a more meaningful illustration of the overall prescribing pattern compared with looking at the trends in each of the Phases separately.

In the results tables, the data were presented in order of prescribing volume in terms of the number of items prescribed. The NSAID data were sorted based on the following classification:

1. Acetic acid derivatives
2. Proprionic acid derivatives
3. Oxicam derivatives
4. Selective cox-2 NSAIDs
5. Anthranilic acid derivatives
6. Miscellaneous NSAIDs
7. Salicylic acid derivatives
8. Topical preparations.

5.1.3 Results

5.1.3.1 Prevalence patterns

NSAID prescribing accounted for 9% (0.6) of all prescribing in Phase I and 7.5% (0.2) in Phase II and a more detailed breakdown of prescribing can be seen in Table 5.12. There were significant differences between the control and study groups ($p = 0.02$) and highly significant differences between countries ($p < 0.001$) and a highly significant country by group ($p < 0.001$) interaction (i.e. the size of the control vs. study effect depended upon country). Overall Portugal and Italy showed the highest NSAID prescribing, with 26% of the total number of drugs prescribed being NSAIDs by the Portuguese control group in Phase I. Exclusion of the Portuguese data from the analysis removed the last two statistical differences above and the difference between the control and study groups became of borderline significance ($p = 0.05$) suggesting that Portugal was an outlier, disproportionately skewing the data.

5.1.3.2 Prescribing performance indicators before and after the intervention

5.1.3.2.1 Concordance with NSAIDs recommended in the European Formulary

The level of prescribing concordance with the NSAIDs recommended in the European Formulary i.e. ibuprofen, diclofenac, naproxen and indomethacin, for new prescriptions can be seen in Table 5.13. There was a trend towards Formulary recommended NSAIDs with the intervention group increasing on average by 7.9% (2.6) compared to the control group which increased by 0.7% (2.7). This difference was of borderline statistical significance ($p = 0.05$). There was no significant difference ($p = 0.26$) found between countries. The larger differences between movement towards the Formulary by the intervention group and movement away by the control group were observed in England, Italy, Northern Ireland and Portugal. In England, this difference was of borderline significance ($p = 0.05$). Overall, the greatest concordance with the EF can be seen in the UK where more than four out of five new NSAID prescriptions were for those recommended in the Formulary. This compares with the prescribing by GPs in Italy and Portugal where just over one in three new NSAID prescriptions were those that were recommended.

The total overall prescribing levels of the four recommended NSAIDs increased by approximately 12% in the intervention group from Phases I to II (Table 5.14). Within the intervention groups of the individual countries, the total prescribing levels increased by a minimum of 10% in Ireland, Italy, Portugal and Spain. Depending on the country, either diclofenac or ibuprofen was the NSAID of choice, other than Belgium where naproxen was the most commonly prescribed NSAID. The largest increases of individual NSAID prescribing from Phase I to Phase II were for ibuprofen in Italy, Northern Ireland and Spain.

For information, Table 5.15 indicates how prescribing of the most commonly used NSAIDs outside the Formulary by the study group GPs of Phases I and II, compares with use of NSAIDs recommended in the European Formulary (Table 5.14). The four most commonly used non-Formulary NSAIDs were nimesulide, piroxicam, mefenamic acid and ketoprofen.

5.1.3.2.2 Proportion of new prescribing covered by the four Formulary NSAIDs

The 90% prescribing target was not achieved by any of the countries in Phase I although the four Formulary NSAIDs covered in excess of 80% of the prescribing in England, Northern Ireland and Scotland (Table 5.14). In Phase II, prescribing of the four NSAIDs combined increased considerably in all the countries except for Belgium. Prescribing in England and Scotland was over the 90% mark.

5.1.3.2.3 Proportion of new prescribing covered by the NSAID of choice

The NSAID of choice varied from country to country but it was always a European Formulary recommended NSAID (Table 5.14 and Table 5.16). In Phase I, no individual NSAID in any of the countries reached the 60% target. In England and Northern Ireland, prescribing of ibuprofen was the closest being just under the 50% mark and in Scotland 47% of NSAID prescriptions were for diclofenac. In Phase II, the 60% mark was achieved in Northern Ireland by the prescribing of ibuprofen.

5.1.3.2.4 The range of drugs prescribed

There was no significant difference in the range of NSAIDs prescribed as new drugs from Phase I to Phase II either between countries ($p = 0.31$) or between the control and study groups ($p = 0.53$) (Table 5.17). There was a trend towards a reduced range of NSAIDs prescribed in the intervention groups of Belgium, Ireland and Northern Ireland compared with their control groups, but none of these changes was statistically significant. The largest ranges of NSAIDs were prescribed in Italy and Portugal and the smallest ranges were found to be prescribed by the UK GP participants.

5.1.3.2.5 Proportion of simple analgesics prescribed compared with NSAIDs

The intervention group as a whole increased its proportion of simple analgesic prescribing from Phase I to II by 5.4% (2) compared with a decrease in the control group by 5.6% (2.6) and the difference was found to be statistically significant ($p = 0.001$) (Table 5.18). There was no significant difference found between countries ($p = 0.07$). Within individual countries, trends towards an increase in prescribing of analgesics by intervention groups compared with control groups can be seen in England, Ireland, Italy, Northern Ireland and Scotland. The largest difference in prescribing of

simple analgesics between control and intervention groups was in Italy and this was highly significant ($p < 0.001$). A statistically significant statistical difference was also found between the control and study groups in Spain ($p = 0.03$), but in Table 5.18 this can be seen to be due to the large decrease in the proportion of simple analgesics prescribed by the control group with the level in the intervention group remaining constant.

5.1.3.2.6 Proportion of consultations resulting in a simple analgesic

The proportion of consultations for conditions listed in Section 5.1.2.2, resulting in the prescription of a simple analgesic increased by 1.9% (0.7) in the intervention group compared with a decrease of -1.2% (0.5) in the control group and this was of statistically high significance ($p < 0.001$) (Table 5.19). No significant difference was found between countries ($p = 0.12$). Belgium was excluded from this analysis as no data were provided on consultations without a prescription. An increased trend towards new prescribing of simple analgesics can be seen in the intervention groups of all countries, except for Portugal where the trend towards prescribing simple analgesics was greater in the control group. The largest increase in consultations resulting in the prescribing of a simple analgesic was found in Italy and this was statistically significant ($p = 0.002$).

5.1.3.3 Comparisons of NSAID prescribing

A total of 10,799 NSAID prescription items was recorded in all countries, both Phases combined (Table 5.20). The majority of these, 5,850 (54%), were new prescriptions varying from 36% in Spain to 65% in Italy (mean 55%, SD 9.2). From the remainder, 2,738 (25%) were regular repeat prescriptions, 1,311 (12%) were prescribed upon request of the patient as a result of having been prescribed on a previous occasion, 759 (7%) were hospital/specialist initiated prescriptions and 141 (1.3%) NSAIDs were not categorised.

5.1.3.3.1 Acetic acid derivatives

The acetic acid derivatives with relatively short half-lives were the most commonly prescribed class of NSAIDs accounting for 37% of those prescribed from all the drug classes collectively (Table 5.20). Prescribing of acetic acid derivatives varied from 27% in Italy to 58% in Spain (mean 37%, SD 9.5). Diclofenac was the acetic acid derivative of choice in all countries accounting for over 75% of the prescribing from within this group. For all drug categories combined, diclofenac prescribing varied from 19% in Italy to 40% in Ireland (mean 30%, SD 7.7) and prescribing of indomethacin, the second most commonly prescribed drug in this group varied from 1.4% in Northern Ireland to 7.7% in England (mean 4.5%, SD 2.2). For new NSAID prescriptions only (Table 5.16), diclofenac use varied from 20% in England to 44% in Ireland (mean 29%, SD 9.3), and new prescribing of indomethacin varied from 0.4% in Northern Ireland to 6.1% in Spain (mean 3.1%, SD 2.1).

Within this NSAID class, aceclofenac use in Spain accounted for 10% of the prescribing overall. In Northern Ireland, two and a half times as much acematacin than indomethacin was prescribed and almost an equal amount of ketorolac as indomethacin was used in Italy.

5.1.3.3.2 Proprionic acid derivatives

Proprionic acid derivatives were the second most commonly prescribed class of NSAIDs accounting for 30% of those prescribed overall, varying from 15% in Spain to 60% in England (mean 37%, SD 17) (Table 5.20). The majority of proprionic acid derivatives tend to also have short half-lives (similar to the acetic acid derivatives). Ibuprofen was the most commonly prescribed NSAID in this group, representing just under 16% of the total number of NSAID prescriptions overall. Twice as much ibuprofen was prescribed as naproxen, the second most commonly prescribed proprionic acid derivative, and four times as much ibuprofen was prescribed as ketoprofen, the third most commonly prescribed NSAID. For all categories combined, ibuprofen use varied from 5.8% in Spain to 43% in Northern Ireland (mean 21%, SD 16) and for new NSAIDs only (Table 5.16) ibuprofen varied from 5.1% in Belgium to 50% in Northern Ireland (mean 24%, SD 18). Prescribing of naproxen varied from 4.6% in Portugal to 28% in Belgium (mean 11%, SD 8.5) for all prescription categories combined and new

naproxen prescriptions (Table 5.16) varied from 3.7% in Ireland to 29% in Belgium (mean 11%, SD 9.1).

In Italy, ketoprofen was the proprionic acid derivative of choice accounting for almost 10% of the NSAID prescriptions overall and in Spain piketoprofen was the proprionic acid derivative of choice there. Piketoprofen is only available in a topical formulation and so for the purposes of NSAID classification was grouped with the topical NSAIDs in Table 5.20.

5.1.3.3.3 Oxicam derivatives

The oxicam derivatives were the third most common group of NSAIDs prescribed (Table 5.20) varying from 1.6% in Ireland to 18% in Italy (mean 7.8%, SD 5.7). The oxicams have been reported as having the longest half-lives of all the different classes of NSAIDs. Piroxicam was the oxicam of choice in all the countries and its use varied from 1.1% in Ireland to 16% in Italy (mean 6.5%, SD 4.6) for all prescription categories combined. For newly prescribed NSAIDs (Table 5.16) only, piroxicam use varied from 0.7% in Ireland to 16% in Italy (mean 5.3%, SD 4.7).

5.1.3.3.4 Selective cox-2 NSAIDs

Of the NSAIDs prescribed in this study, nimesulide was the only one classed as selective inhibitor of cyclo-oxygenase-2 (Cox-2) at the time of data collection. It was a particularly popular choice of NSAID in Italy and Portugal, representing 19% and 16% of the NSAID items prescribed respectively in each of those two countries (Table 5.20). Of the remaining countries it was also available on prescription (at the time of data collection) in Belgium and Ireland. In Italy, for all categories of NSAIDs prescribed, nimesulide use was actually on a par with diclofenac use. In Portugal, nimesulide was comfortably the second most popular NSAID prescribed overall with almost as much being used as for the whole category of proprionic acid derivatives in that country. For newly prescribed NSAIDs, nimesulide was the third most commonly prescribed NSAID overall, representing 10% of the total number of NSAID prescription items (Table 5.16).

5.1.3.3.5 Anthranilic acid derivatives

This group accounted for less than 5% of the total of NSAIDs prescribed from all prescription categories combined, varying from 0% in Belgium to 20% in Ireland (mean 4.9%, SD 6.8) (Table 5.20). Mefenamic acid was the most commonly prescribed NSAID in this group, varying from 0% in Belgium and Spain to 20% in Ireland (mean 4.7%, SD 6.9) for all categories combined and for new NSAIDs (Table 5.16) its use varied from 0% in Belgium, Portugal and Spain to 19% in Ireland (mean 4.6%, SD 6.5).

5.1.3.3.6 Miscellaneous NSAIDs

Prescribing of miscellaneous NSAIDs accounted for 4.3% of NSAID prescriptions for all prescription categories combined (Table 5.20). Their use varied from 1% in England and Ireland to 7.9% in Italy (mean 3.3%, SD 2.6%). Within this group in Italy, morniflumate accounted for 3.8% of NSAIDs prescribed and feprazone 1.8%. Of the NSAID prescriptions in Portugal, clonixin accounted for 1.9% and nabumetone 1.6%; in Spain, nabumetone represented 1.7% of the NSAIDs prescribed there.

5.1.3.3.7 Salicylic acid derivatives

Salicylic acid derivative use (Table 5.20) varied from 0% in Northern Ireland to 10% in Portugal (mean 2.1%, SD 3.6). Lysine aspirin (a chemical derivative of aspirin) was the most commonly prescribed salicylate, accounting for over 10% of the NSAIDs prescribed in Portugal and 4.3% of those prescribed in Belgium. As previously stated aspirin was excluded from this analysis as no dosage information was recorded by prescribers to indicate if prescribed for its anti-inflammatory effect.

5.1.3.3.8 Topical NSAIDs

As previously explained, no proper analysis could be performed categorising topical NSAIDs. However at the time of data collection in this study, some NSAIDs were only available as topical formulations and included etofenamate, niflumic acid, piketoprofen and bendazac. These drugs were prescribed in Belgium and the southern European countries only, etofenamate and bendazac being available in all four countries (Table 5.20). Bendazac was prescribed in only Italy and Portugal and piketoprofen was

only prescribed in Spain. In Spain, etofenamate represented 6.4% of the NSAIDs prescribed and piketoprofen accounted for 7.7%. None of these four topical NSAIDs were prescribed in English speaking countries as they were not licensed and therefore unavailable.

5.1.3.4 Prescribing in different age groups

5.1.3.4.1 NSAID use in patients under 60 years

The bulk of NSAID prescribing in patients under 60 years of age for all drug categories in Phases I and II data combined can be seen in Table 5.21. The drugs recommended in the European Formulary were the mainstay of treatment in all the countries except for in Italy and Portugal. These findings were similar to the results presented in Table 5.13 for new NSAID prescribing only. It can be seen in Table 5.21 that a broader range of NSAIDs were required in Belgium, Italy, Portugal and Spain in order to cover 90% of the prescribing volume. Several of the NSAIDs listed were only prescribed in certain countries such as nimesulide (Section 5.1.3.3.4). Despite being only prescribed in considerable amounts in Italy and Portugal, nimesulide was the third most commonly prescribed NSAID overall. Whilst selective cox-2 NSAIDs have the potential to improve patient care, they may be most appropriate in patients over 60 years of age who are more susceptible to GI side effects from NSAIDs. Other NSAIDs which were also commonly used in patients under 60 years of age included piroxicam, particularly in Belgium and the Mediterranean countries and mefenamic acid, a popular choice in the English speaking countries especially Ireland.

5.1.3.4.2 NSAID use in patients 60 years and over

Levels of Formulary recommended NSAIDs were notably greater in patients of 60 years and over in Belgium, Italy, and Portugal, than in those who were younger than 60 (Table 5.22). Formulary concordance was however below 50% in the latter two countries. In contrast, concordance with Formulary recommended NSAIDs prescribed for Spanish patients over 60 years of age was lower than the level in younger patients. Again, a much narrower range of drugs was prescribed in the English speaking countries

than in the southern European regions in order to achieve a 90% level of prescribing volume.

The aggregate levels of nimesulide and piroxicam were reversed in patients under 60 when compared with patients over 60. In Italy and Portugal, nimesulide use dropped from the third most commonly prescribed NSAID for patients under 60 to the sixth most commonly prescribed for patients over 60. In contrast, piroxicam levels overall almost doubled in use from patients under 60 years to patients over 60 years, especially in Italy where one in five NSAID prescription items was for piroxicam. Piroxicam was the third most commonly used NSAID in patients over 60 years, marginally lower than the level of ibuprofen. Table 5.22 also shows the relatively high prescribing of tenoxicam in Belgium and higher prescribing levels of those NSAIDs only available in a topical formulation for patients over 60 years, notably in Spain. In Ireland, 14% of NSAID prescription items were for mefenamic acid, where it was the third most common choice.

5.1.3.4.3 Diagnoses where NSAIDs were prescribed in patients under 60 years

Pain and arthropathies (both disorders where NSAIDs were recommended in the European Formulary) were the two most commonly occurring conditions for which NSAIDs were prescribed in patients under 60 years (Table 5.23). NSAIDs were also commonly prescribed for musculoskeletal disorders not covered by the Formulary, such as low back pain. NSAIDs were also prescribed for some conditions listed within the Formulary such as throat infections, for which their use was not recommended. Such prescribing occurred particularly in Italy where 14% of the NSAIDs prescribed there were for throat infections. In addition, there appears to be a relatively high level of NSAID prescribing for pre-menstrual syndrome and/or dysmenorrhoea in Scotland. This could be associated with high levels of mefenamic acid prescribing there (Table 5.21), especially as this drug is licensed for this condition and has been promoted accordingly.

5.1.3.4.4 Diagnoses where NSAIDs were prescribed in patients 60 years and over

The range of diagnoses for which NSAIDs were prescribed for patients 60 years and over is considerably reduced compared with their use in patients under 60 (Table 5.24). The disorders being treated in Table 5.24 were notably those characteristic of an elderly population. The top two diagnoses were arthropathies and pain, similar to Table 5.23 but the positions were reversed. The prevalence level of arthropathies for which NSAIDs were prescribed trebled overall in patients 60 years and over compared with patients under 60. Again, there was NSAID prescribing for musculoskeletal conditions not included in the European Formulary such as low back pain and NSAID use for conditions listed in the Formulary but which did not include NSAIDs as part of the recommended drug management, such as neuralgia.

5.1.4 Discussion

In this study, NSAID prescribing represented almost 10% of the total prescribed items overall - confirming that they were a key area for intervention in attempting to educate prescribers and consequently promote more rational prescribing. The majority of drug entities prescribed were for newly prescribed items and although the level was relatively lower than that for antibiotics, this was offset by the large volume of NSAID data available for analyses.

Where an NSAID prescription is considered necessary, patient response will tend to determine the most appropriate one. However, it is preferable for prescribers to prescribe from a small range, selecting NSAIDs that have been marketed for some time and that have a better-than-average safety margin. Using this convention, drug formularies[49,78,81,84] and prescribing guidelines[279] tend to be fairly consistent in selecting ibuprofen as the first-line NSAID of choice, followed by naproxen, diclofenac and indomethacin. It is generally accepted that NSAIDs with shorter half-lives have fewer side-effects than those with longer half-lives[272] although one report[280] of comparative toxicity found fenoprofen with a half-life of three hours to have a greater incidence of serious GI effects than piroxicam with a half-life of 45 hours. Even though this information is widely available to prescribers, keeping up-to-date with newly

published research reporting changes in the relative toxicity of one NSAID compared with another[281,280] is an ongoing and time consuming task for any prescriber.

The three most successful outcomes of the study were:

1. that the difference between the increase by the intervention group compared with the control group in concordance with the Formulary between Phase I and II was of borderline statistical significance.
2. for the simple analgesic and NSAID data combined, there was a highly significant increase in the proportion of simple analgesics prescribed from Phase I to II indicating that to an extent the former were displacing NSAIDs.
3. there was a highly significant increase in the proportion of consultations for conditions within the Formulary for which both simple analgesics and NSAIDs were used.

All these findings suggest that the intervention may have had some impact, especially in England, Italy, Northern Ireland and Portugal where the most positive trends were found. However, the relatively high level of oxicam prescribing and in particular the greater use of piroxicam in all the countries in patients over 60 years of age compared with those under 60, suggests that some advice was ignored.

In this results section, a blanket analysis was performed on general concordance with European Formulary recommended NSAIDs, irrespective of what disorders they were being prescribed for. Should this analysis have been based on concordance with prescribing for the conditions within the Formulary then the volume of NSAID data available would have been considerably reduced, especially that relating to prescribing for patients below 60 years of age. The reason for this is because not only were patients with conditions being prescribed NSAIDs where they were not recommended but many of the musculoskeletal conditions for which NSAIDs were being used for were not included in the European Formulary and Appendix. Therefore the document appeared limited in its coverage. Additionally, sophisticated analyses, comparing differences in NSAID prescribing between osteoarthritis and rheumatoid arthritis for example, would

have been problematic as the majority of GPs tended to record the diagnosis as arthritis only, omitting to specify the type.

There were marked differences in the pattern of NSAID prescribing between countries - for example in Italy, nimesulide was the most commonly prescribed drug, whereas in all other countries diclofenac or ibuprofen were the NSAIDs of choice. Nimesulide, a cox-2 derivative, was an example of an NSAID only available and established in certain countries thus contributing to variations in prescribing patterns between countries. Of the most commonly used NSAIDs, many were actually available in all the countries but there were notable differences in the order of their preference. Possible reasons for the failure of ibuprofen to be the most commonly prescribed NSAID in the study could include: firstly, that it may be cheaper to purchase over the counter compared with the cost payment for a prescription and secondly, as a consequence of its wide availability OTC, some patients may have already experimented with it first, before requiring an alternative.

An aspect of the prescribing that appeared somewhat contradictory was that in Italy and Portugal, for patients under 60 years, nimesulide prescribing was greater than piroxicam and yet the reverse occurred for patients over the age of 60. It would have been expected that the cox-2 NSAID would have been prescribed more for the elderly, to protect against the increased likelihood of side-effects, and piroxicam with its relatively poor safety profile to be prescribed less for the elderly. Three years after the data were collected for this study, Italian epidemiological researchers in Rome have reported that despite being confirmed to be among the most gastrotoxic NSAIDs, piroxicam is still one of the most commonly prescribed.[282] Consequently, they concluded that piroxicam use potentially represents a great public health concern. At the same time in Portugal, because of piroxicam being one of the most commonly prescribed NSAIDs, high levels of reported photosensitivity adverse effects has resulted in dermatological researchers from Porto proposing that piroxicam prescription should be avoided.[283] Drug utilization research in the province of Seville, Spain, has also found piroxicam to be one of the two most commonly prescribed NSAIDs[284], although these findings were not reflected in the Spanish data in this study.

Interventions with respect to NSAID have been found to be successful in both primary and secondary care. The effect of regular audit sessions between prescribers, specialist clinicians and pharmacists resulted in a 40% reduction in NSAID prescribing in the accident and emergency department of a London hospital.[285] In general practice, prescribing formularies have been shown to reduce the range of NSAID prescribing[286] but in this study, there was found to be limited and no significant reduction in the ranges that were prescribed. The smallest ranges of NSAIDs were found in the UK in both patients below and above 60 years of age. Coupled with the high Formulary concordance levels there, this indicates that prescribing was both more consistent as well as more in line with the recommendations than elsewhere. In England, ibuprofen was the most commonly prescribed NSAID followed by diclofenac and then naproxen which compares reasonably well with Department of Health reports of little difference in the number of prescription items for ibuprofen and diclofenac with naproxen falling in to third place.[29] This trend towards consistent prescribing of a relatively small range of NSAIDs therefore seems to be largely mirrored across the whole country.

5.2 URINARY TRACT INFECTIONS

5.2.1 Introduction

In the UK, UTIs account for approximately 2% of GPs' consultations.[287] Urinary tract infection (UTI) is a common condition especially affecting many women at sometime in their lives. Each year around 5% of women present to their GPs with dysuria and frequency.[288] Of these, about half have a urinary tract infection as confirmed by the presence of a threshold number of bacteria in their urine. In males, UTI is uncommon in youth and middle age but the problem becomes more prevalent with increasing age, frequently being associated with an underlying abnormality of the renal tract.

In this results section, a comparison of prescribing patterns between countries for UTIs in women 16 years and over and in males and females overall will be made. UTI management is complicated in men due to the underlying pathology and low prevalences of UTIs in men and limited data from children are unlikely to enable valid comparisons of these groups alone from the database.

5.2.2 Clinical presentation

Anatomically, UTIs may be classed as either lower, the site of infection being the bladder and/or urethra, or upper, occurring in the kidneys and/or ureters.[289] Alternatively, they can be classed according to the likely response of therapy into those that are uncomplicated (the majority) and those that are complicated. Lower UTIs (simple or uncomplicated) are generally ascending bacterial infections from a patient's own gut flora into the bladder via the urethra. Upper UTIs (complicated) involve inflammation of the kidney tissue and response to therapy depends on the presence of certain risk factors including diabetes mellitus, immunosuppressant drugs and pregnancy.[6] An infection is also considered to be complicated, and may have serious consequences, if it affects pregnant women, children, men or the elderly. Recurrent infections are more serious and may be due to relapse but are more often as a result of re-infection. Recurrent episodes are an indication for radiological investigation

especially in children in whom untreated pyelonephritis may lead to permanent kidney damage.[290]

Infection generally presents as either cystitis or acute pyelonephritis. Typical symptoms of cystitis include dysuria, nocturia, frequency and urgency of urination. Suprapubic pain, cloudy or foul-smelling urine, haematuria, or, in elderly patients, confusion may also occur.[288] Acute pyelonephritis typically causes flank pain and fever, often with nausea, vomiting, malaise and/or symptoms of cystitis.

Asymptomatic bacteriuria (significant bacteriuria without symptoms of urinary infection) is found in 15-20% of women aged 65-70 years and does not seem to impair renal function or shorten life.[288] Asymptomatic bacteriuria also occurs in 4-7% of pregnant women but is then associated with premature delivery and low birthweight.[291]

5.2.3 Diagnosing UTIs

In women presenting with uncomplicated cystitis, diagnosis can be based on the history and clinical signs, together with results of urine dipstick testing for nitrites and/or leucocyte esterase.[288] If the nitrite test is positive, it is reasonable to start appropriate antibiotic therapy without accompanying culture of the urine. However, if both tests are negative, urine should be sent for culture. Uncomplicated UTIs are usually caused by single organisms and so culture of urine is not usually necessary although microscopic examination may provide helpful clues.

Urine culture is essential in the management of certain situations including complicated infections, in those who are pregnant and where empirical antibiotic treatment fails. In these circumstances, treatment can be started with the 'best guess' antibiotic before results are available but it may need to be modified after subsequent culture findings.

5.2.4 Rational prescribing for UTIs

The goal of antibiotic therapy is simply to provide resolution of symptoms in the shortest possible time with the minimum of adverse effects, as economically as possible.[292]

5.2.4.1 Current recommendations

Trimethoprim is usually first-line recommended therapy in uncomplicated lower UTIs[6], effective against approximately 70% of urinary pathogens.[293] Nitrofurantoin and oral cephalosporins may be alternative first-line drugs.[6] Resistance of urinary pathogens to older antibiotics is increasing and it has been calculated that around 50% of urinary pathogens are now amoxycillin and ampicillin resistant which makes them both unsuitable for empirical therapy.[293] Up to 90% of urinary pathogens are sensitive to co-amoxiclav, an alternative for infections caused by bacteria resistant to trimethoprim.[293] The fluoroquinolones are effective in uncomplicated cystitis because only 5% of pathogens are resistant[293], although resistance will increase the more these drugs are prescribed. Five-day and seven-day treatment regimens are usually recommended for the treatment of uncomplicated UTIs[191] but three days has been found to be adequate.[288]

In a woman who has recurrent infection with a proven microbial cause and in whom imaging investigation has proved negative, prophylactic trimethoprim, cephalexin, nitrofurantoin or norfloxacin therapy can reduce the likelihood of further attacks.[294] Prophylaxis should be started after successful treatment of infection and continued for 3-6 months.

Patients with acute pyleonephritis should be admitted to hospital if accompanied by vomiting or requiring intravenous antibiotic therapy or rehydration. Treatment should be started blind with trimethoprim, a 'second or third generation' cephalosporin, a fluoroquinolone or an aminoglycoside while waiting for culture results, then changed as necessary but continued for 10-14 days.[288] Severely ill patients are likely to have an underlying complication and should be referred.

Approximately 30% of pregnant women with untreated asymptomatic bacteriuria will develop acute pyelonephritis during the pregnancy.[291] If infection is found and if the causative organism is known to be susceptible, amoxycillin, an oral cephalosporin or nitrofurantoin is the preferred antibiotic for a minimum of 7 days treatment.[295] In the case of a relapse, urine should be cultured 1-2 weeks after stopping treatment.

5.2.4.2 European Formulary recommendations

The following drug treatment strategy was recommended in the European Formulary:

1. Lower UTIs and asymptomatic bacteriuria - trimethoprim, amoxycillin
2. Upper UTIs, initial treatment - trimethoprim, amoxycillin
3. If treatment with first-line drugs fails or when these drugs are contraindicated (after relevant microbiological diagnosis) - norfloxacin or consistent prescribing of an alternative fluoroquinolone depending on availability and comparative cost per country.

The European Formulary Group recommendations in the Appendix included that:

- short courses of trimethoprim and aminopenicillins are first-line treatment for uncomplicated UTIs,
- longer regimens of these drugs are required where renal infections present,
- the newer drugs (cephalosporins and fluoroquinolones) should be used for treatment failure after relevant microbiological diagnostics or when the first-line drugs are contraindicated,
- aminoglycosides should never be used outside hospitals,
- asymptomatic bacteriuria should be treated only in pregnant women and children.

5.2.4.3 Proposed prescribing performance indicators

The following hypotheses were drawn up based on quality indicators which could be adapted to critically explore the UTI prescribing data in the different countries. The hypotheses for UTIs were that:

- low prevalences of UTIs in men and children as well as complications in their underlying pathology indicate that the analysis should focus primarily on prescribing patterns in females of 16 years and above to enable valid comparisons from the database,
- the proportion of antibiotics prescribed which were listed within the European Formulary increased following the educational intervention and the distribution of the Formulary,
- the range of newly prescribed antibiotics would be reduced following the educational intervention and the distribution of the Formulary
- trimethoprim being the established first-line drug treatment for UTIs and effective against approximately 70% of urinary pathogens should thus be found to be prescribed for approximately 70% of UTIs in each country,
- the use of co-trimoxazole should be justified and limited due to its reported adverse toxicity,
- the prescribing of the newer second and third generation cephalosporins (e.g. cefuroxime, cefixime, ceftibuten and cefpodoxime) and the use of fluoroquinolones (e.g. ciprofloxacin) should be based on pharmacoeconomics and reserved for cases where specific sensitivity has been demonstrated,
- the use of combination antibiotic preparations should be limited as they do not allow for flexible dosing and their cost usually exceeds that of the combined cost of the individual entities if they were prescribed separately,
- aminoglycoside antibiotics should not be prescribed outside hospitals.

5.2.5 Data manipulation/methodology

In order to critically evaluate the UTI prescribing by the GP participants in the different countries, all the searches with the exception where specified involved drugs matched to a UTI diagnosis. The following searches were performed within the database:

- UTIs in both sexes all ages combined, no matching of drugs to diagnosis for both Phases combined,
- UTIs in both sexes all ages combined, for both Phases combined,
- UTIs in children less than 16 years of age, for both Phases combined,
- UTIs in women 16 years upwards, no matching of drugs to diagnosis for both Phases combined
- UTIs in women 16 years upwards, for both Phases combined,
- all Phase I new prescriptions for UTIs in women 16 years upwards antibiotic selection only,
- all Phase II new prescriptions for UTIs in women 16 years upwards antibiotic selection only,
- all Phase I new prescriptions for UTIs in all males and females combined, antibiotic selection only,
- all Phase II new prescriptions for UTIs in all males and females combined, antibiotic selection only.

In order to analyse whether there had been any move towards increased concordance with the European Formulary following the educational intervention, searches were performed on 'new' prescribing for UTIs in women from both Phases. New prescribed items were selected, firstly as it was considered that this would be a more realistic measurement of the GPs' prescribing practice, uninfluenced by hospitals or previous prescriptions. Secondly, antibiotics should be seldom given as repeat prescriptions.

For the country by country comparative results section, it was decided to combine all the data from Phases I and II as this is likely to provide a more meaningful illustration of the overall prescribing pattern compared with looking at the trends in each of the Phases separately.

In the results tables, the data were presented in order of prescribing volume in terms of the number of items prescribed. The UTI antibiotic drug data were sorted based on the following classification:

1 Penicillins including:

- amoxycillin combined with clavulanic acid (betalactamase inhibitor)

2 Cephalosporins

3 Tetracyclines

4 Aminoglycosides

5 Macrolides

6 Sulphonamides and trimethoprim

7 Fluoroquinolones

8 Other miscellaneous antibiotic groups combined including:

- bactericidals, lincosamides, nitrofurans and steroidals

9 Other drug entities (not antibiotics) prescribed by the GPs for UTIs

5.2.6 Results

5.2.6.1 Morbidity/prevalence patterns

Urinary tract infections were the fourteenth most commonly occurring diagnosis and accounted for 2.1% of the total number of general practice consultations (Table 5.25). The proportion of UTI consultations varied between 1.5% in Northern Ireland to 2.6% in Ireland (mean 2%, SD 0.36). The majority of these consultations were for females of 16 years and over, varying from 1.1% in Northern Ireland to 1.8% in Portugal (mean 1.4%, SD 0.24). The proportion of patients presenting with a UTI who received treatment varied from 86% in England and Scotland to 96% in Portugal (mean 90%, SD 3.7) and in females of 16 years and over, varied from 89% in England to 96%

in Ireland and Portugal (mean 92%, SD 3.2). Of a total of 2,061 patients in this study presenting with a UTI, 1,825 required a prescription of one or more drug entities and of those requiring treatment 1,339 (73%) were women 16 years and above.

5.2.6.2 Proportion of new antibiotics from all antibiotic categories

Results are detailed in Table 5.26 for new antibiotic drugs only, indicating that antibiotics are seldom prescribed from either of the 'R', 'A' or 'H' categories (Section 3.1.3.5). The intervention group prescribed on average 82% (2.6) of antibiotics as new antibiotics for UTIs in Phase I and 75% (3.1) in Phase II compared to the control group of 77% (2.7) and 74% (3.3) in Phase I and II respectively. There was no significant difference in the proportion of new antibiotics items prescribed between the control and study groups, neither on average ($p = 0.41$) nor between countries ($p = 0.84$).

5.2.6.3 Prescribing performance indicators before and after the intervention

5.2.6.3.1 Concordance before and after dissemination of the European Formulary

The level of prescribing concordance with the first-line drugs in the European Formulary recommended for UTI i.e. amoxycillin and trimethoprim can be seen in Table 5.27. Despite an increase of 5.5% (5.4) in the intervention group as opposed to an increase of only 1.3% (4.9) in the control group, this difference was not significant ($p = 0.24$). Between countries the difference was of borderline significance ($p = 0.05$) though. Within Belgium, Ireland, Italy and Portugal, there appeared to be a trend towards use of Formulary recommended drugs. In Ireland, the difference between the intervention group from Phase I to Phase II was of borderline significance ($p = 0.05$), but the difference between the control and intervention groups was not significant ($p = 0.82$) as there was increased concordance with the Formulary in the control group too.

Overall, prescribing by the GPs in Northern Ireland demonstrated the greatest concordance with the European Formulary, followed closely by England, Scotland and Ireland. Concordance levels in the remaining countries indicated that European Formulary first-line recommended drugs were seldom prescribed.

Of the two first-line antibiotics recommended in the Formulary for UTIs, trimethoprim was the more commonly prescribed (Table 5.28) and was prescribed in preference to amoxycillin in all countries except for Portugal. From study group Phases I to II, there were considerable increases in trimethoprim use in Ireland and Scotland although in the Spanish Phases I and II study groups, neither trimethoprim nor amoxycillin were prescribed.

5.2.6.3.2 Range of antibiotics

There was a slight decrease in the range of newly prescribed antibiotic items for UTIs in both males and females from Phases I to II in both the study and control groups but this difference was not significant ($p = 0.29$) (Table 5.29). The Spanish data were excluded from this analysis due to the number of recorded consultations in Phase II being halved. A borderline significant difference was found between countries ($p = 0.06$). The analysis was repeated for the range of new antibiotics prescribed for females of 16 years and above. The results were similar and again there was found to be no significant difference either between the study and control groups ($p = 0.42$), or between countries ($p = 0.06$). The largest decrease in the range from Phase I to Phase II between the control and study groups occurred in Ireland but this difference was also not significant ($p = 0.17$).

5.2.6.3.3 Prescribing of trimethoprim

The highest use of trimethoprim was in the Phase I study group of Northern Ireland (Table 5.28) where it represented 67% of the antibiotics prescribed for UTIs in females of 16 years and over, compared with 0% in Belgium, Portugal and Spain. Trimethoprim was the single most commonly prescribed new antibiotic for UTIs in females of 16 years and above (Table 5.30) as well as for all prescription categories combined (Table 5.32). For UTI prescribing overall in males and females, all prescription categories combined (Table 5.33), trimethoprim use varied from 0% in Spain to 58% in England (mean 24%, SD 24). The level of prescribing of trimethoprim therefore generally fell considerably below the proposed 70% mark.

5.2.6.3.4 Prescribing of co-trimoxazole

Co-trimoxazole was the fifth most commonly prescribed new antibiotic overall for UTIs (Table 5.30). In Ireland and Portugal, co-trimoxazole was the second most commonly prescribed antibiotic and relatively high levels of its use were also found in Belgium and Italy.

Between study group Phases I to II, the overall level of co-trimoxazole prescribing almost halved (Table 5.31) with a particularly large decrease in Belgium and Ireland. The level in Italy however remained consistent between Phases and there was a three-fold increase in its use from the Phase I study group to Phase II in Portugal.

5.2.6.3.5 Prescribing of cephalosporins

Second and third generation cephalosporins did not feature among the more commonly prescribed new antibiotic items for UTIs (Table 5.30 and Table 5.31).

For UTI prescribing in females of all prescription categories combined (Table 5.32) and overall in both males and females (Table 5.33), the levels of second and third generation cephalosporins were relatively low. Of particular note was that in Italy and Spain the cephalosporins prescribed were not first generation.

5.2.6.3.6 Prescribing of fluoroquinolones

From Table 5.30 it can be seen that of the top 15 newly prescribed antibiotic items for UTIs, nearly half were fluoroquinolones. Of the fluoroquinolones represented in Table 5.30, their use varied from 2.2% in Northern Ireland to 84% in Spain (mean 35%, SD 32). In Northern Ireland, only one fluoroquinolone was used compared with seven in Italy. In Belgium and Portugal, norfloxacin was the drug of choice for UTIs in females of 16 years and over, and in Italy and Spain pipemidic acid was the drug of choice followed by norfloxacin in both countries. From study group Phases I to II (Table 5.31), with the exception of slight changes in preference of fluoroquinolone such as the increased use of nalidixic acid in England, overall use of fluoroquinolones was fairly similar.

5.2.6.3.7 Prescribing of combination antibiotics

Only 239 (18%) of the 1,319 antibiotic drug entities prescribed overall in females of 16 years and over for UTIs belonged to combination antibiotics and of these 214 entities represented co-amoxiclav and co-trimoxazole. In males and females combined, there were 1,783 antibiotic drug entities prescribed for UTIs of which 361 (20%) were part of combination antibiotics and 328 of the 361 entities represented co-amoxiclav and co-trimoxazole (all but 2%). Co-amoxiclav was the most commonly used combination antibiotic varying from 0% in Belgium to 17% in Scotland in females of 16 years and above (mean 7.2%, SD 6.1) and from 0.6% in Italy to 21% in Ireland (mean 8.2%, SD 7.5) in males and females combined. Collectively in the treatment of UTIs, co-amoxiclav was prescribed twice as much as amoxycillin.

5.2.6.3.8 Prescribing of aminoglycosides

Of the 1,042 newly prescribed antibiotic items for UTIs in females of 16 years and above, only six were for aminoglycosides. There were three prescriptions for netilmicin in Portugal and two in Italy, in addition there was one prescription for gentamicin in Italy.

5.2.6.4 Comparisons of antibiotic prescribing

5.2.6.4.1 Sulphonamides and trimethoprim

Prescribing of this group of antibiotics for UTIs in females of 16 years and over varied from 1.7% in Spain to 56% in England (mean 32%, SD 23) (Table 5.32). In both males and females for all ages and categories of prescription combined, their use varied from 2.6% in Spain to 58% in England (mean 33%, SD 21) (Table 5.33). Trimethoprim represented the bulk of prescribed items in this group of antibiotics, although higher levels of co-trimoxazole were prescribed in Belgium, Italy, Portugal and Spain than trimethoprim. Thus, there was a greater use of trimethoprim in combination, in all of the non-English speaking countries.

5.2.6.4.2 Fluoroquinolones

The overall level of fluoroquinolone prescribing for UTIs was marginally below that of sulphonamides and trimethoprim. In females of 16 years and over, fluoroquinolone use varied from 3% in Northern Ireland to 81% of the items prescribed for UTIs in Spain (mean 34%, SD 31) (Table 5.32). In males and females, their use varied from 3.5% in Northern Ireland to 82% in Spain (mean 33%, SD 31) (Table 5.33). The results indicate that in England, Ireland, Northern Ireland and Scotland, fluoroquinolone use was below 10%, whereas in Belgium, Italy and Portugal fluoroquinolones were prescribed for between a third and two thirds of UTIs, and in Spain for over 80% of UTIs. Norfloxacin was the most commonly prescribed fluoroquinolone overall and was the drug of choice in Belgium. In Italy and Spain, norfloxacin and pipemidic acid were of roughly equal first choice and in Portugal norfloxacin and ofloxacin were of roughly equal first choice.

5.2.6.4.3 Penicillins

Penicillins were the third most commonly prescribed group of antibiotics for UTIs varying from 2.1% in Italy to 33% in Northern Ireland (mean 16%, SD 9.5) in females of 16 years and over (Table 5.32). For UTIs overall in all males and females, their use varied from 3% in Italy to 34% in Northern Ireland (mean 17%, SD 11) (Table 5.33). In this group, co-amoxiclav was most commonly prescribed, being the drug of choice in Ireland, Portugal, Scotland and Spain. In the remaining four countries, amoxycillin was the penicillin of choice.

5.2.6.4.4 Miscellaneous antibiotics

This group comprised four drugs, namely: nitrofurantoin, fosfomycin, fusidic acid and clindamycin. Combined, they represented the fourth most commonly prescribed class of antibiotics in females of 16 years and over (Table 5.32) and the fifth most common for UTIs overall, in all males and females combined (Table 5.33). In females of 16 years and over, their use varied from 0.7% in Scotland to 31% in Belgium (mean 9.2%, SD 8.7) and in males and females combined from 0.6% in Scotland to 25% in Belgium (11%, SD 11). Nitrofurantoin was the most commonly prescribed drug in

this antibiotic group in five of the eight countries, with the exception of Italy, Northern Ireland and Spain where fosfomycin was more prevalent.

5.2.6.4.5 Cephalosporins

The level of cephalosporin use was fairly similar to the miscellaneous antibiotic usage. Cephalosporins were the fifth most commonly prescribed antibiotic group for UTIs in females of 16 years and over but (Table 5.32) the fourth most common group for UTIs in all males and females combined (Table 5.33). Prescribing of cephalosporins varied from 0% in Belgium to 26% in Scotland (mean 6.9%, SD 8.5) in females of 16 years and above and in all males and females combined from 0% in Belgium to 25% in Scotland (mean 7.5%, SD 8.1).

5.2.6.4.6 Aminoglycosides

In females of 16 years and above (Table 5.32), aminoglycosides were used in only Italy (1.7%) and Portugal (1.7%). For all prescribing data in males and females combined (Table 5.33), aminoglycoside prescribing for UTIs was only found in Italy (2.1%), Portugal (1.6%) and Spain (0.7%).

5.2.6.4.7 Tetracyclines and Macrolides

In females of 16 years and over (Table 5.32), together they represented 0.6% of antibiotics prescribed and for all males and females in all prescription categories, they accounted for 0.5% of antibiotic use (Table 5.33).

5.2.7 Discussion

Receipt of the European Formulary and participation in the educational intervention appeared to have little impact on antibiotic prescribing for UTIs. There was a slight trend towards greater concordance with first-line recommended drugs in the overall study group compared with the control group but no decrease in the range of newly prescribed antibiotics was found.

In the study, the proportion of consultations varied between 1.5% in Northern Ireland to 2.6% in Ireland and a similar range of UTI prevalence has been reported

within the UK.[287] Over 70% of patients who presented with a UTI were female of 16 years and above and considerably more than 70% of the prescriptions for UTIs were for newly prescribed items. These results are not surprising as UTIs are more common in women.[296] Nevertheless the findings were important as the volume of UTI prescribing data available for analyses in this study was considerably less than that for the two areas of respiratory tract infections for which antibiotic use was also investigated.

The concordance levels for UTI prescribing were disappointing, although the results presented were for first-line Formulary recommended drugs only. If the concordance with the Formulary had additionally taken into account the use of fluoroquinolones (recommended in the Formulary for use where first-line drugs had failed or were contraindicated), then the concordance levels would have undoubtedly been greater. Summation of fluoroquinolone prescribing from Table 5.31 to trimethoprim and amoxycillin use within each of the countries would have still given concordance levels that were disappointing. Despite the Formulary allowing flexibility from country to country with respect to the fluoroquinolone of choice, there was inconsistent fluoroquinolone prescribing in southern Europe with wider ranges used than elsewhere. Overall, there was a notable contrast in the use of fluoroquinolones for UTIs varying from less than 10% of the antibiotics used in the UK to more than 80% of the newly prescribed antibiotic items in Spain. High levels of fluoroquinolone use in Spain have been reported by others[297] and more recently the level of resistance to fluoroquinolones has been found to be considerable in some parts of Spain.[298] Despite there being differences in culture and sensitivity patterns both within and between countries, there appears to be little rationale in the excessive use of fluoroquinolones prescribed for UTIs in southern Europe.

Trimethoprim use was highest in the UK regions and was the drug of choice for UTIs there but the level of prescribing generally fell well below the proposed target figure of 70% in all the countries. One positive outcome is that the intervention may have helped demote the use of co-trimoxazole, particularly in Belgium and Ireland and in both their study groups, there was a corresponding increase in the level of trimethoprim prescribing from Phases I to II. It has been shown that trimethoprim alone

is as good as co-trimoxazole for simple UTIs in general practice and has potentially fewer side-effects.[299]

There are some limitations in investigating the area of antibiotic prescribing for UTIs in this study. Firstly UTIs may present as either simple or complicated infections which are managed in different ways and there is no way of separating the two types in this data set, nevertheless the majority of presentations are of the former type. Secondly, it is not known where urine culture has been carried out with appropriate tailoring of treatment, compared with where a 'best guess' treatment strategy has been selected. Thirdly, as already mentioned culture and sensitivity patterns differ from region to region and this will be partially responsible for some variations in antibiotic prescribing patterns. Fourthly, no data were available comparing the duration of antibiotic treatment regimens which are known to vary.[288] There are also some limitations with respect to recommendations for UTI treatment within the European Formulary. Amoxycillin has been reported to be unsuitable for empirical therapy because of its association with a high failure rate as a result of high levels of resistance[289,293] but it was recommended as first-line treatment in the European Formulary. Secondly, the European Formulary appeared to be limited in its range of treatment options. Nitrofurantoin and an oral first generation cephalosporin (except for cephalexin) which have been recommended elsewhere as alternative first-line drugs[288,289], were excluded.

5.3 RESPIRATORY TRACT INFECTIONS

5.3.1 Introduction

The prescribing of antibiotics for respiratory tract infections (RTIs) has long been and continues to be an area of controversy.[300] Davey *et al*, a general practice research group from Dundee, analysed PACT and SPA data from 1980 to 1991 which revealed that there was an average increase of 5% per year for all antibacterial items prescribed in the community in England and Scotland.[301] The authors speculated that the changes represented an increased tendency to prescribe for respiratory conditions. Despite this increase being of concern, even larger increases in antibiotic prescribing were found over the same time period in other countries (Table 5.34).

Increased prescribing of antibiotic items has major implications for increased cost burdens on different health care systems. In the UK, the Audit Commission in 1994 estimated that £295m could be saved from the NHS drug bill if overprescribing was reduced.[30] Of this, approximately £80m was attributed to antibiotics which at the time represented 45% of the total cost of antibiotic prescribing. Antibiotics are frequently prescribed for viral infections against which they are ineffective; even when they are indicated, the duration of treatment is often unnecessarily long. In addition, research by GPs in 11 general practices in Southampton showed that antibiotic prescribing increases patients' belief in antibiotics and their intention to reconsult, compared with either not prescribing or offering a delayed prescription.[302] Currently the cost of oral antibiotics in England and Wales is £175m.[29]

Unnecessary overprescribing of antibiotics is also a major public health concern as it promotes the building up of resistance and disturbs the balance of micro-organisms in the body which may permit more severe infections to develop. Research between 1991 to 1996 which involved taking samples from patients in England and Wales with meningitis or septicaemia has found that the percentage of *Staphylococcus aureus* samples resistant to beta-lactam antibiotics has increased from 1.5% to nearly 22%.[303] In September 1998, the UK Standing Medical Advisory Committee (SMAC) published a report called the 'Path of Least Resistance' which identified four areas that could

make a significant impact on the volume of antimicrobials prescribed.[304] The report included the following key recommendations that:

- antibiotics should not be prescribed for simple coughs and colds,
- antibiotics should not be prescribed for viral sore throats,
- special consideration should be made when determining the appropriate duration of treatment,
- antibiotic prescribing over the telephone should be limited to exceptional cases.

There is no single antibiotic which is effective against all bacteria. Some antibiotics such as penicillin have a relatively narrow spectrum of activity, while others have a much broader spectrum of activity. It is prescribing of the latter that has been shown to promote most drug resistance. The main problem in prescribing of antibiotics in general practice is that prescribers rarely know the precise organism involved, nor consequently the best drug to use. In spite of widespread use of antibiotics over the last 40 years, many bacterial infections in general practice remain sensitive to the well tried and tested older antibiotics which provides a strong argument against the prescribing of newer antibiotics unless there is a specific indication for their use.

The frequency with which patients with acute respiratory problems present to their GP accounts for 17% of all 'acute' consultations as recorded in one study[148] though antibiotic prescribing for RTIs covers a vast range of presenting diagnoses and symptoms. Respiratory infections have also been reported to be the most frequent reason for primary health care consultation in Spain.[305] For the purposes of this thesis in order to determine any effect of the intervention as well as to compare and contrast differences between the countries, it was decided to group together some of the diagnostic codes as follows:

- Throat Infections
  - acute pharyngitis/tonsillitis and sore throat/throat infection
- Lower Respiratory Tract Infections
  - acute bronchitis, bronchitis, chronic bronchitis and pneumonia

5.3.2 Throat infections

5.3.2.1 Diagnosing Throat Infections

The sore throat syndrome is one of the commonest presenting conditions in general practice and there is strong evidence that the majority are caused by viruses for which the prescription of an antibiotic is inappropriate. Streptococcal sore throat/pharyngitis is difficult to diagnose on clinical grounds alone as it is usually indistinguishable clinically from viral infections. Culture of a throat swab is used conventionally to make a definitive diagnosis. Using throat-swab culture as a method of determining the cause of sore throat has several limitations including errors that can arise when the swab is positive because of carriage rather then streptococcal infection.[306] In addition, the cost of swabbing all acute sore throats routinely in UK general practice would be approximately £40 million annually. The difficulties in establishing the causative agents and the uncertain contribution this information provides in deciding on treatment as well as the time delay makes the choice of treatment controversial.[307] For practical reasons an empirical, epidemiologically based approach is often used by doctors and may be accepted in many cases. Although this approach is inexpensive, using clinical scorecards or symptom clusters to identify individuals who would benefit from treatment is insensitive with low predictive value and therefore this method is not entirely rational.[308]

5.3.2.2 Rational prescribing for Throat Infections

The aim of treatment is to relieve symptoms, prevent complications and limit the spread of the illness by eradicating the infecting strain of streptococcus (if present) from the upper respiratory tract.

A streptococcal throat infection is usually self-limiting and symptoms can be relieved with simple analgesics, though symptoms may resolve more quickly when penicillin is given. Traditionally, bacterial pharyngitis has been treated with antibiotics to prevent serious complications like acute rheumatic fever or acute glomerulonephritis.[306] The rarity of these complications in industrialised countries has led to controversies about the value and cost-effectiveness of treating streptococcal sore throat with antibiotics.[300] Nevertheless, relatively recent outbreaks of rheumatic fever in the US suggest that some streptococcal micro-organisms may still be potentially dangerous for a minority of patients.[309] Immediate treatment may therefore be indicated in patients with severe pharyngitis, with or without exudate but with pronounced systemic features and in those with scarlet fever. Delaying treatment to await the results of culture does not increase the risk of complications but if time is taken to obtain bacteriological results, antibiotics are not necessarily going to shorten the course of the illness.

5.3.2.3 European Formulary recommendations

The following drug treatment strategy was recommended in the EF:

1. Symptomatic - simple analgesics (e.g. aspirin and paracetamol)
2. Antibiotics - phenoxymethylpenicillin or erythromycin

The European Formulary Group (EFG) recommendations in the Appendix included that:

- pharyngitis/tonsillitis can usually be treated with a simple analgesic,
- when a swab confirms a bacterial infection, phenoxymethylpenicillin is the drug of choice or alternatively erythromycin for patients allergic to penicillin,
- prescribing of amoxycillin or cephalosporins (effective broad spectrum drugs) for this condition may favour the emergence of resistant *Haemophilus influenzae* resistant strains in the community.

5.3.2.4 Proposed prescribing performance indicators

The following hypotheses were drawn up based on performance indicators which could be adapted to critically explore the prescribing data for pharyngitis/throat related disorders in the different countries. The hypotheses were that for pharyngitis/throat related disorders::

- the proportion of newly prescribed antibiotics which were listed within the European Formulary would increase following the educational intervention and the distribution of the Formulary,
- the proportion of consultations resulting in an antibiotic prescription would reduce following the intervention and distribution of the Formulary,
- the range of new drugs prescribed would reduce following the educational intervention and the distribution of the Formulary,
- the prescribing of broad spectrum antibiotics would be limited following the educational intervention and distribution of the Formulary as they promote a build up of drug resistance,
- the prescribing of new macrolides e.g. clarithromycin would reduce following the intervention and distribution of the Formulary as they are expensive and should only be used for resistant strains compared with erythromycin which is a reasonable alternative for patients allergic to penicillin,
- the proportion of simple analgesics prescribed which were listed within the European Formulary would increase following the educational intervention and the distribution of the Formulary,
- the proportion of consultations resulting in an analgesic prescription would increase following the intervention and distribution of the Formulary.

5.3.2.5 Data manipulation/methodology

In order to critically evaluate the prescribing for throat infections by the GPs in the different countries, all the searches except where indicated involved a matching of drugs to diagnoses. The following searches were performed in the database:

- all antibiotic prescriptions for throat infections for both Phases combined, no matching of drugs to diagnoses,
- all consultations for throat infections for both Phases combined, no matching of drugs to diagnoses,
- new antibiotic prescriptions for throat infections, Phase I only,
- new antibiotic prescriptions for throat infections, Phase II only,
- new antibiotic prescriptions for throat infections for both Phases combined,
- new analgesic and NSAID prescriptions for throat infections, Phase I only,
- new analgesic and NSAID prescriptions for throat infections, Phase II only,
- new analgesic and NSAID prescriptions for throat infections, both Phases combined,
- all drug prescribing for throat infections for both Phases combined,
- new drug prescribing for throat infections, both Phases combined,
- all study group Phase I new drug prescribing for throat infections,
- all study group Phase II new drug prescribing for throat infections,
- new antibiotic prescriptions for throat infections, no matching of drugs to diagnoses Phase I only,
- new antibiotic prescriptions for throat infections, no matching of drugs to diagnoses Phase II only,
- new analgesic and NSAID prescriptions for throat infections, no matching of drugs to diagnoses Phase I only,
- new analgesic and NSAID prescriptions for throat infections, no matching of drugs to diagnoses Phase II only.

For the country by country comparative prescribing results section, it was decided to combine the data from Phase I and II which is likely to provide a more meaningful illustration of the overall prescribing pattern compared with looking at the trends in each of the Phases separately.

In the results tables, the data were presented in order of prescribing volume in terms of the number of items prescribed. The drug data for throat infections were sorted based on the following classification:

1 Penicillins including:

- amoxycillin combined with clavulanic acid (betalactamase inhibitor)

2 Cephalosporins

3 Tetracyclines

4 Aminoglycosides

5 Macrolides

6 Sulphonamides and trimethoprim

7 Fluoroquinolones

8 Other miscellaneous antibiotic groups combined including:

- bacteriostatics, lincosamides and other individual antibiotics

9 Analgesics and NSAIDs

10 Other drug entities (neither antibiotics nor analgesics) prescribed by the GPs for throat infections

5.3.2.6 Results

5.3.2.6.1 Morbidity/prevalence patterns

The different throat infection diagnostic codes when consolidated represented the fifth most commonly occurring diagnosis and accounted for 3.7% of the total number of general practice consultations. From Table 5.35 it can be seen that the proportion of consultations for throat infections varied between 2.1% in Spain to 5.4% in Belgium (mean 3.9%, SD 1.2). The proportion of patients presenting with a throat disorder who

received treatment varied from 79% in England to 99.8% in Portugal (mean 90%, SD 6.3). Of a total of 3,830 patients presenting with a throat disorder, 3,430 were prescribed 4,235 drug entities of which 3,588 (85%) were new prescriptions and 3,863 (91%) were single non-combination drugs.

5.3.2.6.2 Prescribing performance indicators before and after the intervention

5.3.2.6.2.1 Concordance with antibiotics recommended in the European Formulary

For newly prescribed antibiotic items, both the intervention and control groups moved away by -1.8% (4.1) and -6.7% (4.9) respectively from the Formulary recommendations (Table 5.36). Despite there being a larger movement away by the control group, the difference was not significant ($p = 0.43$). Significant differences were found between the countries ($p = 0.002$) but there was no significant ($p = 0.42$) country-by-group interaction.

In Ireland, there appeared to be some positive movement towards increased prescribing of the Formulary recommended drugs - the difference between the intervention group from Phase I to II was significant ($p = 0.009$) and the difference between the control and intervention groups from Phases I to II was of borderline significance ($p = 0.04$). There was also some positive movement towards the Formulary recommended drugs in Italy, Northern Ireland and Portugal (Table 5.36) but the differences were not statistically significant. Overall, the greatest concordance with the Formulary can be seen to occur in the English speaking countries with little prescribing of the two Formulary recommended antibiotics in Belgium, Italy, Portugal and Spain.

Phenoxymethylpenicillin was markedly the more commonly prescribed antibiotic, of the two recommended in the European Formulary. In both Ireland and Northern Ireland prescribing levels of phenoxymethylpenicillin increased by nearly 15% from study group Phase I to study group Phase II. In contrast there was no prescribing of this drug in Italy, Portugal and Spain (Table 5.37). Erythromycin levels fluctuated between the study groups in the two time periods with increases in all countries except for England and Spain. Of particular note was the increase in prescribing of erythromycin in Portugal from 4.6% to 14%.

5.3.2.6.2.2 Proportion of consultations resulting in a 'new' antibiotic prescription

Overall there was no significant difference in the proportion of patients receiving new antibiotics for throat infections between Phase I and Phase II ($p = 0.18$). Belgium was excluded from the analysis as no data were provided on consultations without prescriptions. The average proportion of consultations resulting in a prescription marginally decreased in the intervention group by 1.2% (3.4) but on average decreased even more in the control group by 8% (3.8) between Phases I and II (Table 5.38). The proportion of consultations resulting in a prescription decreased in the intervention groups of all the countries except for Portugal and Scotland but even greater reductions were seen in all the control groups except for England and Italy. In none of the countries did any of the differences prove to be statistically significant. Overall in Spain approximately one in three consultations for a throat infection resulted in a new antibiotic prescription whereas in Ireland, over 70% of these consultations resulted in a script for a new antibiotic.

5.3.2.6.2.3 Range of new drugs prescribed

There was a very slight decrease in the range of new drugs prescribed in both the intervention and control groups (Table 5.39). Spain was excluded from the statistical analysis due to half the number of consultations having been recorded in Phase II. There was a similar reduction in range between the intervention and control groups and so no significant difference were found between them ($p = 0.16$) but significant differences were found between countries ($p = 0.02$). The largest reduction in the range between the intervention and control groups occurred in Belgium and the difference there was found to be of borderline significance ($p = 0.04$). The range of new drugs prescribed by the Belgian intervention group appeared to be unusually high though compared with the corresponding control group there. Other slight decreases in the range were found in Ireland and Northern Ireland compared with their control groups, but neither of these was found to be statistically significant.

In general, the range of new drugs prescribed for throat infections was lowest in England and Scotland averaging approximately 2.5 drugs per GP compared with Italy and Portugal where the ranges prescribed were more than double this number.

5.3.2.6.2.4 Broad spectrum antibiotic prescribing

The prescribing of amoxycillin for throat infections was 26% overall which was almost equivalent to that of phenoxymethylpenicillin (Table 5.40). Levels of amoxycillin prescribing increased substantially in the intervention groups of Italy, Portugal and Scotland from Phase I to Phase II (Table 5.41) despite the educational intervention discouraging the prescribing of broad spectrum penicillins for sore throat. The greatest drop in amoxycillin prescribing occurred in the intervention group of Northern Ireland from 19% to 12 % (Table 5.41) but levels of ampicillin (another broad spectrum penicillin) remained high there. The level of ampicillin prescribing decreased in the overall study group from Phase I to Phase II which was predominantly due to a decrease in Ireland from 11% to 2.2%. However in Ireland the relative proportion of prescribing of co-amoxiclav nearly doubled from 4.6% to 8.7% from Phase I to Phase II.

Cephalosporins are also broad spectrum antibiotics and are thus discouraged from being prescribed for throat infections. From the intervention groups in Table 5.41 it can be seen that no individual cephalosporin represented more than 1% of the prescribing in England, Scotland and Spain. The level of cefaclor reduced overall from Phase I to Phase II to represent less than 1% of prescribing for throat infections and prescribing levels of cephalexin decreased between time periods in the study groups of the three countries where it was prescribed namely, Ireland, Italy and Northern Ireland.

5.3.2.6.2.5 Prescribing of new macrolides

With Phase I and II new antibiotic data combined, erythromycin prescribing overall was more than double that of clarithromycin, the second most commonly prescribed macrolide antibiotic (Table 5.40). However, in the study groups of Phase I (Table 5.37 and Table 5.41), prescribing of clarithromycin was overall more than erythromycin for all drug categories combined and clarithromycin was the macrolide of choice in Ireland, Italy, and Portugal and of equal choice with erythromycin in Scotland. Between Phase I and II the overall prescribing of clarithromycin in the study groups decreased by a third.

At the same time, the prescribing of erythromycin doubled resulting in it becoming the macrolide of choice in all countries except for Belgium where the level of clarithromycin was five times that of erythromycin (Table 5.40). In Spain, neither erythromycin or clarithromycin were prescribed. Some of these changes in prescribing may have been prompted by the intervention and dissemination of the Formulary.

5.3.2.6.2.6 Concordance with analgesics recommended in the European Formulary

For symptomatic treatment of throat infections, the intervention group appeared to move towards prescribing the European Formulary recommended drugs by 15% (7.5) compared with the movement away by the control group -6.7% (7.3) (Table 5.42). This difference between the control and study groups was found to be highly significant ($p = 0.002$) and there were also found to be significant differences between countries ($p = 0.03$) but no significant country by group interaction ($p = 0.13$). From Table 5.42 it can be seen that there was no new simple analgesic prescribing in the control groups of England and Ireland but even with exclusion of these two countries from the analysis the differences were still statistically significant both between the control and intervention groups ($p = 0.002$) and between countries ($p = 0.02$). The greatest movement towards the prescribing of European Formulary recommended drugs can be seen to occur in Belgium, Northern Ireland and Portugal.

Of all the drugs prescribed for throat infections, paracetamol accounted for 9.3% of the prescribing overall and was the most commonly prescribed analgesic. The prescribing levels of paracetamol increased in the intervention groups from Phases I to II in all the countries except for England and Ireland (Table 5.37). The largest increase in paracetamol prescribing was found in Portugal where levels increased from 3.1% to 19%. There were marginal increases in the prescribing of aspirin in the intervention groups of England, Ireland and Portugal but for the intervention groups combined, aspirin prescribing decreased between Phase I to II.

The most commonly prescribed analgesics for throat infections which were outside the Formulary recommendations can be seen in Table 5.43.

5.3.2.6.2.7 Proportion of consultations resulting in a 'new' analgesic prescription

The combined effect of the European Formulary and educational intervention did not increase the proportion of consultations for throat infections resulting in the prescription of a new analgesic (p = 0.75) (Table 5.44). Significant differences in the proportion of consultations resulting in an analgesic prescription were however found between countries (p = 0.004). The largest difference between control and intervention groups in the prescribing of analgesics was found in Northern Ireland (Table 5.44) but this difference was not significant (p = 0.08). An increase in the prescribing of analgesics was also seen in Italy and Portugal but again neither of these positive trends was statistically significant.

5.3.2.6.3 Comparisons of antibiotic prescribing

5.3.2.6.3.1 Penicillins

Of the antibiotics and analgesics prescribed for throat infections, the penicillins were the most popular group used accounting for 56% of the drugs prescribed from all the drug categories collectively (Table 5.45). Penicillin group prescribing varied from 28% in Belgium and Italy to 80% in Scotland (mean 54%, SD 23). Phenoxymethylpenicillin and amoxycillin were the penicillins of choice depending on the country and together they accounted for approximately 75% of the penicillin prescriptions. For all drug categories combined, phenoxymethylpenicillin use varied from 0% in Italy and Portugal to 43% in Scotland (mean 20%, SD 21) and amoxycillin use varied from 6.7% in England to 29% in Ireland and Spain (mean 19%, SD 7.7). For new antibiotics only (Table 5.40), phenoxymethylpenicillin use varied from 0% in Italy and Portugal to 51% in England (mean 23%, SD.23) and amoxycillin use varied from 7.6% in England to 57% in Spain (mean 29%, SD 15).

5.3.2.6.3.2 Macrolides

Macrolides were the second most common group of drugs prescribed from all drug categories combined for throat infections, accounting for 12% of the drugs prescribed (Table 5.45). Macrolide use varied from 6.1% in Northern Ireland to 18% in Portugal (mean 9.5%, SD 3.7). Erythromycin was the most commonly prescribed macrolide, varying from 2.1% in Belgium to 13% in England (mean 6%, SD 3.2). As a proportion

of 'N' antibiotic prescribing, erythromycin prescribing levels varied from 2.5% in Belgium to 14% in England (mean 8%, SD 3.6) (Table 5.40).

From Table 5.40, it can be seen that in all English speaking countries erythromycin was the macrolide of choice but in the other four countries there was a trend to prescribe the newer antibiotics. In Belgium, clarithromycin was the macrolide of choice being prescribed eight times more frequently than erythromycin. In Italy, seven different macrolides were prescribed. Azithromycin was the macrolide of choice followed by clarithromycin, erythromycin and roxithromycin. Whilst erythromycin was the macrolide of choice in Portugal and Spain, summation of the newer macrolides prescribed in both countries exceeded erythromycin alone.

5.3.2.6.3.3 Cephalosporins

Cephalosporins were the third most common group of antibiotics prescribed varying from 0.5% in Spain to 6.9% in Belgium and Ireland (mean 3.5%, SD 2.6) (Table 5.45). Cephalexin was the most commonly prescribed cephalosporin both from the new antibiotics and from all the drug classes combined (Table 5.40). Despite this, the bulk of the cephalosporin prescribing came from the prescribing of cefaclor, cefuroxime and cefixime, all of which are second generation cephalosporins. Prescribing of these three drugs was found to be most common in Ireland, Italy and Portugal.

5.3.2.6.3.4 Sulphonamides and trimethoprim

Sulphonamides and trimethoprim represented 1.9% of the antibiotics and analgesics prescribed for throat infections, their use varying from 0% in Spain to 4.3% in Belgium (mean 1.6%, SD 1.8) (Table 5.45). Co-trimoxazole accounted for two-thirds of the prescribing in this antibiotic group and was the most commonly prescribed in Ireland and Italy. For new drugs in Ireland and Italy (Table 5.40), co-trimoxazole accounted for 3.6% and 3.9% respectively and for all prescription categories combined it accounted for 3.3% and 2.2%.

5.3.2.6.3.5 Miscellaneous antibiotics

The miscellaneous antibiotics accounted for 1.5% of the drugs prescribed for throat infections. The most commonly prescribed antibiotic in this category was fusafungine which varied from 0% in England, Scotland and Spain to 3.5% in Portugal (mean 0.8%, SD 1.2) (Table 5.45). Fusafungine is active against both some Gram-positive and some Gram-negative organisms and possibly has some anti-inflammatory action. It is used in the form of an aerosol spray in the treatment of throat infections.

5.3.2.6.3.6 Tetracyclines, Fluoroquinolones and Aminoglycosides

When combined, these three groups of antibiotics accounted for only 1.1% of the drugs prescribed for throat infections. From Table 5.45 it can be seen that tetracyclines were most commonly prescribed in Belgium (1.1%) and Ireland (1.4%) fluoroquinolones were most commonly prescribed in Italy (1.3%) and aminoglycosides in Belgium (1.6%).

5.3.2.6.4 Comparisons of analgesic including NSAID prescribing

This drugs category represented just under a quarter of those prescribed for throat infections from all drug categories combined. Their use varied from 4.5% in Ireland to 52% in Spain (mean 28%, SD 19) (Table 5.45).

5.3.2.6.4.1 Analgesics

Analgesic prescribing, excluding NSAIDs varied from 2.7% in Ireland to 45% in Spain (mean 16%, SD 14). Paracetamol was universally the analgesic of choice accounting for over 80% of the analgesic prescribing varying from 1.8% in Ireland to 31% in Spain (mean 13%, SD 9.9) (Table 5.45). Co-codamol was generally the second analgesic of choice depending on the country. From Table 5.43 it can be seen that in the intervention groups from Phases I to II, co-codamol use decreased from 1.9% to less than 1%.

5.3.2.6.4.2 NSAIDs

NSAIDs represented nearly 14% of the total prescribing of antibiotics, analgesics and anti-inflammatories prescribed for throat infections. Their use varied from 0.7% in Scotland to 35% in Italy (mean 11%, SD 13) (Table 5.45). Nimesulide (a cox-2

NSAID) was the most commonly prescribed NSAID despite its prescribing being restricted to Italy and Portugal only. From Table 5.43 it can be seen that prescribing of this drug decreased considerably in the intervention group of Portugal from Phase I to Phase II.

5.3.2.7 Discussion

The difference in prescribing patterns between Phases I and II suggest that the educational intervention may have had some positive effects in improving the management of throat infections as has been found with other similar interventions in primary care.[310-312] The three most successful outcomes of the study were that:

1. there was a highly significant increase in concordance by the intervention group overall compared with the control group, towards EF recommended simple analgesics and within countries the greatest increases were seen in Belgium, Northern Ireland and in Portugal.
2. for antibiotic prescribing, the increase in concordance with the EF by the Irish intervention GPs compared with the control group was statistically significant.
3. there was a significant reduction in the range of new drugs prescribed for throat infections between the control and intervention groups in Belgium.

Throat infections are an example of an acutely presenting condition in primary care and hence 85% of the drug entities prescribed for it in this study were found to be for a newly prescribed item. A combination of such a high proportion of prescriptions belonging to this category and the fact that throat infections represented the fifth most common diagnosis, meant that any effect of the educational intervention would be expected to be more apparent.

Antibiotic concordance with the Formulary in general was disappointing, especially in the non-English speaking countries where the average levels were well below 50%. In these countries, concordance levels with the Formulary recommended simple analgesics were better than those for antibiotics but still lower than concordance levels in the English speaking countries. Patients presenting with throat infections in southern

European countries were found to be more likely to receive a related prescription than elsewhere. However one positive feature of the prescribing patterns for throat infections in Belgium and the southern European countries was that, between one third and half the number of prescriptions issued were for analgesics/anti-inflammatories which was a notably higher proportion than in English speaking countries. It is possible though that patients in the UK may be encouraged to purchase OTC analgesics which are relatively cheap.

Of the antibiotics recommended by the Formulary, phenoxymethylpenicillin prescriptions increased between Phases I and II, from 21% to 36% and from 31% to 44% of all new drugs used in the intervention groups of Ireland and Northern Ireland respectively. Erythromycin prescriptions increased from 4.6% to 14% in Portugal replacing clarithromycin as the main macrolide there. Prescribing of erythromycin also increased after the intervention in the study groups of Ireland, Italy and Scotland to replace clarithromycin as the macrolide of choice there. However with the data for control and intervention groups in both Phases combined, it was noted that seven different macrolides were prescribed by the Italian GPs with azithromycin being the macrolide of choice, followed by clarithromycin. While this is indicative of irrational prescribing, these patterns may be partially explained by the finding of a sharp rise in erythromycin resistant rates in the mid-1990s in North Italy.[313] Common prescribing of macrolides for acute URTIs in primary care has been reported by other Italian researchers.[314] In Portugal and Spain, summation of the newer macrolides prescribed collectively also exceeded the number of erythromycin prescriptions there.

In the study, amoxycillin was both the antibiotic of choice in Belgium, Italy, Portugal and Spain and the level of amoxycillin prescribing overall was almost as high as that of phenoxymethylpenicillin. Although amoxycillin has been found to be as effective as phenoxymethylpenicillin in treating throat infections[315], sore throats should be regarded as potentially indicative of glandular fever and thus broad spectrum antibiotics such as amoxycillin should not be used for 'blind' treatment of a sore throat.[6] There is also little justification for using amoxycillin for throat infections in countries where its cost is greater than that of phenoxymethylpenicillin, such as in the UK where it is almost double the price.[279] Of the other broad spectrum antibiotics

discouraged from being prescribed for throat infections, cephalosporin levels were minimal except for being prescribed by some GPs in Ireland and Northern Ireland.

There are several limitations in investigating the area of antibiotic prescribing for throat infections. Firstly the terminology used by GPs to classify and label the presenting complaint is inconsistent in-part due to the difficulty in making a clinical diagnosis. While it was considered acceptable to clump together codes for acute pharyngitis/tonsillitis and sore throat/throat infections in this analysis, the codes for respiratory tract infections and URTIs were not included. A 'respiratory tract infection' label does not indicate whether the condition was upper or lower and in any case URTIs incorporate acute otitis media and acute sinusitis, for which the recommended antibiotics where necessary, are slightly different. Research has shown that the use of a diagnostic label 'tonsillitis' is more likely to result in a prescription for penicillin than if the diagnosis were 'URTI' which would be more likely to result in symptomatic treatment[316] but it was not possible to investigate this further in this research. A second limitation is that it was not known whether patients were reattending, having experienced side-effects to previous treatment or because it may have failed. This may have accounted for only a relatively small number of antibiotic prescriptions though as one study in Southampton found reattendance rates to be low[302] and another study in Scotland found that of nearly 1000 patients who received at least one prescription for an antibiotic, only 14% of the infections required more than one antibiotic prescription to achieve a successful outcome.[317] Thirdly culture and sensitivity patterns vary both between[318,319] and within countries[320] and this will be partially responsible for variations in prescribing, as with the UTI prescribing patterns.

5.3.3 Lower respiratory tract infections

5.3.3.1 Diagnosing Lower Respiratory Tract Infections

There is considerable variation in the diagnosis classification by which GPs group the different presentations of lower respiratory tract infections (LRTIs). LRTIs overlap with and include many illnesses such as acute bronchitis, infectious exacerbation of chronic bronchitis and pneumonia.[149] LRTIs are frequent community-acquired infections affecting both the paediatric and adult population and are one of the commonest respiratory illnesses observed in daily medical practice.

Acute bronchitis implies acute inflammation of the bronchial tree and it is often associated with a preceding viral nasopharyngitis (common cold). The most common organisms responsible for secondary bacterial infection are *Streptococcus pneumoniae* and *Haemophilus influenzae* but the frequency with which they occur is unclear.[321]

Whilst many LRTIs seen by GPs are self-limiting conditions, between 5% - 10% are pneumonias.[322] In patients with suspected LRTI, there are no firmly established clinical criteria that absolutely exclude pneumonia and prospective studies show that no individual clinical findings or combination of findings will definitely confirm a diagnosis of pneumonia. Again the main organisms responsible are *Streptococcus pneumoniae*, *Haemophilus influenzae* and viruses.[321]

Many acute exacerbations of chronic obstructive pulmonary disease/airways disease (COPD/COAD) are associated with viral infection and the other organisms identified as the most common causes of secondary bacterial infection are *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Moraxella catarrhalis*.[323]

In general practice, the diagnosis of LRTI will nearly always be made on clinical grounds alone and the infecting organism is rarely identified. Clinical features such as older patients with more underlying disease ('typical') and younger patients with more upper respiratory tract findings and less underlying disease ('atypical') are the factors which usually determine the practitioners' strategy despite the unreliability of predicting the causative pathogen.[324]

Blood tests, sputum examination and culture are not usually done in the UK because it is generally considered that test results take too long to influence management. Chest x-rays are also seldom routinely done despite being indicated in certain patients, particularly smokers who are slow to recover or who have a recurrent LRTI. One study found that, even in patients already on an antibiotic, sputum culture results could often guide clinical decisions, such as in patients with chronic lung disease or in whom an antibiotic had failed.[325]

5.3.3.2 Rational prescribing for LRTIs

In the UK, approximately 75% of patients consulting their GP with an acute LRTI receive an antibiotic.[326] The same respiratory medical research team at Nottingham found that between 20-25% seek a second consultation often within a fortnight, usually because of persisting symptoms.[149] A follow up study revealed that nearly two thirds are prescribed a further course of antibiotic but investigation showed that few of these had infections that required such treatment.[327]

There have been several trials comparing a range of antibiotic treatment strategies with that of placebo for different LRTIs but, because of variations in inclusion and exclusion criteria, few studies can be statistically compared, leaving the evidence somewhat inconclusive. Even when a meta-analysis was performed comparing antibiotics used in COPD, the main outcomes measured differed from trial to trial making the analysis difficult.[328] Despite the results being statistically significant, only a small improvement was shown in patients receiving antibiotic therapy for acute exacerbations of COPD.

The majority of healthy adults with few symptoms are unlikely to benefit from antibiotic therapy. In clinical trials involving previously healthy patients with acute bronchitis, 19-36% developed unwanted effects from the antibiotic.[145,329] Resistance to antibiotics is becoming increasingly common in respiratory pathogens and any irrational antibiotic prescribing is likely to potentiate this problem.[330] Initial receipt of an antibiotic prescription for a respiratory infection may also influence patient expectations for future occasions.[331]

At the other end of the spectrum, antibiotic treatment should not be delayed in either adults or in children if pneumonia is suspected.[332] Epidemiological evidence shows that while many episodes of LRTI are due to viruses, bacterial infection, especially pneumococcal infection is more common in those over 60 years old and in those with other underlying medical disorders.[149] If antibiotics are necessary, then the aim of treatment is to treat as specifically as possible while ensuring that the most likely organisms are affected.

5.3.3.3 European Formulary recommendations

The following antibiotic drug treatment strategy based on efficacy, safety, convenience and cost was recommended in the European Formulary:

- amoxycillin
- benzylpenicillin
- doxycycline
- erythromycin

The European Formulary Group (EFG) recommendations in the Appendix included that:

- prescribing of antibiotics for acute bronchitis is almost always unnecessary,
- treating acute exacerbations of chronic bronchitis with antibiotics is controversial,
- previously well children and adults with pneumonia usually recover well with a prescription for a penicillin or erythromycin,
- rare pathogens should be suspected in patients at risk from pre-existing conditions and hospitalisation may have to be considered,
- GPs should prescribe from a small range of antibiotics,
- third generation cephalosporins, fluoroquinolones and new macrolides are relatively expensive and their use should be restricted to selected patients.

5.3.3.4 Proposed prescribing performance indicators

The following hypotheses were drawn up based on quality indicators which could be adapted to critically explore the prescribing data for LRTIs in the different countries. The hypotheses for LRTIs were that:

- the proportion of antibiotics prescribed which were listed within the European Formulary increased following the educational intervention and the distribution of the Formulary,
- the proportion of consultations resulting in an antibiotic prescription reduced following the educational intervention and distribution of the Formulary,
- the range of newly prescribed antibiotics would be reduced following the educational intervention and the distribution of the Formulary
- the prescribing of new macrolides such as clarithromycin would be reduced following the educational intervention and distribution of the Formulary as they are expensive and should only be used for resistant strains,
- the prescribing of fluoroquinolones would be reduced following the educational intervention and distribution of the Formulary for the same reasons as they are also expensive and should only be used for resistant strains.

5.3.3.5 Data manipulation/methodology

In order to critically evaluate the prescribing for LRTIs by the GP participants in the different countries the following searches (both sexes and all ages combined) were performed within the database and except where indicated involved a matching of drugs to diagnoses:

- all LRTI consultations, no matching of drugs to diagnoses for both Phases combined,
- all Phase I new antibiotics prescriptions for LRTIs,
- all Phase II new antibiotic prescriptions for LRTIs,
- all new antibiotic prescribing for LRTIs for both Phases combined,

- all drug prescribing for LRTIs for both Phases combined,
- all Phase I study group new drug prescriptions for LRTIs,
- all Phase II study group new drug prescriptions for LRTIs,
- all Phase I new antibiotics for LRTIs, no matching of drugs to diagnoses,
- all Phase II new antibiotics for LRTIs, no matching of drugs to diagnoses.

For the country by country comparative prescribing results section, it was decided to combine the data from Phase I and II as this is likely to provide a more meaningful illustration of the overall prescribing pattern compared with looking at the trends in each of the Phases separately.

In the results tables, the data were presented in order of prescribing volume in terms of the number of items prescribed. The antibiotic drug data for LRTIs were sorted based on the following classification:

1 Penicillins including:

- amoxycillin combined with clavulanic acid (betalactamase inhibitor)

2 Cephalosporins

3 Tetracyclines

4 Aminoglycosides

5 Macrolides

6 Sulphonamides and trimethoprim

7 Fluoroquinolones

8 Other miscellaneous antibiotic groups combined including:

- lincosamides as well as other individual antibiotics

9 Other drug entities (not antibiotics) prescribed by the GPs for LRTIs.

5.3.3.6 Results

5.3.3.6.1 Morbidity/prevalence patterns

The four lower respiratory tract diagnoses codes when combined represent the second most commonly occurring area of diagnosis overall accounting for 5.1% of the total number of general practice consultations. The proportion of consultations for LRTIs varied from 2.8% in Portugal to 9.5% in Belgium (mean 5.6%, SD 2) (Table 5.46). The proportion of patients presenting with a LRTI who received treatment varied from 89% in Scotland to 97% in Ireland (mean 94%, SD 3). Of a total of 5,190 patients with a LRTI, 4,817 were prescribed 6,773 drug entities of which 3,966 (59%) were new prescriptions and 6,163 (91%) were single non-combination drugs.

5.3.3.6.2 Prescribing performance indicators before and after the intervention

5.3.3.6.2.1 Concordance with antibiotics recommended in the European Formulary

The level of prescribing concordance with the antibiotics recommended in the European Formulary for LRTIs i.e. amoxycillin, benzylpenicillin, erythromycin and doxycycline can be seen in Table 5.47. The intervention and control groups increased their prescribing concordance with the Formulary drugs from Phase I to Phase II, the former moved towards the Formulary by 6.7% (4.4) compared with the latter by 1.4% (3.9). Although the trend of the intervention group towards using the Formulary drugs was greater, this difference was not statistically significant ($p = 0.37$). There were no significant differences found between countries ($p = 0.87$), nor was there any significant country-by-group interaction ($p = 0.54$).

The greatest difference between the control and intervention groups from Phase I to Phase II in the trend towards the use of European Formulary recommended drugs was found in Portugal but this was not significant ($p = 0.12$). There also appeared to be some positive movement towards the European Formulary recommended drugs in Belgium, Ireland and Italy but again none of these changes proved to be statistically significant.

Overall, the greatest concordance with the European Formulary can be seen to occur in England with almost 80% concordance in each of the control and intervention

groups. High levels of concordance were also found in Scotland, Spain and Northern Ireland. The lowest level of Formulary concordance can be found in Italy where less than one third of the new antibiotic drugs prescribed for LRTIs were those recommended in the European Formulary.

Of the four antibiotics recommended in the Formulary, amoxycillin was the most commonly prescribed antibiotic (Table 5.48). From study group Phase I to study group Phase II, there were considerable increases in amoxycillin prescribing with the levels in Belgium, Italy and Portugal more than doubling, compared with doxycycline prescription levels which more than halved in Belgium and Portugal at the same time. Doxycycline was actually preferred to amoxycillin in the Belgian and Portuguese Phase I study groups. It can be seen from Table 5.48 that despite being recommended in the European Formulary, there was found to be no prescribing of benzylpenicillin which is probably because it is commonly administered as an injection and therefore only used in special circumstances.

5.3.3.6.2.2 Proportion of consultations resulting in a new antibiotic prescription

The average number of consultations resulting in a prescription (Table 5.49) did slightly decrease in both the control and intervention groups by 1.6% (3.2) and 2.1% (2.8) respectively (excluding Belgium from the analysis as no data were provided on consultations without prescriptions). However, there was found to be no significant difference in the proportion of patients receiving new antibiotics for LRTIs between Phase I and Phase II ($p = 0.35$). There was a considerable decrease in the proportion of LRTI consultations resulting in a prescription in the intervention group in Northern Ireland compared with a large contrasting increase in the control group but the difference was not significant ($p = 0.23$). The mean number of consultations resulting in a prescription also appeared to decrease in the intervention groups of Scotland and Spain compared with their respective control groups but none of these differences proved to be statistically significant. Overall in England, Ireland, Northern Ireland and Scotland, approximately two thirds of consultations for LRTIs resulted in a new antibiotic prescription whereas in Spain only a third of these consultations resulted in a new antibiotic prescription.

5.3.3.6.2.3 Range of antibiotics prescribed

From Table 5.50, the range of antibiotics prescribed only marginally decreased in both the intervention and control groups and there was no significant difference either between them ($p = 0.39$), or between countries ($p = 0.79$). The Spanish data were excluded from the statistical analysis due to the reduction in the number of patient-doctor consultations recorded in Phase II. Belgium was the only country where the decrease in the range from Phase I to II was greater than the corresponding control group and this difference was not significant. In England, a significant increase in the range actually occurred in the intervention group compared with the control group ($p = 0.04$).

In general, the range of newly prescribed antibiotics for LRTIs was lowest in Portugal, averaging approximately 2 per GP compared with Ireland and Northern Ireland where the ranges prescribed were double this number.

5.3.3.6.2.4 Prescribing of macrolides

With Phase I and II new antibiotic data combined (Table 5.51), erythromycin was the third most commonly prescribed antibiotic and clarithromycin the fourth, although the prescribing volume of erythromycin was half as much again as that of clarithromycin. In the study groups of Phase I and Phase II for all drug categories combined (Table 5.52), erythromycin was again the most commonly prescribed macrolide overall. However, in the Phase I study groups of Belgium and Italy and the Phase II study groups of Belgium, Italy, Portugal and Spain clarithromycin was the macrolide of choice. In Italy both roxithromycin and azithromycin were prescribed in preference to erythromycin (Table 5.51). While clarithromycin and azithromycin levels increased in the study group overall from Phase I to Phase II (Table 5.52), this was not as great as the increase in prescribing of erythromycin which became the macrolide of choice overall (Table 5.48). In addition, the overall level of roxithromycin decreased from 1.2% to less than 1%.

5.3.3.6.2.5 Prescribing of fluoroquinolones

Ciprofloxacin was the eleventh most commonly prescribed new antibiotic, and the only fluoroquinolone to appear among the 17 antibiotics which represented 1% or more of the antibiotics prescribed for LRTIs (Table 5.51). The level of ciprofloxacin

prescribing was fairly low in all countries except for Italy (7%) and to a lesser extent in Portugal (3.1%). In the study group of Phase I (Table 5.52), ciprofloxacin went from being the seventh most commonly prescribed new antibiotic accounting for 2% of prescribing for all countries combined to less than 1% of prescribing in the study group of Phase II post intervention.

5.3.3.6.3 Comparisons of antibiotic prescribing

5.3.3.6.3.1 Penicillins

Of the antibiotics prescribed for LRTIs, the penicillins were the most popular group overall for throat infections accounting for 62% of the drugs prescribed from all drug categories. Penicillin group prescribing (Table 5.53) varied from 29% in Italy to 77% in England (mean 59%, SD 17). Amoxycillin was by far the most commonly prescribed penicillin for LRTIs and was the penicillin of choice in all countries. For all drug categories combined, amoxycillin use varied from 17% in Italy to 67% in England (mean 42%, SD 16) and for the category of new drugs only (Table 5.51), amoxycillin use varied from 17% in Italy to 71% in England (mean 44%, SD 17). Overall, co-amoxiclav was the second most commonly prescribed drug from this antibiotic class. For all drug classes combined, co-amoxiclav use varied from 4.9% in England to 20% in Belgium and Spain (mean 13%, SD 5.7) and for new antibiotics only (Table 5.51), its use varied from 3.8% in England to 19% in Belgium and Scotland (mean 13%, SD 5.6).

5.3.3.6.3.2 Macrolides

Macrolides were the second most common group of drugs prescribed from all drug classes for LRTIs accounting for 16% of the antibiotics prescribed. Macrolide use (Table 5.53) varied from 11% in Ireland, Northern Ireland and Portugal to 35% in Italy (mean 16%, SD 8.4). Erythromycin was the most commonly prescribed macrolide overall varying from 0.5% in Belgium to 11% in England, Scotland and Spain (mean 7.4, SD 4.2). As a proportion of new antibiotic prescribing (Table 5.51), erythromycin prescribing levels varied from 0.6% in Belgium to 11% in Spain (mean 7%, SD 4).

Clarithromycin was the macrolide of choice in Belgium, Italy and Portugal whereas in all the English speaking countries and in Spain, erythromycin was the macrolide of choice (Table 5.51). In the non-English speaking countries there was also an increased

tendency to prescribe a broader range of the newer macrolide antibiotics. For all drug categories combined, clarithromycin use varied from 0.4% in England to 14% in Italy (mean 5.9%, SD 5.1) and as a proportion of new antibiotic prescribing only (Table 5.51) its use varied from 0.4% in England to 14% in Belgium and Italy (mean 6.3%, SD 5.5).

5.3.3.6.3.3 Cephalosporins

Cephalosporins were the third most common group of antibiotics prescribed varying from 4% in England to 19% in Portugal (mean 9.9%, SD 5.1). Cephalexin was the most commonly prescribed cephalosporin both from all the drug categories combined and from the category of new antibiotics only (Table 5.51). For all drug categories combined, cephalexin use varied from 0% in Portugal and Spain to 5.9% in Scotland (mean 2.1%, SD 2.2) and for new drugs (Table 5.51) from 0% in Portugal and Spain to 5.4% in Scotland. The bulk of cephalosporin prescribing for LRTIs was made up by second generation cephalosporins, namely: cefaclor, cefuroxime and cefixime, which mirrored the prescribing for throat infections.

5.3.3.6.3.4 Tetracyclines

Tetracyclines were the fourth most commonly prescribed class of antibiotics for LRTIs varying in use from 1.2% in Spain to 21% in Portugal (mean 8.6%, SD 7.3). In Belgium, Italy, Northern Ireland, Portugal and Spain, the tetracycline of choice was doxycycline whereas in England and Scotland it was oxytetracycline and in Ireland, tetracycline. Doxycycline was the joint fifth most commonly prescribed new antibiotic, together with ampicillin, for LRTIs (Table 5.51).

5.3.3.6.3.5 Sulphonamides and trimethoprim

Sulphonamides and trimethoprim represented 3.5% of the antibiotics prescribed overall for LRTIs. Their use varied from 0% in Spain to 7.4% in Belgium (mean 3%, SD 2.8). Co-trimoxazole was predominantly the most commonly prescribed drug in this group varying from 0% in England and Spain to 5.9% in Belgium (mean 1.9%, SD 2.4). Of the new drugs prescribed co-trimoxazole use varied from 0% in England and Spain to 6.2% in Belgium being most commonly prescribed in Belgium and Ireland (Table 5.51). In the study group Phase I, co-trimoxazole was the seventh most commonly prescribed antibiotic for LRTIs representing 3.1% of the new antibiotics prescribed but

after the intervention prescribing of co-trimoxazole represented less than 1% of the new antibiotics prescribed.

5.3.3.6.3.6 Fluoroquinolones

Prescribing of fluoroquinolones was minimal in all countries except for Italy and Portugal where levels accounted for 10% and 5% respectively of the antibiotic prescribing for LRTIs (Table 5.53). As a group they represented 2.3% of the antibiotics prescribed overall for LRTIs, their use varying from 0% in Belgium to 10% in Italy (mean 2.7%, SD 3.4). Ciprofloxacin accounted for over three quarters of the fluoroquinolone prescribing and where they were prescribed, ciproflxoxacin was the preferred fluoroquinolone in all countries except for Ireland.

5.3.3.6.3.7 Aminoglycosides and Miscellaneous antibiotics

When combined these drug groups accounted for only 0.5% of the antibiotics prescribed for LRTIs. From Table 5.51 and Table 5.53, no individual drug from either of these two groups was regularly prescribed.

5.3.3.7 Discussion

The results indicate that there were some notable improvements in certain aspects of prescribing for LRTIs in some countries but none of the changes towards the recommendations of the European Formulary and educational intervention was statistically significant. There was a positive trend in the concordance level with the Formulary in the prescribing of new antibiotic prescriptions by the intervention group compared with the control group overall, with notable improvements seen in Ireland, Italy, Belgium and Portugal. Concordance with the Formulary varied from approximately 30% in Italy to nearly 80% in England indicating that there was less scope for GPs to improve prescribing practices in the latter.

Of individual antibiotics prescribed for LRTIs, Formulary recommended amoxycillin was the penicillin and antibiotic of choice in all the countries, although the difference between its high use in England and relatively low use in Italy was almost four-fold. Co-amoxiclav was the second most commonly prescribed antibiotic. Similar findings were reported in a questionnaire study of GPs in five European countries.[333] In the Phase I intervention groups of Belgium, Italy and Portugal doxycycline was

actually the antibiotic of choice. From Phase I to Phase II, amoxycillin prescription levels more than doubled in the intervention groups of Belgium, Italy and Portugal. While these differences suggest that the intervention may have had a positive impact, there were equally large decreases in the reduction of Formulary recommended doxycycline prescribing from Phases I to II in the intervention groups of Belgium and Portugal.

Patient consultations for LRTIs were less likely to result in a prescription in the UK than elsewhere, although high prescribing rates were found in all countries. Patient expectations are known to be a considerable influence in the prescribing of antibiotics for lower respiratory tract illness. One study involving over 1,000 patients in Nottingham found that non-clinical factors influenced the decision to prescribe antibiotics in nearly half of those patients receiving a prescription.[331] A survey of GPs from several European countries reported slightly lower prescribing rates[334] than found in this study but this can probably be attributed to the fact that this data set collated details from face-to-face doctor-patient encounters. Considering the proportion of consultations for LRTIs which resulted in a newly prescribed antibiotic, there were decreases between Phases in the intervention groups of Northern Ireland, Scotland and Spain with increases in all of the corresponding control groups. Thus the educational intervention may have also had some impact here.

Erythromycin prescription levels increased in the intervention groups of all the English speaking countries from Phase I to II in line with the Formulary recommendations. While the overall level of erythromycin prescribed for LRTIs was double that of clarithromycin, clarithromycin was the macrolide of choice in the intervention groups of Belgium and Italy in Phase I and in Belgium, Italy, Portugal and Spain in Phase II. In Italy, as with the prescribing for throat infections, a particularly large range of macrolides were prescribed by GPs there.

Of the fluoroquinolones prescribed for LRTIs, ciprofloxacin was the only one to feature in the top 17 new antibiotics used in all the study data combined. A disproportionately high level of ciprofloxacin use was seen in Italy and to a lesser extent in Portugal but its use decreased from Phase I to II.

For all prescription categories combined for the treatment of LRTIs, penicillins were the most commonly used group of antibiotics in all the countries except for Italy

where macrolides were the most common class. Other researchers have found high macrolide prescription levels in Mediterranean countries.[333] One other observation was that cephalosporins (not recommended in the intervention for LRTIs) were the second most commonly prescribed antibiotic class for LRTIs in Ireland and Portugal.

Limitations with analysing LRTIs include firstly, that there are inaccuracies in labelling whether the presenting complaint is of mild severity or otherwise.[321] In the analyses in this study, four different diagnoses codes associated with LRTIs were clumped together. A wide variation in the terms used by GPs to describe the illness has been found by others too.[326] After combining the diagnoses codes for LRTIs, the prevalence of LRTI varied from 2.8% in Portugal to 9.5% in Belgium. Marked differences in the diagnostic tests used for LRTIs and the frequency of their use has been reported from a questionnaire study of GPs across Europe[335] and these are inevitable confounding factors. A second limitation in this study was that no data were available on frequency of patient reconsultations and consequently the initial prescribing of the first-line antibiotic was not known. It has been suggested that approximately one in four patients reconsult within a few weeks of initial management of LRTIs[148,149], which may partially explain why the proportion of drug entities which represented newly prescribed items was lower (59%) compared with the previous two areas of antibiotics investigated in this thesis. Thirdly the analysis has not investigated the management and prevalence of LRTI in different age groups which can be important as there is an increased likelihood of associated co-morbidity.[321] Fourthly, as previously mentioned, there are differences in culture and sensitivity patterns which will account for some of the differences in prescribing practices.[336]

At the time of the study, despite guidelines for the management of lower respiratory tract infections having been published in several European countries[337], wide variations were found in antibiotic prescription by GPs in the different participating countries. This research confirms the findings of Dorca and Torres two Spanish hospital respiratory physicians, that in order to rationalise future prescribing for LRTIs, infections which are most likely to benefit from antibiotic treatment need to be defined and internationally accepted.[338] In addition, the criteria for establishing a specific

diagnosis of pneumonia needs to be identified, the use of newer antibiotics needs to be restricted and general populations need to be better educated.[338]

Table 5.12 Number and percentage (SEM) NSAIDs prescribed out of all drugs

Country	Phase I				Phase II				Phase II - Phase I	
n = total N⁰ NSAIDs	Study *n*	Study % (SEM)	Control *n*	Control % (SEM)	Study *n*	Study % (SEM)	Control *n*	Control % (SEM)	Study % (SEM)	Control % (SEM)
Belgium	116	5.3 (1.2)	93	5.3 (0.3)	67	3.4 (0.6)	105	6.5 (1)	**-1.9 (1)**	+1.2 (1)
England	187	5 (0.6)	160	4.6 (0.6)	188	4.7 (0.6)	178	4.9 (0.5)	**-0.3 (0.2)**	+0.3 (0.7)
Ireland	487	8.4 (0.8)	293	6.2 (0.5)	421	7.9 (0.6)	285	6.6 (0.4)	**-0.5 (0.6)**	+0.5 (0.5)
Italy	635	11 (0.9)	526	10 (0.8)	587	10 (0.9)	588	11 (1.2)	**-1 (1)**	+0.6 (1)
N Ireland	167	7.8 (1.1)	87	5.8 (0.5)	121	5.5 (0.8)	68	4.3 (0.8)	**-2.4 (0.8)**	-1.5 (0.7)
Portugal	463	8.5 (0.7)	1154	26 (4.7)	452	9.1 (0.8)	676	11 (0.6)	**+0.6 (0.7)**	+15 (4.3)
Scotland	347	5.7 (0.5)	181	5.1 (0.6)	305	5.1 (0.6)	161	4.2 (0.4)	**-0.6 (0.6)**	-0.9 (0.7)
Spain *	404	7 (0.5)	501	7.9 (0.7)	226	7.2 (0.6)	267	7.8 (0.6)	**+0.2 (0.6)**	-0.1 (0.7)
Total	2806	7.7 (0.3)	2995	10 (1.2)	2367	7.2 (0.3)	2328	7.7 (3.8)	**-0.5 (0.3)**	**-2.7 (1)**

* In Spain the numbers of all prescriptions recorded were halved in Phase II

Table 5.13 Percentage (SEM) concordance with the European Formulary of new NSAIDs prescribing in all males and females

Country	Phase I				Phase II				Phase II - Phase I	
n = total N^0 new NSAIDs	Study *n*	Study % (SEM)	Control *n*	Control % (SEM)	Study *n*	Study % (SEM)	Control *n*	Control % (SEM)	Study % (SEM)	Control % (SEM)
Belgium	59	71 (9.4)	60	71 (9.4)	27	52 (17)	70	77 (9)	**-19 (22)**	+6.1 (11)
England	97	88 (4.1)	94	94 (3.7)	103	93 (2.2)	91	84 (6.1)	**+4.8 (4.1)**	-10 (6)
Ireland	314	67 (3.7)	147	75 (5.7)	258	74 (4.1)	168	83 (1.9)	**+7.7 (4.9)**	+8.3 (6.2)
Italy	460	33 (3.3)	325	34 (6.1)	379	49 (5.3)	340	38 (7.1)	**+16 (5.5)**	+4.1 (7.4)
N Ireland	98	83 (2.8)	46	79 (9.1)	70	89 (6)	44	66 (18)	**+6 (6.9)**	-13 (12)
Portugal	172	40 (6.5)	598	42 (3.9)	166	51 (7.7)	370	34 (4)	**+10 (9.7)**	-9.1 (5.2)
Scotland	167	87 (3.1)	97	82 (4.9)	158	92 (3.4)	92	84 (4.5)	**+4.8 (4.5)**	+3.7 (6)
Spain	122	67 (5.8)	202	55 (5.9)	92	80 (5.4)	86	66 (7.9)	**+13 (7)**	+12 (9.4)
Total	1489	64 (2.6)	1569	62 (2.9)	1253	72 (2.6)	1261	62 (3.1)	**+7.9 (2.6)**	**+0.7 (2.7)**

Table 5.14 Percentage of new NSAID drugs prescribed recommended in the Formulary from study group Phases I & II, by country

Drug		Belgium	England	Ireland	Italy	N. Ireland	Portugal	Scotland	Spain	Overall
Phase I	**n =**	**59**	**97**	**331**	**501**	**98**	**186**	**174**	**127**	**1573**
diclofenac %		34	16	38	20	34	25	26	47	28
ibuprofen %		5.1	49	25	3.6	46	4.3	40	8.7	18
naproxen %		27	17	3	7.6	2	1.6	15	4.7	7.4
indomethacin %		1.7	6.2	0.3	1.2	0	4.3	4	5.5	2.3
TOTAL%		**68**	**88**	**66**	**32**	**82**	**35**	**85**	**66**	**56**
Phase II	**n =**	**27**	**103**	**258**	**379**	**70**	**166**	**166**	**92**	**1261**
diclofenac %		11	30	43	17	20	40	30	44	30
ibuprofen %		3.7	37	28	20	60	6.6	36	25	26
naproxen %		33	17	4.7	8.4	5.7	4.8	17	3.3	9
indomethacin %		0	9.7	0	1.8	1.4	4.2	7.8	4.3	3.3
TOTAL%^		**48**	**94**	**76**	**47**	**87**	**56**	**91**	**77**	**68**

Table 5.15 Percentage of top new NSAIDs representing 1% or more of overall prescribing from study groups Phases I & II

Drug	Belgium	England	Ireland	Italy	N. Ireland	Portugal	Scotland	Spain	Overall
Phase 1 n =	**59**	**97**	**331**	**501**	**98**	**186**	**174**	**127**	**1573**
piroxicam %	3.3	2.1	0.6	18	4.1	8.6	0	10	8.2
mefenamic acid %	0	6.2	27	0	5.1	0	9.2	0	7.3
nimesulide %	0	0	0	18	0	15	0	0	7.3
ketoprofen %	1.7	0	1.8	8.9	0	2.7	2.3	6.3	4.4
lysine aspirin %	12	0	0	1.6	0	12	0	0	2.3
feprazone %	0	0	0	6	0	0	0	0	1.9
niflumic acid %	0	0	0	3.8	0	4.3	0	0	1.7
morniflumate %	0	0	0	3.8	0	1.1	0	0	1.3
ketorolac %	0	0	0	4.2	0	0	0	0	1.3
tenoxicam %	12	0	0.3	1.2	0	1.1	0	0	1
Phase 2 n =	**27**	**103**	**258**	**379**	**70**	**166**	**166**	**92**	**1261**
nimesulide %	0	0	1.5	19	0	7.7	0	0	6.9
ketoprofen %	7.1	0	3.1	9.8	0	3.6	1.2	3.3	4.6
mefenamic acid %	0	1.9	15	0	5.7	0	3.6	0	4
piroxicam %	3.6	1.9	1.1	7.1	1.4	6	3	1.1	3.9
lysine aspirin %	14	0	0	0.3	0	11	0	0	1.9
morniflumate %	0	0	0	6.3	0	0	0	0	1.9
niflumic acid %	14	0	0	2.4	0	1.2	0	3.3	1.4
ketorolac %	0	0	0	4.2	0	0	0	0	1.3

Table 5.16 Percentage of top new NSAIDs by country representing 1% or more of those prescribed from Phases I & II

Drug	Belgium	England	Ireland	Italy	N. Ireland	Portugal	Scotland	Spain	Overall
Phases I and II n =	**216**	**391**	**940**	**1597**	**272**	**1334**	**593**	**507**	**5850**
diclofenac % *	**32**	**20**	**44**	**18**	**24**	**24**	**27**	**40**	**28**
ibuprofen % *	**5.1**	**44**	**25**	**7.5**	**50**	**10**	**41**	**10**	**19**
nimesulide %	0.9	0	0.4	19	0	23	0	0	10
naproxen % *	**29**	**20**	**3.7**	**6.2**	**7.7**	**4.4**	**15**	**5.1**	**8**
piroxicam %	6	2.6	0.7	16	4.8	6.9	1.5	4.3	7.1
mefenamic acid %	0	4.1	19	0.1	5.5	0	8.4	0	4.4
ketoprofen %	1.4	1.3	2.6	9.6	0.4	2.4	1.9	3.4	4.2
indomethacin % *	**1.9**	**5.6**	**0.7**	**2.7**	**0.4**	**3.7**	**4.1**	**6.1**	**3.1**
lysine aspirin %	5.1	0	0	0.9	0	8.7	0	0	2.4
etofenamate %	3.7	0	0	0.1	0	3.8	0	7.7	1.7
niflumic acid %	5.1	0	0	2.8	0	1.7	0	1.8	1.5
aceclofenac %	0	0	0	0	0	1.4	0	13	1.5
morniflumate %	0	0	0	4.9	0	0.2	0	0	1.4
flurbiprofen %	0.5	0	0.6	3.3	0	0.5	0.3	1.8	1.3
ketorolac %	0	0	0	3.7	0	0	0	0.2	1

* drugs listed within the European Formulary

Table 5.17 Average (SEM) range of newly prescribed NSAIDs in all males and females

Country	Phase I				Phase II				Phase II - Phase I	
n = mean N^0 new NSAIDs	Study *n* (SEM)	Study Mean range (SEM)	Control *n* (SEM)	Control Mean range (SEM)	Study *n* (SEM)	Study Mean range (SEM)	Control *n* (SEM)	Control Mean range (SEM)	Study Mean range (SEM)	Control Mean range (SEM)
Belgium	12 (3.5)	4 (0.8)	12 (1.5)	4 (0.5)	5 (1.5)	3 (0.8)	14 (2.2)	4 (0.6)	**-1.2 (0.7)**	+0.6 (0.9)
England	7 (1.3)	3 (0.3)	8 (1.3)	3 (0.2)	8 (1.2)	3 (0.3)	8 (1.2)	3 (0.2)	**+0.4 (0.4)**	+0.2 (0.4)
Ireland	17 (2)	4 (0.3)	11 (1.1)	3 (0.3)	14 (1.4)	4 (0.3)	12 (1.5)	3 (0.3)	**-0.6 (0.4)**	+0.4 (0.4)
Italy	26 (2.1)	7 (0.3)	19 (1.8)	6 (0.5)	21 (2)	7 (0.4)	20 (2.9)	7 (0.6)	**-0.6 (0.6)**	-0.6 (0.6)
N Ireland	14 (2.5)	4 (0.4)	9 (1)	2 (0.4)	10 (2.1)	3 (0.4)	9 (2.4)	3 (0.6)	**-1 (0.6)**	+1 (0.7)
Portugal	9 (1.1)	5 (0.5)	31 (5.8)	7 (0.7)	9 (1.5)	4 (0.5)	19 (2.2)	6 (0.4)	**-0.7 (0.5)**	-0.8 (0.7)
Scotland	8 (1.1)	3 (0.2)	8 (1.1)	3 (0.3)	8 (1)	3 (0.2)	8 (1.1)	3 (0.3)	**-0.1 (0.3)**	-0.3 (0.4)
Spain *	9 (1.1)	4 (0.4)	13 (2)	4 (0.4)	7 (0.7)	3 (0.4)	5 (0.6)	3 (0.4)	**-0.6 (0.4)**	-1.5 (0.6)
Total	13 (0.8)	4 (0.2)	16 (1.5)	5 (0.3)	11 (0.7)	4 (0.2)	13 (0.9)	4 (0.2)	**-0.5 (0.2)**	**-0.3 (0.2)**

* In Spain the numbers of all prescriptions recorded were halved in Phase II

Table 5.18 Proportion of aspirin and paracetamol use from new prescribing of simple analgesics and NSAIDs for disorders listed in section 5.1.2.2

Country	Phase I				Phase II				Phase II - Phase I	
n = total N^0 NSAIDs and simple analgesics	Study *n*	Study % (SEM)	Control *n*	Control % (SEM)	Study *n*	Study % (SEM)	Control *n*	Control % (SEM)	Study % (SEM)	Control % (SEM)
Belgium	16	23 (12)	29	28 (11)	18	23 (10)	23	10 (7.8)	**0 (18)**	-18 (14)
England	55	12 (7.3)	48	19 (8.6)	79	19 (7.6)	48	11 (5.2)	**+7.3 (2.4)**	-7.6 (12)
Ireland	117	3.6 (2.1)	63	18 (8.7)	88	6.4 (3.3)	65	11 (5.9)	**+2.8 (3.8)**	-6.4 (10)
Italy	193	3.4 (1.5)	146	12 (5.1)	190	20 (5)	139	6.5 (3)	**+16 (4.6)**	-5.4 (3.8)
N Ireland	66	11 (4.7)	37	13 (6.2)	42	31 (14)	24	22 (8.9)	**+20 (14)**	+8.4 (8.3)
Portugal	70	3.4 (2.8)	208	1 (0.6)	87	4.5 (2.2)	133	4 (1.9)	**+1.1 (2.6)**	+2.9 (1.9)
Scotland	86	9 (3.8)	64	8.4 (4.4)	94	9.5 (4.1)	48	5.6 (3)	**+0.5 (5.7)**	-2.9 (4.9)
Spain	102	35 (6.2)	107	32 (6.8)	71	35 (8.4)	46	14 (5.2)	**-0.04 (5.3)**	-18 (5.9)
Total	705	11 (1.8)	702	15 (2.4)	669	16 (2.2)	526	9.2 (1.6)	**+5.4 (2)**	**-5.6 (2.6)**

Table 5.19 Percentage (SEM) of patient consultations for conditions listed in section 5.1.2.2 resulting in a new simple analgesic prescription

Country	Phase I				Phase II				Phase II - Phase I	
n = total N^0 consultations	Study *n*	Study % (SEM)	Control *n*	Control % (SEM)	Study *n*	Study % (SEM)	Control *n*	Control % (SEM)	Study % (SEM)	Control % (SEM)
England	383	3.4 (1.8)	369	3.9 (1)	445	4.2 (1.4)	416	2.2 (1.1)	**+0.8 (0.9)**	-1.7 (1.5)
Ireland	352	2 (1.5)	321	2.5 (1.3)	315	3 (1.8)	281	2.5 (1.2)	**+0.9 (2.3)**	+0.1 (1.4)
Italy	525	1.2 (0.5)	510	4.1 (1.9)	438	8.2 (2.2)	436	2.5 (0.8)	**+7.1 (2)**	-1.6 (1.8)
N Ireland	220	3.4 (1.5)	174	3.3 (1.3)	174	6.6 (2.4)	131	2.5 (0.8)	**+3.2 (2.3)**	-0.8 (1.4)
Portugal	343	1.4 (0.9)	719	0.3 (0.2)	384	1.8 (0.7)	431	1.8 (0.6)	**+0.4 (0.8)**	+1.4 (0.6)
Scotland	580	1.9 (0.6)	523	2.3 (0.8)	536	2.1 (0.7)	307	1.9 (0.9)	**+0.2 (0.9)**	-0.5 (1.2)
Spain	578	8.3 (1.8)	609	7.7 (1.3)	297	9.5 (3.6)	368	2.2 (0.8)	**+1.2 (3.4)**	-5.5 (1.1)
Total	2981	2.8 (0.5)	3225	3.3 (0.5)	2589	4.7 (0.8)	2370	2.2 (0.3)	**+1.9 (0.7)**	**-1.2 (0.5)**

Belgium omitted from table as data not provided on consultations without a prescription

Table 5.20 All NSAID prescribing by drug group, number of prescriptions and percentage drug use in males and females

Country	Belgium	England	Ireland	Italy	N. Ireland	Portugal	Scotland	Spain
Drug Group **N° prescribed items (%)**	375 (100)	728 (100)	1538 (100)	2468 (100)	434 (100)	2761 (100)	1099 (100)	1396 (100)
Acetic acid derivatives	140 (37)	218 (30)	664 (43)	675 (27)	140 (32)	985 (36)	386 (35)	803 (58)
diclofenac *	118 (31)	160 (22)	621 (40)	477 (19)	117 (27)	704 (26)	348 (32)	552 (40)
indomethacin *	15 (4)	56 (7.7)	43 (2.8)	95 (3.9)	6 (1.4)	166 (6)	35 (3.2)	95 (6.8)
Proprionic acid derivatives	144 (38)	438 (60)	517 (34)	655 (27)	241 (56)	454 (16)	579 (53)	215 (15)
ibuprofen *	28 (7.5)	285 (39)	351 (23)	161 (6.5)	188 (43)	209 (7.6)	391 (36)	81 (5.8)
naproxen *	105 (28)	140 (19)	77 (5)	161 (6.5)	36 (8.3)	126 (4.6)	149 (14)	73 (5.2)
Oxicam derivatives	50 (13)	27 (3.7)	24 (1.6)	439 (18)	23 (5.3)	282 (10)	26 (2.4)	112 (8)
piroxicam	29 (7.7)	27 (3.7)	17 (1.1)	388 (16)	23 (5.3)	245 (8.9)	26 (2.4)	98 (7)
Selective cox-2 - nimesulide only	2 (0.5)	0 (0)	7 (0.5)	478 (19)	0 (0)	444 (16)	0 (0)	0 (0)
Anthranilic acid derivatives	0 (0)	30 (4.1)	308 (20)	1 (0.04)	24 (5.5)	32 (1.2)	89 (8.1)	4 (0.3)
mefenamic acid	0 (0)	30 (4.1)	308 (20)	1 (0.04)	24 (5.5)	1 (0.04)	89 (8.1)	0 (0)
Miscellaneous NSAIDs	3 (0.8)	8 (1)	3 (1)	145 (5.9)	6 (1.4)	104 (3.8)	13 (1.2)	47 (3.2)
Salicylic acid derivatives	16 (4.3)	8 (1.1)	3 (0.2)	18 (0.7)	0 (0)	283 (10)	6 (0.5)	2 (0.1)
Topical preparations [1]	20 (5.3)	0 (0)	0 (0)	57 (2.3)	0 (0)	177 (6.4)	0 (0)	213 (15)

[1] NSAID formulation was not recorded but etofenamate, niflumic acid, piketoprofen and bendazac were only available in the topical form at the time

* drugs listed within the European Formulary

Table 5.21 Percentage use of top NSAIDs by country representing ≥1% of those prescribed in patients <60 years from Phases I & II

Drug	Belgium	England	Ireland	Italy	N. Ireland	Portugal	Scotland	Spain	Overall
Phases I and II n =	**235**	**505**	**1055**	**1377**	**289**	**1378**	**704**	**623**	**6166**
diclofenac % *	**33**	**23**	**42**	**17**	**27**	**23**	**30**	**43**	**28**
ibuprofen % *	**8**	**41**	**23**	**6.6**	**45**	**10**	**37**	**6.9**	**18**
naproxen % *	**25**	**19**	**3.2**	**7.1**	**6.9**	**3.9**	**12**	**8.7**	**8.1**
indomethacin % *	**1.7**	**6.1**	**1.5**	**3.3**	**1.4**	**3.5**	**3.4**	**5.3**	**3.3**
TOTAL %	**68**	**89**	**70**	**34**	**80**	**40**	**82**	**64**	**57**
nimesulide %	0.9	0	0.4	23	0	22	0	0	10
piroxicam %	6.8	1.8	1	12	3.5	8	2	4.3	6
mefenamic acid %	0	5.7	23	0	7.3	0.1	11	0	5.9
ketoprofen %	1.7	1.6	2.1	9.5	0.4	2	1.4	2.6	3.6
lysine aspirin %	6.4	0	0	0.4	0	13	0	0	3.2
aceclofenac %	0	0	0	0	0	0.9	0	11	1.4
morniflumate %	0	0	0	5.8	0	0.1	0	0	1.3
niflumic acid %	3.8	0	0	3.1	0	1.4	0	1.3	1.3
etofenamate %	3.4	0	0	0.1	0	2.7	0	5.1	1.3
flurbiprofen %	0.4	0	0.7	3.4	0	0.4	0.3	1.3	1.2
TOTAL %	**23**	**9.1**	**27**	**57**	**11**	**49**	**15**	**26**	**35**

* drugs listed within the European Formulary

Table 5.22 Percentage of top NSAIDs by country representing ≥1% of those prescribed in patients ≥60 years from Phases I & II

Drug	Belgium	England	Ireland	Italy	N. Ireland	Portugal	Scotland	Spain	Overall
Phases I and II n =	**135**	**210**	**461**	**1034**	**140**	**1303**	**372**	**731**	**4386**
diclofenac % *	**28**	**19**	**35**	**23**	**28**	**28**	**34**	**36**	**29**
ibuprofen % *	**5.9**	**36**	**23**	**6.7**	**39**	**5.2**	**33**	**4.7**	**12**
naproxen % *	**35**	**20**	**8.5**	**5.7**	**11**	**5.1**	**16**	**2.6**	**7.9**
indomethacin % *	**7.4**	**11**	**5.6**	**4.6**	**1.4**	**8.7**	**3**	**7.9**	**6.6**
TOTAL %	**76**	**86**	**72**	**40**	**79**	**47**	**86**	**51**	**56**
piroxicam %	9.6	7.6	1.3	20	9.3	9.7	3.2	9	11
nimesulide %	0	0	0.7	14	0	9.5	0	0	6.3
ketoprofen %	2.2	0.5	5	10	1.4	2.4	2.2	3.7	4.6
lysine aspirin %	0.7	0	0	1.2	0	8.1	0	0.3	2.7
etofenamate %	0.7	0	0	0.2	0	4.7	0	7.4	2.7
aceclofenac %	0	0	0	0	0	1.5	0	8.9	1.9
mefenamic acid %	0	0.5	14	0.1	2.1	0	3.5	0	1.9
piketoprofen %	0	0	0	0	0	0	0	11	1.8
tenoxicam %	5.2	0	0.7	1.9	0	1.8	0	1.4	1.5
ketorolac %	0	0	0	4.5	0	0	0	0.7	1.2
nabumetone %	0	0.5	0.9	0	0	1.8	1.9	2.1	1.1
flurbiprofen %	0	0.5	0.4	0.9	0	1.2	1.3	1.4	1
TOTAL %	**18**	**9.6**	**23**	**53**	**13**	**41**	**12**	**46**	**38**

* drugs listed within the European Formulary.

Table 5.23 Percentage of top diagnoses in patients <60 years from Phases I & II representing ≥1% of those for which NSAIDs were used

Diagnosis	Belgium	England	Ireland	Italy	N. Ireland	Portugal	Scotland	Spain	Overall
Phases I and II n =	**199**	**467**	**955**	**1205**	**270**	**945**	**645**	**493**	**5179**
Pain % *	**11**	**22**	**22**	**23**	**31**	**12**	**23**	**27**	**21**
Arthropathies % *	**19**	**22**	**9.1**	**13**	**16**	**30**	**19**	**14**	**17**
Low back pain %	13	20	23	16	22	14	15	16	17
Other M/S disorders (pain+inflammation) %	25	10	12	6.6	6.7	3.8	16	11	9.7
Injury and trauma %	4	5.4	12	1	7.4	5.4	3.9	3.9	5.4
Throat infections % '	1.5	0	0.3	14	1.9	3.6	0	0.8	4.2
Premenstrual syndrome/dysmenorrhoea % *	**3**	**3.6**	**2.9**	**2.2**	**4.4**	**3**	**7.4**	**3**	**3.5**
Headache %	1	2.1	2.9	4.1	0.4	1.7	1.4	0.6	2.3
Neuralgia % '	2	3	1.3	2.7	2.2	1.3	2.8	3.7	2.2
Common cold/flu/coryza %	1.5	0	0.4	3.8	0	4.8	0	0	1.9
Gout and hyperuricaemia % *	**0**	**2.8**	**1.5**	**0.1**	**1.9**	**0.5**	**1.6**	**1.2**	**1**
Dental related conditions %	0.5	0.2	0.5	2.4	0	1.4	0	0.6	1

* diagnoses listed within the European Formulary which included the recommendation of NSAIDs for symptomatic relief

' diagnoses listed in the European Formulary but did not include the recommendation of NSAIDs as part of the drug management

Table 5.24 Percentage of top diagnoses in patients ≥60 years from Phases I & II representing ≥1% of those for which NSAIDs were used

Diagnosis	Belgium	England	Ireland	Italy	N. Ireland	Portugal	Scotland	Spain	Overall
Phases I and II n =	**112**	**196**	**417**	**960**	**123**	**1051**	**340**	**567**	**3766**
Arthropathies % *	**51**	**57**	**56**	**37**	**46**	**63**	**52**	**50**	**52**
Pain % *	**14**	**9.2**	**13**	**26**	**28**	**11**	**16**	**24**	**18**
Low back pain %	8	8.7	12	17	11	8.5	7.4	6.5	11
Other M/S disorders with pain & inflammation %	8.9	7.7	3.6	2.6	2.4	1.2	9.1	3	3.4
Neuralgia % †	1.8	2.6	1.2	3.9	0.8	0.7	3.2	2.3	2.2
Injury and trauma %	2.7	0.5	3.4	0.3	0.8	1.5	0.9	2.5	1.5
Gout and hyperuricaemia % *	**0**	**6.6**	**1.2**	**0.1**	**1.6**	**0.9**	**2.1**	**0.4**	**1**
Eye conditions outside the Formulary %	0	0	0	0.5	0	2.5	0	1.2	1

* diagnoses listed within the European Formulary which included the recommendation of NSAIDs for symptomatic relief

† diagnoses listed in the European Formulary which did not include the recommendation of NSAIDs as part of the drug management

Table 5.25 The mean number and percentage of all patients presenting with a UTI, those who received treatment and proportion who represented females ≥16 years

Country	Mean No (%) patients with UTIs/country	Mean No (%) females UTI patients/country	Mean % (SEM) UTI patients treated for UTIs	Mean % (SEM) female UTI patients treated
Belgium	66 (1.7)	49 (1.3)	100 (--) *	100 (--) *
England	266 (1.8)	182 (1.2)	86 (2.7)	89 (2.3)
Ireland	400 (2.6)	270 (1.6)	93 (1.7)	96 (1.8)
Italy	392 (2.3)	276 (1.6)	90 (2.5)	90 (2.4)
N Ireland	103 (1.5)	74 (1.1)	90 (3)	95 (2.3)
Portugal	259 (2.4)	187 (1.8)	96 (1.8)	96 (1.7)
Scotland	405 (2)	313 (1.5)	86 (2.2)	90 (2.3)
Spain	170 (1.6)	132 (1.3)	91 (2.7)	90 (2.6)
ANOVA	p = 0.002	p = 0.013	p = 0.011	p = 0.045

* Data recorded in Belgium did not include consultations where a prescription was not given and so was excluded from the analysis.

Table 5.26 Percentage (SEM) of new antibiotics from all antibiotics prescribed for UTIs in all males and females

Country	Phase I				Phase II				Phase II - Phase I	
n = total N^0 antibiotics	Study *n*	Study % (SEM)	Control *n*	Control % (SEM)	Study *n*	Study % (SEM)	Control *n*	Control % (SEM)	STUDY % (SEM)	CONTROL % (SEM)
Belgium	11	75 (25)	12	66 (20)	16	78 (11)	20	70 (12)	**+2.7 (17)**	+4.2 (25)
England	52	89 (8.3)	54	75 (9.2)	52	87.4 (5.9)	52	65 (6.9)	**-1.4 (11)**	-9.5 (8.8)
Ireland	121	90 (4.2)	73	82 (2.8)	105	74 (6.3)	71	74 (7.1)	**-16 (7.1)**	-8.1 (6.4)
Italy	85	78 (4.6)	93	71 (7)	86	71 (8.2)	67	69 (8.6)	**-6.8 (9.7)**	-2.4 (8.9)
N Ireland	26	81 (7.8)	16	70 (8.5)	31	72 (13.4)	14	90 (10)	**-9 (14)**	+20 (11)
Portugal	36	88 (9)	99	88 (5.2)	40	72 (11)	49	95 (3.7)	**-15 (13)**	+6.8 (6.6)
Scotland	100	76 (5.2)	72	76 (6.4)	88	73 (7.2)	46	77 (8.5)	**-2.9 (7.2)**	+1.1 (13)
Spain	39	77 (10)	45	71 (9.8)	20	75 (11)	21	51 (13)	**-2.3 (17)**	-20.6 (13)
Total	470	82 (2.6)	464	77 (2.7)	438	75 (3.1)	340	74 (3.3)	**-7.4 (3.8)**	**-3 (3.7)**

Table 5.27 Percentage (SEM) concordance* with the European Formulary of UTI prescribing in females 16 years and above

Country	Phase I				Phase II				Phase II - Phase I	
n = total N^0 antibiotics	Study *n*	Study % (SEM)	Control *n*	Control % (SEM)	Study *n*	Study % (SEM)	Control *n*	Control % (SEM)	STUDY % (SEM)	CONTROL % (SEM)
Belgium	7	0 (0)	4	0 (0)	9	29 (20)	9	0 (0)	**+29 (20)**	0 (0)
England	34	63 (13)	23	78 (7.5)	24	53 (12)	24	63 (15)	**-10 (22)**	-15 (14)
Ireland	68	29 (7)	41	40 (11)	47	56 (8.7)	41	62 (9.9)	**+26 (12)**	+22 (13)
Italy	25	0 (0)	38	3 (3)	33	2.5 (2.5)	31	0 (0)	**+2.5 (2.5)**	-3 (3)
N Ireland	15	72 (18)	6	100 (0)	13	67 (15)	5	50 (29)	**-5.6 (22)**	-50 (29)
Portugal	23	6.5 (4.3)	65	6.9 (4.8)	20	16 (11)	20	0 (0)	**+9.1 (13)**	-6.9 (4.8)
Scotland	52	62 (8.7)	34	29 (13)	45	59 (10)	25	56 (13)	**-2.7 (13)**	+27 (19)
Spain	20	0 (0)	20	3.3 (3.3)	9	0 (0)	8	0 (0)	**0 (0)**	-3.3 (3.3)
Total	244	34 (4.5)	231	30 (4.7)	207	39 (4.6)	163	31 (5)	**+5.5 (5.4)**	**+1.3 (4.9)**

* first-line recommended drugs only

Table 5.28 Percentage use of new antibiotics recommended in the Formulary for UTIs in females ≥16 years from study group Phases I and II

Drug *		Belgium	England	Ireland	Italy	N. Ireland	Portugal	Scotland	Spain	Overall
Phase 1	**n =**	**11**	**40**	**76**	**60**	**18**	**32**	**88**	**41**	**366**
trimethoprim %		0	43	22	1.7	67	0	50	0	25
amoxycillin %		0	13	5.3	0	11	6.3	3.4	0	4.4
Total %		**0**	**56**	**27**	**1.7**	**78**	**6.3**	**53**	**0**	**29**
Phase 2	**n =**	**14**	**39**	**63**	**45**	**23**	**41**	**62**	**12**	**299**
trimethoprim %		7.1	46	49	0	35	2.4	61	0	32
amoxycillin %		29	2.6	7.9	2.2	13	7.3	1.6	0	6
Total %		**36**	**49**	**57**	**2.2**	**48**	**10**	**63**	**0**	**38**

* first-line recommended drugs only

Table 5.29 Average (SEM) range of new drugs prescribed for UTIs in all males and females

Country	Phase I		Phase II		Phase II - Phase I	
	Study	Control	Study	Control	Study	Control
Belgium	1.7 (0.3)	1.5 (0.3)	2 (0.6)	1.8 (0.3)	**+0.3 (0.7)**	+0.3 (0.5)
England	1.8 (0.2)	1.8 (0.2)	2 (0.3)	1.4 (0.2)	**+0.2 (0.3)**	-0.3 (0.3)
Ireland	3.3 (0.4)	2.4 (0.3)	2.4 (0.3)	2.3 (0.3)	**-0.9 (0.5)**	-0.1 (0.3)
Italy	2.5 (0.5)	2.4 (0.3)	2.9 (0.4)	2.3 (0.3)	**+0.5 (0.6)**	-0.1 (0.3)
N. Ireland	1.7 (0.4)	1.8 (0.2)	2 (0.4)	1.6 (0.2)	**+0.3 (0.2)**	-0.2 (0.4)
Portugal	2.3 (0.4)	3.2 (0.5)	1.9 (0.4)	1.5 (0.2)	**-0.4 (0.3)**	-1.7 (0.5)
Scotland	1.9 (0.2)	2.3 (0.4)	1.7 (0.2)	2.1 (0.3)	**-0.2 (0.2)**	-0.2 (0.5)
Spain †	2 (1.3)	1.7 (0.3	1.3 (0.2)	1.1 (0.1)	**-0.8 (0.5)**	-0.6 (0.4)
Total	2.3 (0.1)	2.3 (0.1)	2.1 (0.1)	1.8 (0.1)	**-0.2 (0.2)**	-0.5 (0.2)

† The number of consultations recorded by the Spanish GPs in Phase II was halved

Table 5.30 Percentage use of new antibiotics representing ≥1% of those used for UTIs in females ≥16 years from Phases I & II

Drug	Belgium	England	Ireland	Italy	N. Ireland	Portugal	Scotland	Spain	Overall
Phases I and II n =	**35**	**126**	**220**	**178**	**46**	**155**	**195**	**87**	**1042**
trimethoprim % *	**0**	**57**	**40**	**0.6**	**61**	**1.3**	**46**	**0**	**27**
norfloxacin %	37	0	0	16	0	26	5.6	30	12
co-amoxiclav % *	0	4.8	14	0.6	4.4	5.2	18	5.8	8.5
pipemidic acid %	0	0	0	23	0	0	0	48	8
co-trimoxazole %	11	0	17	9.6	2.2	15	0	0	7.8
nitrofurantoin % *	37	12	4.1	7.3	0	8.4	0.5	0	6.1
cephalexin %	0	5.6	3.2	0	2.2	0	23	0	5.7
ofloxacin %	0	0	4.6	2.8	0	25	0	0	5.1
amoxycillin % *	**11**	**7.1**	**5**	**1.1**	**13**	**3.9**	**3.1**	**2.3**	**4.4**
ciprofloxacin %	2.9	0.8	0.9	9.6	0	8.4	1	5.8	3.9
fosfomycin %	0	0	0	10	2.2	0	0	3.5	2.1
ampicillin %	0	3.2	4.1	1.1	8.7	0.7	0.5	0	2
nalidixic acid %	0	9.5	1.8	0.6	2.2	0	0	0	1.7
pefloxacin %	0	0	0	8.4	0	0	0	0	1.4
lomefloxacin %	0	0	0	6.2	0	0.7	0	0	1.1

* drugs recommended as first-line treatment within the European Formulary

Table 5.31 Percentage use of new antibiotics representing ≥1% of those used for UTIs in females ≥16 years from study group Phases I & II

Drug	Belgium	England	Ireland	Italy	N. Ireland	Portugal	Scotland	Spain	Overall
Phase 1 n =	**11**	**40**	**76**	**60**	**18**	**32**	**88**	**41**	**366**
co-trimoxazole %	27	0	34	8.3	5.6	9.4	0	4.9	11
norfloxacin %	73	0	0	20	0	13	6.8	20	10
pipemidic acid %	0	0	0	18	0	0	0	56	9.3
co-amoxiclav %	0	2.5	11	0	5.6	3.1	17	9.8	8.2
nitrofurantoin %	0	25	3.9	8.3	0	19	1.1	0	6.8
cephalexin %	0	5	2.6	0	0	0	19	0	5.7
ofloxacin %	0	0	3.9	0	0	31	0	0	3.6
fosfomycin %	0	0	0	12	0	0	0	7.3	2.7
ciprofloxacin %	0	0	0	8.3	0	9.4	0	2.4	2.5
ampicillin %	0	7.5	5.3	0	5.6	0	0	0	2.2
pefloxacin %	0	0	0	10	0	0	0	0	1.6
nalidixic acid %	0	5	2.6	0	5.6	0	0	0	1.4
Phase 2 n =	**14**	**39**	**63**	**45**	**23**	**41**	**62**	**12**	**299**
norfloxacin %	29	0	0	8.9	0	20	8.1	17	7.7
co-amoxiclav %	0	2.6	14	0	22	0	9.7	0	7
nitrofurantoin %	29	18	3.2	13	0	2.4	1.6	0	7
co-trimoxazole %	0	0	4.8	8.9	0	29	0	0	6.4
cephalexin %	0	5.1	4.8	0	0	0	16	0	5
ciprofloxacin %	7.1	0	0	6.7	4.3	15	0	25	4.7
nalidixic acid %	0	23	6.3	0	0	2.4	0	0	4.7
fosfomycin %	0	0	0	24	4.3	0	0	0	4
pipemidic acid %	0	0	0	11	0	0	0	50	3.7
ampicillin %	0	2.6	4.8	0	17	2.4	0	0	3
ofloxacin %	0	0	3.2	2.2	0	15	0	0	3
lomefloxacin %	0	0	0	6.7	0	2.4	0	0	1.3
pefloxacin %	0	0	0	6.7	0	0	0	0	1

Table 5.32 All antibiotic prescribing for UTIs by drug group in terms of number of items and percentage drug use in females ≥16 years

Country		Belgium	England	Ireland	Italy	N. Ireland	Portugal	Scotland	Spain
Drug Group	**N° prescribed items (%)**	48 (100)	152 (100)	259 (100)	235 (100)	67 (100)	176 (100)	267 (100)	115 (100)
Sulphonamides & trimethoprim		7 (15)	85 (56)	143 (55)	19 (8.1)	36 (54)	33 (19)	122 (46)	2 (1.7)
trimethoprim *		1 (2.1)	85 (56)	97 (38)	1 (0.4)	35 (52)	2 (1.1)	122 (46)	0 (0)
co-trimoxazole		6 (13)	0 (0)	43 (17)	18 (7.7)	1 (1.5)	30 (17)	0 (0)	2 (1.7)
Fluoroquinolones		20 (42)	13 (8.6)	24 (9.3))	150 (64)	2 (3)	103 (59)	15 (5.6)	93 (81)
Penicillins		6 (13)	21 (14)	60 (23)	5 (2.1)	22 (33)	19 (11)	57 (21)	12 (10)
amoxycillin *		6 (13)	9 (5.9)	11 (4.2)	2 (0.9)	10 (15)	6 (3.4)	9 (3.4)	3 (2.6)
Miscellaneous antibiotics		15 (31)	20 (13)	13 (5)	53 (23)	1 (1.5)	15 (8.5)	2 (0.7)	5 (4.3)
nitrofurantoin		15 (31)	20 (13)	13 (5)	23 (9.8)	0 (0)	15 (8.5)	2 (0.7)	0 (0)
fosfomycin		0 (0)	0 (0)	0 (0)	29 (12)	1 (1.5)	0 (0)	0 (0)	5 (4.3)
Cephalosporins		0 (0)	13 (8.6)	17 (6.6)	2 (0.9)	6 (9)	2 (1.1)	69 (26)	3 (2.6)
second & third generation cephalosporins		0 (0)	1 (0.7)	3 (1.2)	2 (0.8)	3 (4.5)	1 (0.6)	1 (0.4)	3 (2.6)
Aminoglycosides		0 (0)	0 (0)	0 (0)	4 (1.7)	0 (0)	3 (1.7)	0 (0)	0 (0)
Tetracyclines		0 (0)	0 (0)	2 (0.8)	2 (0.9)	0 (0)	0 (0)	1 (0.4)	0 (0)
Macrolides		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.6)	1 (0.4)	0 (0)

* drugs recommended as first-line treatment within the European Formulary

ble 5.33 UTI prescribing of all antibiotic drugs by drug group, number of items and percentage drug use in all males and females

Country		Belgium	England	Ireland	Italy	N. Ireland	Portugal	Scotland	Spain
)rug Group	**N° prescribed items**	64 (100)	205 (100)	367 (100)	332 (100)	86 (100)	245 (100)	332 (100)	152 (100)
)ulphonamides and trimethoprim		16 (25)	119 (58)	183 (50)	25 (7.5)	42 (49)	59 ((24)	148 (45)	4 (2.6)
rimethoprim *		5 (7.8)	118 (58)	119 (32)	1 (0.3)	41 (48)	4 (1.6)	148 (45)	0 (0)
o-trimoxazole		10 (16)	1 (0.5)	60 (16)	24 (7.2)	1 (1.2)	52 (21)	0 (0)	4 (2.6)
luoroquinolones		23 (36)	14 (6.8)	28 (7.6)	220 (66)	3 (3.5)	131 (54)	17 (5.1)	124 (82)
enicillins		9 (14)	29 (14)	110 (30)	10 (3)	29 (34)	25 (10)	80 (24)	14 (9.2)
amoxycillin *		8 (13)	14 (6.8)	20 (5.4)	5 (1.5)	12 (14)	9 (3.7)	14 (4.2)	3 (2)
Cephalosporins		0 (0)	18 (8.8)	28 (7.6)	5 (1.5)	9 (11)	9 (3.7)	83 (25)	3 (2)
second & third generation cephalosporins		0 (0)	1 (0.5)	4 (1.1)	5 (1.5)	3 (3.5)	3 (1.2)	2 (0.6)	3 (2)
Miscellaneous antibiotics		16 (25)	25 (12)	16 (4.4)	62 (19)	2 (2.3)	16 (6.5)	2 (0.6)	6 (3.9)
nitrofurantoin		16 (25)	25 (12)	16 (4.4)	23 (6.9)	0 (0)	16 (6.5)	2 (0.6)	0 (0)
fosfomycin		0 (0)	0 (0)	0 (0)	38 (11)	1 (1.2)	0 (0)	0 (0)	6 (3.9)
Aminoglycosides		0 (0)	0 (0)	0 (0)	7 (2.1)	0 (0)	4 (1.6)	0 (0)	1 (0.7)
Tetracyclines		0 (0)	0 (0)	2 (0.5)	2 (0.6)	1 (1.2)	0 (0)	1 (0.3)	0 (0)
Macrolides		0 (0)	0 (0)	0 (0)	1 (0.3)	0 (0)	1 (0.4)	1 (0.3)	0 (0)

* drugs recommended as first-line treatment within the European Formulary

Table 5.34 Change in antibiotic prescribing between 1980-1991 in three European countries[301]

Country	Increase in antibiotic items 1980-1991
England	46%
France	65%
Germany	78%

Table 5.35 The mean number and percentage of all patients presenting with a throat infection and proportion of those who received a related prescription

Country	Mean No (%) patients with throat infections/GP	Mean % (SEM) patients receiving a prescription for a throat infection
Belgium	20 (5.4)	100 (--) *
England	14 (2.6)	79 (3.7)
Ireland	24 (5.1)	90 (2.
Italy	20 (4.6)	92 (2)
N Ireland	22 (4.2)	88 (2.8)
Portugal	10 (3.4)	99.8 (0.1)
Scotland	17 (3.4)	87 (2.3)
Spain	7 (2.1)	92 (3.6)
ANOVA	$p < 0.001$	$p < 0.001$

* Data recorded in Belgium did not include consultations where a prescription was not given and so were excluded from the analysis.

Table 5.36 Percentage (SEM) concordance with the European Formulary of new antibiotic prescribing for throat infections

Country	Phase I				Phase II				Phase II - Phase I	
n = total N^0 antibiotics	Study *n*	Study % (SEM)	Control *n*	Control % (SEM)	Study *n*	Study % (SEM)	Control *n*	Control % (SEM)	STUDY % (SEM)	CONTROL % (SEM)
Belgium	16	5.6 (5.6)	11	0 (9.6)	27	5.6 (5.6)	19	50 (50)	**0 (0)**	50 (50)
England	52	87 (5.5)	35	84 (12)	67	41 (10)	32	56 (15)	**-45 (13)**	-28 (19)
Ireland	196	32 (8.3)	120	66 (9.8)	219	48 (7.2)	118	63 (11)	**+16 (5.5)**	-3.3 (7.2)
Italy	86	3 (2.3)	63	21 (11)	100	6.7 (2.8)	60	17 (8.7)	**+3.8 (2.7)**	-4.1 (11)
N Ireland	52	53 (18)	20	55 (16)	59	56 (16)	35	45 (5.9)	**+3 (20)**	-10 (19)
Portugal	35	15 (7.6)	178	9.6 (4)	36	24 (11)	86	12 (6.7)	**+8.6 (16)**	+2.6 (7.4)
Scotland	122	64 (8.3)	78	61 (8.8)	135	60 (7.8)	80	33 (12)	**-4.7 (7.8)**	-27 (18)
Spain	4	0 (0)	16	11 (11)	9	0 (0)	10	17 (11)	**0 (0)**	+5.6 (9.3)
Total	563	38 (4.4)	521	40 (4.7)	652	37 (3.9)	440	34 (4.5)	**-1.8 (4.1)**	**-6.7 (4.9)**

Table 5.37 Percentage use of new drugs recommended in the Formulary for throat infections from study group Phases I & II, by country

Drug	Belgium	England	Ireland	Italy	N. Ireland	Portugal	Scotland	Spain	Overall
Phase 1 n =	**89**	**77**	**218**	**215**	**62**	**65**	**133**	**77**	**936**
phenoxymethylpenicillin %	1.1	49	21	0	31	0	62	0	20
paracetamol %	4.5	16	3.2	5.6	1.6	3.1	3.8	21	6.3
erythromycin %	1.1	7.8	1.8	1.4	4.8	4.6	3.8	0	2.7
aspirin %	1.1	6.5	0.5	4.7	1.6	0	0	1.3	2
Total %	**7.8**	**79**	**27**	**12**	**39**	**7.7**	**70**	**22**	**31**
Phase 2 n =	**77**	**93**	**230**	**208**	**66**	**94**	**156**	**17**	**941**
phenoxymethylpenicillin %	0	27	36	0	44	0	48	0	23
paracetamol %	10	13	1.3	10	4.5	19	7.1	24	8.5
erythromycin %	1.3	4.3	3.9	4.3	7.6	14	6.4	0	5.4
aspirin %	0	8.6	0.9	1	0	1.1	0	0	1.4
Total %	**11**	**53**	**42**	**15**	**56**	**34**	**62**	**24**	**38**

Table 5.38 Percentage (SEM) of consultations for throat infections resulting in a new antibiotic prescription

Country	Phase I				Phase II				Phase II - Phase I	
n = total N^0 consultations	Study *n*	Study % (SEM)	Control *n*	Control % (SEM)	Study *n*	Study % (SEM)	Control *n*	Control % (SEM)	STUDY % (SEM)	CONTROL % (SEM)
England	101	59 (7.7)	84	46 (9.5)	110	54 (8)	83	55 (9.6)	**-5.2 (10)**	+8.6 (11)
Ireland	257	74 (7)	173	82 (3.6)	272	73 (6.3)	145	65 (8.8)	**-0.8 (5.1)**	-16 (9)
Italy	206	55 (4.8)	219	40 (5.6)	209	43 (7.4)	170	30 (5.3)	**-11 (5.2)**	-10 (7.5)
N Ireland	77	66 (10)	65	57 (9.9)	84	66 (8)	57	55 (14)	**-0.8 (13)**	-1.9 (19)
Portugal	48	47 (8.8)	195	72 (7.8)	63	61 (9.4)	100	73 (6.8)	**+13 (11)**	+1.4 (7.6)
Scotland	182	64 (6.6)	160	70 (6.3)	229	68 (5.9)	122	50 (10)	**+3.7 (6.8)**	- 20 (13)
Spain	71	32 (7.5)	89	39 (7)	25	21 (9.8)	33	27 (10)	**-11 (13)**	-12 (9.4)
Total	942	57 (2.9)	985	58 (3)	892	55 (3.3)	710	50 (3.6)	**-1.2 (3.4)**	**-8 (3.8)**

Belgium omitted from table as data not provided on consultations without a prescription

Table 5.39 Average (SEM) range of new drugs prescribed for throat infections in all males and females

Country	Phase I		Phase II		Phase II - Phase I	
	Study	Control	Study	Control	Study	Control
Belgium	16 (0.9)	3.8 (1.4)	8.5 (1.7)	2.8 (0.5)	**-7.5 (2.2)**	-1 (0.9)
England	2.8 (0.4)	1.7 (0.3)	3.2 (0.3)	2.1 (0.2)	**+0.3 (0.5)**	+0.4 (0.4)
Ireland	4.9 (0.7)	3.1 (0.6)	4.3 (0.5)	2.9 (0.5)	**-0.6 (0.6)**	-0.3 (0.4)
Italy	6.3 (0.7)	6.7 (1)	5.8 (0.9)	5.5 (0.9)	**-0.5 (1.3)**	-1.1 (1)
N. Ireland	4 (0.7)	3.4 (0.8)	3.6 (0.6)	3.6 (0.2)	**-0.4 (0.6)**	+0.2 (0.7)
Portugal	3.8 (0.8)	6.6 (1)	4.4 (0.9)	6.8 (1)	**+0.6 (1.2)**	+0.1 (1.1)
Scotland	2 (0.2)	3.4 (0.4)	2.7 (0.3)	3.2 (0.7)	**+0.7 (0.3)**	-0.2 (0.5)
Spain †	3.3 (0.7)	3.8 (0.9)	1.6 (0.2)	3 (0.8)	**-1.6 (0.6)**	-0.8 (0.8)
Total	4.5 (0.4)	4.5 (0.4)	4.2 (0.3)	4.2 (04)	**-0.3 (0.4)**	-0.3 (0.3)

† The number of consultations recorded by the Spanish GPs in Phase II was halved

Table 5.40 Percentage use of new antibiotics by country representing ≥1% of those prescribed for throat infections from Phases I & II

Drug	Belgium	England	Ireland	Italy	N. Ireland	Portugal	Scotland	Spain	Overall
Phases I and II n =	**81**	**211**	**675**	**362**	**180**	**366**	**474**	**75**	**2424**
phenoxymethylpenicillin % *	**3.7**	**51**	**36**	**0**	**43**	**0**	**48**	**2.7**	**27**
amoxycillin %	35	7.6	30	40	26	17	21	57	26
erythromycin % *	**2.5**	**14**	**5.9**	**7.2**	**8.3**	**12**	**6.8**	**6.7**	**8**
penicillin %	0	26	0.6	0	2.8	6	18	0	7.1
co-amoxiclav %	14	0.5	5.2	6.9	1.7	16	1.9	12	6.2
clarithromycin %	20	0	0.7	8	0	8.7	1.3	1.3	3.7
ampicillin %	0	0	6.8	0.8	12	0.3	0.2	0	3
co-trimoxazole %	0	0	3.6	3.9	0	1.1	0	0	1.7
roxithromycin %	0	0	0	4.7	0	4.9	0	6.7	1.7
fusafungine %	1.2	0	1.2	2.2	0	5.7	0	0	1.5
cephalexin %	0	0.5	3.7	0.6	3.3	0	0.2	0	1.4
azithromycin %	0	0	0	8.3	0	0	0	0	1.2
benzathine penicillin %	0	0	0	0	0	6.3	0	5.3	1.1
cefaclor %	1.2	0	2.1	1.4	1.7	0.5	0	0	1
benzylpenicillin %	0	0	0.4	0	0	5.7	0	0	1
bacampicillin %	0	0	3.9	3.9	0	1.9	0	0	1

* drugs recommended within the European Formulary

Table 5.41 Percentage use of top new antibiotics for throat infections representing ≥1% of overall prescribing from study group Phases I & II

Drug	Belgium	England	Ireland	Italy	N. Ireland	Portugal	Scotland	Spain	Overall
Phase 1 n =	**89**	**77**	**218**	**215**	**62**	**65**	**133**	**77**	**936**
amoxycillin %	7.9	7.8	34	13	19	11	14	23	18
ampicillin %	0	0	11	0.5	16	0	0	0	3.7
clarithromycin %	0	0	2.3	8.8	0	9.2	3.8	0	3.7
co-amoxiclav %	3.4	0	4.6	1.9	1.6	3.1	2.3	10	3.3
co-trimoxazole %	0	0	5	3.3	0	1.5	0	0	2
penicillin %	0	3.9	0.9	0	1.6	0	9	0	1.9
fusafungine %	1.1	0	1.4	1.4	0	15	0	0	1.8
azithromycin %	0	0	0	6.5	0	0	0	0	1.5
cephalexin %	0	0	4.1	0.9	4.8	0	0	0	1.5
cefaclor %	1.1	0	2.3	0.9	3.2	1.5	0	0	1.2
roxithromycin %	0	0	0	3.3	0	3.1	0	1.3	1.1
Phase 2 n =	**77**	**93**	**230**	**208**	**66**	**94**	**156**	**17**	**941**
amoxycillin %	10	6.5	30	26	12	28	21	18	22
penicillin %	0	36	0	0	6.1	1.1	12	0	6.1
co-amoxiclav %	3.9	0	8.7	2.9	0	2.1	1.3	0	3.5
clarithromycin %	6.5	0	0	2.4	0	9.6	0.6	0	2.1
ampicillin %	0	0	2.2	0	15	0	0	0	1.6
cephalexin %	0	0	3.9	0	1.5	0	0	0	1.1
co-trimoxazole %	0	0	2.6	1.9	0	0	0	0	1.1
azithromycin %	0	0	0	3.4	0	0	0	12	1

Table 5.42 Percentage (SEM) concordance with the European Formulary of new analgesic prescribing for throat infections

Country	Phase I				Phase II				Phase II - Phase I	
n = total N^0 analgesics	Study *n*	Study % (SEM)	Control *n*	Control % (SEM)	Study *n*	Study % (SEM)	Control *n*	Control % (SEM)	STUDY % (SEM)	CONTROL % (SEM)
Belgium	13	23 (15)	4	83 (17)	10	75 (25)	3	25 (25)	**+52 (38)**	-58 (42)
England	13	100 (0)	--	--	17	100 (0)	--	--	**0 (0)**	--
Ireland	6	56 (29)	--	--	5	100 (0)	--	--	**+44 (29)**	--
Italy	61	37 (11)	75	47 (11)	54	31 (9.9)	64	30 (12)	**-6.1 (9.1)**	-17 (6.6)
N Ireland	2	50 (50)	8	63 (3.3)	3	100 (0)	4	50 (50)	**+50 (50)**	-13 (47)
Portugal	8	11 (11)	70	16 (9)	11	78 (15)	47	35 (9.1)	**+67 (17)**	+19 (13)
Scotland	4	100 (0)	9	83 (17)	2	100 (0)	13	92 (8.3)	**0 (0)**	+8.3 (22)
Spain	12	42 (21)	20	69 (16)	9	40 (24)	11	38 (24)	**-1.7 (12)**	-31 (27)
Total	109	48 (7.1)	186	45 (6.7)	111	64 (7.2)	142	39 (6.6)	**+15 (7.5)**	**-6.7 (7.3)**

-- data unavailable

Table 5.43 Percentage use of top new analgesics for throat infections representing ≥1% of those prescribed from study group Phases I & II

Drug	Belgium	England	Ireland	Italy	N. Ireland	Portugal	Scotland	Spain	Overall
Phase 1 n =	**89**	**77**	**218**	**215**	**62**	**65**	**133**	**77**	**936**
nimesulide	0	0	0	7.4	0	6.2	0	0	2.1
co-codamol	0	1.3	1.8	0.5	1.6	0	0	14	1.9
dimethoxanate *	10	0	0	0	0	0	0	0	1
morniflumate	0	0	0	4.2	0	0	0	0	1
Phase 2 n =	**77**	**93**	**230**	**208**	**66**	**94**	**156**	**17**	**941**
dextromethorphan *	23	0	0	0	0	0	0	5.9	2
morniflumate	0	0	0	9.1	0	0	0	0	2
nimesulide	0	0	0	7.2	0	1.1	0	0	1.7
ketoprofen	0	0	0	5.3	0	0	0	0	1.2
niflumic acid	0	0	0	3.4	0	0	0	12	1

* cough suppressants

Table 5.44 Percentage (SEM) of consultations for throat infections resulting in a new analgesic prescription

Country	Phase I				Phase II				Phase II - Phase I	
n = total N^0 consultations	Study *n*	Study % (SEM)	Control *n*	Control % (SEM)	Study *n*	Study % (SEM)	Control *n*	Control % (SEM)	STUDY % (SEM)	CONTROL % (SEM)
England	101	24 (5.9)	84	1.1 (8.3)	110	16 (7.2)	83	8.3 (5.3)	**-8.3 (6.5)**	+7.3 (5.2)
Ireland	257	7.7 (3.7)	173	3.1 (1.6)	272	1.9 (1)	145	7.6 (6.2)	**-5.8 (2.9)**	+4.5 (6.7)
Italy	206	32 (5.6)	219	38 (5.6)	209	38 (6.4)	170	39 (6.9)	**+6.5 (7.5)**	+0.9 (6.8)
N Ireland	77	4 (1.9)	65	18 (10)	84	13 (6.7)	57	9 (6.4)	**+9.1 (7.3)**	-9.5 (5.8)
Portugal	48	20 (7.6)	195	42 (7.6)	63	34 (8.5)	100	50 (7.5)	**+14 (10)**	+8.7 (8.8)
Scotland	182	5.1 (2.8)	160	15 (5.1)	229	4 (2.1)	122	9.9 (4.6)	**-1.2 (2.4)**	-5 (3.5)
Spain	71	51 (9.9)	89	38 (8.1)	25	31 (11)	33	15 (6.1)	**-20 (16)**	-23 (8.7)
Total	942	21 (2.7)	985	24 (2.7)	892	20 (2.8)	710	23 (2.9)	**-0.57 (3.3)**	**-1.3 (2.8)**

Belgium omitted from table as data not provided on consultations without a prescription

Table 5.45 Analgesic and antibiotic prescribing for throat infections by drug group, number of prescriptions and percentage drug use in both sexes

Country	Belgium	England	Ireland	Italy	N. Ireland	Portugal	Scotland	Spain
Drug Group **N° prescribed items (%)**	188 (100)	297 (100)	779 (100)	744 (100)	244 (100)	599 (100)	610 (100)	203 (100)
Penicillins	53 (28)	205 (69)	592 (76)	209 (28)	184 (75)	229 (38)	487 (80)	76 (37)
phenoxymethylpenicillin *	5 (2.7)	125 (42)	258 (33)	0 (0)	98 (40)	0 (0)	264 (43)	2 (1)
Macrolides	21 (11)	37 (13)	50 (6.4)	124 (17)	15 (6.1)	110 (18)	48 (7.9)	15 (7.4)
erythromycin *	4 (2.1)	37 (13)	44 (5.6)	28 (3.8)	15 (6.1)	46 (7.7)	40 (6.6)	7 (3.4)
Cephalosporins	13 (6.9)	2 (0.7)	54 (6.9)	24 (3.2)	11 (4.5)	23 (3.8)	7 (1.1)	1 (0.5)
Sulphonamides and trimethoprim	8 (4.3)	1 (0.3)	28 (3.6)	26 (3.5)	0 (0)	4 (0.7)	3 (0.5)	0 (0)
Miscellaneous antibiotics	1 (0.5)	1 (0.3)	9 (1.2)	13 (1.7)	1 (0.4)	25 (4.2)	0 (0)	6 (3)
fusafungine	1 (0.5)	0 (0)	8 (1)	8 (1.1)	1 (0.4)	21 (3.5)	0 (0)	0 (0)
Tetracyclines	2 (1.1)	1 (0.3)	11 (1.4)	3 (0.4)	2 (0.8)	4 (0.7)	2 (0.3)	0 (0)
Fluoroquinolones	0 (0)	0 (0)	0 (0)	10 (1.3)	0 (0)	1 (0.2)	0 (0)	0 (0)
Aminoglycosides	3 (1.6)	0 (0)	0 (0)	1 (0.1)	0 (0)	1 (0.2)	0 (0)	0 (0)
Analgesics including anti-inflammatories	87 (46)	50 (17)	35 (4.5)	334 (45)	31 (13)	202 (34)	63 (10)	105 (52)
paracetamol *	47 (25)	29 (9.8)	14 (1.8)	65 (8.7)	24 (9.8)	45 (7.5)	54 (8.9)	63 (31)
aspirin *	15 (8)	17 (5.7)	7 (0.9)	32 (4.3)	1 (0.4)	17 (2.8)	4 (0.7)	2 (1)

* drugs listed within the European Formulary.

Table 5.46 The mean number and percentage of all patients presenting with a LRTI and proportion of those who received a related prescription

Country	Mean No (%) patients with LRTIs/GP	Mean % (SEM) patients receiving a prescription for a LRTI
Belgium	36 (9.5)	100 (--)*
England	27 (5.1)	90 (6.9)
Ireland	28 (6.1)	97 (4.1)
Italy	18 (4.1)	96 (5.6)
N Ireland	32 (6.4)	92 (5.8)
Portugal	7.9 (2.8)	96 (8.3)
Scotland	26 (5.3)	89 (16)
Spain	20 (5.9)	95 (7.3)
ANOVA	p <0.001	p <0.001

* Data recorded in Belgium did not include consultations where a prescription was not given and so was excluded from the analysis.

Table 5.47: Percentage (SEM) concordance with the European Formulary of new antibiotic prescribing for LRTIs in all males and females

Country	Phase I				Phase II				Phase II - Phase I	
n = total N^0 antibiotics	Study *n*	Study % (SEM)	Control *n*	Control % (SEM)	Study *n*	Study % (SEM)	Control *n*	Control % (SEM)	STUDY % (SEM)	CONTROL % (SEM)
Belgium	39	58 (12)	38	43 (16)	46	62 (19)	39	45 (13)	**+4.5 (29)**	+2.1 (16)
England	138	77 (9.2)	101	78 (8.7)	143	76 (9.2)	80	78 (9.1)	**-1.1 (9.4)**	-0.1 (7.5)
Ireland	185	37 (6.8)	150	52 (6.3)	191	47 (6.3)	131	59 (5.9)	**+10 (8.8)**	+7.1 (6.4)
Italy	110	23 (8.8)	67	28 (10)	77	40 (8.4)	70	28 (9.4)	**+18 (13)**	+0.6 (13)
N Ireland	63	61 (8.9)	55	55 (9.6)	66	62 (12)	78	71 (7.9)	**+0.4 (12)**	+16 (3.8)
Portugal	6	50 (22)	57	42 (7.6)	22	79 (8.8)	46	28 (11)	**+29 (25)**	-14 (13)
Scotland	161	64 (8)	85	66 (11)	171	73 (6.7)	111	75 (6.1)	**+8.9 (6.3)**	+8.5 (12)
Spain	45	67 (11)	29	77 (14)	18	53 (15)	15	77 (11)	**-14 (16)**	-0.8 (11)
Total	747	53 (3.9)	582	54 (3.8)	716	59 (3.7)	570	55 (4)	**+6.7 (4.4)**	**+1.4 (3.9)**

Table 5.48: Percentage use of new antibiotics recommended in the Formulary for LRTIs from study group Phases I and II, by country

Drug	Belgium	England	Ireland	Italy	N. Ireland	Portugal	Scotland	Spain	Overall
Phase 1 n =	**39**	**138**	**206**	**119**	**63**	**19**	**178**	**54**	**816**
amoxycillin %	21	79	44	12	48	21	50	59	46
erythromycin %	0	5.1	4.4	1.7	1.7	9.5	5.3	12	6.3
doxycycline %	26	0.7	0.5	13	3.2	37	0	0	4.4
benzylpenicillin %	0	0	0	0	0	0	0	0	0
Total %	**47**	**85**	**49**	**27**	**53**	**68**	**55**	**71**	**57**
Phase 2 n =	**46**	**143**	**194**	**77**	**66**	**27**	**190**	**18**	**761**
amoxycillin %	46	72	35	25	52	59	49	44	48
erythromycin %	0	11	9.8	2.6	11	3.7	12	5.6	8.9
doxycycline %	8.7	0.7	1.5	10	4.5	15	0	0	3
benzylpenicillin %	0	0	0	0	0	0	0	0	0
Total %	**55**	**84**	**46**	**38**	**68**	**78**	**61**	**50**	**60**

Table 5.49: Percentage (SEM) of consultations for LRTIs resulting in a new antibiotic prescription

Country	Phase I				Phase II				Phase II - Phase I	
n = total N^0 consultations	Study *n*	Study % (SEM)	Control *n*	Control % (SEM)	Study *n*	Study % (SEM)	Control *n*	Control % (SEM)	STUDY % (SEM)	CONTROL % (SEM)
England	206	64 (5.6)	178	57 (6.8)	192	75 (4)	120	61 (6.1)	**+12 (5.4)**	+4 (6.9)
Ireland	293	67 (6.7)	231	64 (3.2)	266	69 (6)	190	66 (4.8)	**+1.7 (6.7)**	+2.3 (4.2)
Italy	213	56 (5.7)	162	38 (5.8)	143	58 (7.5)	173	42 (6.1)	**+1.2 (8.6)**	+3.9 (7.4)
N Ireland	89	68 (7.8)	77	64 (10)	124	57 (6.2)	106	73 (5.1)	**-11 (9.9)**	+9.2 (12)
Portugal	64	32 (7.2)	97	67 (7.7)	62	19 (6.2)	87	44 (8.5)	**-13 (8.4)**	-23 (11)
Scotland	268	58 (7.7)	132	68 (6)	326	57 (5.1)	141	74 (8.1)	**-0.7 (6.5)**	+5.8 (8.6)
Spain	203	32 (4.9)	206	19 (4.3)	95	23 (6.2)	91	20 (5.9)	**-8.7 (7.4)**	+0.8 (5.3)
Total	1336	53 (2.8)	1083	52 (2.9)	1208	50 (2.9)	908	50 (3.1)	**-2.1 (2.8)**	**-1.6 (3.2)**

Belgium omitted from table as data not provided on consultations without a prescription

Table 5.50 Average (SEM) range of new antibiotics prescribed for LRTIs in all males and females

Country	Phase I		Phase II		Phase II - Phase I	
	Study	Control	Study	Control	Study	Control
Belgium	3.2 (0.5)	3.6 (1.2)	2.8 (0.6)	3.6 (0.9)	**-0.4 (0.9)**	0 (0.7)
England	2.2 (0.3)	2.5 (0.4)	3.1 (0.4)	2.3 (0.3)	**+0.9 (0.5)**	-0.3 (0.3)
Ireland	4.7 (0.5)	4.2 (0.5)	4.6 (0.4)	3.8 (0.4)	**-0.1 (0.6)**	-0.4 (0.4)
Italy	3.1 (0.4)	2.5 (0.4)	3 (0.4)	2.7 (0.3)	**-0.1 (0.4)**	+0.3 (0.5)
N. Ireland	3.6 (0.4)	4.2 (0.9)	3.9 (0.3)	4.2 (0.5)	**+0.3 (0.6)**	0 (0.7)
Portugal	1.2 (0.2)	2.7 (0.4)	2.2 (0.4)	2.3 (0.3)	**+1 (0.3)**	-0.4 (0.4)
Scotland	2.9 (0.2)	2.4 (0.4)	3 (0.4)	3 (0.4)	**+0.1 (0.4)**	+0.1 (0.5)
Spain †	2.3 (0.7)	2.1 (0.5)	1.6 (0.3)	1.4 (0.2)	**-0.7 (0.5)**	-0.7 (0.5)
Total	3.1 (0.2)	2.9 (0.2)	3.1 (0.2)	2.8 (0.2)	**-0.08 (0.2)**	-0.1 (0.2)

† The number of consultations recorded by the Spanish GPs in Phase II was halved

Table 5.51: Percentage use of top new antibiotics by country representing ≥1% of those prescribed for LRTIs from Phases I & II

Drug	Belgium	England	Ireland	Italy	N. Ireland	Portugal	Scotland	Spain	Overall
Phases I and II n =	**162**	**475**	**688**	**345**	**284**	**163**	**625**	**125**	**2867**
amoxycillin % *	**35**	**71**	**41**	**17**	**56**	**28**	**53**	**53**	**47**
co-amoxiclav %	19	3.8	13	7.2	11	16	19	16	13
erythromycin % *	**0.6**	**10**	**8.7**	**2.9**	**8.8**	**3.7**	**9.4**	**11**	**7.8**
clarithromycin %	14	0.4	2.5	14	1.4	4.9	4.3	8.8	4.9
ampicillin %	0	4.4	6.4	0.9	6	0	1.1	0	3.2
doxycycline % *	**15**	**0.6**	**0.7**	**8.1**	**2.5**	**14**	**0.3**	**0.8**	**3.2**
cephalexin %	0.6	1.9	2.9	0.9	2.5	0	5.4	0	2.6
cefaclor %	0.6	0	6.5	0.3	2.8	3.1	0.2	1.6	2.2
co-trimoxazole %	6.2	0	4.7	0.9	1.1	0.6	1	0	1.9
tetracycline %	0	0.2	5.5	0	0	6.1	0	0	1.7
ciprofloxacin %	0	0.6	0	7	1.1	3.1	1.1	1.6	1.5
cefuroxime %	3.1	0	1.2	0.9	1.8	10	0.3	2.4	1.5
oxytetracycline %	0	3.8	1.2	0	1.1	0	1.6	0	1.4
azithromycin %	0	0	0.4	7.8	0.4	0	0.6	0	1.2
roxithromycin %	0	0	0	9	0	1.2	0	0.8	1.2
trimethoprim %	1.2	2.1	0.7	0	2.1	0	1.6	0	1.2
cefixime %	0	0	1.9	3.5	0	1.8	0	0.8	1

* drugs recommended within the European Formulary

Table 5.52 Percentage use of top new antibiotics by country representing ≥1% of those prescribed for LRTIs from study group Phases I & II

Drug	Belgium	England	Ireland	Italy	N. Ireland	Portugal	Scotland	Spain	Overall
Phase 1 n =	**39**	**138**	**206**	**119**	**63**	**19**	**178**	**54**	**816**
co-amoxiclav %	33	4.3	8.3	2.5	19	5.3	24	19	13
clarithromycin %	7.7	0	0.5	19	0	5.3	5.1	7.4	5
ampicillin %	0	6.5	7.3	0.8	4.8	0	1.1	0	3.7
co-trimoxazole %	5.1	0	9.2	0	4.8	0	0.6	0	3.1
cefaclor %	0	0	6.8	0	3.2	0	0	3.7	2.2
cephalexin %	0	1.4	1.5	2.5	0	0	5.1	0	2.1
ciprofloxacin %	0	0	0	10	0	16	0	1.9	2
cefixime %	0	0	2.9	5.9	0	5.3	0	0	1.7
tetracycline %	0	0	5.3	0	0	0	0	0	1.3
trimethoprim %	0	2.2	1.5	0	1.6	0	1.7	0	1.2
roxithromycin %	0	0	0	8.4	0	0	0	0	1.2
azithromycin %	0	0	0	5	0	0	1.1	0	1
Phase 2 n =	**46**	**143**	**194**	**77**	**66**	**27**	**190**	**18**	**761**
co-amoxiclav %	17	3.5	17	12	4.5	3.7	12	11	11
clarithromycin %	17	0.7	5.7	9.1	3	7.4	8.4	11	6.4
cephalexin %	0	0.7	4.1	0	3	0	6.3	0	3
tetracycline %	0	0.7	11	0	0	0	0	0	2.9
ampicillin %	0	4.2	2.6	0	11	0	1.1	0	2.6
cefaclor %	0	0	8.3	0	4.6	3.7	0	0	2.6
oxytetracycline %	0	2.8	0.5	0	1.5	0	4.2	0	1.8
trimethoprim %	4.4	2.8	0	0	3	0	2.6	0	1.7
cefuroxime %	6.5	0	0	2.6	1.5	0	1.1	17	1.5
cefixime %	0	0	1	6.5	0	7.4	0	5.6	1.3
azithromycin %	0	0	1	5.2	0	0	1.1	0	1.1
bacampicillin %	0	0	0	10	0	0	0	0	1.1

Table 5.53: Antibiotic prescribing (all categories combined) for LRTIs by drug group, prescription numbers and percentage drug use in both sexes

Country		Belgium	England	Ireland	Italy	N. Ireland	Portugal	Scotland	Spain
Drug Group	**N° prescribed items (%)**	203 (100)	569 (100)	799 (100)	424 (100)	332 (100)	180 (100)	835 (100)	170 (100)
Penicillins		222 (55)	439 (77)	478 (60)	122 (29)	235 (71)	77 (43)	606 (73)	114 (67)
amoxycillin *		69 (34)	383 (67)	311 (39)	72 (17)	178 (54)	47 (26)	453 (54)	80 (47)
Macrolides		26 (13)	66 (12)	90 (11)	149 (35)	35 (11)	20 (11)	127 (15)	35 (21)
erythromycin *		1 (0.5)	64 (11)	68 (8.5)	12 (2.8)	29 (8.7)	9 (5)	93 (11)	19 (11)
Cephalosporins		10 (5)	22 (4)	111 (14)	54 (13)	31 (9)	34 (19)	53 (6)	15 (9)
Tetracyclines		36 (18)	25 (4.4)	58 (7.3)	43 (10)	16 (4.8)	38 (21)	16 (1.9)	2 (1.2)
doxycycline *		36 (18)	4 (0.7)	6 (0.8)	42 (9.9)	11 (3.3)	28 (16)	2 (0.2)	2 (1.2)
Sulphonamides and trimethoprim		15 (7)	13 (2)	57 (7)	6 (1)	9 (3)	1 (1)	21 (3)	0 (0)
Fluoroquinolones		0 (0)	4 (1)	4 (1)	43 (10)	5 (2)	9 (5)	11 (1)	4 (2)
Miscellaneous antibiotics		3 (1)	0 (0)	1 (0)	3 (1)	1 (0)	0 (0)	1 (0)	0 (0)
Aminoglycosides		2 (1)	0 (0)	0 (0)	4 (1)	0 (0)	1 (1)	0 (0)	0 (0)

* drugs recommended within the European Formulary.

CHAPTER SIX
PRESCRIBING STUDY RESULTS
EFFECT OF THE EUROPEAN FORMULARY IN ISOLATION

6.1 HYPERTENSION

6.1.1 Introduction

It is estimated that there are around 691 million patients with hypertension world-wide[339] and many patients with hypertension already have established cardiovascular disease. Cardiovascular disease is one of the commonest causes of morbidity and death in both developed and developing countries. It is the main cause of death in the United Kingdom, accounting for nearly 300,000 deaths per annum (equivalent to one death in two) of which half are from coronary heart disease.[340] In the last decade, some progress has been made against coronary heart disease for which hypertension is a major treatable risk factor. The ability of antihypertensive therapy to reduce stroke mortality among hypertensive patients remains the most impressive benefit, although stroke is responsible for only one-third as many deaths as coronary heart disease.[339] In England in 1997, cardiovascular drug use represented the largest share of prescription volume and of net ingredient cost. Prescription items increased from 91 million prescription items in 1996 to 97 million in 1997 and net ingredient cost was to £826 million in 1997, an increase of 12% from 1996.[29]

6.1.1.1 Diagnosing hypertension

In recent years, several national and international guidelines on the management of hypertension have been published.[341-346] They provide guidance on the identification and treatment of those at risk and in so doing attempt to promote a reduction in adverse events, particularly increased risk of stroke and coronary heart disease to which hypertensive patients are predisposed. The continuous relationship between the level of blood pressure and the risk of cardiovascular events and the arbitrary nature of the definition of hypertension have contributed to the variation in the definitions issued by various national and international parties. The most recent World Health Organisation - International Society of Hypertension Guidelines (WHO-ISH) for the management of

hypertension[346] attempt to provide more consistent advice to clinicians around the world in order to reduce confusion. The WHO guidelines define hypertension as a systolic blood pressure of 140mmHg or greater and/or a diastolic blood pressure of 90mmHg or greater in subjects who are not taking antihypertensive medication. Guidelines for the treatment of hypertension generally base their recommendations for treatment on cut-off blood pressure levels, although to some extent they all take into account concomitant risk factors.[347]

6.1.2 Rational prescribing for hypertension

The primary goal of treatment of the patient with high blood pressure is to achieve the maximum reduction in the total risk of cardiovascular morbidity and mortality.[346] The decision to treat a patient should be based on an assessment of the patient's overall risk. In patients with additional risk factors for cardiovascular disease, it is sensible to intervene at lower blood pressures than in those with none.[347] Major risk factors include previous cardiovascular disease and end organ damage, for example renal impairment and familial hyperlipidaemia. Other important risk factors include increasing age, cigarette smoking, high blood cholesterol levels, diabetes mellitus and of male sex.[347] All hypertensive patients should be encouraged to adopt lifestyle modifications such as weight loss, smoking cessation, increased exercise and reduction in alcohol and salt intake.[348] These non-pharmacological measures can reduce blood pressure and improve other cardiovascular risk factors.

The six main drug classes used world-wide for treating hypertension are diuretics, β-blockers, calcium antagonists, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II antagonists and α-adrenoceptor blockers.[346] Of these drug groups, diuretics and beta-adrenoceptor blocking drugs (β-blockers) are the only ones for which long term effects on morbidity and mortality have been demonstrated and consequently guidelines usually state that they are the preferred drugs of choice.[347] Several studies suggest that these two well established drug groups are as well tolerated as newer drugs and where diuretics and β-blockers induce metabolic changes in individual patients, the treatment strategy can be tailored accordingly.[347] Trials have provided evidence that

ACE inhibitors are preferable in hypertensive patients with diabetes and therefore can be considered as drugs of first choice here.[349]

Not all drugs indicated for hypertension work well in everyone - a German study found that both hydrochlorothiazide (a thiazide diuretic) and nitrendipine (a calcium channel blocker) worked better in older patients than younger ones.[348] When selecting an antihypertensive, co-existing diseases should also be considered as some drugs are contra-indicated in certain conditions such as β-blockers in asthma, while others may treat a concomitant cardiovascular condition as well as the hypertension, thus simplifying therapy and reducing prescribing costs.

In the elderly, low dose thiazide diuretics are the first-line treatment of choice with β-blockers as a good second choice.[350] Ten trials involving 16,164 patients found that β-blocker therapy only reduced the odds for cerebrovascular events, whereas diuretic therapy was superior and effective in preventing cerebrovascular events, fatal stroke, coronary heart disease, cardiovascular mortality and all-cause mortality.[351] Meta-analyses have indicated that the benefits of hypertension treatment in the elderly may actually be greater than those in younger persons[352], and more recently it has been suggested that antihypertensive drugs may be particularly beneficial in patients over 80 years old.[353]

Selection of the most suitable drug to prescribe should be based on published scientific evidence for the efficacy of lowering blood pressure in preventing stroke and coronary heart disease. There are also important differences in the side-effect profiles between drug classes. Without adequate evidence that newer antihypertensive drugs significantly alter outcomes, it is difficult to justify the greatly increased cost of their more widespread use. Ultimately however, the choice of drug should be tailored to the individual patient.

6.1.2.1 European Formulary recommendations

The Formulary recommended that non-drug treatment should be initially considered in the management of hypertension. Drug treatment may be added in a stepwise fashion until the necessary control has been achieved. The drug treatment strategy recommended in the European Formulary was based on efficacy, safety, cost and availability as follows:

1.	Initial treatment	hydrochlorothiazide, atenolol
2.	If not effective or if side-effects	hydrochlorothiazide + atenolol
3.	If no effect, if side-effects or if contraindicated	verapamil, nifedipine or enalapril

In special situations, the European Formulary endorsed prescribing of the following:

• hypokalaemia	hydrochlorothiazide + amiloride/triamterene
• elderly	hydrochlorothiazide, verapamil/nifedipine/enalapril
• pregnancy	oral methyldopa, or atenolol (from third trimester)
• hypertensive crisis	oral nifedipine or sodium nitroprusside infusion

The European Formulary Group (EFG) recommendations in the Appendix included that:

- thiazide diuretics are considered to be the best initial therapy especially in elderly patients,
- the optimal dose is the lowest possible one,
- potassium sparing diuretics are unnecessary unless hypokalaemia develops,
- β-blockers can be used as first-line treatment or together with a thiazide if the latter is not effective alone,
- calcium antagonists and ACE inhibitors should only be considered when thiazides or β-blockers fail, or are poorly tolerated, or for co-existing indications,
- vasodilators, α- blockers and centrally acting drugs should be reserved for patients whose blood pressure is not controlled by, or who have contra-indications to diuretics, β-blockers, calcium antagonists and ACE inhibitors.

6.1.2.2 Proposed prescribing performance indicators

The following hypotheses were drawn up based on quality indicators which could be adapted to critically explore the prescribing data for hypertension in the different countries. The hypotheses were that:

- the proportion of antihypertensives prescribed which were listed within the European Formulary increased following its distribution,
- the range of drugs prescribed for hypertension would be reduced following the distribution of the Formulary,
- diuretics (thiazide) and β-blockers represented the majority of antihypertensives prescribed,
- calcium channel blockers and ACE inhibitors represented the third and fourth largest groups of antihypertensives prescribed,
- use of vasodilators, α-blockers and centrally acting drugs should be limited,
- potassium sparing diuretics as a proportion of overall diuretic prescribing should be minimal,
- the use of combination antihypertensive drugs should be limited.

6.1.2.3 Data manipulation/methodology

In order to critically evaluate the prescribing data for antihypertensive drugs, all the searches except the first involved drugs matched to a diagnosis code of hypertension. The following searches involving both sexes and all ages combined were performed within the database:

- all hypertension consultations for both Phases combined, no matching of drugs to diagnosis,
- all hypertension consultations for both Phases combined,
- hypertension consultations, selection of single component drugs only,
- hypertension consultations, selection of single component drugs Phase I only,
- hypertension consultations, selection of single component drugs Phase II only,

- hypertension consultations, selection of all drug entities Phase I only,
- hypertension consultations, selection of all drug entities Phase II only.

In the results tables, the data are presented in order of prescribing volume in terms of the number of items prescribed. The antihypertensive drug data were sorted based on the following classification:

1. Diuretics (thiazides, loop and potassium-sparing)
2. β-blockers (cardioselective and non-cardioselective)
3. Calcium channel blockers (CCBs)
4. Angiotensin-converting enzyme (ACE) inhibitors
5. α-blockers
6. Centrally acting antihypertensives
7. Vasodilator antihyprtensives
8. Other antihypertensive drugs (serotonin antagonists, ganglion blockers, adrenergic neurone blockers)
9. Potassium supplements
10. Other cardiovascular drugs

6.1.3 RESULTS

6.1.3.1 Morbidity/prevalence patterns

Hypertension was the most commonly occurring diagnosis overall accounting for 9.4% of the total number of general practice consultations. The proportion of consultations (Table 6.54) varied between 4.4% in England to 16% in Portugal (mean 9.8%, SD 5.4). Of a total of 9,514 patients with hypertension, 8,955 were prescribed 12,841 drug entities. The majority of these, 10,297 (80%), were repeat prescriptions. From the remainder, 1,007 (7.8%) were newly prescribed items, 804 (6.3%) were hospital-initiated prescriptions and 534 (4.2%) were prescribed upon request of the patient as a result of having been prescribed on a previous occasion. Of the drug entities prescribed, 9,697 (76%) were single non-combination drugs (Table 6.54).

6.1.3.2 Prescribing performance indicators

6.1.3.2.1 Concordance before and after dissemination of the European Formulary

As hypertension is an example of a chronic disorder involving long term medication, reflected by less than 8% of the drug entities being new prescriptions for it, in this study (section 6.1.3.1), concordance levels were measured using all prescription categories combined. To assess the concordance with the Formulary, two analyses were performed. Firstly, the level of concordance with both single component and combination drugs was measured; and then secondly, an analysis was performed on single component drugs only. The reason for this was because some antihypertensive drugs, for example hydrochlorothiazide, occur in both single component and combination drug formulations, of which only the former was recommended in the European Formulary. Consequently, concordance with the European Formulary cannot purely be based on analysis of all drug entities together as this does not separate the prescribing of combination drug entities from non-combination drug entities. In comparison however, measuring the level of concordance with the European Formulary on antihypertensive prescribing of single component drugs only is likely to give artificially higher concordance levels because of the total number of drug entities being lower.

For both combination and single component drugs, with all prescription categories combined, no significant differences were found either in the concordance with drugs recommended in the EF (Table 6.55) between intervention and control groups from Phases I to II ($p = 0.21$) or between countries ($p = 0.91$). In Belgium, there appeared to be considerable movement towards use of the Formulary drugs by the intervention group and movement away from the Formulary recommendations by the control group but this difference was not statistically significant ($p = 0.28$). Prescribing by the GPs in Spain demonstrated the greatest concordance with the European Formulary averaging approximately 60% in each of the subgroups compared with Ireland at the other extreme which averaged approximately 25% concordance in each of its subgroups.

For single component drugs only, with all prescription categories combined, again there was found to be no statistically significant movement towards the use of European Formulary (Table 6.56) recommended antihypertensive drugs in control and

intervention groups from Phases I to II (p = 0.19). No statistically significant difference was found between countries either (p = 0.94). The sub-groups of Spain had the greatest concordance with the Formulary and those in Ireland demonstrated the least concordance with the Formulary, similarly to Table 6.55.

The change in *n* values between Table 6.55 and Table 6.56 indicates the difference in prescribing of single drug components compared with combination drug entities and particular differences were seen in Ireland, Italy and Portugal. In Italy and Portugal, the subgroups displayed notably higher levels of Formulary concordance in Table 6.55, compared with Table 6.56. From this one can infer that Formulary recommended hydrochlorothiazide was being prescribed in combination form in both countries, thus artificially increasing the levels of concordance observed in Table 6.55.

6.1.3.2.2 Range of drugs prescribed

For both combination and single component drugs, with all prescription categories combined, there was no significant difference (p = 0.61) in the range of drugs prescribed for hypertension from Phase I to Phase II between control and study groups (Table 6.57). The difference between countries was of high statistical significance (p <0.001). Within countries, there was no statistically significant difference between control and intervention groups in changes in the range of drugs prescribed. The largest range of drugs prescribed for hypertension was in Italy which was nearly three times greater than the ranges used in England, Northern Ireland and Scotland.

For single component drugs only (Table 6.58), the results largely mirrored those of all drug entities in Table 6.57. There was no significant difference (p = 0.53) in the range of drugs prescribed for hypertension between control and study groups from Phases I to II and no significant difference between countries (p = 0.31). Within countries, the greatest difference between study and control groups after dissemination of the Formulary occurred in Belgium but the difference was not statistically significant (p = 0.42). Again the largest range of drugs prescribed for hypertension occurred in Italy, three times greater than the ranges used by the UK cohort of GPs.

6.1.3.2.3 Prescribing of diuretics and β-blockers

Of the drugs prescribed for hypertension, the diuretics were marginally the most popular group overall, accounting for 31% of prescribed items (Table 6.59). β-blockers were the fourth most commonly prescribed class of antihypertensives representing 15% of the drugs used (Table 6.59). Within countries, diuretics were the main antihypertensive drug class used in the four English speaking countries and Spain. They were the second most popular in Italy and Portugal. In contrast, β-blockers were the main drug class used in Belgium and the second most common in each of the four English speaking countries.

6.1.3.2.4 Prescribing of CCBs and ACE inhibitors

CCBs were the third most popular group of antihypertensives representing 16% of the drugs used (Table 6.59). In the three southern European countries, they were the third most commonly used group there and in the remaining five countries they were the fourth most commonly used antihypertensive group. In contrast, the ACE inhibitors were the second most abundant group of drugs prescribed for hypertension accounting for 31% of the drugs prescribed, fractionally less than the proportion of diuretics (Table 6.59). They were the third most commonly prescribed class of antihypertensives in England, Ireland, Northern Ireland and Scotland and were even more popular in all the other countries.

6.1.3.2.5 Prescribing of vasodilators, α-blockers and centrally acting drugs

Together, these groups combined represented less than 3% of the antihypertensive drugs used overall. Of the three groups, α-blockers were the most commonly prescribed and in Spain they accounted for 4% of prescribing for hypertension (Table 6.59). Prescribing of centrally acting antihypertensives was greatest in Belgium where they accounted for 3.7% of the drugs used there. Use of vasodilator antihypertensives was minimal in all countries.

6.1.3.2.6 Prescribing of potassium sparing diuretics

Overall, potassium-sparing diuretics represented almost 18% of the total diuretic prescribing. In general the levels of potassium-sparing diuretics were low in England and Scotland and relatively high in Belgium, Italy and Portugal (Table 6.59). The proportion that potassium-sparing diuretics represented of the total diuretic prescribing varied from 4.1% in Scotland to 31% in Belgium (mean 16%, SD 9.5).

6.1.3.2.7 Prescribing of combination antihypertensives

Of the 12,841 drug entities prescribed for hypertension in the study, 3,144 (24%) were part of combination drugs (Table 6.54). This varied from 5.6% of the antihypertensives prescribed in England to 37% of those prescribed in Ireland (mean 20%, SD 11). Relatively high levels of combination drugs for hypertension were also prescribed in Italy and Portugal.

6.1.3.3 Comparisons of antihypertensive drug classes prescribed

6.1.3.3.1 Diuretics

Diuretic group prescribing (Table 6.59) varied from 17% in Belgium to 34% in Spain (mean 30%, SD 5.5). This class of antihypertensive drugs were the most commonly prescribed in England, Ireland, Northern Ireland, Scotland and Spain. Of the diuretics, thiazides were the most commonly prescribed subgroup varying from 11% in Belgium to 29% in England (mean 24%, SD 6). Hydrochlorothiazide was the most popular diuretic accounting for 12% of the overall prescribing, however bendrofluazide which was only found to be prescribed in each of the four English speaking countries was predominantly the diuretic of choice there (Table 6.60 and Table 6.61). hydrochlorothiazide prescribing varied from 1% in Scotland to 24% in Spain (mean 8.3%, SD 8.2). Potassium-sparing diuretics were the second most popular sub-group of diuretics representing 5.5% of the drug prescribing for hypertension, varying from 1.3% in Scotland to 7.8 % in Portugal (mean 4.6%, SD 2.2). Amiloride was the most commonly prescribed potassium-sparing diuretic and was nearly always prescribed as part of a combination. Amiloride prescribing (Table 6.60 and Table 6.61) varied from 0.7% in Scotland to 5.6% in Italy (mean 2.9%, SD 1.9). Frusemide accounted for

nearly all loop diuretic prescribing (Table 6.60 and Table 6.61), its use varied from 1.1% in Belgium to 2.7% in Italy (mean 1.8%, SD 0.5).

6.1.3.3.2 ACE inhibitors

This class of drugs was the most commonly prescribed in Italy and Portugal (Table 6.59). ACE inhibitor use varied from 18% in England to 38% in Italy (mean 27%, SD 8). Enalapril was the most commonly used one (Table 6.60 and Table 6.61) representing 9.7% of the drugs prescribed and its use varied from 0.9% in Ireland to 16% in Spain (mean 7.7%, SD 5.2). Captopril accounted for 8.2% of the antihypertensive drug prescriptions and it was clearly the ACE inhibitor of choice in Ireland and Portugal. Lisinopril was the third most commonly used ACE inhibitor and it appeared to be the one of choice in Belgium and Northern Ireland.

6.1.3.3.3 CCBs

Their use varied (Table 6.59) from 9.4% in Ireland to 20% in Spain (mean 16%, SD 3.4). Nifedipine was the CCB of choice and was markedly the one most commonly prescribed in all the countries (Table 6.60 and Table 6.61). Nifedipine use accounted for nearly 10% of the prescriptions for hypertension, its use varied from 6.4% in Ireland to 13% in Northern Ireland (mean 10%, SD 2.7). Amlodipine, diltiazem and verapamil were the second, third and fourth most commonly used calcium channel blockers respectively, but even when combined their use was lower than the level of nifedipine use (Table 6.60 and Table 6.61).

6.1.3.3.4 β-blockers

Their use varied (Table 6.59) from 6.8% in Spain to 36% in Belgium (mean 21%, SD 11). β-blockers were the most popular class of antihypertensives in Belgium only. Over 80% of the β-blockers prescribed were cardioselective of which atenolol was predominantly prescribed (Table 6.60 and Table 6.61). Atenolol use varied from 5.4% in Portugal to 24% in England (mean 15%, SD 8.8) and it was the one of only two β-blockers to feature in the top drugs prescribed for hypertension (Table 6.61). Propranolol was the most commonly prescribed non-cardioselective β-blocker, however its use represented less than 1% of the antihypertensives prescribed.

6.1.3.3.5 α-blockers

α-blockers represented 1.6% of the drugs prescribed for hypertension (Table 6.59) and their use varied from 0.1% in Portugal to 4% in Spain (mean 1.7%, SD 1.1). Doxazosin accounted for over three quarters of the α-blocker prescriptions and it was the fifteenth most commonly prescribed antihypertensive drug used overall, although it was neither prescribed in Belgium, nor Portugal (Table 6.60 and Table 6.61).

6.1.3.3.6 Potassium supplements

Potassium supplements were used in combination with diuretics and they were predominantly prescribed in Ireland where they represented 8.4% of the drug entities prescribed for hypertension (Table 6.59). Their use elsewhere was found to be minimal.

6.1.3.3.7 Centrally acting drugs, vasodilators and other antihypertensives

When combined, these drug groups accounted for less than 1.5% of the drug entities prescribed for hypertension (Table 6.59). Their use varied from 0% in Northern Ireland to 4.3% in Belgium (mean 1.5%, SD 1.3).

6.1.3.3.8 Other cardiovascular drugs

These cardiovascular drugs represented 2.5% of the drugs associated with hypertension (Table 6.59), their prevalence varied from 1% in Scotland to 3.5% in Ireland (mean 2.5%, SD 1). These cardiovascular drugs were ones not officially indicated for hypertension but were nevertheless linked up to a diagnosis of hypertension in the prescribing data. It can therefore be inferred that they were being prescribed for related co-morbid conditions.

6.1.4 Discussion

In this data set, hypertension was the most commonly occurring diagnosis overall. High prevalence levels of hypertension have been found in studies from many European countries[354-361] and the cardiovascular system has been found to be the main therapeutic area in terms of number of prescription items in England.[29] These findings together with the fact that hypertension is almost exclusively managed by general practitioners made antihypertensive drug utilization patterns an ideal area to investigate.

Interpretation of these data is however particularly complex for several reasons. Firstly, due to the chronic nature of the disease, drugs are prescribed for use in the long term and therefore the numbers of newly prescribed drugs were relatively small. Thus when investigating any possible effects of the Formulary dissemination it was not realistic to investigate the potentially more meaningful cohort of new prescriptions in isolation. Secondly, the therapeutic management of hypertension varies with its severity but it was not possible to analyse this in any more detail. The diagnostic coding frame used did not include a breakdown of different levels of hypertension severity and in any case the majority of GPs were found to record a diagnosis of hypertension only. Thirdly, there are a number of recognised risk factors associated with cardiovascular diseases such as ethnicity[346] which can effect treatment management but this collation of data does not permit such investigation. Fourthly, the analyses did not consider in detail the area of concomitant use of two or more antihypertensives by patients and whether prescribing practices were tailored in patients with co-morbidities. Fifthly, it was not possible to identify which drugs (if any) had been tried previously on some patients as well as the variations in dosage, formulation and strength of medications prescribed, something which was problematic in all areas investigated in this thesis.

In this study, there was found to be no significant differences either in concordance with the Formulary or in the range of antihypertensives prescribed between the intervention and control groups from Phases I to II following dissemination of the European Formulary. The only country where there appeared to be any slight trend towards a positive change in prescribing was in Belgium. Formulary concordance was below the 50% level in all countries, with the exception of prescribing by the Spanish GPs. Relatively large ranges of drugs were prescribed by GPs in all countries, except

for the cohort of GPs from the UK. Therefore, one can conclude that dissemination of the Formulary and thus receipt of written material alone appeared to have virtually no impact on the prescribing for hypertension within the frame of this project.

On observing the prescribing for hypertension in the different countries, more consistent prescribing of different antihypertensive drug classes between the different countries can be seen compared with individual drug use. For example, diuretics were the main antihypertensive drug class in five countries and the second in two others. Also CCBs were the third most commonly used group in the three southern European countries and the fourth, in the remaining five other countries. The relative prescribing of these two important antihypertensive drug classes could be said to reflect fairly rational prescribing and consequently prescribing patterns may actually reflect higher levels of concordance with national guidelines within countries than with a multinational consensus based European Formulary. Different national guidelines for the treatment of hypertension exist and many have been available for about 25 years having undergone periodic updating.[362] Whilst the general principles of the European Formulary management of hypertension were sound, the individual drugs recommended may have been too rigid and inflexible for the diversity of antihypertensive drugs available. For example bendrofluazide is the most cost-effective thiazide diuretic in the UK and Ireland and was the diuretic of choice there but was excluded from the Formulary. In contrast though, Formulary recommended atenolol and nifedipine were the β-blocker and CCB of choice most distinctly in all the countries. Levels of β-blocker prescribing were notably low though in southern European countries and ACE inhibitors appeared to be overprescribed in their place. The prescribing of these drug classes support what others have reported in Spain.[363,364]

Patterns of prescribing for hypertension do vary from country to country especially with respect to individual drug use. Within countries, ideally there should be more standardisation of prescribing within the different antihypertensive drug classes and a consequent reduction in the range of drugs used. Combination antihypertensive drugs which were found to be prescribed particularly in Ireland, Italy and Portugal should be minimised as they do not allow for flexible dosing. Also the level of β-blocker use should be increased in southern European countries as these drugs together with

diuretics are currently the only ones for which long term effects on morbidity and mortality have been consistently demonstrated.

6.2 ASTHMA

6.2.1 Introduction

Asthma is a common inflammatory condition of the airways which may present as acute attacks or as a chronic disorder with exacerbations. It continues to be the commonest chronic condition of any sort in children and the commonest chronic respiratory problem at all ages. Persistently high levels of asthma morbidity and mortality have been shown in studies from many countries.[365-372] Recent evidence has shown that the prevalence of symptoms of asthma in children varies widely, to a twenty fold extent, between countries - from 1.6% in Indonesia to 36.8% in the UK.[373] Many of these children have not been diagnosed formally as having asthma by doctors and thus many do not receive the appropriate treatment they need. Even amongst those who have been diagnosed, undertreatment remains a particular problem in several European countries (Denmark, Finland, France, Italy, Netherlands, Switzerland and the UK)[374-380] and beyond[371,381-383] Suboptimal treatment in the community, where the vast majority of asthma care is delivered, is likely to result in greater use of emergency facilities. In the UK, asthma morbidity and mortality data has not improved in the past 25 years and it features in the top 20 medical lead causes of death.[384] Of those that die, studies have indicated that 80% or more of these could be preventable.[385,386] Ironically non-concordance with recommended standards is probably a major cause of avoidable deaths from asthma.

Despite underdiagnosis and undertreatment, the requirement for prescriptions in asthma care is massive - in the UK for example about 7% of all NHS prescriptions are for asthma.[387] The total annual costs of asthma in the UK were estimated to be between £322M and £686M in 1990[388], of which 20-25% of the direct costs are due to hospitalisation. The costs due to asthma in France, in 1995 were approximately 1% of direct and indirect health care costs combined, equivalent to 7 thousand million French francs (approximately £700M)[389] and in the USA at the beginning of this decade they accounted for 5.5 billion dollars (approximately £3,440M).[390]

Since consensus statements on asthma management have emerged in various countries and international agreement on treatment has been possible,[391] it is reasonable to hope that prescribing in the community should be in line with recognised guidelines in order to minimise the impact of asthma on both the people who suffer its consequences and the health services who serve them. As the majority of asthma is diagnosed and treated solely in primary care it was rational for the condition to be included in the European Formulary and Appendix. The two documents contained discussion about both non-drug treatment and drug treatment.

In this results section, an investigation of asthma drug utilisation will indicate whether the dissemination of written prescribing recommendations alone can improve prescribing. In addition, prescribing patterns between countries for children 0-15 years of age and adults 16 years and over will be compared.

6.2.2 Rational prescribing for asthma

To improve asthma management, regional[392], national[393] and international guidelines have been introduced.[391] The aim of asthma management is to reduce the symptoms and restore normal long term function of the airways and reduce as far as possible the risk of severe attacks.[262] In the most recent British Thoracic Society (BTS) guidelines published in 1997, the most significant change was the urging of prescribers to begin management of asthmatic patients with high dose inhaled steroids, stepping down the dose once asthma control is established.[393,394] The BTS guidelines recommend a stepped pharmacological approach to asthma therapy.

6.2.2.1 European Formulary Recommendations

Asthma management guidance in the European Formulary reinforced the BTS stepwise approach and the following drug treatment strategy was recommended:

- salbutamol or any alternative short acting β_2 agonist
- ipratropium bromide
- beclomethasone
- prednisolone
- sodium cromoglycate

6.2.2.2 Proposed quality indicators

The following hypotheses were drawn up based on quality indicators which could be adopted to critically explore the prescribing data for asthma in the different countries. The hypotheses for asthma prescribing were that:

- the proportion of drugs prescribed for asthma which were listed within the European Formulary increased following the distribution of the Formulary,
- the range of drugs prescribed for asthma would be reduced following the distribution of the Formulary,
- the level of use of inhaled corticosteroids increased following the distribution of the Formulary,
- a high level of inhaled medications should be prescribed as they are associated with a rapid onset of action and fewer side-effects for a given therapeutic effect,
- the use of combination drugs should be limited as they do not allow for flexible dosing.
- the use of antibiotics in managing an acute attack should be minimised as there is no clear evidence of any resulting benefit.

6.2.2.3 Data manipulation/methodology

In order to critically evaluate the prescribing data for asthma, all the searches except where specified involved drugs matched to a diagnosis code of asthma. The following searches involving both sexes were performed within the database:

- all asthma consultations for both Phases combined, no matching of drugs to diagnoses,
- asthma consultations in children <16 years of age, for both Phases combined,
- asthma consultations in children <16 years of age for both Phases combined, no matching of drugs to diagnosis,
- asthma consultations in adults ≥16 years, for both Phases combined,

- asthma consultations in adults ≥16 years, no matching of drugs to diagnosis for both Phases combined,
- all Phase I prescriptions for asthma in all ages combined,
- all Phase II prescriptions for asthma in all ages combined,
- all Phase I study group new drug prescriptions for asthma in all ages combined,
- all Phase II study group new drug prescriptions for asthma in all ages combined,

For the country by country comparative prescribing results section, it was decided to combine the data from Phases I and II as this was likely to provide a more meaningful illustration of the overall prescribing patterns compared with looking at the trends in each of the Phases separately. In the results tables, the data were presented in order of prescribing volume in terms of the number of items prescribed. The drug data for asthma were sorted based on the following classification:

1 Short acting β_2 agonists

2 Long acting β_2 agonists

3 Inhaled corticosteroids

4 Oral corticosteroids

5 Cromoglycate and related therapy

6 Antimuscarinic bronchodilators

7 Antihistamines

8 Antibacterials

9 Theophyllines

10 Nasal sprays

11 Drug entities prescribed for asthma present in combination form only

12 Asthma appliances (peak flow meters, spacers and nebulisers)

13 Miscellaneous group of drugs prescribed for asthma including: expectorants mucolytic agents; cough suppressants and sympathomimetic decongestants.

14 Other drug entities prescribed for asthma

Although included in the overall denominator because of being matched to asthma diagnoses, categories 7, 10, 11, 13 and 14 were merged into one group, as they imply related morbidity. The resulting mixed group was heavily weighted in terms of the number of prescribed items, towards categories 13 and 14 and so it could largely be defined as consisting mainly of drugs of limited proven clinical value. For discussion purposes, it was decided to keep groups 8 and 12 as separate.

6.2.3 Results

6.2.3.1 Morbidity/prevalence patterns

Asthma was the sixth most common diagnosis overall accounting for 3.5% of the total number of consultations in general practice. The proportion of asthma consultations varied from 1.8% in Italy to 5.8% in Ireland (mean 3.4%, SD 1.6) (Table 6.62). The proportion of patients presenting with asthma who received treatment varied from 84% in Scotland to 98% in Portugal and Spain (mean 92%, SD 5.5).

6.2.3.2 Prescribing performance indicators

6.2.3.2.1 Concordance with drugs recommended in the European Formulary

No significant differences were found either in the concordance with drugs recommended in the EF Table 6.63 between study and control groups from Phases I to II ($p = 0.83$) or between countries ($p = 0.34$). The largest difference between the control and intervention groups from Phase I to Phase II in the trend towards European Formulary recommended drugs was in England which was found to be statistically significant ($p = 0.02$). The concordance levels were measured using all prescription categories combined because of the 5,159 prescriptions for asthma in the study, only 1,405 (27%) were for newly prescribed items.

Overall, the greatest concordance with the European Formulary can be seen to have occurred in England with a level of almost 90%, followed by Scotland and Northern Ireland with approximately 80% concordance. The lowest level of Formulary concordance was found in Italy where the level was just below the 50% mark.

Of the drugs recommended in the Formulary for asthma, short acting β_2 agonists were the most commonly prescribed (Table 5.48). Salbutamol was the short acting β_2 agonist drug of choice in all the countries, as well as being the most commonly prescribed drug overall for asthma. From study group Phases I to II, there were substantial increases in the prescribing of salbutamol in Belgium and Italy. In Belgium, from Phases I to II, the reduction in prescribing of fenoterol almost equated to the increase in salbutamol use there. From Phases I to II, the level of beclomethasone use increased by nearly 30% overall; within countries, notable increases in its use were found in England and Northern Ireland but these were not statistically significant Although terbutaline remained the fourth most common drug used overall in the study groups from Phase I to Phase II, in Northern Ireland its level decreased from 21% to 8.7%.

6.2.3.2.2 Range of drugs prescribed

The reduction in the range of drugs prescribed from Phases I to II was greater in the study group compared with the control group overall (Table 6.65) but this was not found to be statistically significant ($p = 0.10$). No significant difference was found between countries either ($p = 0.34$). Nevertheless, the reduction of the range within the study group from Phases I to II was found to be significant ($p = 0.02$), whilst the reduction in the control group was not significant ($p = 0.62$). The Spanish data were excluded from these analyses due to the number of recorded consultations in Phase II being halved.

Within countries from Phases I to II, there was a trend towards a greater reduction in the range within the study groups of Belgium, England, Northern Ireland and Scotland compared with their corresponding control groups. Of these, the greatest difference between study and control groups occurred in Belgium but this difference was not significant ($p = 0.09$).

Approximately eight different items were prescribed on average for asthma by each of the GPs in Ireland which was the largest range found to be used. Excluding Spain for the above reasons, the smallest range was found in Portugal where just over four different items were prescribed on average per GP.

6.2.3.2.3 Prescribing of inhaled corticosteroids

Using the number of patient consultations as a proxy for the number of patients seen (it was clearly possible for a single patient to be seen on more than one occasion), the percentage of treated asthma patients on inhaled corticosteroids for all ages combined (Table 6.62) varied from 23% in Italy to 47% in Northern Ireland (mean 35%, SD 9.7). The Spanish data were not included in this comparison as the formulation of the steroids could not be inferred.

As previously mentioned, for the study group overall, from Phases I to II, the level of beclomethasone use increased by nearly 30% (Table 5.48) and within countries, its use increased considerably in England and Northern Ireland. For the other inhaled corticosteroids (Table 5.52), the level of budesonide decreased in all the study groups from Phases I to II, except for an increase in its use in Scotland. Fluticasone levels remained fairly constant in the study groups from Phases I to II, except for a notable increase in Belgium.

6.2.3.2.4 Prescribing of inhaled medications

Relatively high levels of prescribing of inhaled medications (Table 5.48) recommended in the Formulary were found to occur in England followed by Northern Ireland and the other English speaking countries. The only drug in Table 5.48 not to be in an inhaled formulation was prednisolone.

6.2.3.2.5 Prescribing of combination drugs for asthma

Of the 5,159 drug entities prescribed for asthma in all the countries combined, only 252 (4.9%) entities belonged to combination drugs. In children up to 15 years of age, of 1,538 entities prescribed for asthma, 20 (1.3%) represented combination drugs and in adults 16 years and over, of 3,621 items prescribed for asthma, 232 (6.4%) formed part of combination drugs. The proportion of drug entities representing combination drugs was therefore relatively small.

6.2.3.2.6 Prescribing of antibiotics

The only antibiotic to be prescribed in notable volume was amoxycillin. From Table 5.51, it can be seen that amoxycillin was the eleventh most commonly prescribed drug for asthma in the study with greatest use in Scotland. In study groups from Phases I to II, its use marginally decreased overall. Within countries, the highest level of use was found in Belgium in Phase I and Scotland in Phase II.

6.2.3.3 Comparisons of prescribing for asthma

6.2.3.3.1 Prescribing in children

Prescribed inhaled medications (Table 6.68) varied from 72% of all prescribed items for asthma in Ireland and Portugal to 87% in Northern Ireland (mean 77%, SD 5.6). As stated above, the formulation of the steroids could not be inferred from the Spanish data above and so it was excluded from the above comparison. Inhaled corticosteroid usage varied from 12% in Portugal to 34% in Northern Ireland (mean 21%, SD 8.2). Use of individual corticosteroids also varied widely; Spain used no beclomethasone, instead using budesonide in 28% of asthma prescriptions. Northern Ireland used fluticasone in 4.5% - more than three times the frequency in any other country. In all other countries, beclomethasone was the steroid of choice accounting for 15% of all asthma prescriptions. $Beta_2$-agonist use (long and short acting combined) varied from 24% of all prescribed items for asthma in Italy to 67% in Spain for children (mean 45%, SD 13).

Combination drug items accounted for less than 1.3% of asthma prescriptions for children. Cromoglycate use alone varied from 0% in Spain to 7.3% in Italy (mean 3.6%, SD 2.7). Methylxanthine use varied from none in England to 8.8% in Ireland (mean 3.8%, SD 3). Antibiotic prescribing in children at consultations for asthma varied from none in Spain and Portugal to 7.3% in Belgium (mean 2.9%, SD 2.5).

6.2.3.3.2 Prescribing in adults

Prescribed inhaled medications (Table 6.69) varied from 54% in Italy to 78% in England (mean 68%, SD 9.1), with the Spanish data again being excluded from the

comparison. Inhaled corticosteroid usage varied from 14% in Italy to 31% in Northern Ireland (mean 23%, SD 6.7). Spain used beclomethasone in 6% of asthma prescriptions but budesonide in 22% and Northern Ireland used beclomethasone in 16% but budesonide in 13%. In all other countries, beclomethasone was again the steroid of choice accounting for 17% of asthma prescriptions overall. $Beta_2$-agonist use (long- and short -acting combined) varied from 27% in Belgium to 48% in Spain (mean 40%, SD 7).

For adults, combination drug items accounted for less than 6.4% of prescription items for asthma. Methylxanthine use varied from 0.8% in England to 23% in Italy (mean 10%, SD 9). Antibiotic prescribing for adults varied from 0.6% in Portugal to 5% in Scotland (mean 2.9%, SD 1.3).

6.2.4 Discussion

It is clear from the data that despite the real progress made in international consensus on asthma management[391], patterns of asthma prescribing in general practice vary considerably as does the frequency of asthma diagnosis. If prescribing were more in concordance with the European Formulary and other published guidelines[392,393], one would expect more consistent asthma treatment, minimal antibiotic use and no prescribing of drugs of limited clinical value. The variation in proportions of patients with asthma suggests that there may well be differences in the diagnostic labelling of asthma as indicated by other studies.[376,379,395,396]

Some cautions should be considered in interpreting this data. Firstly, this study has used the prescribed item as a unit of prescribing volume which in reality gives no consistent indication of the quantity of drug prescribed. Secondly, another important confounder is the difference in organisation of general practice in the various countries and the difference in distribution of asthma patients between the primary and secondary care sector, which make it difficult to compare the patient populations in the various countries.

The results detailed are not easily comparable with other published research as the drug and morbidity data presented are solely based on consecutive face-to-face consultations with GPs. A highly significant difference in the mean percentage of

patients consulting GPs with asthma was found between countries. Despite the variation in the number of participating GPs between countries (Table 6.62), this study appears to be consistent with others in that similar trends of high asthma prevalence in the UK and Ireland and low in the southern European countries have been reported.[373,393,395] Different studies have varying methods of data collection, sample sizes and age groups with some studies relying only on GP and patient recall and/or questionnaires. Whilst this study avoided these sources of bias, there remains a problem with GP-labelled asthma diagnosis in all such studies.

The mean percentage of asthma patients who received a drug prescription for asthma was very high in all the countries as might be expected but there was still a significant difference between them (Table 6.62). The data indicate that asthmatic patients in the UK are approximately 10% less likely to receive a prescription than in the other countries (excluding Belgium). The converse to this was found in the European Community Respiratory Health Survey published in 1996[396] where patients with a diagnosis of asthma in Italy and Spain were 10% less likely to be using asthma medication than in the UK. This difference could be due to a higher level of undertreatment in Mediterranean regions compared with UK centres resulting in less asthma medication use, as found in the ECRHS study. The difference in this study, could be due to a greater emphasis on reviewing asthmatic patients in the UK compared with Mediterranean countries with a consequent greater proportion of prescription-less consultations for asthma. In addition, there is a greater likelihood of high prevalence of associated co-morbidity amongst populations where asthma is more prevalent - as in the UK. Therefore, some of these patients may be consulting for treatment of any one of an associated co-morbid condition and the recording of asthma by the GP may only be part of the patient's medical history without requiring a prescription at that time.

When investigating the prescribing performance indicators, all the prescription categories were combined rather than using just the new prescription subset, as only 27% of the 5,159 asthma drug entities were for newly prescribed items. For the two main indicators, the Formulary concordance and the range of drugs prescribed, there were found to be no significant differences between control and study groups from Phase I to Phase II. In England, a significant difference was found between the control and study groups with a trend towards increased Formulary concordance but this can

only be explained as coincidental. From these results, it can be inferred therefore that the provision of written prescribing recommendations alone appeared to have little impact on influencing prescribing for asthma. Overall, levels of concordance with the European Formulary were generally found to be higher in the UK than in the other countries. Also the largest average range of drugs prescribed was found in Ireland but this could be explained by the higher prevalence of the condition there.

The figures for the percentage of treated asthma patients receiving inhaled corticosteroids - a potential quality marker, varied considerably (Table 6.62), with the levels in Belgium and Northern Ireland being approximately double those in Italy and Scotland. Prescribing for asthma could be of a better quality in countries where higher levels were found, however the figures for inhaled corticosteroid use may be contaminated in some countries by the oral use of steroids such as budesonide. In addition, presenting the ratio between prescribed beta-2 agonists compared with the country's total percentage for inhaled drugs would not have been an entirely accurate measure as a small but possibly varying proportion of beta-2 agonists may have been oral formulations.

Of the remaining prescribing indicators, generally higher levels of inhaled drugs were prescribed in the English speaking regions which is important as inhaled drugs act directly on the airways and are associated with a more rapid onset of action and fewer side-effects for a given therapeutic effect.[6] Prescribing of combination drugs is an indicator of inappropriate prescribing in the treatment of asthma, as they do not allow for flexible dosing.[279] From this study, less than 5% of the 5,159 drug entities prescribed for asthma represented part of combination medicines. Lastly, of the antibiotics used for asthma, amoxycillin was the only one to be of notable use (Table 5.51) and the lowest levels of it were found in Italy, Portugal and Spain. Relatively higher levels of antibiotics were found to be prescribed for children in Belgium and Ireland and for adults in Italy and Scotland (Table 6.68 and Table 6.69). Overall, considerably lower levels were found in Portugal and Spain than elsewhere. One reason for this could be, as mentioned earlier, that where the prevalence of asthma is greater, there is an increased likelihood of co-morbidity presenting and consequently an artificial link made of drugs (for these associated conditions) with a diagnosis of asthma.

The levels of inhaled drug use appear to be fairly high in all the countries for children, which may be considered satisfactory. In adults, there appears to be a much greater variation in the level of inhaled drug use between countries, with high levels in the UK centres and low levels in the other countries. There was a low prevalence of inhaled steroids (both for children and adults) in Italy with a high prevalence in the UK, which is consistent with data reported in the ECRHS.[396] Inhaled bronchodilator use is also broadly similar between our study and the ECRHS.

In Belgium, Italy and Portugal where particularly low levels of inhaled anti-asthmatics were found in adults, there appeared to be high levels of oral methylxanthines prescribed. This may suggest inappropriate prescribing of these drugs as low levels of more severe night-time related asthma symptoms have been reported in these areas compared with the British Isles.[397] High levels of aminophylline and theophylline prescribing have also been reported in other countries.[398,399] The prescribing of oral methylxanthines does have a place within asthma guidelines but not as major drug management.

High levels of 'all other drugs prescribed for asthma' were found in Belgium, Italy and Portugal. This group consisted largely of drugs of limited clinical value and thus may also be perceived as indicators of inappropriate prescribing.

With the continued introduction of new and revised guidelines for the management of asthma, both in consensus[391,393,400] and evidence-based[392] form, the therapeutic management of most cases of asthma should now be relatively straight-forward - although many challenges remain in the organisational management of this condition especially in long term patient management. The considerable variation in most aspects of asthma prescribing between the countries sampled in this study suggests that there is still much room for improvement.

Table 6.54 The mean number (%) of patients presenting with hypertension, the number (%) of single component and combination drugs prescribed per country

Country	Mean No (%) patients with hypertension/GP	Number (%) of single component drugs	Number (%) of combination drugs
Belgium	40 (10)	487 (88)	67 (12)
England	24 (4.4)	748 (94)	44 (5.6)
Ireland	28 (5.9)	981 (63)	566 (37)
Italy	71 (16)	2524 (66)	1305 (34)
N Ireland	26 (4.9)	346 (84)	67 (16)
Portugal	44 (16)	1940 (74)	669 (26)
Scotland	25 (4.8)	904 (84)	170 (16)
Spain	52 (15)	1767 (87)	256 (13)
ANOVA	$p < 0.001$		

Table 6.55 Percentage (SEM) concordance with the European Formulary in prescribing of all drug entities for hypertension

Country	Phase I				Phase II				Phase II - Phase I	
n = total N^0 drugs for hypertension	Study *n*	Study % (SEM)	Control *n*	Control % (SEM)	Study *n*	Study % (SEM)	Control *n*	Control % (SEM)	Study % (SEM)	Control % (SEM)
Belgium	125	44 (8.3)	177	39 (7.9)	112	55 (12)	140	29 (4.4)	**+11 (17)**	-9.6 (6.1)
England	140	48 (6.5)	223	48 (5.5)	179	49 (4.5)	222	48 (5.5)	**+0.1 (9)**	+0.5 (6.9)
Ireland	423	25 (3.3)	421	25 (4)	340	25 (2.8)	321	25 (5.3)	**+0.3 (3.2)**	-0.2 (4)
Italy	813	44 (2.6)	943	50 (2.6)	888	44 (2.5)	959	49 (2.8)	**-0.5 (3.1)**	-1 (3.2)
N Ireland	87	34 (7.1)	111	43 (5)	72	32 (7.2)	125	30 (6.4)	**-2.2 (7)**	-13 (5.2)
Portugal	678	39 (2.4)	396	34 (3.9)	719	37 (2.7)	436	37 (3.8)	**-1.9 (2.7)**	+2.7 (3)
Scotland	322	48 (4.1)	175	55 (4.5)	320	43 (5.3)	183	52 (3.6)	**-4.7 (5.8)**	-3.4 (5.4)
Spain	592	57 (4.2)	667	64 (2.2)	338	57 (4.6)	375	60 (3.5)	**+0.1 (3.2)**	-3.5 (3.6)
Total	3180	42 (1.7)	3113	46 (1.9)	2968	42 (1.8)	2761	44 (2)	**-0.9 (1.9)**	**-2.1 (1.7)**

Table 6.56 Percentage (SEM) concordance with the European Formulary of single component antihypertensive drug prescribing

Country	Phase I				Phase II				Phase II - Phase I	
n = total N^0 drugs for hypertension	Study *n*	Study % (SEM)	Control *n*	Control % (SEM)	Study *n*	Study % (SEM)	Control *n*	Control % (SEM)	Study % (SEM)	Control % (SEM)
Belgium	113	45 (9.9)	132	35 (7.3)	108	54 (13)	134	28 (5.1)	**+9.7 (18)**	-7.3 (4.9)
England	131	50 (6.8)	216	48 (5.5)	165	48 (4.7)	208	49 (6.1)	**-1.5 (9.2)**	+0.5 (7)
Ireland	246	26 (3.6)	271	30 (4)	205	25 (4.2)	239	24 (6.1)	**-1 (4.5)**	-5.4 (5.9)
Italy	542	40 (3.2)	639	48 (3.5)	590	37 (2.7)	613	44 (3.6)	**-2.6 (3.7)**	-3.7 (4.3)
N Ireland	68	32 (7.4)	101	44 (5)	57	32 (8.7)	108	30 (6.9)	**-0.3 (5.9)**	-14 (6.9)
Portugal	496	33 (2.6)	290	30 (3.9)	578	34 (3.3)	321	33 (5.3)	**+0.8 (3.4)**	3.4 (4.4)
Scotland	269	48 (4.4)	153	54 (6.2)	266	43 (5.9)	149	52 (3.7)	**-4.9 (6.1)**	-1.9 (7.3)
Spain	524	58 (4.2)	579	68 (2.4)	283	58 (4.9)	342	62 (3.5)	**+0.3 (3.7)**	-5.8 (3.6)
Total	2389	41 (1.8)	2381	46 (2.1)	2252	40 (2)	2114	43 (2.2)	**-1.1 (2)**	**+3.5 (2)**

Table 6.57 Average (SEM) range of both combination and single component drugs prescribed for hypertension

Country	Phase I		Phase II		Phase II - Phase I	
	Study	Control	Study	Control	Study	Control
Belgium	12 (2.5)	14 (2.2)	9.8 (1.4)	13 (2)	**-2.4 (1.4)**	-1 (5.6)
England	5.6 (0.7)	6.7 (1)	6 (0.7)	7.2 (0.6)	**+0.4 (0.7)**	+0.5 (1)
Ireland	12 (1.1)	13 (1.2)	10 (0.7)	10 (1.2)	**-1.3 (0.9)**	-2.4 (1)
Italy	17 (1.1)	17 (0.8)	18 (1.2)	17 (1.5)	**+0.4 (1.3)**	-0..4 (1.5)
N. Ireland	6.9 (1.9)	8.6 (1.6)	7 (1.5)	11 (1.4)	**+0.1 (2.1)**	+2.6 (0.9)
Portugal	13 (0.7)	13 (1.3)	14 (1)	15 (1.2)	**+1.1 (0.8)**	+2 (1.7)
Scotland	6.4 (0.6)	6.4 (0.6)	6.2 (0.5)	6.5 (0.7)	**-0.2 (0.7)**	+0.1 (0.9)
Spain *	12 (0.7)	14 (1)	9.8 (0.7)	11 (1)	**-2.6 (1)**	-2.9 (1.5)
Total	11 (0.5)	12 (0.5)	11 (0.5)	11 (0.6)	**-0.3 (0.4)**	-0.6 (0.5)

* In Spain the numbers of all prescriptions recorded were halved in Phase II

Table 6.58 Average (SEM) range of single component drugs prescribed for hypertension

Country	Phase I		Phase II		Phase II - Phase I	
	Study	Control	Study	Control	Study	Control
Belgium	11 (1.9)	12 (1.9)	9.2 (2.8)	13 (2)	**-1.4 (1.5)**	+1.2 (2.7)
England	4.9 (0.7)	6.2 (0.8)	5.5 (0.6)	6.5 (0.6)	**+0.6 (0.6)**	+0.4 (0.7)
Ireland	7.8 (0.9)	9.6 (0.9)	6.8 (0.6)	8.4 (1.1)	**-0.9 (0.8)**	-1.1 (0.9)
Italy	14 (1.1)	15 (0.7)	14 (1.2)	14 (1.5)	**+0.2 (1.3)**	-0.6 (1.4)
N. Ireland	5.4 (1.4)	7.4 (1.6)	5.6 (1.2)	8.6 (1.2)	**+0.1 (1.2)**	+1.2 (0.6)
Portugal	10 (0.7)	10 (0.9)	12 (0.8)	12 (1.3)	**+1.3 (0.8)**	+1.8 (1.5)
Scotland	5.5 (0.5)	5.7 (0.6)	5.3 (0.4)	5.4 (0.5)	**-0.2 (0.6)**	-0.3 (0.8)
Spain *	11 (0.6)	11 (0.8)	8.7 (0.5)	9.4 (0.7)	**-2.1 (0.8)**	-1.9 (1.1)
Total	8.8 (0.4)	9.9 (0.4)	8.6 (0.4)	9.7 (0.5)	**-0.2 (0.3)**	-0.3 (0.4)

* In Spain the numbers of all prescriptions recorded were halved in Phase II

Table 6.59 All prescribing for hypertension by drug group in terms of number of items and percentage drug use in males and females

Country		Belgium	England	Ireland	Italy	N. Ireland	Portugal	Scotland	Spain
Drug Group	**Nº items (%)**	539 (100)	785 (100)	1,516 (100)	3,788 (100)	409 (100)	2,568 (100)	1,070 (100)	1,980 (100)
Diuretics		94 (17)	258 (33)	505 (33)	1147 (30)	131 (32)	779 (30)	342 (32)	665 (34)
thiazides		59 (11)	229 (29)	396 (26)	780 (21)	108 (26)	540 (21)	300 (28)	551 (28)
potassium sparing		29 (5.4)	15 (1.9)	78 (5.1)	262 (6.9)	16 (3.9)	201 (7.8)	14 (1.3)	85 (4.3)
ACE inhibitors		122 (23)	140 (18)	285 (19)	1369 (36)	96 (23)	988 (38)	254 (24)	656 (33)
Calcium channel blockers		80 (15)	131 (17)	142 (9.4)	647 (17)	65 (16)	468 (18)	131 (12)	395 (20)
Beta-adrenoceptor blocker		195 (36)	214 (27)	341 (22)	404 (11)	97 (24)	212 (8.3)	319 (30)	135 (6.8)
cardioselective		173 (32)	202 (26)	309 (20)	342 (9)	89 (22)	163 (6.3)	304 (28)	116 (5.9)
non-cardioselective		22 (4.1)	12 (1.5)	32 (2.1)	62 (1.6)	8 (2)	49 (1.9)	15 (1.4)	19 (1)
Alpha-adrenoceptor blockers		9 (1.7)	11 (1.4)	28 (1.8)	58 (1.5)	8 (2)	3 (0.1)	8 (0.7)	80 (4)
Potassium supplements		0 (0)	0 (0)	128 (8.4)	12 (0.3)	4 (1)	0 (0)	0 (0)	10 (0.5)
Centrally acting antihypertensives		20 (3.7)	8 (1)	18 (1.2)	47 (1.2)	0 (0)	13 (0.5)	3 (0.3)	8 (0.4)
Vasodilator antihypertensives		3 (0.6)	1 (0.1)	14 (0.9)	0 (0)	0 (0)	19 (0.7)	2 (0.2)	8 (0.4)
Other antihypertensive drugs		0 (0)	0 (0)	2 (0.1)	1 (0)	0 (0)	8 (0.3)	0 (0)	0 (0)
Other cardiovascular drugs		16 (3)	22 (2.8)	53 (3.5)	103 (2.7)	8 (2)	78 (3)	11 (1)	23 (1.2)

* 186 drug entities were prescribed associated with a hypertension diagnosis but were not related to its therapy

Table 6.60 Percentage use of the top drugs for hypertension by country representing ≥2% of those prescribed from Phases I & II

Drug	Belgium	England	Ireland	Italy	N. Ireland	Portugal	Scotland	Spain	Overall
Phase 1 n =	**289**	**379**	**861**	**1965**	**216**	**1091**	**569**	**1283**	**6653**
hydrochlorothiazide %*	**4.5**	**1.1**	**4.9**	**15**	**4.2**	**13**	**1.1**	**23**	**12**
atenolol %*	**24**	**25**	**13**	**7.5**	**17**	**6.5**	**26**	**5.7**	**11**
nifedipine %*	**8.7**	**14**	**6.3**	**9.8**	**16**	**12**	**11**	**12**	**11**
enalapril %*	**4.5**	**6.6**	**0.5**	**13**	**2.3**	**6.7**	**11**	**17**	**9.7**
captopril %	2.4	2.1	7.8	5	3.7	18	1.6	8.6	7.6
bendrofluazide %	0	31	15	0	16	0	20	0	5.9
amlodipine %	4.2	2.4	3.1	6.2	2.8	3.5	5.6	3.7	4.4
amiloride %	1	0.8	2.3	6.2	3.2	6.3	0.5	4.1	4.2
chlorthalidone %	4.5	0.3	4.6	3.2	3.7	2.8	5.8	3	3.4
lisinopril %	7.6	3.2	1.2	2.6	12	4.5	4	1.6	3.2
indapamide %	0.7	0	1.7	2.5	0.9	5.1	0.5	0.3	2
frusemide %	1	1.6	2	2.6	1.9	1.2	2.6	1.6	2
Phase 2 n =	**250**	**406**	**655**	**1823**	**193**	**1477**	**501**	**697**	**6002**
hydrochlorothiazide %*	**2.4**	**2**	**4**	**15**	**3.1**	**13**	**1**	**27**	**12**
atenolol %*	**22**	**24**	**15**	**8.2**	**17**	**4.6**	**30**	**5**	**11**
enalapril %*	**5.6**	**7.4**	**1.4**	**15**	**3.6**	**6.9**	**6.8**	**15**	**9.6**
nifedipine %*	**6**	**15**	**6.6**	**7.9**	**9.8**	**11**	**9**	**9.3**	**9.1**
captopril %	3.2	2.2	8.1	3.3	2.1	23	0.4	7.6	8.9
bendrofluazide %	0	23	14	0	20	0	20	0	5.3
amlodipine %	5.2	4.2	3.5	7.8	5.7	3	7.8	3	5.2
lisinopril %	7.2	6.7	2.4	2.2	13	2.6	8	3.4	3.8
amiloride %	2.4	0.7	2.7	4.9	2.6	5	0.8	3.2	3.7
chlorthalidone %	5.6	1.2	3.7	3.5	3.1	3	6.4	3	3.5
diltiazem %	0.4	3	2.1	0.7	2.1	4.7	1	1.3	2.1
indapamide %	1.2	0	1.7	2.2	0.5	4.2	0.2	0.7	2.1

* drugs listed within the European Formulary

Table 6.61 Percentage use of the top drugs for hypertension by country representing ≥1% of those prescribed from Phases I & II

Drug	Belgium	England	Ireland	Italy	N. Ireland	Portugal	Scotland	Spain	Overall
Phases I and II n =	**539**	**785**	**1516**	**3788**	**409**	**2568**	**1070**	**1980**	**12,655**
hydrochlorothiazide % *	**3.5**	**1.5**	**4.5**	**15**	**3.7**	**13**	**1**	**24**	**12**
atenolol % *	**23**	**24**	**14**	**7.8**	**17**	**5.4**	**28**	**5.5**	**11**
nifedipine % *	**7.4**	**14**	**6.4**	**8.9**	**13**	**11**	**9.9**	**11**	**9.9**
enalapril % *	**5**	**7**	**0.9**	**14**	**2.9**	**6.8**	**9.2**	**16**	**9.7**
verapamil % *	**0.2**	**0.1**	**0.6**	**1.7**	**0.5**	**0.7**	**0.8**	**5.3**	**1.6**
TOTAL %	**39**	**47**	**26**	**47**	**44**	**37**	**49**	**62**	**44**
captopril %	2.8	2.2	7.9	4.2	2.9	21	1	8.2	8.2
bendrofluazide %	0	27	14	0	18	0	20	0	5.6
amlodipine %	4.6	3.3	3.3	7	4.2	3.2	6.6	3.5	4.8
amiloride %	1.7	0.8	2.5	5.5	2.9	5.6	0.7	3.7	3.9
lisinopril %	7.4	5	1.7	2.4	12	3.4	5.9	2.2	3.5
chlorthalidone %	5	0.8	4.2	3.3	3.4	2.9	6.1	3	3.5
indapamide %	0.9	0	1.7	2.4	0.7	4.6	0.4	0.5	2
diltiazem %	0.4	1.9	2.1	0.7	2.2	5.2	1.1	1.1	2
frusemide %	1.1	1.8	1.9	2.7	1.7	1.5	2.2	1.4	1.9
doxazosin %	0	0.6	1.4	1.5	1.5	0	0.3	3.8	1.3
potassium salts %	0	0	8.4	0.3	1	0	0	0.5	1.2
quinapril %	1.5	0	1.3	1.8	0.2	0.2	0.1	2.1	1.1
metoprolol %	2.4	0.6	3.4	0.8	1.5	0.7	0.6	0	1
triamterene %	2.8	1.1	2.4	0.3	1	1.8	0.5	0	1
aspirin %	0.7	2.3	2.4	0.9	2	0.5	0.7	0.8	1
TOTAL %	**31**	**47**	**59**	**34**	**55**	**51**	**46**	**31**	**41**

* drugs listed within the European Formulary

Table 6.62 The overall number and frequency (%) of asthma consultations in each country

Country	Total N° (%) patients with asthma/country	Mean % (SEM) asthma patients with a prescription for asthma	% of treated‡ asthma patients receiving inhaled corticicosteroids
Belgium	89 (2.3) *	100 (--)*	46
England	622 (4.2)	88 (1.6)	40
Ireland	965 (5.8)	94 (1.4)	31
Italy	324 (1.8)	94 (2.7)	23
N. Ireland	351 (5.2)	87 (2.2)	47
Portugal	204 (1.9)	98 (1)	30
Scotland	811 (3.9)	84 (2)	27
Spain	229 (2.2)	98 (0.7)	48
ANOVA	p <0.001	p <0.001	

* Some GPs fell short of recording consecutive face to face consultations until 200 had resulted in a prescription.
* Belgium data was excluded from this analysis as it did not include consultations where a prescription was not given.
‡ The number of treated asthma patients was used in this calculation in order to enable comparison with the Belgium data.

Table 6.63: Percentage (SEM) concordance with the European Formulary of all the drugs prescribed for asthma

Country	Phase I				Phase II				Phase II - Phase I	
n = total N^0 prescription entities for asthma	Study *n*	Study % (SEM)	Control *n*	Control % (SEM)	Study *n*	Study % (SEM)	Control *n*	Control % (SEM)	STUDY % (SEM)	CONTROL % (SEM)
Belgium	95	53 (6.1)	32	48 (9.8)	33	60 (13)	38	62 (10)	**+7.4 (9.8)**	+12 (12)
England	196	83 (3.4)	209	90 (2.8)	164	91 (3.5)	230	88 (3.8)	**+8.6 (3.7)**	-2.4 (2.1)
Ireland	412	71 (4.3)	357	76 (2.7)	375	75 (4.1)	303	77 (3.5)	**+4.8 (2.5)**	+1.3 (4.5)
Italy	108	47 (7.1)	99	46 (6.5)	102	44 (6.4)	107	45 (7.3)	**-3.2 (8.2)**	-1.1 (8.3)
N Ireland	89	74 (8.6)	101	86 (5.2)	161	73 (5.5)	80	78 (7.8)	**-1.1 (7.2)**	-7.2 (9.8)
Portugal	66	53 (8.1)	73	38 (9.7)	85	52 (8.9)	59	56 (10)	**-1.6 (10)**	+18 (15)
Scotland	290	79 (2.7)	173	85 (3.5)	269	80 (3.3)	176	86 (3.3)	**+0.9 (3.4)**	+1.4 (3.3)
Spain	113	55 (5.9)	98	64 (7.3)	83	47 (7.9)	69	56 (6.9)	**-8.2 (6.8)**	-7.9 (9.4)
Total	1369	66 (2.3)	1142	68 (2.9)	1272	67 (2.6)	1062	68 (2.8)	**+0.8 (2.2)**	**+0.5 (2.9)**

Table 6.64: Percentage use of drugs recommended in the Formulary for asthma from study group Phases I and II, by country

Drug	Belgium	England	Ireland	Italy	N. Ireland	Portugal	Scotland	Spain	Overall
Phase 1 n =	**95**	**196**	**426**	**136**	**89**	**93**	**291**	**123**	**1449**
salbutamol %	13	49	39	18	25	29	36	34	34
beclomethasone %	15	17	13	16	5.6	9.7	20	4.9	14
prednisolone %	1.1	11	8.2	2.2	11	0	11	0.8	7.1
terbutaline %	0	2.6	5.6	0	21	3.2	5.8	5.7	5.2
sodium cromoglycate %	2.1	0.5	3.3	4.4	2.2	3.2	3.1	0.8	2.6
ipratropium bromide %	12	0.5	2.8	0.7	0	2.2	0.3	1.6	2.1
fenoterol hydrobromide %	13	0	0.9	2.2	0	1.1	0.3	0	1.4
orciprenaline sulphate %	0	0	0.7	0	1.1	0	0	0	0.3
procaterol %	0	0	0	0	0	2.2	0	0	0.1
clenbuterol %	0	0	0	0	0	1.1	0	0	0.1
Total %	**56**	**81**	**74**	**44**	**66**	**52**	**77**	**48**	**70**
Phase 2 n =	**33**	**164**	**375**	**103**	**161**	**99**	**269**	**83**	**1287**
salbutamol %	24	51	38	28	32	32	38	29	37
beclomethasone %	9.1	27	17	13	19	13	22	3.6	18
prednisolone %	0	8.5	9.6	0	9.9	1	13	0	8
terbutaline %	0	0	5.3	0	8.7	0	6.3	3.6	4.2
ipratropium bromide %	12	3	2.4	1	1.9	1	0.4	6	2.3
sodium cromoglycate %	0	0	4.8	1	0	0	1.1	0	1.7
fenoterol hydrobromide %	6.1	0	0.8	0	0	3	0	1.2	0.7
orciprenaline sulphate %	0	0	0.8	0	0.6	0	0	0	0.3
procaterol %	0	0	0	0	0	4	0	0	0.3
clenbuterol %	0	0	0	0	0	1	0	0	0.1
Total %	**51**	**90**	**79**	**43**	**72**	**55**	**81**	**43**	**73**

Table 6.65: Average (SEM) range of items prescribed for asthma

Country	Phase I		Phase II		Phase II - Phase I	
	Study	Control	Study	Control	Study	Control
Belgium	9.2 (1.6)	5.5 (2)	4.4 (0.5)	6.5 (1.6)	**-4.8 (1.3)**	+1 (3)
England	4.9 (0.6)	4.7 (5.2)	4 (0.5)	5.2 (0.7)	**-0.9 (0.6)**	+0.5 (0.7)
Ireland	8.1 (0.6)	8.5 (0.8)	6.3 (0.6)	8.2 (1)	**-1.8 (0.8)**	-0.3 (1)
Italy	5.2 (1.1)	4.2 (0.6)	5.1 (0.5)	4.9 (0.6)	**-0.1 (1)**	+0.7 (0.6)
N. Ireland	5.3 (0.9)	5.6 (0.8)	6.6 (0.6)	5.2 (0.8)	**+1.3 (1.1)**	-0.4 (0.8)
Portugal	3.8 (0.5)	5.3 (1.2)	4 (0.6)	4 (1.2)	**+0.3 (0.7)**	-1.3 (1.2)
Scotland	5.9 (0.5)	5.8 (0.7)	5.3 (0.4)	5.2 (0.7)	**-0.6 (0.7)**	-0.7 (0.8)
Spain †	4.5 (0.4)	3.9 (0.5)	3.9 (0.6)	3.2 (0.6)	**-0.6 (0.7)**	-0.7 (0.7)
Total	5.8 (0.3)	5.4 (0.3)	5 (0.2)	5.2 (0.3)	**-0.8 (0.3)**	-0.2 (0.3)

† The number of consultations recorded by the Spanish GPs in Phase II was halved

Table 6.66: Percentage use of top items for asthma by country representing ≥1% of those prescribed from Phases I & II

Drug	Belgium	England	Ireland	Italy	N. Ireland	Portugal	Scotland	Spain	Overall
Phases I and II n =	**202**	**807**	**1491**	**471**	**440**	**398**	**968**	**383**	**5159**
salbutamol % *	**15**	**45**	**37**	**24**	**27**	**29**	**36**	**34**	**34**
beclomethasone % *	15	23	17	16	16	10	21	5.8	17
prednisolone % *	**0.5**	**12**	**9.7**	**1.1**	**13**	**1.3**	**14**	**0.3**	**8.7**
theophylline %	14	0.2	8.7	15	1.4	7	0.6	5	5.6
budesonide %	4.5	2.2	2.7	0	13	4.5	6.2	22	5.6
terbutaline %	**0**	**1.4**	**5.1**	**0**	**16**	**1.8**	**6.7**	**6.5**	**4.9**
salmeterol %	1.5	2.5	0.7	6.6	3.2	0.8	1.9	6.8	2.4
ipratropium % *	**10**	**1.6**	**2.7**	**0.6**	**1.4**	**1.3**	**0.9**	**3.1**	**2.1**
sodium cromoglycate % *	**3**	**0.9**	**3.4**	**2.3**	**0.9**	**1**	**1.7**	**0.3**	**1.9**
appliances %	0	5	0.7	0	0.7	0	3.6	0	1.7
aminophylline %	1	0.2	1.8	2.8	0.5	8.8	0.5	0.3	1.7
amoxycillin %	1.5	2	1.5	0.8	1.6	0.3	2.7	0.8	1.6
fenoterol %	**10**	**0**	**1.1**	**1.1**	**0**	**1.3**	**0.2**	**0.3**	**1**

* drugs recommended within the European Formulary for asthma

Table 6.67: Percentage use of top items for asthma by country representing ≥1% of those prescribed from study group Phases I & II

Drug	Belgium	England	Ireland	Italy	N. Ireland	Portugal	Scotland	Spain	Overall
Phase 1 n =	**95**	**196**	**426**	**136**	**89**	**93**	**291**	**123**	**1449**
theophylline %	15	0.5	8.2	18	1.1	8.6	0.3	7.3	6.5
budesonide %	1.1	2.6	3.5	0	18	9.7	4.1	25	6.1
appliances %	0	9.7	0.7	0	1.1	0	6.2	0	2.8
salmeterol %	1.1	2	0.7	4.4	1.1	0	2.7	4.1	1.9
amoxycillin %	3.2	1.5	2.1	0	2.2	0	2.7	1.6	1.9
aminophylline %	1.1	0	2.1	4.4	0	5.4	1	0	1.7
ketotifen %	2.1	0.5	0.5	3.7	0	6.5	0.3	0	1.2
fluticasone proprionate %	0	2	0.2	0	5.6	0	1.4	0	1
Phase 2 n =	**33**	**164**	**375**	**103**	**161**	**99**	**269**	**83**	**1287**
budesonide %	0	0.6	2.4	0	11	3	7.1	24	5.4
theophylline %	15	0	9.1	13	3.1	9.1	0.4	2.4	5.4
salmeterol %	6.1	1.8	0.3	5.8	3.7	1	1.1	12	2.5
appliances %	0	4.3	2.1	0	0	0	3.3	0	1.9
amoxycillin %	0	1.8	0.3	2.9	2.5	1	3	0	1.6
aminophylline %	0	0	0.8	1	0.6	10	0.7	1.2	1.4
fluticasone proprionate %	9.1	1.8	0.3	0	5	0	0.7	0	1.3
nedocromil sodium %	0	0	0.3	6.8	0	0	0	9.6	1.2

Table 6.68: Asthma prescribing by drug group in terms of the number of items prescribed per country in children 0-15 years

Country		Belgium	England	Ireland	Italy	N. Ireland	Portugal	Scotland	Spain
Drug Group	**N° prescribed items (%)**	41 (100)	273 (100)	568 (100)	41 (100)	223 (100)	52 (100)	322 (100)	18 (100)
Short acting β_2 agonists		12 (29)	139 (51)	286 (50)	10 (24)	105 (47)	19 (37)	147 (46)	10 (56)
Long acting β_2 agonists		3 (7)	6 (2)	0 (0)	0 (0)	7 (3)	0 (0)	4 (1.2)	2 (11)
Inhaled corticosteroids		6 (15)	68 (25)	73 (13)	8 (20)	76 (34)	6 (12)	86 (27)	5 (28)
Oral corticosteroids		1 (2.4)	27 (9.9)	66 (12)	2 (4.9)	17 (7.6)	2 (3.9)	36 (11)	0 (0)
Cromoglycate & related therapy		5 (12)	2 (0.7)	43 (7.6)	14 (34)	4 (1.8)	12 (23)	12 (3.7)	0 (0)
Antimuscarinics		4 (9.8)	2 (0.7)	4 (0.7)	0 (0)	2 (0.9)	0 (0)	1 (0.3)	0 (0)
Methylxanthines		2 (4.9)	0 (0)	50 (8.8)	1 (2.4)	3 (1.4)	3 (5.8)	4 (1.2)	1 (5.6)
Antibiotics		3 (7.3)	8 (7.3)	27 (4.8)	1 (2.4)	4 (1.8)	0 (0)	12 (3.7)	0 (0)
Asthma appliances		0 (0)	20 (0.4)	7 (1.2)	0 (0)	2 (0.9)	0 (0)	18 (5.6)	0 (0)
All other drugs prescribed for asthma		5 (12)	1 (0.4)	12 (2.1)	5 (12)	3 (1.3)	10 (19)	2 (0.6)	0 (0)

Table 6.69 Asthma prescribing by drug group in terms of the number of items prescribed per country in adults 16 years and above

Country		Belgium	England	Ireland	Italy	N. Ireland	Portugal	Scotland	Spain
Drug Group	**N° prescribed items (%)**	161 (100)	534 (100)	923 (100)	430 (100)	217 (100)	346 (100)	646 (100)	364 (100)
Short acting β_2 agonists		39 (24)	234 (44)	374 (41)	110 (26)	84 (39)	128 (37)	265 (41)	146 (40)
Long acting β_2 agonists		4 (2)	14 (3)	10 (1)	39 (9)	8 (4)	3 (0.9)	14 (2)	27 (7)
Inhaled corticosteroids		35 (22)	151 (28)	209 (23)	60 (14)	68 (31)	53 (15)	182 (28)	102 (28)
Oral corticosteroids		10 (6.2)	74 (14)	104 (11)	33 (7.7)	41 (19)	11 (3.2)	102 (16)	15 (4.1)
Cromoglycate & related therapy		6 (3.7)	6 (1.1)	15 (1.6)	21 (4.9)	0 (0)	14 (4.1)	8 (1.2)	21 (5.8)
Antimuscarinics		17 (11)	11 (2.1)	52 (5.6)	4 (0.9)	4 (1.8)	7 (2)	12 (1.9)	12 (3.3)
Methylxanthines		28 (3.1)	4 (0.8)	107 (12)	98 (23)	5 (2.3)	68 (20)	7 (1.1)	19 (5.2)
Antibiotics		5 (3.1)	17 (3.2)	31 (3.4)	16 (3.7)	6 (2.8)	2 (0.6)	32 (5)	6 (1.7)
Asthma appliances		0 (0)	20 (3.8)	4 (0.9)	0 (0)	1 (0.5)	0 (0)	17 (2.6)	0 (0)
All other drugs prescribed for asthma		17 (11)	3 (0.6)	17 (1.4)	49 (11)	0 (0)	60 (17)	7 (1.1)	16 (4.4)

CHAPTER SEVEN
RESULTS FROM THE TWO-STAGE DELPHI PESCRIBING INFLUENCES QUESTIONNAIRE STUDY

7.1 QUESTIONNAIRE NUMBER ONE

7.1.1 The response rate

Of the 241 stage one questionnaires sent out to the GP participants in the eight countries (Section 3.2.3), 181 (75%) responses were returned. Although nearly 60% of the questionnaires were returned on the first mailing, a follow up reminder was necessary. Of the 181 replies, eight (3%) questionnaires (3 Belgian, 3 English and 2 Portuguese) were returned uncompleted and could not be used in the analysis. Of these eight GPs, five had changed addresses, two had retired and one had died. The remaining 173 (72%) completed questionnaires (Table 7.70) were used for the various analyses. Within the individual countries, the responses for stage one were all above 60%, except for Portugal (55%).

7.1.2 Age and gender profiles of participating GPs

Table 7.71 shows that 113 (65%) of the 173 GPs were male and 60 (35%) were female. There were considerably more male than female GP participants in all the countries, except for England and Portugal. The majority of GP respondents 89 (51%) fell into the 40-49 year age band in all of the countries, apart from Spain.

7.1.3 Practice type and location

Most of the GP respondents, 123 (71%) were found to be working in group practices/health centres with other GPs (Table 7.72). Group practices appeared to be overwhelmingly the norm in Belgium, Spain and in the UK, whereas in Italy, all the GPs with one exception, worked alone. A more mixed style of practice was found in Ireland and Portugal, although there were more group practices in Ireland than in Portugal.

In the study, 86 (50%) of the GPs described the location of their practice as urban (Table 7.72). Within individual countries, the majority were consistently urban based except for GPs in Ireland where most were situated in a mixed urban/rural environment. For all the countries combined, only 9 (5%) GPs overall said they worked exclusively in a rural setting and the remaining 45% were fairly evenly split between a mixed urban/rural or inner city type of practice.

7.1.4 GPs involvement in training doctors and the time period since qualification

In this study, 113 (65%) GPs were involved in training doctors (Table 7.72). Within individual countries, the majority of GPs were involved in this way except for those in Italy, Northern Ireland and Portugal.

From Table 7.72, it can be seen that the average number of years the GP respondents had been qualified varied from on average 15 years in Spain to 22 years in Ireland and Scotland (mean 19 years, SD 2.5).

7.1.5 Age of consulting patient population

Of the 173 doctor respondents, 147 (85%) had patients under the age of 14. Of the 26 remaining GPs, 19 were in Spain and their replies indicated that their patient population did not include children under the age of 14; the remaining five GPs were in Italy and stated likewise. The majority of GPs 167 (97%) in this study saw patients over the age of 65 years old.

7.1.6 Hours worked/week, patients seen/week and patient consultation length

The mean number of hours worked in primary care in one week (Table 7.73) varied over two fold from 28 hours in Italy to 58 hours in Ireland (mean 42, SD 8.9). There were broad similarities in the mean number of patients consulted in one week in each of the countries (excluding Belgium and Ireland, 101 and 168 respectively), varying from 116 in Portugal and Scotland to 134 in Spain (mean 121, SD 6.6). The mean duration of each patient consultation varied from 8 minutes in Spain to 19 minutes in Belgium (mean 12, SD 4).

7.1.7 Consultations with pharmaceutical sales representatives and patients

The mean number of pharmaceutical industrial representatives seen in four weeks (Table 7.74) varied from 0 in Belgium and England to 32 in Portugal (mean 12, SD 13) . A relatively high number of pharmaceutical representatives were also seen in Italy and Spain. Comparing the mean number of patients consulted with that of drug industry representatives over a four week period produced a marked contrast in ratios from one drug representative seen for every 5,648 patients consulted in Belgium to one pharmaceutical representative seen for every 15 patients in Portugal. The ratios highlighted notable differences between countries indicating that in southern European regions particularly high numbers of drug company representatives were seen there by GPs, while by comparison, relatively little communication appeared to take place between drug representatives and GPs in Belgium and in the UK.

7.1.8 The most important influence on prescribing

Of the 173 GPs who returned questionnaire stage one, in response to the open ended question, 167 cited a top main influence on their personal prescribing. Of these responses:

- the most popular was medical literature selected by 26 GPs,
- the second most popular was the efficacy of a drug selected by 15 doctors,
- the third was a practice formulary/prescribing policy as selected by 11 doctors,
- nine GPs stated that personal experience and familiarity with the drug as the top influence, while nine others sited budgets and government health policy first,
- three groups of eight GPs each selected: the cost of a drug, using a regional/national formulary and the opinions and pressure of discussion with colleagues, as their number one influence.

For the remainder of the open ended question responses, 164 GPs stated a second main prescribing influence, 160 provided a third, 141 listed a fourth, while 114 GPs recorded a fifth main influence on their prescribing since the start of the prescribing study.

All the responses received were separated into seven categories/themes of likely influence (Annex 9) namely:

1. drug factors
2. education/information factors
3. patient factors
4. pharmaceutical industry factors
5. general medical practitioner factors
6. regulatory factors
7. work related factors

7.2 QUESTIONNAIRE NUMBER TWO

7.2.1 The response rate

For the stage two questionnaire, 154 (64%) responses were received which was slightly lower than the stage one response (Table 7.70). For this second round, two follow up reminder questionnaire mailings were necessary in order to bring the overall response rate to above 60%. There were three countries, namely Portugal, Scotland and Spain where a 60% level was not reached.

7.2.2 Overall rank order of the different categories of influence

For all GPs combined, 'drug factors' were perceived to be the most important category of influence, whereas pharmaceutical industry related factors were considered the least influential category (Table 7.75). Although there was an evident gradation in the hierarchy of the remaining categories, opinion was less distinct. Patient factors received the second greatest number of first preferences but summation of the scores for the different ranked positions, resulted in education/information factors being marginally the second most important category of influence overall and patient factors the third. For the fifth and sixth most important categories of influence, despite twice as many GPs indicating that workplace factors were the least (seventh) important category of influence compared with regulatory factors, their overall weighted totals were

similar. Overall, regulatory factors were perceived as slightly more influential in fifth place, than workplace factors in sixth position.

As a consequence of there being different numbers of GP respondents from the various countries, those countries with greater numbers could produce a slight bias in the overall ranking of the different categories of influence overall (Table 7.75). Nevertheless by comparing the overall ranking of the categories of influence with their ranking in the individual countries, inter-country variations would be identified.

7.2.3 Rank order of the categories of influence in the different countries

Drug factors were the number one category of influence in most countries, but in Belgium and England they were second (Table 7.76). Pharmaceutical industry related influences were the least influential category in most countries, except for Portugal and Italy where they were fifth and sixth respectively. General practitioner factors were the fourth most influential category in most countries apart from England and Scotland where they were positioned in third place, whereas workplace factors were considered to be the fifth most influential category in all the countries except in Ireland and Italy. For the remaining three categories of influence: education/information; patient; and regulatory factors, there was slightly less agreement between the countries as to their precise order. Finally, the order of the perceived influence of workplace, regulatory; and industrial factors were fifth, sixth and seventh positions respectively by GPs in Belgium, England, Northern Ireland, Scotland and Spain.

When comparing Table 7.75 with Table 7.76, in the former, regulatory factors were the fifth most important category for all the GPs combined, whereas in the latter, workplace factors were consistently perceived to be more influential than regulatory factors.

7.2.4 Comparison of the GP ranking profiles in the different countries

In Table 7.76, with the exception that GP factors in England were perceived to be equally as important an influence as patient factors there, the Belgian and English doctors appeared to be the most similar in what they perceived to influence their prescribing.

For the Irish GPs, their category rank order was identical to that of all the GP respondents combined in Table 7.75. The first four categories of influence occurred in the same order to those of the Portuguese and Spanish GPs.

In Italy, the GPs perceived patient influences to be the equally most important influential category together with drug factors. Pharmaceutical industry influences were in sixth place and considered more influential than workplace factors.

Patient influences were also ranked fairly high by the GPs in Northern Ireland and Scotland where they were the second most important category. The order of the four least important categories of influence were the same in Northern Ireland as those of the GPs in Belgium and Spain.

The Portuguese GPs rated the influence of pharmaceutical industry factors more highly than in any other country. These influences were ranked to have as equal an impact as workplace factors and to be more important than regulatory factors. In Portugal, regulatory factors were perceived to be less influential than in any of the other countries.

Scottish GPs rated general practitioner factors in third place (similar to their English counterparts), which was higher than elsewhere. Education/information factors were rated in fourth place which was lower than elsewhere.

Spain was the only country in which the ranking for each of the influential categories was consistent with the collective ranking of the other countries.

7.3 DISCUSSION

The overall response rates were above 60% in both questionnaires one and two which met the target level. Portugal was the only country where the 60% target was not attained for both questionnaires and consequently it is possible that non-responders could have modified the response there. Due to the geographical distance over which the research was taking place, it is difficult to know how the response rate could have been improved as one reminder was sent out for the first questionnaire and two reminders subsequent to the second questionnaire. In addition, copies of the first

questionnaire were included with all mailings of the second questionnaire to GP non-responders from the first stage.

From the GPs age category breakdowns, the Belgian and Spanish doctors were on average the youngest from all the countries. This appeared to link up fairly well with the number of years since qualification, where the Belgian and Spanish GPs were noted to have the lowest mean number of years recorded, thus confirming a degree of accuracy in the way responders were completing the questionnaire.

In the study, the workplace distribution of the GPs was partially influenced by the location of the co-ordinators who generally worked in towns or cities. With the exception of GPs in Italy, Northern Ireland and Portugal, the majority were also involved in training doctors to become GPs. These two factors support the fact that the participants were unlikely to be entirely representative of the GP populations within their countries.

The style of general practice (single-handed/group practice) and the differences in the age profiles of the patients who consult GPs varied from country to country. They are indicative of fundamental differences in health care practice between European countries which can influence prescribing patterns.[210,213] Although where both single handed and group practices exist within a country, the GP may choose between them.

From the ranges of hours worked and patients seen per week in the different countries, it is likely that some of the GP participants worked part-time. Of the different participating countries surveyed, Belgium is the only one which had an open access health care system. An abundance of doctors, associated with the probability of increased pressure to satisfy patients there, would be likely to result in a greater instance of home visits in Belgium than in the other countries. The Belgian GPs also recorded a longer than average length of doctor-patient consultation time than was found in the other countries. This helps to explain why the mean number of patients seen in one week were lowest in Belgium.

The mean number of pharmaceutical industrial representatives consulted over a four week period revealed extreme differences between countries. The relatively high number of drug representatives seen on average in southern European countries,

suggests that the GPs appear to have relied on them as a major source of drug information.

From the second questionnaire, of the seven different categories of influence, a fairly clear pattern emerged of which were positioned the top, middle and bottom ranked categories. As a consequence of there being different numbers of GP respondents from the various countries, those countries with greater numbers could produce a slight bias in the overall ranking of the different categories of influence overall. For example, the number of Irish and Italian GPs responding, represented almost a third of the total respondents in the second questionnaire and there was a corresponding bias towards regulatory factors by the GPs in these two countries. This explained the difference between the order of this category and workplace factors in Table 7.75 for the overall data combined compared with Table 7.76 for that of the individual countries.

Within the individual countries, the most notable findings were firstly that Italy was the only country where GPs perceived patient factors to be the joint most important influence on their prescribing. Secondly in Scotland, education and information factors were rated lower than elsewhere. Thirdly, regulatory factors which could be interpreted as the only category which formally controls the GPs prescribing, were relatively low down the category rank order in all of the countries. Lastly, industrial factors were perceived to be the least influential category in all the countries except for two of the three southern European regions which could be associated with the high number of sales representatives seen (and honestly admitted) by GPs there.

Table 7.70 Response rate to postal questionnaires 1 and 2 by country

Country	No. of GPs mailed in each round	No. (%)of GPs completing questionnaire 1	No. (%) of GPs completing questionnaire 2
Belgium	17	14 (82)	11 (65)
England	26	23 (88)	22 (85)
Ireland	35	30 (77)	25 (71)
Italy	40	27 (68)	25 (63)
N Ireland	13	12 (92)	11 (85)
Portugal	40	22 (55)	20 (50)
Scotland	40	26 (65)	23 (58)
Spain	30	19 (63)	17 (57)
Total	**241**	**173 (72)**	**154 (64)**

Table 7.71 Age and gender profiles of the respondents

Country	N°. of GPs	Males	Females	*30-39 years	40-49 years	50-59 years	≥60 years
Belgium	14	11	3	5	9	0	0
England	23	10	13	6	11	5	1
Ireland	30	27	3	6	13	10	1
Italy	27	19	8	7	13	3	4
N. Ireland	12	9	3	5	5	2	0
Portugal	22	6	16	1	20	1	0
Scotland	26	18	8	8	9	7	2
Spain	19	13	6	10	9	0	0
Total	**173**	**113**	**60**	**48**	**89**	**28**	**8**

* There were no GPs aged under 30 years old

Table 7.72 Mean (SD) number of years qualified, GPs involved in training doctors and the proportion of GPs working in group practices and their location

Country	Number of GPs	Mean Nº. (SD) years qualified as doctors	Number (%) GPs involved in training doctors*	Number (%) GPs working in a group practice*	Nº. rural practices	Nº. urban / rural practices	Nº. urban practices	Nº. inner city practices
Belgium	14	16 (5.5)	14 (100)	14 (100)	0	5	7	2
England	23	20 (8.3)	18 (78)	22 (96)	1	5	9	8
Ireland	30	22 (9.9)	18 (60)	21 (70)	3	16	6	5
Italy	27	21 (9.8)	10 (37)	1 (4)	0	1	19	7
N. Ireland	12	19 (5.7)	4 (33)	12 (100)	1	3	5	3
Portugal	22	19 (2.2)	9 (41)	8 (36)	4	8	9	1
Scotland	26	22 (8.3)	21 (81)	26 (100)	0	2	17	7
Spain	19	15 (3.3)	19 (100)	19 (100)	0	0	14	5
Total	**173**	**20 (7.6)**	**113 (65)**	**123 (71)**	**9**	**40**	**86**	**38**

* The remaining GP participants represent the converse

Table 7.73 Comparison of the mean (SD) number of hours worked and patients seen per week and mean consultation length

Country	Nº. of GPs	Mean Nº. (SD) hours worked in primary care/week	Mean Nº. (SD) patients seen in one week	Mean duration in minutes (SD) of the consultation
Belgium	14	48 (9.6)	101 (47)	19 (2.8)
England	23	42 (19)	119 (45)	9 (1.1)
Ireland	30	58 (15)	168 (54)	10 (3)
Italy	27	28 (10)	120 (42)	13 (4.1)
N Ireland	12	39 (11)	123 (42)	9 (1.2)
Portugal	22	38 (5.6)	116 (39)	16 (5.8)
Scotland	26	43 (12)	116 (33)	10 (0.7)
Spain	19	38 (2.4)	134 (37)	8 (1.7)
Mean	22	42 (15)	127 (47)	12 (4.6)

Table 7.74 Comparison of the minimum, maximum and mean (SD) number of drug reps seen compared with patients over four weeks

Country	Nº. of GPs	Min. and Max. number of drug reps seen in four weeks	Mean Nº. (SD) drug reps seen per GP in four weeks	Mean Nº. (SD) patients seen in one week	Ratio of Nº. patients consulted for each drug representative seen
Belgium	14	0-1	0.07 (0.3)	101 (47)	5648:1
England	23	0-2	0.3 (0.6)	119 (45)	1596:1
Ireland	30	1-24	9.7 (5.8)	168 (54)	70:1
Italy	27	1-80	23 (17)	120 (42)	21:1
N Ireland	12	1-12	4.3 (2.9)	123 (42)	115:1
Portugal	22	0-70	32 (21)	116 (39)	15:1
Scotland	26	0-4	1.6 (1.2)	116 (33)	288:1
Spain	19	4-70	23 (20)	134 (37)	22:1
Mean	22	1-33	12 (17)	127 (47)	972:1

Table 7.75 Overall rank order of the seven categories of influence (based on the influences generated in questionnaire stage one) for all countries

No. GPs selecting the rank of each category	Category of Influence	Drug	Education / information	Patient	General practitioner	Regulatory	Workplace	Industry
First		63	36	44	9	5	5	1
Second		44	37	34	21	6	7	2
Third		24	39	27	31	14	15	3
Fourth		11	17	20	50	23	28	7
Fifth		7	20	18	26	38	26	18
Sixth		4	4	10	12	53	43	24
Seventh		1	1	1	5	15	30	99
Weighted Total		**899**	**806**	**802**	**651**	**468**	**458**	**263**
Percentage		**21%**	**19%**	**18%**	**15%**	**11%**	**11%**	**6%**

Table 7.76 Rank order of the seven categories of influence selected by the GPs in all the participating countries

No. GPs selecting the rank of each category	Category of Influence	Drug	Education / information	Patient	General practitioner	Workplace	Regulatory	Industry
Belgium		2	**1**	3	4	5	6	**7**
England		2	**1**	3	3	5	6	**7**
Ireland		**1**	2	3	4	6	5	**7**
Italy		**1**	3	**1**	4	**7**	5	6
Northern Ireland		**1**	3	2	4	5	6	**7**
Portugal		**1**	2	3	4	5	**7**	5
Scotland		**1**	4	2	3	5	6	**7**
Spain		**1**	2	3	4	5	6	**7**

CHAPTER EIGHT
DISCUSSION

8.1 INTRODUCTION

The fundamental purpose of the European Formulary Research Project was to establish the degree of acceptability and use of the European Formulary by GPs in different countries in order to further the development of a final version which was intended to be published. Being the only full-time employee associated with the study enabled me to develop a range of research questions and hypotheses which I have explored. Consolidation of this work constitutes the submission of this thesis for an academic research doctorate. In my independent research I have:

- performed background literature reviews on drug formularies and prescribing patterns, factors influencing prescribing, quality prescribing and European health care systems,
- created the primary hypothesis for the main prescribing study,
- developed the diagnosis and drug coding frames,
- collated and coded the drug and diagnosis/symptom data as well as entering the data using purpose written software,
- provided annual feedback on the project data to the co-ordinators in the different participating countries,
- taken part in debating the final content and format of the educational intervention,
- conducted all the necessary prescribing analyses as appropriate,
- created a second major hypothesis which formed the basis of a two-stage Delphi prescribing influences questionnaire study which I designed and carried out.

The subsidiary questionnaire study was linked to the main prescribing study by involving the same GP participants and attempted to establish perceived influences on GP prescribing in the different countries. By exploring these perceived influences, it

was anticipated that this would contribute and support constructive explanation of the variations in drug utilization found in the main prescribing study.

In this chapter, each study is discussed in turn from three main perspectives, namely *theoretical considerations*, *methodological considerations* and *practical considerations*. Firstly, the *theoretical considerations* section reflects on the two main hypotheses which formed the basis of the two separate studies and discusses the extent to which these were achieved. This step is facilitated by unraveling the hypotheses into discrete components which form natural subheadings for discussion. Secondly, the critique of the methodological design and procedure of the two studies forms the *methodological considerations* section. The limitations of each study are also discussed. Thirdly, the *practical considerations* heading incorporates discussion of the interpretation of the results and what the implications of these are. In addition, a summary is made of the key messages that should be conveyed to the main players associated with disease and medicines management, namely: doctors, pharmacists, policy makers, the pharmaceutical industry and patients. The chapter closes with some suggestions for future research and a final conclusion to the thesis. Discussion of the main findings from the results and how they relate to other published literature was included at the end of each results section.

There may be alternative ways of discussing the interpretation of the data than this proposed format and, not surprisingly, some of the issues raised tend to overlap with the different section headings. However, by adopting this proposed structure, an appropriate level of focus can be applied to the different aspects of the work in this thesis.

8.2 THEORETICAL CONSIDERATIONS

Two hypotheses were drawn up which formed the basis of the two studies. The first study was designed to capture GP prescribing data from two distinct time periods with an educational intervention mid-way between.

8.2.1 The prescribing study

The first major hypothesis postulated that*: the planned implementation of a multinational consensus-based European Formulary in primary care will result in more rational prescribing.*

8.2.1.1 The multinational consensus-based European Formulary

The first study involved up to 40 GPs from eight European countries being randomised into control and intervention groups. As part of an educational intervention to improve certain aspects of prescribing, the GPs in the intervention group each received a copy of the multinational consensus-based European Formulary.

For the above hypothesis to be investigated, a formulary based on sound pharmacological and therapeutic principles had to be produced which would recommend the most cost-effective drug or group of drugs for a specific indication. This production task proved to be highly complex (as explained below) and it took approximately six years (1987-1993) to develop a framework formulary with an additional two years to produce a European Formulary acceptable for field testing.

The aim (Section 2.1.7) was to produce a handy reference manual which included recommendations of both drug and non-drug treatments most appropriate for the majority (90%) of conditions presenting in primary care. Some leeway (10%) was allowed for conditions requiring specialist treatment. It was proposed that the manual should be widely acceptable and useful for the diverse groups of GPs throughout Europe. The concept of a formulary was not new though, as many general practice formularies were already widely established in some parts of Europe, (Section 2.1.5) yet certain countries such as Portugal had no national, regional or local formularies in use at the time. Although different countries had different needs and requirements, it became crucially apparent that what was consistently lacking was an explanation of why

particular preparations are recommended. Consequently, it was decided to also develop a second more detailed Appendix document, which included references from national drug and therapeutics bulletins as well as reputable journals supporting the drugs selected in the European Formulary.

With continuing political integration of the European Community, the concept of a multi-national European Formulary to promote standardisation of quality prescribing and control drug expenditure throughout the continent was both revolutionary and desirable and the acceptability of the free movement of doctors would also be facilitated. It has been established that the most successful formularies are ones which have involved multi-disciplinary collaboration[100,101,130,401] and so it seemed logical for a team of general practitioners, pharmacists and clinical pharmacologists to form the European Formulary Group. Hospital formularies, which are often more sophisticated documents, commonly involve additional experts such as microbiologists who provide advice on local antibiotic sensitivity patterns and help recommend the most cost-effective antibiotics for inclusion within their formulary.[402-405] With the intention that the European Formulary should cover such a large geographical area, the efficacy of antibiotics was likely to vary greatly and consequently the need for local microbiological expertise was reduced.

There were approximately 50 major contributors from 17 countries involved in the development of the European Formulary, of whom 10 individuals formed the Editorial Board and three had the responsibility for compiling the final draft for field testing. The various contributors worked in teams on separate therapeutic sections based on where they perceived their areas of expertise and knowledge to be most relevant. The most up-to-date reputable drug and therapeutics literature sources in the relevant area of therapy were reviewed and specialist advice was consulted where necessary. When completed, the therapeutic sections were presented at meetings and the Editorial Board had the responsibility for updating the work in the light of the discussions that had taken place.

Prior to the 1990s, many of the studies reported in the literature which compared the cost-effectiveness of drugs, were often sponsored by the pharmaceutical industry which exposed them to potential and usually unquantifiable bias.[406] Since the European Formulary development process of a decade ago, there has been a growing

cultural move towards more evidence-based medicine using meta-analyses and systematic reviews in the development of prescribing guidelines.[120,407,408] Nevertheless, the strategy of consensus-based agreement such as that adopted in the construction of the European Formulary demonstrated a valuable stage in the process of change towards independent review which is what is both needed and perceived by GPs to be the way forward.[409]

Although drug selection in the European Formulary was primarily based on the principles of efficacy, safety and cost, the reality was that the consensus-based development process was very much compromised. Apart from the immediate problems of geography, communication and language, the European Formulary Group operated in a part-time voluntary capacity and members found that it was difficult to maintain the momentum of formulary development with the relatively fast rate of change in therapeutics, such as in the area of lipid-regulating drugs. Due in part to the lack of financial backing, membership of the European Formulary Group changed but this had various advantages and disadvantages. The main disadvantage of a fluctuating membership was the erosion of continuity. With fewer people involved, another disadvantage was that a high level of contribution was required by all concerned, but an advantage was that the decision making process was made relatively more efficient. Whereas increased numbers of members from a wider geographical range had the advantage of requiring a lower level of individual contribution. To reach a consensus decision satisfying all concerned, was much more complex with a larger number, and although this was potentially a useful development, there was a need for careful control and undoubtedly more resources.

Frequency of doctor-patient encounters, resulting diagnoses, subsequent prescribing and drug consumption are all influenced to a certain degree by different cultural and societal biases. In the United States for example, the heart is viewed as a mechanical pump and physical blockage is largely believed to be responsible for heart pathology[24], but in Germany, the heart is considered to be an organ that has life on its own and pulsates in response to a number of different stimuli, including emotions. In 1981, total sales (in German marks) of nitrates used for angina in countries with roughly similar populations and age distributions were 176 million DM in West Germany, compared

with 73 million DM in France and 18 million DM in the UK.[24] Around that time, the American rates of frequency for coronary bypass operations were 28 times that of some European countries.[24] One consequence of this difference in cardiovascular medical culture was that pharmaceutical industrial research and development of heart drugs in Germany was particularly vigorous which consequently resulted in greater use of these drugs. Another reason for high use of heart drugs is because *Herzinsuffuzuenz* (cardiac insufficiency) and low blood pressure are diagnoses which are routinely made and treated in Germany[410,411], but are neither accepted nor treated in most other countries.[412] Furthermore, low blood pressure is perceived to be a proxy for longer life in most developed countries.[24]

The management of intermittent claudication was one area of particular controversy in the development of the European Formulary. Although a universally recognised diagnosis, it is one where the issue of prescribing cerebro-vascular dilator drugs is highly controversial since the few controlled-studies carried out have shown little improvement in walking distance ability for those so treated.[6] On a European scale, a formulary which omitted cerebro-vascular dilators would not be readily acceptable in France, Germany and the southern European countries, whereas in several northern European countries, including the Netherlands, Scandinavia and the UK, a formulary which included such drugs would have less credibility. The consensus reached by the European Formulary Group was to recommend pentoxifylline for use in severe cases only. This compromise, though still unsatisfactory to many, was based on the philosophy that if a drug was going to be prescribed then it is more rational to be consistent and just prescribe one, preferably the most cost-effective.

Huge differences exist in drug availability throughout European countries. At the time of the first European Formulary meeting in 1988, Germany had 11,000 drugs in the Rote Liste compendium (Red List) and the UK had approximately 3,000 licensed medicinal products prescribable on the National Health service.[16,24,413] Similarly, there were wide differences in the numbers of licensed medicinal products for sale to the public in the different countries. Of the countries participating in the study, the number of licensed medicinal OTC products at the end of the 1980s varied from 3,382 in

Portugal to 8,747 in Belgium.[414] In the former West Germany, there were 21,000 licensed medicinal products available for sale - the highest number anywhere in Europe.

Associated with the widely differing numbers of medicines available in EU member countries, there are differences in the legal status of medicines in those countries and the ways in which they are controlled. Since the early 1990s, there has been a programme of deregulation of selected medicines for human use from prescription only to non-prescription status in several European countries. Increasing the range of medicines available from pharmacies without a prescription has occurred as a result of the attempt by governments and health care systems to increase patient self medication[415,416], thereby reducing the cost burden on insurance or national health care systems. Such changes have taken place in most European countries and there has been particular promotion of self-medication in France, Germany, Netherlands, Norway, Spain and the UK.[18] Increasing the number of OTC drugs available has advantages such as in providing a more integrated primary health care role for the community pharmacist and relative ease of their availability for the patient but negative consequences include an increased risk of potential drug interactions and the danger of patients wanting 'a pill for every ill'.[417] Attitude towards these changes by doctors and pharmacists varies according to whether they perceive them to be complementary or counterproductive in relation to their practice in their indigenous health care system. In Belgium, France, Ireland, Italy and Spain, doctors are largely opposed to such moves, whereas in Germany, the Netherlands and the UK, doctors are fairly supportive towards the belief that people should take more responsibility for their health.[418] In nearly all countries, pharmacists have a positive attitude towards these reforms as long as the availability of medicines remains essentially through the pharmacy.[418] For example, in the Netherlands, where there is now competition between pharmacies and drug stores for the distribution of OTC medicines, pharmacists are less positive. While the Royal Pharmaceutical Society of Great Britain supports the appropriate deregulation of selected medicines being switched to be under the supervision of a pharmacist, there are reservations about medicines being later added to the general sales list (GSL). Ibuprofen was first deregulated from prescription only medicine (POM) to pharmacy (P) status in 1983 but in 1995, when ibuprofen was deregulated to GSL (general sales list)

status[419], it became available from a range of outlets including petrol stations, newsagents and supermarkets which prompted a request to the Medicines Control Agency to review its current practice.[420]

Traditionally, drug availability has depended upon how rigorous the regulatory measures are within a country. In 1992, the medicines classification Directive 92/26/EEC was implemented with the intention of unifying the distribution of medicines in Europe.[418] Although this has formed the basis for which medicines have been switched from one legal classification to another, the number of medicinal classes varies from country to country. Despite there not having been the same degree of promotion of self-medication in countries such as Belgium, Ireland and Portugal, it may well be that several of the drugs which have been deregulated in other countries in recent years are already available without a prescription in these three countries. Many medicines when deregulated are only available to the public in a restricted quantity and the strength is often lower than that of the prescription version. Important examples of drugs available without a prescription in some European countries include certain: antifungals, bronchodilators, H_2-receptor antagonists and a range of NSAIDs.[418] Particular problems for the European Formulary Group included instances where, for example bendrofluazide which was only available in certain countries had become accepted as the drug of first-line treatment there.

The range of different formulations of drugs which exist includes oral capsules, tablets, powder sachets, suspensions and syrups as well as topical creams, drops, gels and ointments. The availability of different formulations of the same active drug also varies from country to country, for example fluoroquinolones such as ciprofloxacin are used topically in the treatment of eye infections but eye drop preparations are not available in all countries.[20] Occasionally, the availability of different formulations of combination drugs varies too from country to country reflecting differences in both licensing applications and licensing practice. The same drug can have different marketing authorisation indications from country to country and even within a country the licensed indications can depend on whether the drug is prescription only or not. Marketing authorisation indications may extend and dosage of a drug may also change with time as experience of drug use develops.

In developing the European Formulary, there were difficulties in standardising dosages for treating conditions as these were often found to differ from country to country. For example in the management of pain, there was debate over the appropriateness of the level of opioid content in compound analgesics and the consequent total daily dose. Standardising dosages is made easier where accepted definitions and guidelines have already been generated by special bodies or interest groups on an international scale - for example in the areas of asthma[391] and hypertension[346]. Similarly, standardising the duration of treatment is also an issue that has to be considered, for example in the treatment of urinary tract infections where three day, five day and seven day courses of antibiotics are prescribed.[288] The duration of treatment can also be associated with the strength of the active drug and hence the degree of aggressiveness of the treatment strategy. The age of the patient is also a dependent factor.

In January 1994, EC Directive 92/27/EEC came into force requiring the use of the Recommended International Non-proprietary Name (rINN) for medicinal substances to be phased in.[6] One of the aims of the European Formulary was that drugs should be presented by their generic name. However, generic names approved in countries may not always be synonymous with the rINN. Where they are not identical, some generic drug names, for example cephalexin and lignocaine in the UK, are easily substituted with their rINNs - cefalexin and lidocaine. However, other substitutions have the potential to cause confusion, for example adrenaline and dothiepin become rINNs epinephrine and dosulepin respectively. In addition, prescribing by generic drug name was not routinely practised in some European countries, including Italy, Portugal and Spain at the time of this study[421-423], and so many prescribers would not have been familiar with either the rINN or their national equivalent approved name. The situation is further complicated by the way in which brand names of the same drug from the same manufacturer often differ between countries. Although the European Formulary Group agreed to use generic name terminology, the fact that there was no standard uniform drug nomenclature which European GPs would be guaranteed to be familiar with, was a problem.

Probably one of the most disruptive and unpredictable factors in developing the European Formulary was the inconsistency of drug prices between countries which nevertheless influence prescribing. The extent of this was not fully appreciated by members of the European Formulary Group in the initial stages of the Formulary development process. Government and industrial price and profit controls are largely responsible for determining the cost of drugs in different countries.[21] Difficulties have been reported with drug prices varying markedly within countries too, especially between primary and secondary care causing problems with the provision of seamless patient care upon admission to hospitals and later discharge back into the community.[130,279] Differences in drug prices caused a particular dilemma for the European Formulary Group in the area of antibiotic drug selection where it is recognised that resistance to antibiotics is a global problem. When considering the third-line treatment of urinary tract infections, the European Formulary Group wanted to limit the recommendation of fluoroquinolones in order not to jeopardise their future effectiveness but in Spain, for example, nalidixic acid was the most cost-effective fluoroquinolone compared with norfloxacin in the UK.[423] Ironically the Spanish GPs appeared to prescribe norfloxacin in preference to nalidixic acid in the treatment of UTIs.(Section 5.2) Co-amoxiclav was another example of an antibiotic that was relatively cheap to prescribe in Spain in comparison with the UK cost.

Despite the difficulties faced by the European Formulary Group, a European Formulary and Appendix were developed recommending treatment for 66 conditions, deemed to be the most commonly presenting conditions in primary care (Annex 4). There were 126 drugs recommended in the European Formulary which were available in all the European countries where its use was being implemented and tested. In certain places where recommended drugs represented examples of a therapeutic group in which various drugs could serve as alternatives, a special clause was used which enabled the selection of equivalent drugs depending upon their availability and comparative cost in a country. An example was the use of fluoroquinolones for the third-line management of UTIs. In certain situations however, such as in the first-line management of hypertension, the European Formulary appeared to be fairly rigid in the selection of hydrochlorothiazide as the choice of thiazide diuretic. In the UK, hydrochlorothiazide is

more expensive than bendrofluazide and appears to offer no significant clinical advantage.[6]

With the complex nature of developing the European Formulary, the Editorial Board were faced with deciding whether the Formulary was intended to be a 'jack of all trades' i.e. a rough guide to prescribing in general practice, or a 'master of some' i.e. to focus and become an authority on certain specified areas of prescribing which when targeted could have a significant impact on prescribing practice. Ultimately, it was the objective of the European Formulary Group to publish the European Formulary and Appendix by marketing them both as educational tools and as a foundation upon which practitioners throughout Europe could develop their own formulary tailored to local requirements and in so doing foster a degree of ownership (Section 2.1.5).

One of the fundamental questions, which I believe was not properly addressed, was whether the purpose of the European Formulary was to be diagnosis-led or drug-led. If it was intended to be diagnosis-led then should symptoms commonly presenting in general practice but which tend to lack credibility as definite diagnoses, for example fatigue, itching, and pyrexia of unknown origin, be included? If the European Formulary was to be drug-led, then should conditions be included where there is no real controversy over the choice of therapy once the diagnosis is made, for example hypothyroidism and hyperthyroidism? Also should conditions where drug therapy is not routinely recommended first-line, for example sprains and strains, be included?

All the shortcomings discussed above may therefore have diminished the potential influence of the European Formulary and Appendix. Other factors can also determine the level of success of a formulary such as its launch and promotion and how these aspects of the European Formulary were managed are now discussed in the next section.

8.2.1.2 The planned implementation

With the development of a consensus-based European Formulary in 1995, the members of the Editorial Board were now in a position to use this draft for field testing among GPs in Belgium, England, Ireland, Italy, Northern Ireland, Portugal, Scotland and Spain. To achieve maximum success, planning the implementation should have involved in detail how best to optimise the behaviour change of the prescribers. Ways

to achieve such behaviour changes have been considered by others.[424-426] The more lines of communication involved when trying to implement change then the more the messages are likely to get distorted.[427] As the validity of a rigorously designed uniform intervention did not form part of the remit of the study, it has not been possible to adequately test this aspect of the hypothesis. However, the proposal for BIOMED funding did state that a standard formulary and information pack concentrating on antibiotics and NSAIDs would be made available for the GPs in the intervention group prior to the second data collection. Additionally, the doctors in the intervention group in each country would either attend a one day meeting or would each be visited by their co-ordinator. The precise nature and details of the intervention were to be agreed at a later date.

At the annual co-ordinators weekend meeting in April 1995, I participated in establishing the strategy for the planned implementation of the European Formulary and educational intervention. It was agreed that the intervention protocol needed to be standardised so that the same procedure would occur in each country. Whilst it was recognised that certain additional factors, such as the individual performing the exercise (i.e. the co-ordinator), would differ, the co-ordinators were all respected opinion leaders within their localities. The intervention was to consist of the European Formulary, together with all the sections of the Appendix relevant to antibiotics and NSAIDs and a refined list summarising the most important prescribing messages from the Appendix associated with each drug group. It was decided that the intervention group GPs would receive the educational package between one and two weeks prior to the date of an agreed meeting.

Subsequently, the actual implementation of the educational intervention did however vary from country to country, although all GPs were mailed with the same educational literature. The method and extent of communication varied between countries. In England, communication was via the telephone with one of the partners in each of the intervention practices. In Spain, the co-ordinator met all the intervention group GPs at the various GP centres on five separate occasions. Each of these five workshops lasted for one hour's duration and enabled debate and discussion about the educational material. The thoroughness of the implementation process depended on the dedication and enthusiasm of the GP participants as well as the commitment and

persistence of the different co-ordinators trying to fit in with the busy daily schedules of the GPs.

8.2.1.3 Primary care

This research has concentrated on addressing the prescribing practices of primary care doctors in eight European countries. With the exception of Belgium, a gatekeeping system operates in the project countries where GPs control access to all other levels of health care (Annex 1). Consequently these countries have a similar organisational structure with the general practitioner often at the centre of health care, although the delivery of that care may be variable.

In Italy for example, there are community-based paediatricians and children under twelve years old have to be registered with one[266] and in an attempt to co-ordinate care, prescriptions written by specialists such as paediatricians have to be endorsed by the patient's own GP. In Spain, there are additional support units in primary care as well as the network of GPs.[266] These units include maternity and child health centres, mental health centres, physiotherapy units and family planning centres. Whilst GPs still act as gatekeepers to these services, the responsibility for children's prescribing lies with community-based paediatricians and this potentially can have a marked effect on the prescribing profiles of GPs. For example, research has shown that the prescribing levels (in terms of the number of items) in children up to four years of age are not reached again till the 45 to 54 year old age group.[428,35] Also prescribing volume and cost is known to be greater in females up to the age of 55 years old and hence the availability of maternity and family planning centres is also likely to have an effect on the prescribing volume of GPs.

Other characteristics of general practice have also been found to vary widely between countries (Annex 1). The duration of the consultation has been proposed as a simple proxy measure of quality of care with longer consultations being more thorough and relevant to the patients needs.[211] Shorter consultations have been associated with the more frequent use of a prescription to terminate the consultation[30] whereas those GPs who allow ten minutes or more for each consultation have been found to prescribe fewer antibiotics.[211] The reported duration of GP-patient encounters in the project

countries varied from four minutes in Spain to eleven minutes in Belgium and this may have influenced the pattern of prescribing.

Even within the primary care setting of a country, variations in health care practice have been found to have a marked effect on factors such as prescribing volume. Until recently in the UK, GP practices could chose whether they wanted to be fundholders or non-fundholders. Fundholding practices were allocated extra budgets to pay for a patient's secondary care in addition to their primary care needs.[266] As a result of such incentives, fundholding was found to contain increases in prescribing costs in the short term[214] but longer term effects were not as positive.[216]

Although primary care is only part of the entire health care delivery system, targeting general practitioners prescribing behaviour is necessary as it is widely reported that in the region of 85% of the prescribing volume in the UK takes place in primary care.[30] Consequently, this represents the bulk of drug expenditure which is considered to equate to 80% of the cost of all medicines[236] and despite differences in health care practice it is probable that this dominance prevails generally in western Europe, especially where a gatekeeping system exists (Annex 1).

8.2.1.4 More rational prescribing

Over 25 years ago Parish first defined rational prescribing as being 'appropriate for the patient, effective, safe and economical'.[37] Although others have since contributed to this definition, the general interpretation by Parish is still widely accepted today. However, difficulty has been found in finding adequate tools which can be used to measure and compare rational prescribing.[58] Even when valid measures have been identified, it is rarely possible to apply them to prescribing on a large scale. Consequently, one of the attractions of using the proportion of drugs prescribed generically as a crude indicator of rational prescribing is that it can be potentially measured on a continuous basis for all GPs in the UK. Unfortunately, as already noted, generic prescribing was not routinely practised throughout Europe, so the generic prescribing rate could not be used as an international quality indicator.

Formularies are a standard against which rational prescribing can, to a large extent, be practically and more meaningfully assessed, especially as their development is generally based on the core principles of rational prescribing, namely efficacy, safety and cost. The effect of formularies in a variety of settings has been widely documented in the UK since the early 1980s. Studies of formularies have highlighted that: formulary development need not restrict drug choice[122], involvement can be associated with higher levels of prescribing recommended agents[124], adherence is higher with new prescribing for acute conditions than with repeat prescribing for established therapies[124], implementing recommendations have generated considerable cost savings[123], use can reduce the range of drugs prescribed[286], development can educate prescribers[90], adoption can improve patient compliance[127] but that formularies which are not regularly updated eventually stagnate and become obsolete.[72]

The research presented in this thesis has assessed the degree of rational prescribing before and after the educational intervention by using core and miscellaneous prescribing performance indicators. The core indicators were:

- concordance with Formulary recommended drugs for a particular condition
- the diversity of prescribing measured by the range of drugs used
- whether consultations resulting in a prescription reduced where appropriate.

Regarding the diversity or range of prescribing, physicians in general can only keep up-to-date with the profiles (contra-indications, dosages, formulations, indications, interactions, side-effects, strengths and treatment duration) of a limited number of medications. The rationale behind drug selection by doctors has been found to become increasingly inefficient when presented with a larger number of choices of therapy.[429] High quality prescribing is therefore associated with the use of a relatively limited number of drugs.[72,242] The miscellaneous prescribing performance indicators used were ones specifically tailored to the area of prescribing being investigated. For example, the use of combination drug forms such as potassium-sparing diuretics, can confuse prescribers as problems may arise when changes in dosage schedules are needed and hence their use should be minimised. Although combination drugs may contribute to and improve patient compliance, it is difficult to justify their use as the

combined cost of the drug entities prescribed separately is usually more economical.[279] The prescribing analyses focused in particular on the category of new prescriptions as it was perceived that current prescribing would be more likely to change data subsequent to the educational intervention, as opposed to influencing a review of repeat prescribing.

8.2.1.5 Conclusion

The first major hypothesis in this thesis was partially proven. The hypertension and asthma results sections indicate that receipt of the European Formulary alone had little effect in improving prescribing. Whereas the NSAID and antibiotic data (for throat infections in particular) indicate that for some of the prescribing performance areas considered there were statistically significant improvements after the educational intervention in some countries. Occasionally there was also the odd perverse result where the control group appears to have demonstrated a greater improvement in prescribing compared with the intervention group. Therefore it is important to add an element of caution in the interpretation of these results and one has to bear in mind that there are a number of variables interacting having an impact on the results. With respect to the educational intervention, it was not possible to identify whether the catalyst for change was provision of the referenced Appendix, or verbal discussion and debate of the main prescribing messages between the co-ordinators and their intervention group GPs singularly or collectively combined.

8.3 METHODOLOGICAL IMPLICATIONS

8.3.1 The prescribing study

The European prescribing study described was successful in obtaining prospective prescribing data of **138,615 diagnoses** and **130,657 drug entities** from **101,544 doctor-patient consultations** over two distinct time periods from 235 GPs in eight European countries (3 centres within the UK). Half of the GPs received an educational intervention between the two periods of data recording and there were 218 GPs who completed both phases of the study.

The draft multinational consensus-based European Formulary and Appendix documents used for field testing in the intervention were original. There had never

previously been an enterprise to produce a formulary over such a wide geographical scale involving so many countries and cultures. In 1994 when funding was made available to investigate whether use of the European Formulary would improve cost-effective prescribing, very few international multi-centre primary care based drug utilization studies had been previously initiated before, nor have there been since.

In order to attempt to prove or disprove the first hypothesis, a controlled-study design was necessary with two groups exposed to the same conditions within a country differing only for the intervention group which received the educational package (including European Formulary) half-way through the experiment. Consequently, any change in prescribing behaviour that ensued between the control and intervention groups could be said to be attributable to the educational intervention. As others have done[430], this study was also designed for data to be recorded by the GPs in the different countries at precise intervals (Autumn 1994 and 1995) working to a similar time scale. This was necessary as it is recognised that there are seasonal fluctuations in diagnostic patterns, hence different types of drugs may be prescribed and the quantities in which some drugs are utilized can be very variable.

The prescribing data recorded comprised those drugs which were issued and their prescription category linked to diagnoses, together with patient age and gender. Such information is unique as data sets with this linkage are not routinely available for comparative purposes on a wide scale in any country to date. (Section 2.1.3.2) This enabled a more meaningful evaluation of the range of prescribing scenarios, including for instance whether or not a NSAID is deemed necessary or whether the choice of antibiotic is the most suitable for a presenting infection. Recording of the drugs being prescribed to patients for other conditions provided the possibility of greater insight into therapeutic management decisions - for example, the prescribing of an ACE inhibitor for first-line management of hypertension when the patient was also a diabetic.[349] Information available on the age of patients treated by the GPs allowed a consideration of the different safety profiles of drugs, for example the degree to which NSAIDs with longer half-lives often associated with more serious side-effects were being prescribed for the elderly. The recording of the sex of the patient was important in order to

determine, for example, the prevalence of urinary tract infections in females compared with those in males.

A medical statistician was consulted about appropriate sample sizes of GPs who should be recruited in each country. The proposed target of 40 GP participants per country proved somewhat difficult to achieve, as primarily there was no financial incentive for GPs to take part in this study. This proved to be a crucial prerequisite in some countries, such as Germany. The recording of data was a time consuming task for already busy doctors and the control group doctors did not have the added benefit of receiving the educational intervention, although they were promised a copy of the European Formulary upon completion of the study. Consequently the GPs who were recruited were mostly enthusiastic volunteers, many of whom were known personally to the co-ordinators and were either interested in prescribing or were keen to participate in research. In Northern Ireland, an attempt was made to obtain a random sample and the net result was that only 13 GPs agreed to participate out of a target of 40, which exemplified the difficulties experienced with this recruitment method. The overall sample was therefore less likely to be truly representative of the GP populations within the different countries, with the possible exception of Northern Ireland. Any potential bias occurring as a consequence of recruiting potentially more enthusiastic GPs could have tended to produce artificially better results and the levels of drug utilization found would be likely to reflect more informed use. Thus there could be an underestimation of the variations that really exist.

Recruitment was generally restricted to the geographical regions of the local co-ordinators. However in Belgium, the GP subjects were from a wide geographical radius as a regional formulary was already well established in the immediate locality of the co-ordinator which it was feared might bias results and also make recruitment of doctors more difficult. Other regional formularies were known to exist in the immediate vicinity of co-ordinators in England, Northern Ireland and Scotland but it was not possible to avoid these areas as formularies are generally widely available in these countries. The locality of a GP is likely to determine the socio-economic mix of his/her patient population and studies have shown that social deprivation is linked to morbidity and therefore prescribing.[431] Consequently, the actual location of the co-ordinator in each country could indirectly have influenced the data collected and collated. The

North East of England, for example, is generally more deprived than other areas of England; unemployment in the North East was 9.8% in 1997 compared with 6.9% for the whole of England.[432] Recruitment of GPs in the Newcastle upon Tyne region, in the North East of England, could therefore result in prescribing patterns which may be atypical of those in the country at large.

To enable easier administration of the educational package, the co-ordinators attempted to select GPs in group practices or health centres where possible. This could have potentially been a confounding factor as those factors which influence prescribing by GPs in group practices have been found to be different from those influencing solo practices. For example, commercial information has been found to be preferred by doctors who were practicing alone.[156] Once recruited to the study, the doctors were randomized between control and intervention group practices in order to minimise potential bias. Overall, the study had a remarkably low drop out rate; only 17 GPs (7.2%) from Phase I did not participate in Phase II. This was attributed to the high level of enthusiasm of the participants and it is probably unlikely that such a high level of involvement would have been achieved with a completely random, representative sample of the GP population.

Whereas there was a multidisciplinary group of individuals involved in the development of the European Formulary, the co-ordinators in the prescribing study were all GPs associated with either academia or GP training bodies except in Portugal. In Portugal there were two co-ordinators, one a pharmacist and the other a physician, both of whom were based in teaching hospitals but importantly they had good links with community-based family doctors. All the co-ordinators were members of the Editorial Board and/or were co-authors of the two documents. Although the educational intervention strategy was agreed by all the co-ordinators, its success could have varied depending on the personality of the individual co-ordinator administering the intervention but the study had no real control over this aspect. It would have been impractical to standardise this procedure by having the same individual administering the intervention in all the countries on a similar time scale. Even though all the GPs were provided with project guidelines, translated as appropriate, and no language barriers existed between each co-ordinator and his/her cohort of recruited GPs, there were still occasional anomalies in the prescribing data supplied. The most common

misinterpretation was the fact that several GPs fell short of recording 200 consecutive patient consultations where a prescription was issued in addition to those intervening consultations where no prescription was issued. Instead, some just recorded information from 200 consecutive consultations, irrespective of prescriptions. GPs also appeared to be uncertain about whether to include appliances, dressings, reagents and vaccinations within the 200 consecutive prescriptions requested. The study design did not anticipate the fact that some consultations which did not result in a prescription may have actually involved GP advice for patients to purchase OTC medicines, such as dispersible aspirin 75mg tablets for antiplatelet use. Although the guidelines issued to the GPs were translated as appropriate from English by the co-ordinators, ideally they should have been back-translated for validation purposes.

As a result of financial and time constraints, the European Formulary and Appendix which formed the core part of the educational intervention were only printed and available in English which was probably a potentially important confounding factor. Even where GP participants had a good understanding of the English language, this aspect could have decreased its level of user-friendliness and effectiveness as a rapid consultation guide during patient consultations which was one of the main objectives of the European Formulary. As previously mentioned, all the drugs were listed in their generic name form only which may not have been easily recognisable in southern European countries where generic prescribing has not been routinely practised. Nevertheless all the drugs recommended in the documents were well established ones which were available in all the participating European countries.

The data collected in this study were from face-to-face consultations with GPs and so there was probably a bias towards patients with more acute problems and possibly those who were less compliant with treatment regimens who needed to revisit their GP. This created some difficulties when trying to compare morbidity patterns and drug consumption data within the study with other published findings[433] because of the differences in data collection. It proved necessary for all the data recording consultations to be made on paper as unfortunately, those countries with electronic prescribing were unable to submit data in a usable format as their systems did not readily adapt to the requirements of the project. Electronic data were generally unable to include either patient consultations where no prescription was issued or identify the

category of the prescription required. This was disappointing as one study has shown that the recording of data electronically in general practice can be highly accurate with 100% of all consultations where a prescription was issued being logged onto the computer.[434] Electronic transfer of information could have enabled the data collection process to have been significantly faster and less tedious than by manual processing.

Some important prescribing data were not always routinely collected which would have enabled more detailed accurate and meaningful analyses to have been performed, including the dosage, treatment duration, formulation, quantity prescribed and strength of the medication. Although linkage of drugs to diagnoses enabled determination of whether the drugs were being prescribed for appropriate indications, it is possible that the dosage frequency and duration of treatment of an appropriate drug may have been contrary to the European Formulary or to a manufacturer's guidelines. The omission of such additional information meant that this extra analysis was not possible. Each pharmaceutical preparation has a recommended dose and dosage frequency which in the UK is found in the drug data sheet.[191] Although the manner in which a drug is prescribed is at the discretion of the prescriber, it is advisable that the guidelines set out in the data sheet are used as they are set following the result of stringent testing by manufacturers and are part of the marketing authorisation.

Associated with the duration of treatment, it would have been useful to have known the date on which medication on repeat prescriptions was first started, in order to confirm whether this was rational. However it was not intended that the data revealed the complete current medical history of each patient but represented a snap shot of prescribing at a point in time i.e. the data recorded were prescription(s) that patients were receiving for specified conditions at the time of the consultation. Where a drug was prescribed which was recommended in the European Formulary but in a formulation that was not endorsed by the Formulary, it was not possible to make the necessary adjustment to the data analyses. For example where diclofenac was prescribed in a modified release preparation or as a topical gel, this artificially enhanced the level of concordance with the European Formulary because the study was concerned only with the recording, classification and coding of generic drug names. Nevertheless

it was possible to separate the data into single entity non-combination drugs as well as combination drugs for analyses if necessary.

Data were collected on the type and origin of the prescriptions (N,A,R or H) though these categories were sometimes problematic in interpretation. 'N' drugs were clearly defined but many drugs which were recorded as repeats would have originally been initiated by hospital doctors, for example insulin. The results recorded in this study for hospital prescriptions do not completely reflect all hospital-initiated prescribing and are generally lower than has been reported elsewhere.[30] Spain recorded the highest 'H' prescription rates which may be as a result of the combination of short consultations and high referral rates which seem to characterise primary care in that country. In this study, there were lower numbers of 'R' prescriptions recorded than some others have found.[30] This probably reflects the fact that only face-to-face prescriptions were recorded. Systems by which patients are transferred onto repeat prescription registers may also vary between countries as well as the way in which they are monitored. For example, patients requiring repeat prescriptions for asthma in the UK may be reviewed by practice nurses in asthma clinics without the need for intervention by the GP. Thus the mechanism for repeat prescribing is likely to influence the numbers of 'R' prescriptions recorded. Despite the difficulties in this study with prescription categories, their inclusion was highly important in the prescribing analyses performed as it was considered that the new prescribing category would be the most likely to be influenced following the educational intervention. Where prescribing data are available across countries, such as PACT data in England, these do not indicate which prescriptions are new as distinct from repeats and so lacks sophistication in this respect.[65]

The methodology was developed from previous studies which had a more localised setting of prescription data capture.[124] International data sources which were available were assessed to see if they could be useful in this survey. The methods derived and used were considered to be the most comprehensive and practical for the constraints of manpower and the time frame available for the study.

8.3.1.1 Limitations

If this study were to be repeated then it would be imperative that a random, representative sample of GPs should be recruited in all the participating countries, although the number of participants likely to drop out between Phase I to Phase II would probably be higher than it was with volunteers. A rewrite of the European Formulary would be required which took into account the clinical conditions presenting in primary care that the present edition omitted to include. Consideration as to whether some of the most commonly prescribed non-Formulary drugs should be included would also be required. In order to make the European Formulary more acceptable to its users, it would need to be translated into the various national languages and also back-translated in order to validate the process. Also in order to optimise the quality of data collection a larger scale pilot involving GPs independent of the research should be carried out initially and with respect to validating the data management process, an error rate should be established.

Rational prescribing takes time to implement and initiatives to improve prescribing need to be regularly reinforced in order for the proposed effect to be first achieved and secondly sustained.[90,154,167,223] If this study was to be repeated, ideally a greater volume of prescribing data should be analysed over a prolonged period to explore any sustained change in prescribing behaviour and to assess how a positive improvement could be subsequently maintained after a more robust series of interventions. If the same volume of data were collected then in order to increase the volume of data specific to the areas being investigated, one should consider whether the recording of 200 consultations associated with new prescriptions for antibiotics and/or NSAIDs only for example would be of more value.

A shortcoming of the type of information collected in this study is that it lacks outcome data i.e. we do not know the ultimate success or failure of the present treatment strategy for a given condition. Nor do we know whether first and second-line drugs have previously been tried and found to be ineffective or produced undue side-effects, for example in the antibiotic treatment of bacterial infections. It is conceivable that the same patient could have revisited the GP before inclusion in the requested quota of data on 200 consecutive patient consultations and because the patients were number coded

for anonymity, this was not known. In Belgium, the likelihood of a patient returning to the same doctor before 200 consecutive patients have received prescriptions could be less likely as there is no patient registration system with GPs (Annex 1). Ultimately, a knowledge of previous drug outcomes would have been particularly beneficial when critically evaluating the level of rational prescribing within the different countries. Some indication of this would have been possible if an appropriate additional category of prescription to those discussed earlier had been included in the methodology.

To minimise some of the limitations in this study considerably more financial resources would have been required. For example in order to deliver a more successful, uniform intervention, ideally a salaried academic detailer trained to make use of the marketing techniques used by pharmaceutical industrial companies should be located in each country. The content of the intervention should also be reviewed because with varying antibiotic sensitivity patterns around Europe for example, antibiotics may not have been a particularly suitable area to attempt to analyse, even though a global or European strategy is urgently needed to contain increasing antimicrobial resistance.[435]

These identified methodological limitations should be kept in perspective as in practice, many GPs did provide additional prescribing information and it was possible to infer the formulation of many of the drugs prescribed. As different formulations of the same generic drug name often appear in different therapeutic classification systems, where for example an antibiotic was in an oral form as opposed to a topical form, it was possible to code these separately. Unfortunately to request any additional information at the recording stage was not feasible. It would have made the processing of data even more complicated and time consuming and some of the GPs may not have been as willing to participate if required to supply additional data.

Future use of more sophisticated computers and computer software in general practices should facilitate better recording of patient information and easier electronic transfer of data. This could prevent GPs having to put unnecessary time and effort into manually recording the necessary information and would therefore limit finances otherwise incurred to pay for their participation. Those responsible for maintaining computer patient medical records in general practices should be able to add extra information specially for research purposes with relative ease, such as consultations

where no prescription was issued and if prescribed medication was hospital-initiated. It should also be possible to have access to complete current medical histories to patients' to enable a more accurate assessment of rational prescribing as well as confirming whether patient referral was necessary. One major advantage would be that inclusion of information such as the drug dosage, formulation, strength and duration of treatment would enable use of internationally accepted Defined Daily Doses (DDDs) as a unit of comparative drug utilization measurement. Should information on consecutive patient consultations still have to be manually recorded then arguably the most desirable piece of additional information would be the duration of treatment. Knowledge of this together with the other fields of information recorded in this study would still enable measurement of DDDs and would not require much more effort on the part of GPs alongside coding, data entry and data analyses.

Finally for a comprehensive drug utilization study, it would be necessary for OTC medicine use especially deregulated medicines, to be included.[436] To facilitate such an investigation on a wider scale, increased compatibility and standardisation of computer software are needed with internationally recognised measures of patient outcomes.

8.4 PRACTICAL CONSIDERATIONS

8.4.1 The prescribing study

There were indications that in some countries marked changes did occur whilst virtually no changes were found in others. Three generic indicators were used to measure the prescribing performance and issues around these will be discussed in turn.

With respect to concordance with the European Formulary for overall prescribing, there was found to be a highly statistically significant difference in the movement towards the Formulary by the study group compared with the control group, although this difference of a 4.2% swing may appear modest. The concordance levels between countries varied between approximately 35% in Portugal and 60% in England but are likely to be an overestimate of the true concordance for the reasons previously explained (Section 3.1.3.11). This was lower than anticipated as one of the aims of the Formulary was to provide appropriate treatment for a minimum of 90% of patients with common conditions requiring a drug prescription. One regional formulary in Scotland (Grampian

Formulary) has reported up to 90% concordance[132] by its users, although the study did not measure the concordance of drugs linked to their appropriate indications. There are several reasons for the poor relative performance of the European Formulary. Firstly, the reason for the higher concordance level with the Grampian Formulary was because it was neither developed nor intended for use on a geographical scale comparable to that of the European Formulary. Secondly, general practice formularies are usually tailored to local requirements, for example to reflect regional differences in antibiotic sensitivity, whereas the European Formulary, intended for use over such a large geographical scale, could not easily adapt in that way. Thirdly, the Formulary and Appendix were not translated into all the different languages of the project countries but distributed in English and this would have presented a major barrier in its use to some GPs. Fourthly, the average percentage of presenting diagnoses in each country covered by the European Formulary was lower than 70% everywhere confirming that the content of the Formulary was deficient in some areas. Fifthly, the average levels of diagnoses covered by the Formulary per country were higher than the average drug concordance levels suggesting that either the Formulary was too restricted in the drugs that were recommended and/or a proportion of the GPs prescribing was inappropriately outside the Formulary recommendations.

With the more specific drug and diagnostic areas investigated in this thesis there was a more definite link of drugs prescribed with their indication and consequently the concordance levels were more accurate. Comparing these levels between the countries revealed that prescribing in the UK regions was consistently more in line with the recommendations of the European Formulary in all the areas investigated except in the prescribing for hypertension where the concordance levels were relatively low everywhere. As a result of these higher concordance levels, there was less scope for improvement by UK GPs compared with those from the other countries and as a consequence there were more notable trends (some statistically significant) towards increased use of the Formulary by the Belgian, Italian and Portuguese GPs in particular.

The second main prescribing performance indicator was the diversity of prescribing and there was found to be a highly significant reduction in the range of drugs prescribed after the educational intervention between the study and the control group overall. Spain recorded the highest average range and this still remained high in Phase II even

though the Spanish GPs recorded only half the requested number of consultations resulting in a prescription. Other countries with a high recorded range included Portugal, Italy and Belgium. It is postulated that differences in the range of drugs prescribed by the GPs in the different countries could be due to three principal factors. Firstly in some countries, where the number of drugs available on the market is high there is likely to be more choice of both combination and single entity products.[16] Secondly, the total number of active drug entities recorded and coded in the data would inevitably increase as a result of more combination products being available and used in Belgium and southern European countries. Thirdly, in English speaking regions GPs have already been encouraged to use fewer combination products in the promotion of better prescribing.[279]

The higher the range of drugs used, the greater is the diversity of prescribing which is also usually indicative of both poorer quality[242] and even potentially 'dangerous' prescribing.[437] However, this indicator of prescribing is dependent on the number of consultations; the lower the number of consultations, the higher in proportion the range is likely to be and this can be seen in the Spanish data from Phase II. Within the areas investigated in this thesis, the English, followed by the Scottish and then Northern Irish GPs prescribed from the smallest ranges of drugs. Therefore the Belgian, southern European and to a lesser extent the Irish GPs again had more scope to improve in their prescribing practices compared with the GPs from the UK regions. After the educational intervention, positive changes with respect to prescribing from a smaller range were especially evident in Belgium.

The third main indicator measured was the percentage of doctor-patient consultations which resulted in a prescription. This was found to be higher in southern European countries than elsewhere which compares well with published OECD data[250] which indicates that there is a relatively higher number of prescription items per person in these countries than in northern Europe. One of the main reasons for these differences is likely to be associated with the duration of patient-doctor consultations. For example, GPs in Spain are known to have characteristically short patient consultations[266] where there may be a strong tradition of terminating a consultation by issuing a prescription. In English speaking regions, there are relatively longer doctor-

patient consultations resulting in less priority being given to the issue of a prescription but a greater emphasis placed on patient counselling. In open access health care systems such as in Belgium where GPs are paid a fee-per-service, due to greater competition between doctors there is more pressure on satisfying the patient. This is likely to increase the percentage of doctor-patient consultations which result in a prescription and although this aspect could not be measured from the Belgian data, comparing the average number of prescriptions per capita from countries with open access health care systems from OECD data supports this argument.[250]

In the areas of UTI, throat infection and LRTI prescribing, there was a marked decrease in the use of co-trimoxazole in both the study and control groups from Phase I to Phase II. The prescribing of co-trimoxazole was strongly discouraged by the European Formulary but during the early part of data collection in this study the UK Committee on Safety of Medicines also issued a cautionary warning about the sulphamethoxazole component.[438] Which of these two medicines had the greater impact on the GP prescribing in this respect in this study is difficult to determine. However, this does prove that the European Formulary was right up-to-date in its advice in this area and that in principle its potential for influence was appropriate but that the study limitations may have reduced its impact.

General factors which contribute to differences in antibiotic prescribing are regional drug sensitivity data and regional price variations. As previously mentioned (Section 8.2.1.1), for the third-line management of UTIs, the European Formulary Group were forced into recommending consistent prescribing of the most cost-effective fluoroquinolone in a country instead of specifically naming one. Despite this, the message to constrain fluoroquinolone prescribing did not appear to have any impact as their use varied from over two-thirds of newly prescribed antibiotics for UTIs in southern European countries to less than 10% in the UK.

From the prescribing patterns that were recorded for throat infections and NSAIDs, the educational intervention appeared to have some success. Importantly, there was a highly significant increase in simple analgesic use by the intervention group compared with the control group in both areas of prescribing. However for throat infections, there were inappropriately high levels of amoxycillin used particularly in Ireland, Italy,

Portugal, Scotland and Spain and this is indicative of irrational prescribing. For NSAIDs, it appeared that the European Formulary only covered about 60-65% of the diagnoses for which these drugs were prescribed and therefore with this shortcoming, the Formulary could only ever expect to have limited success in changing prescribing practices. The intervention appears to have had a mixed impact on the prescribing for LRTIs and little impact on the prescribing for UTIs.

The areas of hypertension and asthma were also investigated to determine whether receipt of the European Formulary alone may have any impact on prescribing. The study found that the 'passive' dissemination of the Formulary and thus receipt of written material alone appeared to have virtually no impact on the prescribing for either condition, compared with the 'active' verbal communication by the co-ordinators about the rational prescribing of antibiotics and NSAIDs. Other researchers have also reported that printed material has limited success in isolation and that there is a need to reinforce this with other methods of education and communication such as by face-to-face interaction.[154,439] Interventions involving feedback associated with practitioner performance has been found to be particularly effective[439] but due to the volume of data and only one researcher employed full-time on the study, this was not possible. There were limitations with the two therapeutic areas selected when assessing the 'passive' effect of the Formulary. For example, despite hypertension being the most commonly occurring diagnosis and almost exclusively managed by GPs, the number of newly prescribed antihypertensives were so small that all the prescription categories had to be combined when measuring the effect of the Formulary. With the asthma data, again all the prescription categories were combined as the number of newly prescribed items were relatively low. Also, there are problems with GP-labelled asthma and hypertension, for example it was suspected that where some patients consulted for treatment of an associated co-morbid condition, occasionally subsequent treatment was just recorded under a label of either asthma or hypertension.

Medicines are obtained by consumers within different health care systems via a variety of routes. As more medicines are being switched from prescription only to non-prescription status in different European countries[18], patients are being encouraged to visit the pharmacist before seeking the advice of the general practitioner.[440] As a

consequence, there is evidence to suggest that OTC medicine use is increasing.[440,441] In the NSAIDs results section, diclofenac was the most commonly prescribed but it is not known whether for economical reasons prescribers were recommending the use of OTC NSAIDs and/or other medicines to patients in some cases. Thus it is not possible to assess what impact the educational intervention may have had on the increased consumption of OTC simple analgesics and NSAIDs. With the range of OTC NSAIDs available in different European countries (Table 8.1 overleaf), it is likely that inclusion of this data would have altered the NSAID utilization patterns.

Table 8.1 Non-steroidal anti-inflammatory drug status in different European countries[18]

Ingredient	France	Germany	Italy	Netherlands	UK
Diclofenac (oral)	+	Rx	+	Rx	Rx
Etofenamate (topical)	N.R.	+	+	N.R.	N.R.
Ibuprofen (oral)	+	+	+	+	+
Ibuprofen (topical)	+	+	+	+	+
Ketoprofen (topical)	+	+	+	+	+
Naproxen (topical)	N.R.	Rx	+	Rx	N.R.
Piroxicam (topical)	Rx	+	+	Rx	+

+ = Available OTC, Rx = Prescription-only, N.R. = Not registered or not marketed

Another important factor which may explain differences between the countries is that health care professionals in English-speaking countries have the added advantage of a relatively long history of prescribing support both at a local level and nationally in comparison to most other European countries.[4] These include:

- well established drug formularies,[6,78,80,81,]
- the production of monthly information bulletins such as the Drug and Therapeutics Bulletin, the MeReC Bulletin and Bandolier which review the cost-effective management of topical therapeutic areas,
- the provision of regular feedback in the form of PACT data to GPs on their prescribing practices,[40]
- a network of prescribing advisers which attempt to contain prescribing costs,[51,63]

- pharmacists, in recent years based in GP practices reviewing prescribing.[102]

All these initiatives attempt to increase the awareness and knowledge of the prescriber with the intention of rationalising prescribing and containing prescribing costs. The higher concordance with many of the drug recommendations of the European Formulary probably echo messages previously given to the GPs in the English speaking regions in the study. Drug regulation in the UK is under stricter control than Belgium and the southern European countries which is reflected in the narrower range of more effective and safer drugs licensed in the UK for a given condition. Finally, health care professionals in English-speaking countries have the added advantage that the most international reputable journals are all primarily published in the English language. These factors are likely to have increased the extent to which drug choice was more in agreement with the European Formulary by GPs in the UK and to a lesser extent in Ireland.

Whilst other European countries explore the potential for adopting some of these initiatives, the effort devoted to optimising the cost-effectiveness of the health care service in the UK continues unabated. Advances in the use of information technology in the UK have enabled electronic PACT data (ePACT) to be available via an electronic link directly form the Health Authority to the individual GP practice.[32] This electronic PACT data provides a breakdown of GP prescribing profiles down to individual drug level for analytical and comparative purposes and it can be provided on a monthly basis. In 1997 an on-line version of the BNF became available. This has the added advantages of being easily accessed in the doctor-patient consultation as well as in the pharmacy and facilitates regular update of the text compared with the printed version which is produced every six months. In 1998 the PRODIGY project was launched in the UK.[171] This system provides the GP with a software program providing decision support for which drugs to prescribe, based on the evidence of efficacy, safety and cost. This project was based on a study in the Netherlands called PRESCRIPTOR[166] which was terminated due to limited success there. Results from the PRODIGY project to date appear to be positive but this in-part has been as a result of the heavy financial backing by the DoH in the UK.

The last few years has seen a change both in the way information is disseminated and in the way we communicate. Today most of the reputable sources of health related information are available on the Internet either freely or accessible via subscription. To help push forward the boundaries of health care practice in primary care in the new millennium, the DoH in the UK has developed the NHS intranet as a medium of communication and information access and strives to have all GP practices on-line in the near future.[6] In order to improve the effectiveness of medicines management and to promote more rational prescribing, the NHS intranet may allow pharmacists and general practitioners to have access to each others relevant information while maintaining patient confidentiality. The Royal Pharmaceutical Society of Great Britain has set up a working party looking at the use of computer technology in primary care with the view to the standardisation of all general practice and pharmacy systems.[442] This would allow interchange of data between pharmacies, general practice surgeries / health centres, the Prescription Pricing Authority and preferably hospitals. Such a system could eliminate the paper-based prescription form. The implications of this technology for future studies of this nature are that the data may be directly downloaded from computer systems, eliminating the time-consuming process of data recording, collection, coding and subsequent entry.

To achieve this level of sophistication on a Europe wide scale, many hurdles need to be overcome starting with an agreed drug and morbidity classification system, followed by accepted tools which can measure rational prescribing adequately. Five years ago, it was estimated that in the UK every 1% reduction in prescribing costs would release £34 million to spend on other aspects of health care.[30] It is first necessary to know more about patient health outcomes, including how quality of life factors, can be suitably measured to assess whether more rational prescribing has been achieved. These factors are becoming increasingly important and need to be recognised in the future development of drug formularies.

Some important international collaborative developments in the field of drug utilization have taken place and continue to do so. The World Health Organisation Anatomical Therapeutic Chemical (ATC) and the Defined Daily Dose (DDD) coding systems were establishment nearly 30 years ago and undergo continuous updating.[229]

The ATC classification and the DDD methodology have become widely accepted on an international level and their use includes drug consumption statistics; monitoring of adverse drug reactions; drug catalogues and reimbursement schemes.[443] Even in the UK where the Read Code classification system is institutional[253], DDDs as a unit of measurement are being increasingly adopted by health authorities. While each country has its own regulatory body, in 1995 an EU Directive has provided pharmaceutical companies with alternative procedures for obtaining marketing authorisations through a centralised procedure or Mutual recognition which has resulted in the opening of the European Medicines Evaluation Agency (EMEA) whose aims include the facilitation of the free movement of drugs within the European Union.[444] More recently, there has been a move to standardise international drug nomenclature[6] which would also facilitate the further development of a European Formulary. European legislation now requires the production of standardised patient pack medicines which should contribute to better patient concordance with treatment.

Drug consumption can be expressed in a variety of ways including cost, volume, prescribed daily dose and defined daily dose.[229] In this thesis, all analyses are concerned with the number of drugs (or the active ingredients of combination products) as a measure of volume. While this is a measure of GP prescribing practice, it does not contain enough information on the volume to allow the direct calculation of costs.[229] However, measuring frequencies linked to morbidity, as has been done in this research is of value as it provides descriptions of prescribing patterns[229] and measures certain aspects of rational prescribing, which are indicators of cost-effectiveness. As mentioned earlier, this thesis lacks information on outcome data with respect to efficacy and safety of GP selected drugs in individual patients. Outcome measures, including patient concordance with drug regimens as well as any differences between drugs prescribed and drugs actually dispensed, would have been invaluable. In an ideal situation, measuring patient-centred indicators, such as the rate of relief of symptoms in those with acute self-limiting diseases, would be valuable in relation to the effect of formulary implementation. The face-to-face patient consultations in general practice which were recorded in this study were not necessarily fully representative of the population at large, which makes comparisons difficult with those from different studies as well as

with different national morbidity data sets. Consequently, reviewing the literature to identify appropriate quality indicators compatible with the data set has also proved difficult.

8.5 THEORETICAL CONSIDERATIONS

The second study involved the same GP participants who provided information on factors perceived to influence their prescribing to help explain some of the findings in the first study.

8.5.1 The Delphi prescribing influences study

The second major hypothesis postulated that: *explanation of the varying effects of the European Formulary and the educational intervention in the different countries will be assisted by identification of the main influences on the participating GPs' prescribing.*

8.5.1.1 The effects of the European Formulary and educational intervention

The educational intervention involved three different types of potential influence.

- The distribution of the Formulary to all the GPs in the intervention group.
- The distribution of parts of the Appendix associated with the areas specifically being targeted in the educational intervention to all the intervention group GPs.
- Verbal discussion between the co-ordinators and their intervention group GPs which involved debating the main messages of the educational intervention.

From the prescribing study, there were two general main findings. **Firstly**, some aspects of the intervention appear to have been successful in certain countries and **secondly**, analyses of the collated data revealed that there were wide variations between countries in presenting diagnoses / symptoms and drug prescribing patterns. Consequently the following three questions were raised:

1. What are the reasons for the variable effects of the European Formulary and the variations in prescribing patterns?
2. Are the differences in health care systems between countries, in particular the drug regulatory factors, responsible for the variations in prescribing?
3. How far can the drug and diagnosis data be critically compared and contrasted when it represents a snapshot of prescribing at a limited point in time?

To help explore these questions, it is necessary to consider what information was already available.

From the literature review on health care systems across Europe (Annex 1), it is known how care is co-ordinated in each country. In Belgium, an open access system exists where there is no patient registration with GPs and the patient has a free choice of GP or specialist (the latter may also work as a GP in their spare time). In the remaining participating countries, a gatekeeping system exists where GPs control access to most other levels of health care. The type of health care system has implications for prescribing research. Where there is greater competition between doctors, such as in an open access system, one would expect that the pressure to satisfy patients needs is greater, one consequence of which is that there may be a high number of patient consultations that result in a prescription. One may also expect there to be a lower patient referral rate by GPs in this type of system where doctors are generally remunerated on a fee-for-service basis because of the resulting incentive to provide as wide a range of services as possible in primary care.[445,446]

Between countries there may be differences in drug availability and the market authorisation of drugs may also change over time. These factors have been traditionally determined by the regulatory bodies within a country whose actions are dictated by health policies and national legislation although since the establishment of the EMEA[444], this is now changing. Government health policy also largely dictates the nature of a countries' health care system and consequently there are differences in per capita spending on health care as well as differences in the percentage of Gross Domestic Product (GDP) spent on drugs and health care between countries.[250] While these issues are likely to contribute to variations in prescribing patterns between countries, up to 80% of patients consulting GPs have common conditions which can potentially be treated in standard ways.[30] In addition, all the drugs recommended in the European Formulary were available in all of the participating countries which could help to limit the problems of GPs faced with different drug choices from country to country.

However, it is important to recognise that the intervention in this study was an educational/information-type of influence as distinct from the multitude of other factors which potentially influence GP prescribing behaviour.

8.5.1.2 The main influences on GPs prescribing

The factors that influence the prescribing-decision making process have been discussed in (Section 2.2). There appear to be no published reports of research which have investigated the factors perceived to influence the prescribing practices of a pan European group of GPs. Also, there does not appear to be anything published on how GPs rate the perceived importance of different prescribing influences, with the exception of GPs having rated their use of different information sources.[156]

Within a country, health care system/regulatory influences are generally going to be standardised but largely out of the control of the GP. Between countries these factors will be much more significant and should help to explain the differences.[447] Consequently for the purposes of undergoing an investigation of perceived influences on GP prescribing between countries, I propose that they could broadly be divided up into health care system/regulatory influences and those independent of this. Alternatively, this can be described as influences which GPs are potentially in control of and those factors which are outside their control. If the majority of GPs perceive health care system/regulatory factors to be amongst the most important influences, then the value in critically comparing and contrasting prescribing data between countries is limited. Whereas if the converse is found and health care system/regulatory factors are found to be of minimal importance, then this coupled with the equal availability in all the countries of drugs recommended in the European Formulary means that critically evaluating all the prescribing data can be justified.

8.5.1.3 Conclusion

The main hypothesis for the prescribing influences study could neither be proven nor disproven. Attempting to establish a causal relationship by statistically correlating the findings from the two-stage Delphi questionnaire exercise with the GPs drug and diagnosis data from the previous study was not advised because of differences in sample

sizes between countries and the volume of prescribing data per individual GP not being large enough.

8.6 METHODOLOGICAL IMPLICATIONS

8.6.1 The Delphi prescribing influences study

The first stage prescribing influences questionnaire was successfully completed by 173 GPs, representing a response rate of 72% and the second stage Delphi questionnaire achieved an overall response rate of 64% (154 GPs). These were considerable achievements as response rates to questionnaire surveys among general practitioners are declining.[448] This study was original in obtaining a consensus-based list of categories of influences ranked in order of perceived importance.

In order to minimise bias and due to the countries having markedly different health care systems, an appropriate method of data collection had to be used in order to obtain information on the perceived factors influencing the GP participants prescribing. When selecting the method used, the exceptional geographical spread of the GP participants had to be recognised and taken into account. By using questionnaires, as well as perceived influences on prescribing, information on other factors known to be an influence, such as the demographic profiles and the working environment of the GPs, could also be obtained simultaneously. Collecting this wide ranging information by face-to-face interviews with the GPs would not have been feasible for a variety of reasons, including lack of finances, language barriers and time factors as well as the difficulties associated with follow-up interviews. Verbal communication with each GP via the telephone would not have been practical either, principally because of the language barriers.

In the development stage of the first questionnaire, initially a four page questionnaire was developed. This needed to be validated and so was piloted among 20 university researchers in the Department of Primary Health Care (Newcastle University Medical School). Following some amendments another pilot was performed, on this occasion being distributed to the European Formulary GP participants from the Newcastle region. Subsequent to this process, instead of attempting to require the GPs in the different European countries to complete the questionnaire with sentences in

English, it was designed with closed questions answered by ticking boxes, or numerical or one word answers with the exception of one open-ended question. To avoid the problem of language barriers, the questionnaire needed to be translated, which it was thought would increase the likelihood of questionnaires being completed and hence the response rate. By reducing the length of the questionnaire and condensing it to fit onto one page of A4 paper, it was anticipated that this might optimise the response rate but consideration had to be given to ensure that some important questions were not lost.

In order to determine the amount of time the GPs invested in primary care, the GPs were asked the number of days they worked each week. This was considered to be a relatively crude measure and so the question was amended to ask how many hours a GP worked each week. From the two pilot questionnaires it was also thought that by introducing a list of potential influences for GPs to rate, there could be an element of bias as this could possibly lead GPs in a certain direction. Additionally by presenting GPs from different health care systems with a predetermined list of influences developed in the UK, this would be likely to be associated with a UK health care perspective and thus could bias responses too. Ultimately it was decided to ask the GPs what they perceived to influence their personal prescribing and then, in order to establish consensus agreement on these perceived factors, it was decided to adopt a two-stage Delphi technique as effectively used by others.[264,449]

The refined prototype questionnaire required translation into Dutch, French, Italian, Spanish and Portuguese. Due to the specialist nature of the questionnaire, translation ideally needed to be performed by individuals with the relevant knowledge of the appropriate health care practice terminology. This was made possible by my approach to a number of pharmacists and physicians independent of the research at an overseas conference who co-operated and performed the initial translations. The relevantly translated questionnaire was subsequently sent to the appropriate co-ordinator (from the previous prescribing study) in each country for back translation as has been done with other international questionnaire studies.[333] Obtaining accurate translations was important as this had been a major limitation to the implementation of the European Formulary. The process also enabled confirmation of the appropriateness of the terminology used and the relevance of the questions in the context of primary care in the different countries. For example, the terms 'fundholding' and 'non-fundholding' were

irrelevant as these were only applicable in the UK and 'family doctor' as opposed to general practitioner is the standard terminology in Portugal. As GPs may either not realise or may not be forthcoming about disclosing the extent of the influence of the pharmaceutical industry upon their prescribing, an additional question was considered necessary. This question asked the GP how many industrial sales representatives he/she had met up with in the past four weeks.

The second stage questionnaire, to be completed by the same GPs, was based on the responses to the open question in the first questionnaire regarding perceived influences on their own prescribing. These responses had been translated where necessary. From the responses to the open-ended question 86 different influences were cited by the GPs. From this list, there was some degree of overlap and the list was condensed to 59 factors under seven category themes of influence which were identified. In the second stage Delphi questionnaire, the GPs were supplied with the composite list and had to rate the seven categories of influence in order of decreasing importance.

If the study had only involved GPs in the UK, a category heading related to hospital influences would have been appropriate and necessary. As many specialists in southern European countries are community-based, these related factors seemed to fit best under the heading of general medical practitioner factors as it is down to their clinical discretion whether, for example, hospital/specialist influences are adopted or not. Although the different influences were classified under the most appropriate category headings, this process was not entirely precise. For example, whilst hospital/regional/national and international formularies were all classified under the education/information factors category, a practice formulary was considered to be more of a work-based factor associated with practice policy and prescribing protocols despite being a means of education and information. There were also some subtle differences of emphasis between various factors such as the cost of a drug which was classed as a 'drug factor' but a GPs drug budget was a 'regulatory factor'. Some influences were specific to certain countries such as, the presence of a practice pharmacist in the UK. Nevertheless, it was considered that all the categories contained factors which had some degree of influence on prescribing in any country and therefore the GPs were asked to rate the seven categories in order of importance.

The entire list of influences were what the GPs themselves perceived to influence their prescribing and so it was possible that it did not necessarily encompass all the factors that could be said to be influential. For example, there was no mention of cultural or media influences and whilst many GPs referred to the safety, side-effects and tolerability of drugs, there was no mention of drug interactions being a perceived influence. A few GPs did mention polypharmacy prescribing being a potential influence and this could be associated with drug interactions and/or patient compliance.

Translations of the standard cover letters which were mailed with the questionnaires and the reminder letters sent to non-responders were also made by the co-ordinators. As the second stage Delphi questionnaire only consisted of one question (related to the open-ended question from the first questionnaire) no back translation was considered to be necessary. With no financial incentive for the GPs to complete the questionnaires, an appreciative feedback in the form of a six page summary of the main prescribing study was mailed to all participants and the cost of the return postage for the questionnaire was included.

All these various procedures were performed as it was necessary to produce standard questionnaires and to optimise the response rate in order to best fulfil the proposed aims and objectives (Section 3.2.1) of the study.

8.6.1.1 Limitations

This study involved identifying the perceived prescribing influences on the GP participants from the previous study but as already mentioned the volunteer nature of the GPs meant that they were not representative of the populations from within their countries. However, while future studies should if possible obtain random samples of GPs, the primary purpose of this follow up study was an attempt to explain some of the findings from the former study.

This two-stage Delphi questionnaire study was mailed between August 1998 - February 1999, four years after the initial prescribing data collection period. This was potentially problematic in that the GPs were asked to list the main perceived influences to have acted on their prescribing from Autumns of 1994 and 1995 when they recorded the prescribing data. There may have been an element of recall bias here, especially as

health care practice changes and reforms are constantly taking place which can affect prescribing behaviour. For example at the time of initial data collection, generic prescribing was not practised in Belgium, Italy, Portugal and Spain. Since that time it has become possible for GPs in all four countries to prescribe a limited number of medicines generically.[18,266]

In the Delphi research model, it is recommended that initial and follow-up questionnaire mailings should be sent out at precise six weekly intervals in order to allow adequate time for responses while maintaining the momentum of the study.[264] The timescale of this Delphi exercise had to be extended because of the geographical distance involved and extra time for postal delivery and return of the questionnaires and reminders.

When questioning the GPs about the number of hours worked and patients seen in one week, there could have been discrepancies in GPs working part-time, home visits as opposed to office-based consultations and those working on-call. In order to obtain an indication of the amount of time invested by GPs and their workload, this question had to cover all these aspects of primary care as it was not practical to ask about each area due to the restricted length of the questionnaire. As doctor-patient consultations in Belgium tend to take place in peoples' homes, office-based consultations do not exist in the same way there as in other countries and so a general question was of more relevance.

Although the overall response rate from the first questionnaire was 72% and from the second stage it was 64%, which was highly acceptable, not all countries achieved these levels. Portugal, Spain, Scotland and Italy were below 70% in stage one and Portugal, Spain and Scotland were below 60% in stage two. It is feasible that information on non-responders from these countries could have affected the results. One possible reason for a lower response rate in Spain was that although the questionnaires were translated into Spanish, all the participants were actually from the Catalan region which has a different language in everyday use. Although bilingual, the GPs may have been more receptive to the questionnaire if it had been translated into the Catalonian language. In Scotland, it was only possible to obtain the contact name of the senior partner in each of the practices from where GPs had been recruited in order to

preserve anonymity. As it was not possible to write personally by name to the Scottish GPs, this seems to have adversely affected the response rate, despite enclosing the necessary numbers of covering letters, questionnaires and stamped addressed envelopes.

8.7 PRACTICAL CONSIDERATIONS

8.7.1 The prescribing influences study

From the first questionnaire, it was evident that the majority of GPs in the different countries were working in group practices, with the exception of practitioners in Italy and Portugal. The published information available which compares the style of practice in different countries[219,445,450] corresponds well to that found in this study, except for Belgium and Spain. Inevitably the nature of practice is liable to change and evolve with time and this can affect comparisons with earlier data. These differences are often dependent upon a variety of factors including the type of health care reforms within a country, the locality of the practice and the age of the GP. In Spain for example, there used to be a fairly even mix of solo and group practices but, as a result of health reforms in the early-mid 1990s[266], there was a move towards a network of primary care health centres with GPs working in groups. This trend could explain the anomaly between previous reported levels and the fact that all the Spanish GP respondents were working in groups. In countries where there is a mixture of solo and group practices, the solo practices are more likely to be found in rural settings such as in Ireland, where the population is more scattered and therefore smaller for a given distance, when compared with more urban areas.

The work place distribution of the GPs was likely to be influenced by the location of the majority of co-ordinators who were based in towns or cities, as earlier communication with the co-ordinators had indicated that one of the criteria for GP selection was geographical convenience for them. This fits in well with the questionnaire responses where half the GPs described the location of their practice as urban. The GP participants were all volunteers and associated with the fact that they were enthusiastic and likely to be more informed than the average was the finding that in all the countries except for Italy, Northern Ireland and Portugal, the majority were involved in training doctors to become GPs.

Analysis of the age of the patient populations consulting GPs in the different countries confirmed that all the Spanish GPs and almost 20% of the Italian GPs did not have patients under 14 years of age. This is likely to influence GP prescribing patterns, especially in terms of the prescribing volume for treating conditions often presenting in children, such as acute respiratory tract infections.[35] The fact that children are seen by GPs in some European countries and not in others is indicative of fundamental differences in health care practice between countries in the management of children in primary care.

Comparing the GP workloads revealed that the average number of hours worked per week was greatest in the English speaking countries and Belgium and lowest in the southern European regions. At the extreme, the average number of hours worked in Ireland was more than double those in Italy. This could be subject to a number of variables such as the number of GPs working part-time and it is not known whether the number of hours worked included home visits and time spent on-call. The mean number of patients seen in one week by each of the GPs in the different countries is fairly similar except in Ireland, but this correlates to the higher number of reported hours worked there. Comparing the ratio of hours worked to patients seen suggests that there is a greater number of patients seen by GPs in Italy and Spain during their working week i.e. shorter consultation times. The lowest number of patients seen for the hours worked occurred in Belgium which may be associated with the perceived need to retain patient loyalty in the absence of a patient registration system and to ask questions otherwise previously recorded in a registration system.

The duration of the consultation has been proposed as a simple proxy measure of quality of care.[211] Longer consultations have been found to be more thorough and relevant to the patients needs and those GPs who allow 10 minutes or more for each consultation have been found to prescribe less antibiotics. From the data collected, the mean duration of the consultation in the different countries was found to vary widely. The average Belgian patient-doctor consultation lasted over twice the length of consultations in England, Northern Ireland and Spain. Although the figures in our study indicate that the consultations were much longer than previously reported data from these countries[219,445,450], the relative positions of the countries in comparison with

each other are similar. Belgium is the only country in the study with an open-access health care system with no patient registration and consequently patient consultations may tend more often to incur GP visits to patients homes, resulting in longer times spent with patients than office-based appointments. GPs in open access systems are paid on a fee-per-item basis and so there is a tendency to provide a wider range of services in primary care which may also lead to longer consultations. Currently, there is a surplus number of doctors in Belgium and this may be associated with additional pressures to satisfy patients with consequently longer consultations. In contrast, the Spanish GPs reported relatively short average consultation times and thus a high number of patients were seen by GPs per week during their time spent in primary care. Also, in northern European countries there may be more of an emphasis on patient counselling and thus longer consultations than the norm in southern Europe. Such time constraints are also likely to result in greater use of the prescription to terminate the consultation as confirmed by others.[30] These factors may all contribute to influencing the characteristics of prescribing and prescription volume.

Within the UK, research has found that more highly qualified groups of doctors are not as greatly influenced by commercial sources of information as their less qualified colleagues.[156] However it may be that the system for progressing to post-graduate qualifications is closely associated with the medical culture within a particular country. Therefore, this may not necessarily be exclusively either a reflection of the knowledge base or motivation of GPs, or be indicative of the extent in any other country of continuing education opportunities available to practitioners. Nor may it be related to the fact that older GPs will have had more time to obtain post-graduate qualifications. Nevertheless in this study, the highest number of qualifications were recorded by the English speaking GPs and may be compared with the southern European GPs who met a relatively high proportion of drug representatives on whom they presumably relied as a routine source of drug information. The number and frequency with which GPs meet pharmaceutical industrial representatives is likely to be an influence on some aspects of prescribing practice. Research has shown that the more drug representatives who are seen, the greater the likelihood of prescribing more newly introduced drugs and the wider the range of products that a GP is likely to prescribe than otherwise (Section 2.2.8). There is also a tendency for those GPs who see drug representatives

regularly to be older and in single-handed practices. Attempting to statistically correlate these published findings with the GPs and their prescribing data in this study was not possible because of the sample sizes and the volume of data available.

In the second stage of the Delphi questionnaire, of the seven categories of influence, there was sufficient consensus between the countries to establish a structured order from the category of most importance to the category of least importance. The rank order reflected some of the findings from the first stage questionnaire which reinforced its validity. For example, whilst six of the eight countries indicated that pharmaceutical industrial influences were the least important category, the Italian GPs considered that work-based factors were least important and the Portuguese regulatory factors. Work-based factors are mainly associated with health care professional interaction and, as all but one of the Italian GPs were single-handed, it is not surprising that this category was perceived to be the least important prescribing influence. Also, the relatively high number of drug representatives seen by Italian and Portuguese GPs explains why they perceived industrial influences to be of more importance than elsewhere.

Probably the most revealing finding from the second questionnaire was that, regulatory factors were considered to be the least important category in Portugal, the least important category but one in five other countries and ranked in fifth position in Ireland and Italy. This is of professional significance and importance because GPs are capable of controlling the majority of influences within the remaining categories which may affect their decision making. The critical evaluation of prescribing data between these countries from this perspective is thus justified.

In summary, identification of the main influences on prescribing has assisted discussion of prescribing behaviour and highlighted difficulties which have affected the uptake of the European Formulary and the associated educational intervention in the different participating countries.

8.8 RECOMMENDATIONS

From the research which has been conducted, the following list of recommendations are made.

- Any future edition of a European Formulary should be translated into different European languages and would be more credible if its development process shifted from consensus-based to evidence-based.
- Different international drug and diagnosis classification systems do exist but all have limitations and consequently specific coding systems were developed for this research. In future international agreement would be beneficial in order to standardise research methodology and facilitate comparisons between studies.
- Any future educational intervention of the type conducted in the prescribing study would need to be better standardised to reinforce the educational material in order to facilitate comparisons of the outcomes.
- GP prescribing patterns were found to vary widely in this research (despite the majority of doctors being volunteers having an active interest in prescribing) which suggest that there is a definite need for international evidence-base guidelines.
- In order to optimise the analysis of future drug utilization and prescribing studies, it is crucial that prescribed drugs should be linked to patient morbidity.
- Prescribing quality indicators need to be developed further to include patient and treatment outcomes (quality of life etc.) and they also need to be linked to morbidity.

- A future European Formulary should place more emphasis on the use of equivalent drugs depending on availability and the comparative cost in a country (e.g. hydrochlorothiazide in most European countries and bendrofluazide in the UK).
- The Delphi study identified that patient influences were perceived by GPs to be an important influence on prescribing. One avenue for future prescribing interventions should be to improve patient education.
- A greater use of independent sources of drug information should be encouraged in southern European countries where GPs reported relatively high contact rates with pharmaceutical industry representatives compared with their northern European colleagues.

In making these recommendations it is acknowledged that the influences on the prescribing process are multifactorial and the potential influence of a European Formulary should be seen in that context.

8.9 FUTURE WORK

The research in the prescribing study has concentrated on comparing and contrasting prescribing patterns as well as attempting to improve aspects of prescribing. The latter has involved assessing the prescribing performance by using a variety of measures including, the level of concordance with the European Formulary and the range of drugs used. Future research needs to involve international collaboration to establish accepted outcome measures for assessing rational prescribing which can be converted into quality indicators, such as the optimum range of drugs that a prescriber should use to treat a condition. They need to be produced in all therapeutic areas incorporating prescribing for both acute as well as chronic disorders and their development should also include patient outcomes, such as quality of life factors, and rational use of new drugs. In addition, they should be flexible enough to be applied to OTC drug use where appropriate as well as to prescribed drug consumption. Most importantly clear agreement is necessary on the use of a generally accepted diagnostic and therapeutic classification system. This sort of international collaboration could be co-ordinated through groups such as WONCA (World Organisation of Family Doctors) and FIP (International Pharmaceutical Federation) and the WHO.

Once developed, internationally agreed quality indicators could be used to assess just how successful different types of interventions are in inducing changes in prescribing habits. GPs recruited to future research studies should be consulted over which areas of their prescribing they would like to see improved and/or identify those areas where evidence-based guidance is lacking. Studies should encompass GPs from a variety of European countries to determine the level of success of different types of intervention (including the effect of an internationally accepted formulary available on the world wide web) as well as to identify whether interventions are more successful in those with gatekeeping or open access health care systems.

The two-stage Delphi questionnaire study has compared what GPs perceive to influence their prescribing in participating countries. To compliment this study, it would be very useful to determine to what extent patients in different countries expect to receive a prescription as well as the expectations of patients who receive prescribed medication. Although there has been some research on this in the UK[202,207], by

comparing patients' expectations in the different countries, cultural influences on prescribing could be better identified.

Of the different categories of influence rated by the GPs, patient factors were cited as one of the most important influences on general practitioners prescribing in all the countries. Further research is needed to investigate how the potential to promote rational prescribing may be affected and constructively influenced by patient influencing factors. Identification of what consumers/patients' expectations and knowledge are of OTC and prescribed medicines could help in the development of patient educational interventions to promote more appropriate and rational use of antibiotics for example and encourage greater patient participation in their own healthcare.

If a similar study were to be repeated with adequate resources, then by recruiting an appropriate sample size of GPs in different countries and with an adequate volume of prescribing data, an attempt could be made to establish whether a causal relationship exists between perceived influences and the corresponding prescribing of GPs.

8.10 OVERALL CONCLUSIONS

The first study is original in collating prescribing data in such detail from face-to-face doctor-patient consultations in primary care in Belgium, England, Ireland, Italy, Northern Ireland, Portugal, Scotland and Spain. The results indicate that there was an improvement in the prescribing practices within certain therapeutic areas by GPs after the educational intervention which included distribution of the European Formulary. These changes were mainly in increasing the proportion of prescribed drugs which were listed in the Formulary and reducing the range of items prescribed. The findings therefore indicate that some aspects of the methods employed in this study were capable of bringing about a change in clinical practice but also suggest that sustained prescribing support is essential as well as the need for innovative prescribing support in the future.

With respect to formularies, it is important to recognise that they can only have an impact in certain ways and their influence will always be affected by cultural beliefs, government policy and actions and reimbursing procedures. The variations in prescribing by GPs in different European countries are likely to be multifactorial, but can in part be explained by differences in drug availability, drug prices, marketing authorisations, medical education and training, pre-existing availability of national, regional and practice formularies, profit controls and industrial promotion. While these differences remain, the role of a European Formulary maybe partly limited. However should there be a move towards standardization in these areas, a multidisciplinary European prescribing initiative such as a future edition of the European Formulary is feasible. Future potential compilers of European Formularies need to take these factors into consideration. The present European Formulary can still serve as a reference document for the development of both future European Formularies and for national and regionally tailored formularies. The Portuguese Department of Health has confirmed that it is undertaking further trials of the European Formulary as a potential national formulary. Meanwhile interventions to improve drug utilization are most likely to be successful when pursued at local and national levels.

The second study is also original in having collated perceived influences on GP prescribing from Belgium, England, Ireland, Italy, Northern Ireland, Italy, Portugal, Scotland and Spain. The results indicate that there are differences in demographic

characteristics that can explain variations in prescribing behaviour and that there was a fairly consistent consensus between countries with respect to perceived influences on prescribing following categorisation into separate themes of influence.

While there are differences in health care systems between countries, GPs implied that the factors which are most important in influencing their prescribing are factors which are of a common professional character between doctors wherever they are in practice. This adds to evidence confirming that there is a continuing place for promoting rational prescribing through education and information such as in the development and use of prescribing guidelines, provided that such initiatives are realistic in their objectives, are executed appropriately and maintained with adequate resources.

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ANNEX ONE
HEALTH CARE SYSTEMS ACROSS WESTERN EUROPE

A1.1 INTRODUCTION

Health care systems vary widely across Europe with both public and private health facilities coexisting in all European countries. Each country's health care system has evolved not only as a result of medically related factors but greatly determined by other aspects of its society, especially its social, religious, political and economic organisation.[25] Other key influencing factors in their development include: geography, climate, and the demographic characteristics of the population.[451] The most significant influencing factors have been and continue to be national wealth (and the proportion of it given to health care) and the extent of social deprivation and inequality.[445]

This section will focus particular attention on comparing and contrasting the differences and similarities between primary care as part of the overall health care systems in the countries from where doctors participated in this European Formulary Project (including France, Germany, the Netherlands and Norway which were unable to provide adequate data for analysis). In addition, the characteristics of primary care doctors as part of the primary health care team will also be reviewed. Comparisons will also be made with the United States (US) where appropriate.

Cross-national comparisons of health care system data may be subject to distorting factors but the data referred to in this section are obtained from a range of reference sources which appear to be fairly consistent.[21] While changes in health care as a result of government interventions, for example, do occur from year to year between European countries[447], their general position with respect to one another in terms of cost and pharmaceutical consumption has remained surprisingly stable over the past three decades.[21] One important explanation for this is that the differences between European countries' prescribing patterns are based on deep rooted variations in medical culture and training rather than just the effects of contrasting price and profit controls for medicines.[25,24]

A1.1.1 Primary Care

Primary care is only a part of the entire health care delivery system, which also includes secondary and tertiary care. Before primary health care services are utilised, self-care is widely practised and it is important to recognise that in Europe, as in North America, between 80 - 90% of all health related activities, including diagnosis, treatment and rehabilitation as well as prevention and health promotion are conducted by individuals without professional advice.[452] This is substantiated by data on the volume of use of non-prescription remedies which greatly exceeds that of prescribed medicines.[418]

At the World Health Organisation (WHO) conference at Alma Ata in 1978[453], primary health care was defined as,

'essential health care based on practical, scientifically sound and socially acceptable methods and technology, made universally available in the community through their full participation and at a cost that the community and country can afford to maintain at every stage of their development in the spirit of self reliance and determination. It forms an integral part both of the country's health system, of which it is the central function and main focus, and of the overall social and economic development of the community. It is the first level of contact of individuals, the family and the community with the national health care system bringing health care as close as possible to where people live and work, and constitutes the first element of a continuing health care process.'

Alternatively, primary care can simply be defined as the most basic and most accessible form of professional health care available to the population of a country.[266] However, this definition does not encompass all the aspects of primary health care in developed countries, such as those of Western Europe where the organisation, equipment and staffing can be sophisticated and complex.

The primary care doctor, general practitioner (GP) or family doctor, although often at the centre of activities is only one of several health care professionals belonging to a multidisciplinary primary health care team network. Other primary health care professionals include: community pharmacists, dentists, health visitors, midwives, nurses, opticians and physiotherapists. The concept of the primary health care team is most developed and established in the Netherlands, Scandinavia, Spain and the UK.[266]

Primary health care can be said to involve three elements of modern health care:

- prevention of disease
- early diagnosis, subsequent treatment and/or referral
- treatment of all ailments requiring non-hospitalisation or non-specialist treatment.[266]

Problems with this categorisation arise when it is applied to different health care systems. It can easily be applied to health services in for example Italy, Spain and the UK, where patients visit a GP or another member of the primary care team who responds to their symptoms and treats their presenting problem. If their condition merits specialist care, they will then be referred to a specialist or hospital for the necessary treatment. In these countries, GPs are responsible for the patient, act on their behalf and provide co-ordination of care.

In other countries for example Belgium, France and Germany, the situation is different. The patient has a free choice of doctor or office-based specialist for their first point of contact with the system and as the patient is not registered with one particular doctor, there is less co-ordination of care. Instead of primary, secondary and tertiary levels of care, a more appropriate way to define the levels of care in these countries might be as ambulatory and in-patient care. In this situation, ambulatory care encompasses all primary care-based services as well as services from office-based specialists and hospital visits on an out-patient basis.[266]

A1.1.2 Primary care led health services

Primary health care is emerging as the focus of future health care in many developed countries, whereas traditionally the major decisions about health care provision have been made at higher levels within the system, especially where no gatekeeper roles exist. In some European countries, such as the UK, this focus is already evident with primary care groups managing their own budgets and having increased commissioning powers.[4]

Health care reforms in Italy and Spain over the past 20 years have had the effect of devolving decision and policy making power more to regions. Changes in other European countries are more gradual and continue to be so, for example in France primary care is still relatively fragmented and has little influence. In Germany, whilst the number of GPs per

10,000 population has risen since 1960, the percentage of doctors who are GPs has fallen. The financial status of doctors who are GPs is poor; doctors are paid on a per treatment basis which rewards procedures on the basis of their complexity and specialisation.[450] Doctors in Germany thus have a financial incentive to develop a specialisation of some description in order to generate a higher income level.

The main problems currently facing all health care systems world-wide are the challenges of rising expectations, escalating costs, budget limitation and an increasing proportion of older people resulting in uncontrolled demand.[454] Medical costs in 10 Western European countries rose by an average of 4.1% in real terms each year between 1970 and 1990, while real economic growth during the same period increased by only 2.7% annually.[451] In Belgium, government spending for health care increased by a staggering 45% during the 10 years since 1984.[451]

The key drivers for changes in primary health care are developments in diagnostic, pharmaceutical and surgical technology and the rising costs associated with a combination of these developments and limitless demand.[451] In the early 1990s, primary care services in the UK represented over 90% of all health care activity and yet consumed less than 19% (including drug costs) of total NHS expenditure.[455] In contrast, the provision of hospital and community health services consumed at least 70% of NHS expenditure. With statistics such as these, governments are increasingly recognising that primary care is capable of being a more cost-effective sector for the provision of health care than secondary or tertiary care. Most population health needs can now be met in primary care and this is likely to continue to increase with major pharmaceutical innovations such as treatment for gastrointestinal ulcers which previously required surgery but can now be treated and often cured with a GP's prescription. In addition, the potential role of primary care in disease prevention and early detection will possibly provide even greater opportunities to contain health care expenditure in many areas.

As the focus of health care provision shifts towards primary care, it is inevitable that there will be increased demands and expectations placed upon the GP in co-ordinating patient care. To compensate for this increased workload burden, the roles of other members of the primary health care team are developing and diversifying; for example, there is an increasing role for the community pharmacist in managing the treatment of minor illnesses, providing prescribing advice and reviewing patient prescribed medication.[4

Renewed recognition of the treating of minor ailments has been facilitated by the deregulation of the prescription-only status of selected medicines.[18] The availability of these medicines without prescription from pharmacies has helped to move the cost of treatment onto the patient.[456] Changes in the legal classification of selected medicines and promotion of self-medication by government regulatory agencies have occurred particularly in northern European countries.[418]

A1.2 COMPARISON OF HEALTH CARE SYSTEMS

A1.2.1 Health care organisation

All the health care systems in Western Europe are planned centrally by one or more government ministries. The ministry provides planning and legislative support and controls the financing of the system. Below this level, the number of layers of management and how health care is controlled are particular to each country. In France and the UK, the system is controlled centrally, subsequent layers of management are directly responsible to the ministry of health and have little independence. In Germany, Spain and Italy, the system is decentralised and national plans are implemented by independent local bodies which have a degree of autonomy and are able to pass their own legislation. In all of the systems, the health care providers are organised into national bodies which negotiate pay levels and lobby the government over relevant current issues.[450]

A1.2.2 Health care funding

The major differences between health care systems in Europe depends upon their method of funding. Belgium, France, Germany and the Netherlands rely upon some form of social insurance, with both public and private providers. Italy, Scandinavia, Spain, and the UK rely upon taxation, with providers controlled directly by the health service. Each national system differs in detail and in Italy, social security and state funds provide health care funding whereas in Spain and the UK most of the health care is paid out of general taxation. In Scandinavian countries where hospitals are owned and run almost exclusively by the state or local government, private nursing homes also exist.[457]

In Germany, social insurance for health was first introduced under Bismarck in the 19th century and in those countries which have a social insurance system it is carried out

via a number of independent companies called Sick Funds under the regulation of the national government.[457] Enrolment in an insurance scheme is usually obligatory for all low paid workers and funds are collected from salaried workers and the self-employed by means of national social security contributions. Insurance-based health care is not however an example of a free market in health; in all these countries, as well as exerting some control over running the schemes, the government plays a major part in determining the premiums paid by workers and the fees paid by the schemes to doctors and hospitals.[266] Typically there is a system of annual negotiation among all the parties involved, in particular government, sickness funds, private insurers, hospitals and medical associations at which the premiums and benefits for the next year are agreed.

In the UK and Spain, the government has direct control over the level of spending and allocates a budget to the system. This leads to greater control over spending and appears to produce a more efficient system.[266] One major difference between the member states of the EU and the United States is that all countries in the EU have accepted for many years the principle of health care provision as a right for the whole population.

A1.2.3 Health care expenditure

For most countries in Europe, per capita health spending averages approximately £900 (Table 1).[250,458] Germany and France have the highest expenditure on health in Europe. In 1995, Germany spent 10.4% of its Gross Domestic Product (GDP) and France 9.8%, which equates to £1,286 and £1,178 per capita respectively. They were second only to the US, which spent 14.2% of GDP in 1995, equating to £2,229 per capita. From the countries considered in this thesis, Spain, Ireland and the UK were the lowest spenders, each spending under 7% of GDP in 1995, amounting to £648, £666 and £751 respectively per capita.[250,458]

There are many factors influencing the expenditure on health. These include the expectations and demands of patients, demography, morbidity, health care professionals salaries compared with the rest of the population and the overall efficiency of the system including administrative costs.[446] In the German and French systems of social insurance, both public and private providers have some degree of flexibility in the prices charged

which is in contrast with the more highly regulated system and standard pricing for services in Ireland, Italy, Spain and the UK.[266]

It has been suggested that the higher the percentage of GDP a country is prepared to spend on health, the richer and more developed the society becomes.[451] Despite this, the wide variation between 6% and 11% in the percentage of GDP spent on health care does not entirely correlate with national wealth or even with the state of a nation's health.[459] There is an observable slight trend for richer countries to spend more of their GDP on health than poorer ones and in cash terms they will usually spend more on medicines.[250] Yet less affluent countries like Portugal spend more on pharmaceuticals relative to their total health budgets than do wealthier members of the European Union (EU).[250] In general, the EU nations with the highest medicine prices at home also have the most successful foreign trade records (the Netherlands is an exception) and the lowest volumes of domestic prescribing (Germany is an exception).[21] On a country by country basis, the Netherlands is an unusual example of a nation that combines lower than average domestic pharmaceutical consumption and spending, with relatively high medicine prices. France by contrast has relatively low pharmaceutical prices but high domestic usage with over five times more prescriptions per capita/annum than in the UK (Table 2) and proportionately high medicine costs per head. These differences are reflected in the proportion of the Netherlands gross national product and percentage of GDP spent on medicines (0.46%) which is half that of France (0.94%) (Table 1).

In northern EU states, such as Germany, the Netherlands and the UK, over the counter medicine (OTC) sales accounted for nearly a fifth of the total value of the medicines market at the end of the 1980s.[21] At the same time in France, Italy, Portugal and Spain OTC sales represented only 5-10% of sales. By 1993, as a result of expansion of the OTC market, OTC sales in the northern EU states represented nearly a third of the total value of the medicines market and sales in France and the Mediterranean countries had risen to between 10 - 20% and continue to rise to this day.[18]

The UK combines relatively modest domestic consumption of and spending on medicines with a strong balance of trade and unusually high research spending. Largely because of Department of Health controls introduced in the 1970s it has unusually low levels of domestic spending on pharmaceutical promotion. Overall, about 10% of all

national health service (NHS) pharmaceutical revenue goes on promotion; equivalent European figures are about 15 - 20%.[21]

A1.2.4 Characteristics of primary care doctors

A1.2.4.1 Remuneration

Member countries within the EU have different systems for remunerating GPs. Doctors in general practice may be paid on a capitation basis (the level of which often depends on the age and morbidity characteristics of the practice population), fee-for-service (in which the procedure or item of service is the unit of payment), salaried or they may be paid by a combination of these methods sometimes involving allowances (fixed payments for certain overhead costs, such as personnel and office expenses, additional services and continuing professional development (CPD) (Table 1).[445,446] Cultural, political, professional and social factors influence the method of paying GPs and where payment modes are mixed, physicians are paid differently depending on the type of service rendered.

Different types of remuneration systems have been known to influence the working behaviour of practitioners.[459] For example, GPs who were paid a fee-for-service increased their provision of services resulting in reduced referral rates, compared with those GPs who were paid on a capitation basis.[460]

A1.2.4.2 Gatekeeping and co-ordination of care

A GP acts as a gatekeeper when he/she has the authority to restrict the patients use of other parts of the health care system. In Ireland, Italy, the Netherlands, Norway, Portugal, Spain and the UK, a gatekeeping system exists where GPs control access to most other levels of health care. Whereas in Belgium, France and Germany, an open access system exists where the patient has a free choice of doctor and specialist. The level of control the GP has over the patient's use of other health care services thus varies from country to country. In EU countries, the gatekeeping role ranges from being non-existent (France) to major (UK and Netherlands).[266] There is an inverse relationship between the importance of the gatekeeping function and the emphasis that is placed on the role of primary care in the health care system of each country. Where the influence of primary care providers is considerable as in the UK, gatekeeping is important but where primary care is not

emphasised as in France, neither is a gatekeeping function at any level of health care provision.[266]

Gatekeeping systems represent the single most important mechanism for containing the largest costs in any health care system, namely those for hospital services[455] because a GP's prescription or referral is required for diagnostic services, visits to specialists and hospital visits. Also, when GPs screen patients before referring them to specialists, the incidence of true disease among patients seen by specialists is increased and the role of the specialist is more heavily focused on more differentiated and more severe diseases.[461] This may be seen as contributing further to their specialist expertise and efficiency.

In countries where GPs act as gatekeepers, patients are required to register with a GP to receive any service from the medical system. Patients have a free choice of GP within a geographical area as long as there is a choice available. In certain countries for example Italy and the UK, patients can change their GP, whereas in others for example Spain, special circumstances are required. Gatekeeper GPs also have the responsibility of providing co-ordinated care for the patient; they also keep records of their patients and are required to pass them on when the patient changes doctor.

As well as the GP being part of the primary care team, in countries where they act as gatekeepers, team work also takes place between GPs and specialists across the primary-secondary care interface. A recent qualitative study by an academic GP in the South West of England has found a high level of respect between the two branches of the medical profession with both expressing a desire and enthusiasm to work together.[462] Such teamwork is much more limited in open access systems where relationships are likely to be much more transient and distant. Formal co-ordination of primary and secondary care in Italy requires a specialist's prescription to be endorsed by the GP, a system which is stricter than elsewhere.[266]

In Belgium, France and Germany, the situation is entirely different and patients have the choice of 'shopping around' for a GP or an office-based specialist as required. This system leads to problems in the co-ordination of care as there is no organised system of transferring patient medical records between physicians. In Germany, larger GP practices are being encouraged with the intention of providing a greater range of services and there is also an increased focus on improving training for GPs.[463] In France, patients often visit

their doctor with a fixed outcome in mind and there is even anecdotal evidence of patients visiting a succession of doctors until they receive their required diagnosis or prescription.[266] This uncontrolled system may be a contributing factor to the high number of script items per capita per annum dispensed in France (Table 2).[250] In Belgium, France and Germany, patients need a physician's referral for hospital stays, except in an emergency. In Germany, patients will be frequently supervised in hospital by the same office-based physician whom they first visited.[266]

A1.2.4.3 Practice organisation and workload

There is a gradual trend across Europe of GPs joining together in group practices to share facilities or work in health centres owned by a health insurance agency or their government. Group organisation is favoured as it offers practitioners greater flexibility and stability, enhances the likelihood of multi-disciplinary teamwork and increases the range of facilities available under one roof for the needs of patients.

Health centres are more common in public vertically integrated systems; solo practice is the modal form in countries where GPs are paid a fee for service (Table 1), with the exception of Italy (capitation but 90% of GPs work in solo practices).[445] In countries with mixed group practice and solo practice, the relative proportions of each varies. This also varies with time and even some of the most up-to-date published figures rapidly become outdated with changes in health policies. For example in Spain, where almost half of GP practices were solo practices, this has been steadily decreasing since the mid 1990s with changes in health care reforms that have seen a move towards multidisciplinary primary care health centres.[266]

There is a considerable variation in the numbers of GPs and the proportion of GPs among all doctors both between and within countries, with Belgium and France at one extreme and Spain and the Netherlands at the other.[454] In Belgium, France and Germany where there are no defined practice populations, GPs tend to be located in and around the cities. Countries with defined practice populations are more likely to have community involvement of practitioners which could be because they are more likely to know about community health problems and to become involved with addressing these problems.

Historically GPs in the Scandinavian countries, Portugal and Spain combine work as a family physician and a public health officer.[445]

Many other characteristics of general practice have been found to vary widely between countries including: consultation time, number of consultations per week, patient list sizes, population per GP, physician contacts per patient per year, prescribing of generic drugs, prescription items dispensed per patient per year, roles of the GP, membership of GP organisations and education and training.[21,219,250,445,450,458,464] However, considerable variation has also been found within nations, especially when comparing characteristics of GPs or their practices between urban and rural locations.[445,465]

A1.3 SUMMARY AND CONCLUSION

Health service provision in isolation cannot compensate for the result of social inequality but health services can positively influence health and can reduce the impact of social inequality on health.[445] On the other hand, access to primary care services may have little impact on health when other social services are underdeveloped and where resources for public health education are relatively inadequate.[466]

Primary health care has been found to be most developed and successful in Scandinavia, the Netherlands and the UK which involve patient registration and control of access to health care by GPs.[465] There is some evidence that countries with gatekeeping systems have better health levels, increased patient satisfaction and lower costs.[467] A study in 1991 by Starfield, a medic in the Department of Health Policy Management, The John Hopkins University School of Medicine, Baltimore, compared data of 12 reputable indicators of health (mortality figures, death rates, life expectancies and birth weights) in seven Northern European countries, Australia, Canada and the USA and found the best results were in the Netherlands and Sweden.[466] Disappointingly, the UK which also operates a gatekeeping system was found to have the second worst results overall.

The past two decades have seen substantial growth in health expenditure in all EU countries with the exception of those in Scandinavia, which has applied some restraints towards the EU average. Health expenditure per capita has grown in the UK but the rate of growth has been slow compared with most countries.[446] However, from the aforementioned health indicators study[466], per capita spending does not guarantee high

performance with respect to health indicators as the US has the highest level of spending per capita in the world[250] and yet was ranked only joint seventh out of the ten countries compared by Starfield.[466]

There are many underlying reasons for the considerable diversity in general practice between European countries which involve human resources, the organisation of health systems, the status of the discipline in individual countries and systems and levels of payments which have evolved over the years.[454] Countries with essentially market-orientated systems are depending more on regulation and cost containment and countries with health systems based on careful planning and control are adopting more market-based structures.[454] In an attempt to curtail the extremes in diversity, to limit health care costs and to promote the free movement of doctors[468], a number of charters[469], directives and policies[21] have been proposed and implemented in order to reform the different health care systems. In the most extreme circumstances, the French implemented independently developed mandatory prescribing guidelines for GPs in 1994, fining doctors £2,000 who do not comply.[470]

In the past couple of years, the US has succeeded in preventing health care costs from rising for the first time in two decades. This seems to be associated with the wide distribution of managed care plans in which much of the population has been encouraged to invest in.[457] Managed care is about managing individual episodes of care in order to reduce costs and possibly raise quality and it has similarities with GP fundholding in the UK. However, others would consider managed care to be a form of negative rationing with reduced costs stemming from restrictions imposed on patients with little choice. Nevertheless, The World Bank considers that managed care holds the biggest hope for developing health services in the developing world and only time will reveal if this delivery of health care is exported and emerges in the form of European-style health maintenance organisations.[471]

A1.4 IMPLICATIONS FOR PRESCRIBING RESEARCH

Health care systems are different and their rate of change is primarily dependent upon the political agenda within a country. Consequently, the results from research related to this field have to be interpreted in the light of the variations that exist. The most important confounding factors with respect to prescribing research appear to include: the presence or not of a gatekeeping system; drug availability and regulation; the cost of medicines to the consumer and how well established local and national prescribing initiatives are.

It is likely that the prescribing practices of GPs in countries where a gatekeeping system exists are more comparable than otherwise because of the organisation of care and reduced competition between doctors as explained previously. For the purposes of the research in this thesis, a gatekeeping system operated in all countries except for Belgium.

Drug availability from country to country is problematic both in terms of the differing degrees to which GPs are potentially overwhelmed by large choices and with respect to drug costs which are not comparable between countries and thus cause difficulties when attempting to assess cost-effectiveness. Also, OTC availability will inevitably contribute to differences in prescribing patterns and drug utilization from country to country as governments increasingly attempt to push the expenditure onto the consumer resulting in patients self-medicating. In addition, the contribution consumers/patients have to make towards the cost of the drugs bill varies from country to country. An improvement in cost-effective prescribing in some countries, for example the UK, may generate more money for other areas of healthcare. Whereas in other countries, for example Belgium and Portugal, cost-effective prescribing is more notably in the patients immediate interest, as it saves them money.

Finally, in countries where systems for prescribing support are well established such as in the UK, GP prescribing tends to be more conservative than otherwise. The implications with respect to this study are that access to a European Formulary, whilst presenting new messages for doctors in some countries may only repeat what has already been stated in others. Therefore other than serving as a possible means of reinforcement, prescribing interventions on this scale would be expected to have variable degrees of impact in different countries. However, if it is agreed that efficacy and safety of medicines are primarily two of the most important criteria upon which drug selection should be based, all

other things being equal then there could be a place for a European Formulary developed on the principles of evidence-based medicine.

Table 1 Population, health care expenditure, health care organisation and general practice remuneration[21,219,250,445,450,458,464]

Country	Population (million)	Per capita spending on health (UK£)	Health care expenditure % of GDP	% of GDP spent on drugs	GP acts as a gatekeeper	Solo practices (%)	Method of payment
Belgium	10	1,003	*	0.71	No	85	F
France	56.4	1,178	9.8	0.94	No	55	F
Germany	78.7	1,286	10.4	0.87	No	82	F
Ireland	3.5	666	6.4	0.79	Yes	59	C/F
Italy	57.7	908	7.7	0.95	Yes	95	C
Netherlands	15	1,041	*	0.46	Yes	54	C
Norway	4.3	*	*	*	Yes	12	S/A/F
Portugal	10.5	623	8.2	1.48	Yes	5	S
Spain	39.4	648	7.2	0.67	Yes	40	F
United Kingdom	57.2	751	6.9	0.67	Yes	6	C/A/F

* data unavailable, S = salary; C = capitation; A = allowance; F = fee-for-service.

Table 2 Characteristics of general practice and health outcome[21,219,250,445,450,458,464]

Country	List size	Average N° consultations per week	Duration of the encounter (minutes)	Script items dispensed per capita/anum	Referrals per 1000 direct encounters	Infant mortality rate (per 1000)	Perinatal mortality (per 1000)
Belgium	1200	135	11	9.5	37.5	9.2	10.4
France	1500	82	14	52.2	37.5	7.5	9.2
Germany	2000	220	9	12	55.1	7.5	6.5
Ireland	1800	135	*	11	42	9.7	10.4
Italy	850	115	7.6	5.2	66.2	9.5	12.3
Netherlands	2350	142	9.1	11	44.2	7.6	9.2
Norway	1300	60	*	6.9	80.5	*	*
Portugal	1500	81	8.2	21	55.6	14.9	15.3
Spain	2500	134	4.7	*	54.6	9	10.6
United Kingdom	1800	128	5.8	10	47.2	9.5	9.1

* data unavailable

ANNEX TWO

European Formulary
General Practice Prescribing Study

Guidelines for completion of enclosed forms

PLEASE RECORD ALL FACE TO FACE PATIENT CONTACT, whether a prescription is issued or not, until you have collected 200 patients who have received a prescription.

Please do not write in shaded areas.

COLUMN 1

The first column is for numbering those patients receiving a prescription of any kind, please include but do not number any patient who does not receive a prescription. **We need 200 patients receiving a prescription.**

COLUMN 2

The second column specifies gender - M (male) F (female) I (inter sex). (this will be very rare!)

COLUMN 3

The third column is for the age of the patient.

COLUMN 4

The fourth column is for diagnosis. **Please use a separate line for each different diagnosis.** If diagnosis is certain please specify. Where diagnosis is not certain please give general nature of the problem e.g. **SORE THROAT** is better than diagnosis of **PHARYNGITIS; ABDOMINAL PAIN** is better than **IRRITABLE BOWEL SYNDROME** unless this has been clearly diagnosed. In some cases diagnoses are even more unclear. In the UK patients often present as 'Tired all the Time' (TATT) or 'Run down' meaning feeling generally unwell with no specific symptoms, please specify these as **ill** with no defined symptoms. Your co-ordinator will translate these diagnoses from your own language as nearly as possible into the English equivalent. **Please record a diagnosis for every drug prescribed, even if there is more than one drug for the same diagnosis. You may use ditto marks (") where appropriate.**

COLUMN 5

Please leave blank for coding later.

COLUMN 6

The sixth column is for drug treatment. Please indicate clearly which drug is associated with which diagnosis. You do not need to include directions for use. **Always use a new line for every drug prescribed**. If a patient asks for a drug on repeat prescription please include + diagnosis in Column 4. Please use generic names where possible.

N.B. Please indicate the formulation of NSAIDs.

COLUMN 7

Please leave blank for coding later.

COLUMN 8

This column indicates whether or not a prescribed drug is a combination. Please put a bold **C** when a combined drug is prescribed e.g. paracetamol + codeine. If not a combination drug please put **NC.**

COLUMN 9

This column is for Category of Prescription:

N If a drug is prescribed for a patient's new problem uninfluenced by any previous prescription the patient has received, put a bold **N**.

A If a drug is prescribed and requested by the patient, as a result of having been prescribed on a previous occasion by another doctor, put a bold **A**.

R If a drug is prescribed as a regular repeated prescription, put a bold **R**.

H If a drug was prescribed as directed by a hospital or specialist, please put a bold **H.**

Thank you for your co-operation.

ANNEX THREE

Data entry form for Prescribing study

Physician Number _____ *Please do not write in shaded areas*

Page _____

Patient No	Sex	Age	Diagnosis BLOCK CAPITALS	Code	Drug BLOCK CAPITALS	Code	Com	Cat
1	F	59	ACUTE PHARYNGITIS		PARACETAMOL		C	N
			ACUTE PHARYNGITIS		CODEINE		C	N
2	M	29	ANXIETY		DIAZEPAM		NC	H
	M	16	COMMON COLD					
3	F	75	OSTEOARTHRITIS		IBUPROFEN CREAM		NC	A
			HYPERTENSION					
4	F	47	DYSPEPSIA		ALUMINIUM HYDROXIDE		NC	R

Note : please write CLEARLY in BLOCK CAPITALS and do not write in the shaded area

R = repeat **H** = hospital influenced **A** = previous influence **N** = new (no previous influence)

ANNEX FOUR

DIAGNOSES - FORMULARY

GASTROINTESTINAL SYSTEM

001	Non-ulcer dyspepsia (incl. epigastric pain)
002	Oesophagitis
003	Nausea/vomiting (+vertigo)
004	Peptic ulcers
005	Irritable bowel syndrome
006	Constipation
007	Diarrhoea
008	Ulcerative colitis/Crohn's disease
009	Anal discomfort
010	Cholecystitis/gallstones

CARDIOVASCULAR SYSTEM

013	Hyperlipidaemia (hypercholesterolaemia)
014	Hypertension
015	Angina pectoris
016	Secondary prevention of MI
017	Arrhythmias
018	Heart failure
019	Intermittent claudication
020	Hypotension
021	Venous disorders
022	Acute myocardial infarction

RESPIRATORY SYTEM

027	Cough (croup)
028	Lower RT infection (chest, acute bronchitis)
029	Asthma

ALLERGY

031	Allergy

CENTRAL NERVOUS SYSTEM

032	Pain (sore, ache)
033	Migraine
034	Epilepsy
035	Neuralgia (sciatica, carpal tunnel)
036	Parkinson's disease
037	Insomnia
038	Anxiety (agitation)
039	Depression
040	Psychosis
041	Dementia (+ memory disorders)
042	Acute ischaemic stroke
043	Secondary prevention of stroke/TIA

TERMINAL CARE

046	Terminal care

OTHER COMMON SYMPTOMS

048	Fatigue

SELECTED PROBLEMS IN INFECTIOUS DISEASE

057	Anti-viral therapy

URINARY SYSTEM

059	Urinary infections
060	Renal colic/Calcinosis (stones)

GENITAL TRACT

062	Sexually transmitted diseases
063	Vaginal discharge

ENDOCRINE SYSTEM

066	Non-insulin dependent diabetes
067	Hypothyroidism
068	Hyperthyroidism
069	Goitre
070	Contraception
071	Premenstrual syndrome/dysmenorrhoea
072	Postmenopausal osteoporosis

BLOOD

074	Deficiency anaemia

CONNECTIVE TISSUE, JOINTS & BONES

076	Arthropathies
077	Gout and hyperuricemia

EYES

079	Eye conditions in EF

EAR, NOSE AND OROPHARYNX

080	Acute otitis media
081	Acute pharyngitis/tonsillitis
082	Acute sinusitis
083	Mouth disorders

SKIN

086	Acne vulgaris
087	Eczema/dry skin (+dermatitis)
088	Psoriasis
089	Fungal infections
090	Warts (verruca)
091	Parasitic skin infestations

PLACEBOS

095	Placebos

DOCTOR'S BAG

097	The doctor's bag

ANNEX FIVE

DIAGNOSES - NON-FORMULARY

GASTROINTESTINAL SYSTEM

101	Colon + urinary disorders
102	GI bleeding (haemoptysis)
103	GI protection
104	Other GI disorders (hiatus hernia, pancreatitis etc.)
105	Abdominal pain (colic, cramp)
106	Biliary colic
107	Duodenitis
108	Gastritis
109	Reflux

CARDIOVASCULAR SYSTEM

170	Ascites/Oedema
171	Other CV disorders/disease (arteritis, atherosclerosis, bypass, cardiopathy)
172	Peripheral vascular disease (Raynaud's syndrome)
173	Valve disorders
174	Ischaemic heart disease
175	Thrombosis/Embolism
176	Lymphadenopathy

RESPIRATORY SYTEM

240	Other respiratory disorders (pleurisy, respiratory failure etc)
241	Chronic bronchitis (COPD/COAD)
242	Pneumonia
243	Toxic inhalation/ingestion/overdose
244	Upper RT infection
245	Respiratory tract infection
246	Bronchitis
247	Catarrh/Exudate/Sputum/Block
248	Common cold/"Flu"
249	Rhinitis

ALLERGY

385	Drug allergy (ADRs, S/Es, iatrogenic conditions)

CENTRAL NERVOUS SYSTEM

051	Headache
310	Abuse/Addiction/Dependency
312	Neuritis/polyneuritis
313	Neuropathy/other CNS disorders
	(dyskinesia, paralysis, paraesthesiae, tremor etc)
314	Neurosis
315	Cerebrovascular disorders
316	Confusion/Senile
352	Behaviour/Personality problems

INFECTIONS

380	Cellulitis
381	Viral infections/illness
382	Intestinal parasites
383	Tuberculosis
384	Ulcer (not mouth/GI)
386	Tooth/dental problems
387	Cyst/swelling
388	Abscesses (not teeth)
389	Other systemic infections

URINARY SYSTEM

458	Other renal disorders
521	Colostomy disorder
520	Incontinence

GENITAL TRACT

390	Itch/discomfort/inflammation
519	Gynaecological infection

ENDOCRINE SYSTEM

311	Liver disorders/disease
450	Addisons syndrome
451	Growth disorders
452	Hepatitis
453	HRT/Menopause (post)
454	Hyperglycaemia
455	Insulin depend diabetes
456	Hypoglycaemia
457	Osteoporosis (men)
459	Other womens problems
460	Other mens problems
461	Other endocrine conditions (diabetes insipidus)
462	Diabetes (not specified)
463	Exocrine disorders

BLOOD

660	Pregnancy/ante natal
661	Other blood disorders (glandular fever)

CONNECTIVE TISSUE, JOINTS & BONES

056	Low back pain
728	Anatomical/congenital disorders (hereditary)
729	Disc problems (prolapsed etc)
730	Weird M/S disorders (e.g. cracks, degeneration)
731	Dystrophy/Multiple Sclerosis
732	Fractures (where "pain" not written)
733	M/S disorders (pain + inflammation)
734	Other M/S disorders (e.g. cramps + spasm etc)
737	Hernia related
738	Injury + trauma (excl eye)
739	Trauma?

EYES

800	Other eye conditions (glaucoma etc)

EAR, NOSE AND OROPHARYNX

869	Ear? (otitis, discharge, earache)
870	All other ear conditions (otitis externa, hearing deficiency etc)
871	Other mouth/throat related disorders
873	Sore throat/throat infection (hoarseness)
872	Other nasal conditions

SKIN

736	Wounds/burns/lacerations/lesions (including infections)
940	Hair problems (include folliculitis)
941	Other skin infections/problems (incl nails)
942	Rash (not allergic)

MALIGNANT DISEASE & IMMUNOSUPPRESSION

589	Neoplasm/Hyperplasia/Polyp
590	Cancers (malignant)
591	Non-malignant tumours
592	Organ transplants
801	Immune response related disorders

MISCELLANEOUS

049	Itching
050	Fever
056	Prophylaxis of infectious diseases (vaccines including malaria)
350	Weakness (asthenia)
351	Ill/TATT (no definite symptoms)
352	ME (post viral fatigue)
735	Surgery (ectomy) + post op conditions
888	Stress
889	Other diagnoses (vasovagal attack, faint, blackout)
996	Uncertain diagnosis (prescriber is unsure)
997	Unidentifiable/untranslated
998	Diet/nutrition/weight disorders

ANNEX SIX

Prescribing influences and your working environment

Note: please write in **BLOCK CAPITALS** and use numerals where possible.

1 Male ❒ Female ❒

2 Age (years) <30 ❒ 30-39 ❒ 40-49 ❒ 50-59 ❒ 60+ ❒

3 Do you work i) alone ❒ or ii) in a group practice ❒

4 Which of these best describes the location of your working practice? (please tick only **one**)

rural ❒ mixed urban/rural ❒ urban ❒ inner city/city centre ❒

		Yes	**No**
5	Are you involved in training doctors to become GPs?	❒	❒
6	Do patients who consult you include i) children < 14 years?	❒	❒
	ii) adults > 65 years?	❒	❒

7 Number of years since qualification as a doctor? _____years

8 Please list all the post-graduate qualifications you have and the year of the achievement?

_____

_____

9 How many drug industry sales representatives have met with you in the last **4** weeks?____

10 On average how many **hours** do you work in primary care in **one** week? _____hours

11 On average how many **patients** do you see in primary care in **one** week? _____patients

12 How long (in minutes) is your average consultation with each patient? _____minutes

13 Please list in **order** of importance the **five** main influences which you believe have acted on your personal prescribing since the autumn of 1994.

i)_____

ii)_____

iii)_____

iv)_____

v)_____

THANK YOU for taking time to complete this questionnaire. The individual questionnaires will remain confidential. **Please return the questionnaire to Guy Jepson in the enclosed envelope.** (Dept. Primary Health Care, The Medical School, Newcastle upon Tyne, NE2 4HH, UK)

ANNEX SEVEN

August 1998

Doctors Name
Work Address
City
COUNTRY

Dear Dr

European Formulary Research Project

Thank you for participating in the European Formulary project (August 1994 - July 1997) and for providing your invaluable prescribing data. The educational intervention which included distribution of the European Formulary resulted in more rational prescribing in Belgium, Italy and Portugal. A short summary of the project final report is enclosed for your interest.

To help me explain why variations into the effect of the Formulary occurred in the different countries, I should like to ask for your help in answering this brief and simple **one page questionnaire**. As well as perceived influences on prescribing, the questionnaire also asks for a few working environment and demographic details so that the profiles of the participants from the different countries can be compared. All the answers to the final question will be combined in a list and categorised under different themes of influence. In a few weeks time you will receive a brief follow up questionnaire asking you to rank the influencing categories in order of decreasing importance which you believe have acted on your personal prescribing since the autumn of 1994. The results of these questionnaires will contribute to the completion of a PhD thesis which should also help to raise the profile of the European Formulary.

Please will you post the questionnaire back to me in Newcastle upon Tyne in the **reply paid envelope enclosed**. All replies will be treated in complete confidence. Should you have any queries about the questionnaire, please contact me in Newcastle upon Tyne by telephone on: +44 191 222 5891 or fax on +44 191 222 7892.
Thank you for your response.

Yours sincerely

Guy Jepson
Research Pharmacist
E-mail: G.M.H.Jepson@newcastle.ac.uk

ANNEX EIGHT

Prescribing influences follow up questionnaire

Please rank the influencing categories in order of decreasing importance (score from ① to ⑦) which you believe have acted on your personal prescribing since the autumn of 1994. Examples of individual influences which fall into each of these seven categories can be found on the attached page.

Influencing category	**Category rank order from ① to ⑦;** **① = category of most influence** **⑦ = category of least influence**
a) ***Drug factors***	
b) ***Education/information factors***	
c) ***Patient factors***	
d) ***Pharmaceutical industry factors***	
e) ***General medical practitioner factors***	
f) ***Regulatory factors***	
g) ***Work based factors*** ***(health centre/ practice/surgery)***	
Please write any additional comments here:	

THANK YOU for taking time to complete this questionnaire. The individual questionnaires will remain confidential. **Please return the questionnaire to Guy Jepson in the enclosed envelope.** (Dept. of Primary Health Care, The Medical School, Newcastle upon Tyne, NE2 4HH, UK).

ANNEX NINE

European Formulary project participants list of factors influencing prescribing

a) Drug factors	c) Patient factors
Cost	Clinical indication/diagnosis/symptoms
Cost-effectiveness	Other diagnoses/symptoms of the patient
Dosage frequency	Treatment outcome
Efficacy	Patient age
Formulation	Patient compliance/palatability/tolerability
Perception that drugs are: liable to abuse, unnecessary or useless	Patient acceptability/expectation/feedback/ pressure/request
New drugs	Patient education
New indications for a drug	Patient's family
Number of treatment days	Patient's finances
Polypharmacy	Patients need
Safety/side-effects	**d) Pharmaceutical industry factors**
b) Education/information factors	Industrial agent/detailer/representative
Conferences/courses/lectures/meetings/ personal research/training/training period	Industry: advertising/marketing/promotion/publicity
Continuing Medical Education (CME)	Pharmaceutical company literature/data sheet
Evidence-based medicine	**e) General medical practitioner factors**
Formularies: hospital/regional/national/international	Colleagues/partners/peers - discussion, opinions, pressure
Guidelines/protocols/standards/ - local, national, new, evidence-based, scientific, therapeutic	Discussion/sessions with community pharmacists
Literature - drug and medical journals, drug information bulletins, newsletters, scientific publications, textbooks, medical newspapers	Hospital/specialist directed - discharge medication/letter
Local/national drug advice/information units	Convenience
Small group learning	Custom/experience/familiarity
Involvement in training doctors	Knowledge
University/University organised GP health centre training	Scepticism of new drugs
g) Work based factors (health centre/office/practice/surgery)	Membership of prescribing/therapeutics committee
Computer access	Consultation length/time pressure
Fundholding	**f) Regulatory Factors**
Group meetings	Budgets/indicative prescribing scheme
Practice agreement/behaviour/policy	Equal drug availability internationally
Practice audit/clinical targets	Generic prescribing
Practice formulary/prescribing protocols	Government policy
Practice nurse	Health authority/board/region prescribing advisers
Practice pharmacist	Incentive payments/schemes
Working in a group environment	Prescribing feedback data

ANNEX TEN

January 1999

Doctors Name
Work Address
City
COUNTRY

Dear Dr

European Formulary Research Project

Enclosed please find a very short **final** follow up questionnaire further to the one you received last August on *Prescribing influences and the doctors working environment.* After analysing the responses to this questionnaire, I have managed to separate all the factors influencing prescribing into **seven** different categories/themes of influence.

Please can you rank these categories of influence in order of **most important-①** to **least important-⑦,** which you believe have acted on your personal prescribing since autumn 1994. Thus score a ① by the category which has had the **most influence**, a ② by the influencing category which has had the **second greatest influence** and continue on till you have scored a ⑦ by the category which has had the **least influence** on your prescribing. Examples of individual influences which fall into each of the categories can be seen separately on the attached sheet.

Please will you post the questionnaire back to me in Newcastle upon Tyne in the **reply paid envelope enclosed**. All replies will be treated in complete confidence. Thank you for taking time to help me with this final stage of my PhD research.

Happy New Year.

Yours sincerely

Guy Jepson

PRESENTATIONS AND PUBLICATIONS SINCE JOINING THE DEPARTMENT OF PRIMARY HEALTH CARE

Oral Presentations

Drug Utilisation Research Group (DURG) Annual Meeting, Royal Society of Medicine, *The Role of a Practice Pharmacist in a GP Surgery.* London, December 1995.

Young Pharmacists Group (YPG) Regional Conference, *Partnerships with Pharmacy.* Manchester, March 1996.

European Formulary Bio-Med Project Conference, Annual feedback to European co-ordinators including presentations on: *Prescribing of antibiotics, non-steroidal anti-inflammatory drugs (NSAIDs) and drugs of limited proven clinical value.* Newcastle, April 1995, 1996 and 1997.

European Drug Utilisation Research Group (DURG) Meeting (plenary presentation), *Evaluation of NSAIDs in a European Prescribing Study.* Lake Balaton, Hungary, June 1996.

Association of University Departments of General Practice (AUDGP) Conference(Workshop), *Optimising General Practice Prescribing Data and Analysis.* Newcastle, July 1996.

Northern Primary Care Research Network (NoReN) Annual Research Presentation Day, *Evaluation of NSAIDs in a European Prescribing Study*. Durham, November 1996.

European Association of Clinical Pharmacology and Therapeutics (EACPT) 2nd Congress, *The effect of a European Formulary on prescribing in general practice medicine*. Berlin, Germany, September 1997.

British Pharmaceutical Conference (BPC), *An evaluation of the impact of a European Formulary on primary care prescribing.* Eastbourne, September 1998.

British Thoracic Society (BTS) Winter Meeting, *Patterns of general practice prescribing for asthma in 8 European countries.* London, December 1998.

Publications

Jepson. G. The Role of a Practice Pharmacist in a GP Surgery. *Community Pharmacists' Group Bulletin* 1996; 6: 2-3.

Jepson GMH. Evaluation of NSAIDs in a European Prescribing Study. *European Journal of Clinical Pharmacology* 1996; conference proceedings.

Gregory DA, Jepson GMH, Butler TJ. The effect of a European Formulary on prescribing in general practice medicine. *European Journal of Clinical Pharmacology* 1997; 52: (Suppl) A35.

Jepson GMH, Gregory DA, Butler TJ, Jones KP. An evaluation of the impact of a European Formulary on primary care prescribing. *Pharmaceutical Journal* 1998; 261: (Suppl) R15.

Jepson GMH. Glossy image open for debate (letter). *Pharmaceutical Journal* 1998, 261: 860.

Jepson G, Butler T, Gregory D, Jones K. Patterns of general practice prescribing for asthma in 8 European countries. *Thorax* 1998; 53: (Suppl 4) A74.

Jepson GMH, Butler TJ, Gregory DA, Jones KP, Patterns of general practice prescribing for asthma in 6 European countries. *Respiratory Medicine* (accepted and in press 2000).