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PHARMACOECONOMIC EVALUATIONS AND PRIMARY CARE PRESCRIBING

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ABSTRACT

Background

The goal of effective prescribing with the aim of improving the quality of prescribing in primary care is both a clinical and economic challenge. There are wide variations in prescribing in primary care that cannot be fully accounted for by demographic patterns. Over the years, numerous educational and policy initiatives on improving primary care prescribing in the NHS have been developed and implemented. However, in order to achieve both clinical and cost effectiveness, a wider perspective must be adopted. Focusing solely on the reduction of purchasing costs of drugs is not only ineffective, but may result in increased expenditure in the longer term due to the cost of treating hidden adverse complications.

Aims

This study aimed to investigate the effect of incorporating adverse drug reactions in economic analyses of drug therapies. Subsequently, the impact of this information on prescribing in primary care is explored.

Literature Review

The literature related to the clinical and economic burden of adverse drug reactions was reviewed. Adverse drug reactions have been shown to incur substantial clinical and economic burdens to health care systems. Although different drugs have different adverse events profile, no drugs are free of adverse drug reactions and all result in additional costs. The economic consequences associated with adverse drug reactions have often been neglected.

Evidence about the impact of economic information on primary care decision making is sparse. Several surveys have attempted to investigate the use and the role of economic evidence in primary care practice, but these studies are limited by their methodology.

However, the findings of these studies are in general agreement that there is an awareness and interest in economic information among general practitioners, but there is no indication of successful implementation in changing day-to-day practice. Several barriers to implementation of economic evidence have been identified.

Methods

In order to achieve the aims of the study, three main studies were conducted. In the first study, an economic analysis was conducted to estimate the comparative costs of a large UK population (N = 98 887) given nonsteroidal anti-inflammatory drug (NSAID) therapy alone and in combination of gastrointestinal (GI) protective agents including concomitant prescriptions of H_2 blockers, omeprazole and misoprostol. The study population was divided into four groups: NSAID only sub-cohort (N = 49 212), NSAID and co-prescribed H_2 blockers/omeprazole sub-cohort (N = 2 113), NSAID and co-prescribed misoprostol sub-cohort (N = 212) and the general population comparator cohort (N = 47 350). Direct healthcare costs associated with each individual were calculated at days, six months and 12 months. In addition to the total costs, the sex and age-specific costs, and the relative cost of high and low risk groups associated with NSAID therapy alone and in combination with GI protective agents were also calculated.

The second study was a pharmacoeconomic analysis, using data from the literature and local expert opinion, of three commonly prescribed classes of drugs in primary care - NSAIDs, selective serotonin reuptake inhibitors (SSRIs) and angiotensin converting enzyme (ACE) inhibitors for the treatment of rheumatoid arthritis, depression and hypertension respectively. The total cost of drug therapy, taking into account the cost of the drugs and the cost of treating possible associated drug-induced adverse drug reactions (ADRs) - termed the 'shadow cost' were calculated.

Finally, the results from the pharmacoeconomic analysis were disseminated to GPs in a local Health Board to explore the impact on influencing primary care prescribing. The prescribing trend over a six-month period was analysed using routine data from Prescription Cost Analysis for Scotland. A postal and email survey and qualitative interviews were also undertaken to help better understanding of these findings.

Results

The results from both economic analyses showed clearly that drug associated adverse clinical events may add substantially to the cost of drug therapy.

In the first study using the population database, almost all event rates and costs showed significant differences between any two groups. Over a period of 12 months, the incremental cost of the NSAID-only group was £253 compared to the general population; similarly, the incremental cost of the NSAID and misoprostol group, and NSAID and H2/omeprazole, over the NSAID group was £417 and £543 respectively. The costs of prescriptions and cardiovascular (CV) admissions constituted the bulk of the total costs in all groups. Surprisingly, GI endoscopies only accounted for 8% of the incremental costs. Sensitivity analysis showed that the conclusions were robust and that differences in costs was not due to differences in sex, age, or previous history of hospital admissions.

In the second study eight NSAIDs, four SSRIs and seven ACE inhibitors were evaluated. The economic impact of drug-induced ADRs was particularly apparent among NSAIDs, when the shadow cost (cost of managing adverse events) accounted for 12% (ketoprofen) to 59% (diclofenac sodium) of the total cost of therapy. In some cases, drugs that may be more costly to purchase in the first place, resulted in savings in the long term. This was observed among NSAIDs such as naproxen, ketoprofen and indomethacin, and ACE inhibitors such as trandolapril.

The findings of the pharmacoeconomic analyses were presented to 12 GPs within a local healthcare co-operative (LHCC). Prescribing volume of NSAIDs, SSRIs and ACE inhibitors were monitored and comparisons were made between the three months pre- and post-dissemination. General practitioners in the same LHCC but who did not participate in the study acted as controls and did not receive any interventions. No change in prescribing trends of the three classes of drugs was observed. The subsequent postal and email survey confirmed the general lack of use of economic information. Qualitative interviews have revealed that GPs do not believe that such information should be considered at a practice level.

Conclusions

Economic analyses based on various data sources have shown that the total cost of drug therapies are often much higher than the purchasing cost alone. There is much value in taking into account the clinical and economic impact of drug-induced ADRs when conducting pharmacoeconomic evaluations. However, this is often restricted by the availability of some of the data that are required to complete the economic model. The necessary data do exist, but linked clinical data for this type of analysis are not readily available for research purposes.

General practitioners were generally supportive of economic evaluations and the exploratory study on disseminating pharmacoeconomic information. However, the dissemination exercise had failed to demonstrate a positive relationship. In addition to the barriers highlighted in the literature, it was found that GPs do not feel that there is a role for the implementation of economic information in primary care.

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AUTHOR'S DECLARATION AND ACKNOWLEDGEMENTS

This thesis and the work it describes are entirely the work of the author. Elements of the research reported in this thesis have been presented at the following meetings:

1. Pharmacoeconomic modelling of a population database. Oral presentation at the Medicines Monitoring Unit, University of Dundee (1998).

2. Identifying a high cost sub-population of NSAID takers in Tayside. Wu O, Knill-Jones RP, McMahon AD, MacDonald T. Poster presentation and abstract at the annual meeting of the British Society of Gastroenterology (1998).

3. Are 'cheaper alternatives' a false economy? Wu O, Knill-Jones RP. Poster presentation at the 75th Anniversary Scientific Meeting, Department of Public Health, University of Glasgow (1998).

4. The cost of managing treatment emergent adverse drug reactions: an example with NSAIDs. Oral presentation at AstraZeneca, Kings Langley (2000).

5. The impact of economic information on medical decision-making in primary care. Wu O, Knill-Jones RP. Poster presentation and abstract at the annual meeting of the International Society of Pharmacoepidemiology (2002).

The following publication has been based on parts of the research contained in this thesis:

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DEFINITIONS OF TERMS AND GLOSSARY

ACE Inhibitors	Angiotensin Converting Enzyme Inhibitors
ADRs	Adverse Drug Reactions
AT1 Receptor Blockers	Angiotensin I Receptor Blockers
BNF	British National Formulary
CCOHTA	Canadian Co-ordinating Office for Health Technology Assessment
CHI	Community Health Index
CMR	Continuous Morbidity Recording
CNS	The Central Nervous System
COX II	Cyclo-oxygenase II
CSM	Committee of Safety of Medicines
CV	Cardiovascular
DALYs	Disability Adjusted Life Years
DDD	Defined Daily Dose
Direct Costs	Costs related to the use of resource due to either the disease or its treatment. They include costs to the health care system, costs to social services and to patients themselves or relatives.
DSRU	Drug Safety Research Unit
EC	European Commission
ECG	Electrocardiogram
EDI	Electronic Data Interchange
EED	Economic Evaluation Database
EMEA	European Agency for the Evaluation of Medicinal Products
ENT	Ear, Nose and Throat
EQ	Electronic Questionnaire

FBC	Full Blood Count
FOB	Faecal Occult Blood
GI	Gastrointestinal
GP	General Practitioner
GPASS	General Practice Administrative System for Scotland
GPRD	General Practice Research Database
HTBS	The Health Technology Board for Scotland
ICD 9	International Classification of Disease
Iatrogenic Costs	The cost associated with the treatment and prevention of adverse drug reactions and any substitution treatment following discontinuation from the prescribed medication.
Indirect Costs	Cost related to loss of production, due to either the disease or its treatment, which occur to society.
IPS	Indicative Prescribing Scheme
ISD	Information Statistics Division
IVP	Intravenous Pyelogram
LFT	Liver Function Test
LHCC	Local Healthcare Co-operatives
LOS	Length of stay in hospital
MCA	Medicines Control Agency
MEMO	Medicines Monitoring Unit
MPAs	Medical Prescribing Advisers
NIC	Net Ingredient Cost
NICE	The National Institute for Clinical Excellence
NSAIDs	Non-steroidal Anti-inflammatory Drugs
OA	Osteoarthritis
OP	Outpatient
OPCS	Office of Population Census Surveys (OPCS)

PACT	Prescribing Analysis and Cost
PCTs	Primary Care Trusts
PEM	Prescription Event Monitoring
PPAs	Pharmaceutical Prescribing Advisers
PRDIGY	Prescribing Rationally with Decision Support in General Practice Study
PRISMS	Prescribing Information Systems for Scotland
QALYs	Quality Adjusted Life Years
RA	Rheumatoid Arthritis
SCIEH	Scottish Centre for Infection and Environmental Health
Shadow Costs	The cost associated with the treatment and prevention of adverse drug reactions and any substitution treatment following discontinuation from the prescribed medication.
SIGN	The Scottish Intercollegiate Guidelines Network
SMR 1	Scottish Morbidity Record 1
SPA	Scottish Prescribing Analysis
SSRIs	Selective Serotonin Reuptake Inhibitors
TCAs	Tricyclic Anticholinergics
U&E	Urea and Electrolytes
UHDs	Ulcer-healing Drugs
WBC	White Blood Count
WestNet	The West of Scotland Primary Care Research and Development Network
WHO	World Health Organisation
XR	X-ray

1 INTRODUCTION

INTRODUCTION

1.1 BACKGROUND TO THIS STUDY

National Health Service (NHS) expenditure is rising constantly, and today, the concept of scarce healthcare resources is widely accepted by all. Although administrative inefficiency, managerial paralysis, more experimental technical advances and the ageing population have frequently been blamed for this, there are many other interacting factors contributing to escalating healthcare costs.

The expenditure on drug treatment has increased by approximately five-fold over the past 30 years and currently forms about 12% of all NHS expenditure [1]. In the last decade, the rate of increase averaged almost 9% annually [2], well above inflation, faster than any other sector in the NHS (Figure 1). The reason for this trend may be explained, in part, by the rise in unit cost per prescription and volumes per capita. The introduction of new therapeutic interventions by the pharmaceutical industry has led to significant increases in drug expenditure within the NHS. More and more effective drugs are becoming available to provide better treatment or deal with conditions which until recently could not be treated at all. It has been estimated that 55% of the increased expenditure is due to new products replacing existing agents and 30% due to an increase in number of medicines consumed by patients [3].

The government has committed itself to 'a primary care based NHS'. Over the years, the government has introduced strategies (reviewed in Appendix I) in attempts to contain the costs in prescribing. Various approaches to cost containment have been introduced and adopted throughout the years, ranging from the "stick" approach (e.g. restricted list) to the "carrot approach" (e.g. incentives with a prescribing message on them). However, there is often a lack of rigorous evidence because interventions were implemented as part of a strategic decision rather than on a formally evaluated basis. In addition, most of these methods appear only to have short-term benefits. Cost containment strategies could only generate a finite amount of savings, which would reach a plateau in the long term. In order to achieve cost effectiveness in healthcare, a wider perspective needs to be adopted.

At the time of the work for this thesis, general practice is the core of primary care, and the majority of primary care is delivered by general practice-based teams. The prominent role of general practice in primary care has been strengthened since the 1991 reforms, which have given purchasing responsibilities to general practitioners (GPs). It has given GPs budgets to purchase hospital care as well as contracting them to provide both clinical and preventive primary care for their registered patients. It has allowed them to keep savings made from economies in prescribing for use in providing other services. It has shifted NHS resources from secondary to primary care, and it has achieved a subtle but undeniable increase in the influence of GPs over their colleagues in hospital practice.

General practitioners occupy a prominent role in the rationing process within the NHS, but decision making has become increasingly complex. The constant rise in cost and demand for healthcare has led to the need for optimum use of limited resources in the face of continuous and increasing demand. More recently, economic considerations, especially cost effectiveness, have become an integral part of clinical decision making, and may be essential to the survival of the NHS.

1.2 PRIMARY CARE

General practitioners are often described as "gate-keepers" as general practice is the first port of call for all patients. The most frequent contact with the health service, for most people, is through their GPs in primary care, where drug therapy is the most common therapeutic approach adopted for treatment. In Scotland, 3066 consultations per 1000 practice population were recorded in the year 1999 (based on data from 51 practices) [4]. It is believed that up to 70% of GP consultations result in a prescription, either as a one-off treatment or as part of long-term management of chronic illness [5].

In spite of a fairly steady population growth, the total quantity of drugs issued and their costs rise year after year. A total of 60.9 million NHS prescriptions – equivalent to 11.3 prescriptions per head – were dispensed in 1999/2000 in Scotland [4], representing a 3.6% increase from the previous year, at a cost of £713 million. A combination of factors is responsible for the rise in prescribing expenditure every year. This includes the 3% to 4% annual increase in the number of prescriptions issued, the changes in the price of drugs, the

introduction of new and often more expensive drugs, and changes in prescribing practice. The average net ingredient cost per prescription dispensed in Scotland over the past 15 years has risen from £3.94 in 1985 to £10.11 in 2000 (compared with an increase to £6.46 if price inflation alone was taken into account). The substantial increases in the volume and cost of prescriptions over the past seven years are shown in Figure 2.

The quality of prescribing has a direct impact on the quality of patient care and total NHS expenditure. Although many GPs are generally efficient in their role, inappropriate prescribing does occur in general practice [6]. The Accounts Commission Report published in September 1999 [2] highlighted current attempts at improving the quality and cost effectiveness of prescribing, which it claimed would lead to annual savings in the region of £26 million in Scotland if half of these improvements were achieved. These include:

- Generic prescribing

The prescribing of generic drugs has continued to rise from around 40% in 1992/1993 to almost 67% in 1998/1999. Although this increase was already 3.5% higher than previous year, there was still significant variation among Health Boards, ranging from 50% in Shetland to 74% in the Lothian area [7]. Substantial savings have been generated through increased generic substitution, especially in the mid 1990s. However, the House of Commons Select Committee on Health recently reported on the increase in the price of generic drugs, and as much as 500% increase has been observed, possibly related to the shortage of some generic drugs [8].

- Substitution of therapeutically similar drugs

Where efficacy and safety are not compromised, cheaper alternatives should be considered. However, well-conducted pharmacoeconomic evidence, assessing all aspects of cost implications, is essential to assist such prescribing decisions.

- Avoid premium priced preparations

Preparations such as slow release or effervescent preparations which are more expensive than the basic formulations should be avoided. They do not offer pharmacological advantages to the majority of the patients for whom they are

prescribed and should be reserved for a more highly selected patient group who would benefit the most.

- Reduce prescribing of drugs of limited clinical value

Since 1999, a category of drugs considered by the Joint Formulary Committee to be "less suitable for prescribing" has been included in the British National Formulary (BNF)[9]. These are drugs that are not normally considered as a first choice for treatment, although their use may be justifiable in certain patient groups and specific combinations of disease states (co-morbidity). The main drugs in this group included combination analgesics, peripheral vasodilators and compound bronchodilators. Social audit has estimated that over £100 million is spent on preparations that the BNF deems less suitable [9]. This has provided an indication of the level of potentially inappropriate prescribing.

- Reduce the use of over-prescribed drugs

Antibacterials, hypnotics and anxiolytics are all classes of drugs recognised as having been over-prescribed. In addition to cost implications, over-prescribing has an adverse clinical impact. For instance, the over-prescribing of antibacterial agents may hasten development of resistance by micro-organisms. This has become a growing concern nationally and internationally. In the case of antibacterials indicated for lower respiratory tract disorder, a recent Scottish Intercollegiate Guideline Network (SIGN) guideline [10] has suggested that a 40% reduction in prescribing would generate over £1 million savings for the NHS in Scotland. The estimated figure did not take into account of savings that may be made from reduced GP consultations and reduced management of adverse drug reactions.

- Improved management of repeat prescribing systems

Repeat prescribing has long been target for improvement. Unnecessary treatment should be avoided and reduce the risk of side effects and adverse effects from drug interactions.

General practitioners generally agree with the principles of rational prescribing, however, they also recognise that there are circumstances when rational prescribing is impractical. Instead of being an outcome of the consultation, a prescription may be viewed as a problem-solving tool that could be used to manage a variety of patient situations. There may be instances when prescriptions may be used as a means to cope with a busy workload, to manage a distressing patient situation or to maintain a doctor-patient relationship.

In primary care, the Primary Care Trusts (PCTs) have budgets to manage, and GPs are the individuals responsible for prescribing decisions. The process of drug selection and usage is complex. In addition to making choices based on efficacy and safety, GPs have to account for related cost issues. They are expected to work within resource constraints, make optimum use of available resources and recognise the effect their decisions may have on the resources and choices available to others.

There is a general acceptance among GPs that costs should be accounted for when prescribing, and prescribing costs could be reduced without affecting care. However, there is a lack of awareness and a poor perception of the cost of drug therapies among some GPs – the cost of cheap drugs is often over-estimated, while expensive ones, underestimated [11]. Therefore, it is important that GPs understand both the evidence for new interventions and the potential for cost containment. A report from the King's Fund [12] has called for more responsibility from health professionals for deciding how money should be spent. It is believed that promoting cost awareness may influence GPs' prescribing decisions [13].

1.3 THE ROLE OF ECONOMIC EVALUATIONS IN HEALTHCARE

1.3.1 Economic Evaluations

Traditionally, when considering cost issues in the NHS, the purchasing cost of new drugs was simply compared to existing alternatives. The present healthcare culture demands proper consideration of the economic aspects of drug therapies. Health economics is now a common term in public policy documents, scientific literature and even the lay press. 'Value for money' is becoming a major concern for health policy makers, and economic

evaluations have become an important tool in assisting clinical decision-making. Economic evaluation is also an accepted tool for the appraisal of healthcare programmes, and there is a growing volume of economic analyses of healthcare worldwide.

An economic evaluation in healthcare has been defined as "a comparative analysis of alternative courses of action in terms of both their costs and consequences" [14]. Economic analyses are comparative analyses and are applied to explicit alternatives. Whatever the alternatives, all the direct (associated with resource use) and indirect (associated with loss of production to society) costs related to all aspects of managing the disease should be considered. These should then be weighed against the benefits, in terms of improvement on the length or quality of life.

Depending on the perspective of the study and the question posed, different types of economic evaluations can be adopted:

- Cost-consequence analyses – when effectiveness is measured in different disease-specific measures, generally used to describe costs and outcomes. For instance, cost-consequence analysis may be used to determine whether a primary care dermatology liaison nurse should be introduced into a health authority [15].

- Cost-minimisation analyses – generally used to compare treatments within the same disease when the effectiveness of comparators are equal. For instance, the treatment of deep vein thrombosis by in-hospital treatment with unfractionated heparin may be compared to at-home therapy with low molecular weight heparin. Data from a clinical trial has demonstrated that the group sent home to self-inject with low molecular weight heparin would experience similar rates of bleeding or deep vein thrombosis recurrence as those kept in hospital. Since the clinical outcomes have been proven to be equivalent in the two groups, analysis may be limited to analysing only the costs [16].

- Cost-effectiveness analyses – when the outcomes or consequences of different interventions vary but can be measured in identical natural units, then inputs are costed. Interventions are compared in terms of cost per unit of consequence. Therefore, the intervention associated with the minimum cost per unit outcome, or the maximum outcome per unit cost would be the most cost effective option. For

instance, the prescribing of antibiotic prophylaxis may be compared with no routine prophylaxis in women undergoing caesarean section [17]. The cost per adverse outcome averted was calculated and compared between the two groups.

- Cost-utility analyses – when effectiveness is measured as combined survival and quality of life (quality-adjusted-life years); generally used to compare treatments for different diseases. For instance, cost-utility analysis may be used to determine whether resources should be allocated to the treatment of established osteoporosis to prevent fractures, considering other uses for the equivalent resources [18].

- Cost-benefit analyses – when both the inputs and outcomes or consequences of the comparative interventions are expressed as monetary benefit (such as willingness-to-pay); generally used to compare investments in the health care sector with investments in other sectors. For instance, this may be used to determine the willingness to pay for carrier screening for a congenital deafness gene from the perspective of pregnant women [19].

All methods of economic evaluation value both inputs and outcomes or consequences and follow the same three steps relating to both inputs and outcomes: (1) identification, (2) measurement and (3) valuation. There are potential difficulties in conducting all three phases of the evaluation. Identification may be difficult as some health care interventions have hidden or unknown costs and consequences. For instance, when evaluating drug therapies, in addition to the acquisition cost, cost associated with administration and management of associated side effects (termed 'iatrogenic costs' or 'shadow costs') [20,21] should be taken into account. This may include costs incurred by extra GP consultations, drug changes, additional prescriptions, investigations, laboratory investigations, outpatient referrals and possibly hospital admissions. The costs of managing adverse drug reactions (ADRs) are substantial, and will be discussed in a later section.

Measurement of outcomes is not always straight forward as there are costs and consequences that cannot be measured in appropriate physical units due to intangible outcomes such as the reduction of pain. Valuing inputs and consequences is the most difficult aspect of conducting an economic evaluation and the most difficult for health care professionals to interpret, as in reality the only readily available measures of value, prices,

exist only where there are true markets, and these cover only a minority of health inputs and consequences.

This thesis focuses on the economic analyses of the 'iatrogenic costs' or the 'shadow costs' associated with drug treatments – non-steroidal anti-inflammatory drugs (NSAIDs), selective reuptake serotonin inhibitors (SSRIs) and angiotensin converting enzyme (ACE) inhibitors for the management of rheumatoid arthritis (RA), depression and hypertension, respectively. These drugs, each within their own pharmacological family share the same mechanism of action and have been demonstrated in clinical trials to have equal efficacy.

1.3.2 Perspective Worldwide

In response to recognising the role of economic evidence in clinical decision making, many countries have made it mandatory by law to include proof of cost effectiveness when applying for licensing of new drugs. Some, such as the UK, have chosen to set up specialised groups to assess current and new therapies, with economic analysis an integral part of such assessment.

Australia was the first country to make submission of proof of cost effectiveness an official requirement before pharmaceuticals can be reimbursed for the Australian Pharmaceutical Benefits Scheme in 1993 [22]. This policy was enacted at the time when drug prices and the annual increase in the Australian drugs bill were below the developed world average. In November 1994, Canada was the next to follow suit. The Canadian Co-ordinating Office for Health Technology Assessment (CCOHTA) issued a set of national guidelines for economic evaluations of drugs [23]. Since September 1995 applications to Ontario's provincial drugs reimbursement formulary would be considered incomplete if they do not include economic analysis of the drug in question. In 1997, the World Health Organisation (WHO) produced a draft working party document arguing that "sharper questions must be asked about final impact of new products before any decision is taken on investing public funds in their use" [24]. To date, countries including New Zealand, Finland, Norway and the Netherlands have made the submission of proof of cost effectiveness a mandatory requirement for all new drugs, introducing a 'fourth hurdle' to the three existing assessment criteria for new therapies – efficacy, safety and effectiveness.

The National Institute for Clinical Excellence (NICE)

Although the Department of Health has been promoting cost-effective initiatives in the pharmaceutical field, this has not yet extended to licensing. Over 95% of the drugs on the UK market are authorised by the licensing authority, acting through the Medicines Control Agency (MCA). A small number are now licensed throughout the EC via a centralised procedure, regulated by the European Agency for the Evaluation of Medicinal Products (EMEA). Prior to authorisation, the EMEA or MCA assess the safety, efficacy and quality of a drug. New drugs must be shown to be at least as safe as existing therapies, and also show comparable efficacy. If no suitable comparator exists, then efficacy must be shown to be superior to placebo. While the regulators consider the overall clinical benefit, they do not consider the cost effectiveness of the drug.

In April 1999, the National Institute for Clinical Excellence (NICE) was set up in the UK to evaluate clinical and cost effectiveness of new and existing pharmaceuticals and health technologies, and to prepare guidance on how they should be used appropriately by the English and Welsh NHS. The role of the institute is to promote the use of cost-effective treatments, while ensuring that the availability of these treatments does not vary by geographical distribution or postcode. Existing and new evidence contained in the manufacturers' submissions for drugs and technologies are reviewed before recommendations are disseminated to health professionals.

The first NICE recommendation to the NHS was issued in 1999, against the prescription of zanamivir for the treatment of influenza virus infection [25]. Although zanamivir was approved by the MCA for its indication, NICE cited evidence which showed only modest benefit in otherwise healthy individuals with influenza and at a significant cost. In addition, NICE decided that insufficient evidence was available for recommendations on the use of zanamivir in high-risk patient groups.

Although NICE has not formed a complete barrier to the reimbursement of new drugs, since the beginning of 2002 [26], health authorities are obliged to fund treatments based on their recommendations. Some of the recommendations have been controversial and health authorities have shown reluctance in allocating additional resources to implement the guidance [27].

Health Technology Board for Scotland (HTBS)

The Health Technology Board for Scotland (HTBS) was set up in November 1999. The objective of the board was to act as a national resource of information and independent advice on clinical and cost effectiveness on new and existing health technologies to decision makers in local Drugs and Therapeutics Committees (DTC), Health Boards, NHS Trusts, and the Scottish Executive Health Department. The Health Technology Board for Scotland was designed to undertake assessment on health technologies that have not been reviewed by NICE and provide advice and guidance on NICE technology appraisal in the Scottish context.

To date, the HTBS has completed 14 health technology assessments and made over 20 comments on NICE guidance. However, its approach to health technology assessment and its efficiency in producing comments and guidance have been heavily criticised. The Health Technology Board for Scotland has adopted an open and consultative process to assessing new health technologies in attempt to reflect voices of individual healthcare sectors within the NHS in Scotland. Specialised experts in appropriate areas of expertise have been invited to review HTBS assessment reports. However, these experts are often not representative of general clinical practice. There have also been doubts about the practical applications of the HTBS comments that are issued generally six to ten weeks after the NICE guidance documents are published.

In October 2002, the HTBS merged with the Clinical Standards Board for Scotland and the Scottish Health Advisory Service to create the Quality and Standards Board for Health in Scotland. It is believed that the objectives and functions of the HTBS would remain similar to those when it was founded in 1999.

SUMMARY

The expenditure on drugs in primary care will continue to rise. In response to this, literature on prescribing management is growing and budgetary reforms are introduced.

The establishment of NICE and HTBS in the UK have highlighted the importance of economic evaluations at national policy level. However, their impact on clinical practice and health costs has been difficult to measure. In addition, the optimum strategy for the design and effective dissemination of these economic materials is still unclear.

1.4 STRUCTURE OF THE THESIS

This thesis reports on two closely related areas of research. Firstly, it describes the economic burden of ADRs; then it describes the impact of economic information on decision making in primary care. These distinct themes are reported in such order throughout the thesis.

In order to explore the clinical and economic burden of ADRs in different classes of drugs, this thesis used three different classes of drugs as examples – NSAIDs, SSRIs and ACE inhibitors in the management of RA, depression and hypertension, respectively. Due to the limited financial scope of the PhD, two different types of ADR data had to be used. Firstly, this thesis reports on a large-scale population study, which estimated the substantial costs resulting from drug-associated adverse events while on NSAIDs. This is followed by three meta-analysis-based economic analyses of NSAIDs, SSRIs and ACE inhibitors. It is worth noting that the cyclo-oxygenase II inhibitors that selectively target specific inflammatory receptors are not included in these analyses due to the different mechanism of action from the "traditional" NSAIDs.

The impact of economic information on decision making in primary care was explored in a dissemination exercise and a postal survey, and are reported in subsequent chapters of this thesis. On reviewing the results, an additional qualitative study was introduced to explore in-depth, the implications of the findings of the dissemination exercise and the postal survey.

To avoid excessive fragmentation of the text in the chapters, all the tables and figures have been located at the end of the thesis.

2 AIMS AND OBJECTIVES

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2.1 STUDY AIMS

An initial literature review showed that despite the growing literature on economic evaluations on healthcare, there is limited evidence on the role of economic information on medical decision-making, in particular, relating to prescribing issues. This study was planned to examine the role of pharmacoeconomic information in primary care prescribing. In doing this, two broad aims were developed:

- the first aim was to investigate the effect of incorporating adverse drug reactions in economic evaluations of drug therapies;

- the second aim was to investigate the impact of this information on prescribing in primary care.

2.2 STUDY OBJECTIVES

This study had seven objectives, which were developed from the study aims. The first five objectives relate to the first aim while the remaining two objectives address the second aim of the study. The study objectives were:

1. to evaluate the cost associated with the use of NSAID therapy in a Scottish population based on epidemiological data from a population database;

2. to evaluate the cost associated with NSAID therapies in the treatment of rheumatoid arthritis, based on data reported in clinical trials and expert opinion;

3. to evaluate the cost associated with SSRI therapies in the treatment of depression, based on data reported in clinical trials and expert opinion;

4. to evaluate the cost associated with ACE inhibitor therapies in the treatment of hypertension, based on data reported in clinical trials and expert opinion;

5. to examine the use of data from a population database compared to randomised controlled trials;

6. to investigate the effect of disseminating economic information on primary care prescribing;

7. to examine the role of economic information on primary care prescribing from the perspective of GPs.

2.3 STUDY HYPOTHESES

A limited set of hypotheses was developed from the above objectives. These have been expressed as experimental hypotheses. The first three hypotheses address the first aim of the study while the remaining two objectives focus on the second aim of the study. The study hypotheses were:

1. some drugs of the same pharmacological family have been shown to have equal efficacy, however, these drugs may have different adverse drug reaction profiles;

2. the cost associated with treating adverse drug reactions is substantial;

3. drugs that are the cheapest to purchase are not necessarily the most cost effective to use;

4. targeted dissemination of pharmacoeconomic information can be used to help influence primary care prescribing;

5. general practitioners believe that economic information has a role in medical decision making.

3 ECONOMIC EVALUATION AND MEDICAL DECISION MAKING: A CRITICAL LITERATURE REVIEW

ECONOMIC EVALUATION AND MEDICAL DECISION MAKING: A CRITICAL LITERATURE REVIEW

3.1 INTRODUCTION

This literature review is split into two main sections according to the aims – the inclusion of ADRs in economic evaluation of drug therapies (Section 3.2), and the impact of economic information on decision making in primary care (Section 3.3).

The review in Section 3.2 has been designed to address the following questions:

- What is the incidence of ADRs?
- What are the clinical and economic consequences associated with ADRs?

The first section first looks at the broad issue, and then specific sections are given to the three classes of drugs focused by this thesis – NSAIDs, SSRIs and ACE inhibitors.

The published evidence on the incidence of ADR-related morbidity and mortality is reviewed. Section 3.2.1 discusses and evaluates the various sources of ADR data. Section 3.2.2 assesses the ADR incidence reported by studies of spontaneous reporting systems, the ADR incidence in hospital patients, including ADR-related hospitalisations, inpatient ADR incidents and ADR-related death found in studies of hospital patients and the ADR incidence in primary care. The clinical and economic consequences associated with ADRs are discussed in Section 3.2.3.

The next section (Section 3.3) discusses the findings of the studies that investigated the impact of economic information on medical decision making in primary care. The extent of knowledge (Section 3.3.1) and use (Section 3.3.2) of health economics in primary care decision makers, in particular among GPs are reviewed. In addition, the source of such information is examined (Section 3.3.3). Finally, the barriers to implementing economic information in primary care are discussed (Section 3.3.4).

The extensive literature review conducted on ADRs associated with NSAIDs, SSRIs and ACE inhibitors is described in the methods section (Section 4.3.1) and the results section (Section 5.3).

3.2 THE INCLUSION OF ADVERSE DRUG REACTIONS IN ECONOMIC EVALUATIONS

All drugs undergo a lengthy process of evaluation on efficacy, safety, effectiveness and cost effectiveness prior to licensing. Even when used according to its indication and at recommended daily doses, no drugs are entirely safe and without a toxicity profile. Optimal drug use is dependent upon the risk-benefit balance. Adverse drug reactions (ADRs) refer to adverse effects resulting from appropriate use of medicine, rather than due to medical error. The World Health Organisation has defined ADR as: "*a response to a drug that is noxious and unintended and occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease, or for modification of physiological function*" [28]. In the UK, the Committee of Safety of Medicine (CSM)/Medicines Control Agency (MCA) defines an ADR as: *an unwanted or harmful reaction experienced following the administration of a drug or combination of drugs under normal conditions of use and suspected to be related to the drug"* [29]. This thesis refers to ADRs based on these definitions and does not include events that resulted from inappropriate use of drugs, non-compliance and medical negligence.

Adverse drug reactions are generally mild (e.g. mild sedation from antihistamines); although rare, serious ADRs (e.g. haemorrhage from anticoagulation therapy) may lead to hospitalisation and occasionally death. Therefore, ADRs are a serious issue and management of these events may be associated with a substantial health and economic impact to the health service and to society. This is discussed in later sections of this chapter.

3.2.1 Source of Adverse Drug Reaction Data

Drug safety takes an equally important role alongside drug efficacy in pre-marketing drug development. Similarly, ADRs are monitored post-marketing alongside the effectiveness of drug therapies. All developed countries have some form of spontaneous reporting scheme to monitor adverse drug reactions continuously since the thalidomide disaster in 1961. In the UK, the Yellow Card Scheme has been set up to encourage reporting of suspected ADRs by healthcare professionals such as doctors, dentists, coroners, pharmacists and the pharmaceutical industry. This scheme was later extended to include reporting by nurses,

midwives and health visitors in 2002, and a pilot patient reporting scheme was introduced in 2003.

An alternative to the Yellow Card Scheme is prescription event monitoring (PEM) undertaken by the Drug Safety Research Unit (DSRU) at Southampton [30]. The DSRU focuses on a limited number of drugs (10 to 12) at any one time. The Prescription Pricing Authority (PPA) in England receives records of all dispensed prescriptions in England and forwards all the records of prescriptions for the drugs of interest to the DSRU. A 'green form' is then sent to the prescribing GP enquiring details of any ADRs in the patients who were prescribed the drugs of interest. Unlike the Yellow Card Scheme, both the numerator (returned 'green forms') and denominator in the ADR incidence rate calculation (number of dispensed drugs of interest) are known and overall, the PEM scheme is less limited by under-reporting.

Despite not being designed with the objective of monitoring ADR, there are several epidemiological databases that contain data that may be potentially used for researching in ADRs.

One of the most extensive database of this kind is the General Practice Research Database (GPRD) which contains both prescribing and diagnostic data [31]. The GPRD currently receives data from approximately 525 practices (3.4 million patients, over 30 million years of prescribing histories), recording every prescription and all significant morbidity. This database can be analysed to provide information on patients with selected diseases prescribed specific drugs. Although diagnoses are based solely on clinical judgement, the data have been found to be reliable and accurate when compared to other sources (e.g. consultants' letters, hospital discharge letters, or questionnaire surveys with GPs).

Mediplus is a second dynamic primary care database, most commonly used by the pharmaceutical industry [32]. It contains extensive data on patient demographics, morbidity, prescribing and mortality. Over 148 practices serving approximately 1.8 million patients participate in this data collection system. Although under-represented in Scotland, the data are believed to be representative of the UK as a whole. The data has been captured – during primary care consultation and from other information received in the practice – systematically, encoded and stored electronically in formatted records and updated monthly. The main data set contains details of patients, prescriptions, diagnoses, symptoms,

observations and tests in primary care, secondary referrals and main outcome of referral. Linkage between diagnosis and prescriptions is possible, but inappropriate linkage may cause problems with interpretation of data. The major limitation to Mediplus however, is the cost of accessing the database. Mediplus is a privately owned database and subscription to the database may cost as much as £25 000 per year. Therefore, Mediplus is primarily used by the pharmaceutical companies for marketing purposes.

In Scotland, the development of the General Practice Administration System for Scotland (GPASS) [33] and Continuous Morbidity Recording (CMR) [34] in recent years has shown positive signals in producing a comprehensive database for primary care research. Over 80% of all practices in Scotland participate in a national Scottish computer system for general practice – GPASS, which was set up primarily to collect data for administrative functions. Data from individual practices such as patient registration, repeat prescriptions, call and recall, health promotion and immunisation have been captured via Electronic Questionnaires (EQ). Reports on the practice data can be generated, in particular, on areas of health promotion, chronic disease management and patient summaries, which has been extremely useful to GPs. Based on the original EQ, the GPASS Data Evaluation Project (GDEP) has redeveloped the data capture system to collect anonymous data at patient level from over 400 practices (approximately 2.8 million patients). The GPASS Data Evaluation Project has created an extensive primary care database, where relevant patient data can be extracted, interpreted and compared regionally and nationally, with the aid of software utilities such as Prescribing Analysis Tools [35], Practice Report Utility [36], among others. Feedback on individual practice, regional and national data has been distributed bi-annually.

Continuous Morbidity Recording is a three-way collaboration between the Information and Statistics Division (ISD), Department of General Practice at the University of Aberdeen and the Scottish Centre for Infection and Environmental Health (SCIEH), which began as a pilot project in 1992. The project has now evolved into an invaluable national source of primary care morbidity data from over 60 practices throughout Scotland [34], and participating practices cover all but two health board areas – Orkney and the Western Isles.

Continuous Morbidity Recording is generating a database of active morbidity and GP workload. Morbidity information is collected on a continuing basis from all face-to-face consultations between patients and GPs. Based on the development of the EQ, the CMR

project has been developed to collect and analyse additional data from the daily work of general practice: the patients, symptoms, disease, consulting and prescribing behaviour and geographical and socio-economic patterns, including deprivation. Details of each doctor-patient contact – at surgeries, home visits or clinics - has been recorded. However, no data are collected about prescribing, direct data entry (health promotion and administration) or nurse-led clinic activities. CMR data provide insight into demand for GP services and can be extrapolated to provide estimates of workload at national level. However, due to the small number of participating practices at present, the patient population covered is not representative of Scotland as a whole in terms of age, geography and deprivation.

3.2.2 The Incidence of Adverse Drug Reactions

Spontaneous Reporting

Since 1964, when the scheme was set up, over 400 000 suspected ADRs have been reported. In the year 2000 alone, over 33 000 reports were submitted to the Yellow Card Scheme, most were associated with the Meningitis C vaccine [37]. Despite some success in identifying ADRs such as remoxipride and aplastic anaemia, the main limitation of under-reporting remain. A large retrospective review of case notes has revealed that only 2% to 4% of all ADRs [38] are reported through spontaneous reporting. Similarly, it has been reported that only 10% of serious ADRs are reported through spontaneous reporting [39].

In 2002, 1369 suspected ADRs were reported to the CSM in Scotland [40]. Assuming that due to under-reporting only 2% to 4% of all ADRs are reported [38], the expected number of ADRs is approximately 34 225 to 68 450. In the same year, approximately 66.2 million prescription items were dispensed in Scotland (equivalent to 12.4 prescriptions per patient on GPs' list) [41], giving an ADR incidence rate of approximately 0.05% to 0.10% of all prescriptions. However, the severity of the ADRs and the proportion of patients who seek or require medical treatment are unclear.

Incidence of ADR in Hospital Patients

Although data from spontaneous reporting schemes gives an indication of the incidence of ADRs, the risk, management and cost of ADRs associated cannot be determined. In order to examine these issues, specifically designed studies need to be undertaken. The risk, management and cost of ADRs are not widely investigated. Studies that have attempted to investigate the incidence of ADRs in the medical literature, have focused primarily on serious events that led to hospitalisation or ADRs that occurred in patients whilst in hospital.

An early systematic review (1993) [42] of drug-related hospital admissions (defined as admissions resulting from a patient's non-compliant or unintentionally inappropriate drug use), examined the findings of 36 studies published between 1966 and 1989. The prevalence of the pooled admissions resulting from ADRs was 5.1% (95% CI 4.4% to 5.8%). Of these ADR admissions, 71.5% were classed as "side effects", 16.5% "excessive effects", 11.3% hypersensitivity reactions and 0.4% idiosyncratic; 5% of admissions due to ADR resulted in mortality.

In a meta-analysis of 39 prospective studies published from 1966 to 1996 from US hospitals [43], serious ADRs were defined as those requiring hospitalisation, were permanently disabling or resulted in death. The incidence of serious ADRs that led to hospitalisation (4.7%; 95% CI 3.1% to 6.2%) was combined with the incidence of ADR whilst in hospital (2.1%; 95% CI 1.9% to 2.3%) to determine the overall incidence of serious ADRs in hospital patients (6.7%; 95% CI 5.2% to 8.2%). Fatal ADRs were estimated in 0.32% of all hospitalisations. A similar overall ADR incidence (6.7%; 95% CI 6.6% to 6.8%) was estimated in a more recent systematic review and meta-analysis of data from 69 studies conducted worldwide published between 1966 and 1999 [44] (US studies = 21, European studies excluding UK and Ireland = 21 and studies based in the UK and Ireland = 7). However, when the analysis was stratified by geographical setting, it was found that ADR incidence based on data from the UK (7.5%; 95% CI 7.2% to 7.8%) and Europe (14.1%; 95% CI 13.8% to 14.3%) were significantly higher those reported from North American studies (4.6%; 95% CI 4.5% to 4.7%).

Beijer and de Blaey (2002) [45] conducted a systematic review on the rate of ADR-related hospitalisation. Sixty-eight studies from the US (n = 25), Europe (n = 19) and Australia (n

= 15) were included in the review. Adverse drug reactions were defined according to the WHO definition. The studies reviewed varied considerably in sample size (ranging from 41 to 24 000) and observed ADR-related hospitalisation (ranging from 0.2% to 41.3%). Aggregated ADR incidence rates calculated from two different methods were presented: (1) a proportion calculated by the number of total ADR-related hospitalisations across all studies divided by the total number of hospitalisations across all studies (4.9%; 95%CI 4.8% to 5.0%); (2) an average of the proportions of ADR-related hospitalisation as published in individual studies (12.5%; 95%CI 9.9% to 15.1%).

Although no formal analysis of heterogeneity was undertaken, it is apparent that much inconsistency exists between the individual studies included in the reviews. However, the estimated overall incidence of ADR in hospital patients was relatively consistent among the systematic reviews, with overlapping confidence intervals. Therefore, it is reasonable to suggest that the incidence of ADRs in hospital patients fall within the range of 4.4% to 15.1%.

Incidence of ADR in Primary Care

To date, no systematic review has been conducted to evaluate the incidence of ADRs in general practice and little is known. However, the lack of data reflects on the difficulty in conducting research in this area. The largest survey of ADRs (based on the WHO definition) in general practice in the UK was conducted by Lumley CE et al (1986) [46], when data were collected from 24 training practices in a health region (former South West Thames) in England, over a period of four weeks (n = 100). Of 36 470 consultations evaluated, 1.7% reported ADRs (n = 638 consultations). In approximately half of these cases (0.8%), the ADR was the cause of the GP consultation. However, only 1.6% of ADRs reported (arising in 0.027% of consultations) were judged to be serious. Cardiovascular drugs and diuretics were the most frequently involved drugs (23%), while gastrointestinal (GI) disturbance was the most frequently observed ADR (13%).

The most recent study was conducted by Lacoste-Roussillon C et al (2001) [47]. A prospective study of the incidence of serious ADRs (based on the WHO definition) in 254 GPs was conducted in France. During a five-day period, 13 validated serious ADRs (two were fatal) were observed, representing an "incidence density" of 10.2 (95% CI 5.4 to 17.5)

per 1000 days of practice. If this was extrapolated to the 60 000 active GPs in France, it could be estimated that 123 000 (95% CI 65 400 to 210 000) serious ADRs are seen each year by GPs in France. In this study, antineoplastic and anticoagulant agents were the most frequently involved drugs (seven cases), while blood dyscrasia and bleeding were the most frequently observed ADRs.

This thesis focuses on three different classes – NSAIDs, SSRIs and ACE inhibitors – of drugs with different mechanisms of action for their intended effects. These drugs are associated with different ADR profiles, which are discussed below.

Non-steroidal Anti-inflammatory Drugs

Non-steroidal anti-inflammatory drug therapy is the dominant treatment in arthritis and musculoskeletal conditions. The use of these drugs is extensive. In the UK alone, over 20 million prescriptions are made for NSAIDs annually, accounting for approximately 5% of all the NHS prescriptions [48].

These drugs are extremely effective in appropriately maintained dosages. Currently, there is no established method to predict which NSAID will be the most effective for an individual patient, but minor differences in efficacy have been found. Statistically, all NSAIDs are similar in potency despite consistent but unexplained inter-patient variability in both efficacy and adverse drug reactions profiles. However, attention has been increasingly focused upon inherent safety problems, and the size of the problem associated with NSAID-induced adverse drug reactions is highly significant. In 1986, the CSM reported that 25% of all the 'yellow card' reports received in the UK are NSAIDs-related [49]. The most frequent, as well as the most severe adverse drug reactions, are located in the GI tract, other adverse events are related to the central nervous system (CNS), the kidneys, the liver, the blood and the mucocutaneous system [50,51]. There is emerging evidence of substantial differences in toxicity between in NSAIDs [52].

A number of studies have been dedicated to NSAID-induced GI toxicity. Gastropathy induced by the treatment with these drugs is undoubtedly the most common adverse reaction related to the regular use of NSAIDs [53-56].

Mild GI complications are common, such as dyspepsia, diarrhoea, constipation and gastric mucosal damage (with endoscopic evidence of gastritis). It has been suggested that 5 to 50% of the patients on NSAID therapy would experience dyspepsia [57,58].

Serious and often life-threatening events have also been reported such as peptic ulcer disease and upper GI bleeding [59]. The incidence of peptic ulcers (gastric and duodenal) range from 10 to 40% of patients who are on NSAID therapy [60]. Clinically important peptic ulcer caused by NSAIDs can occur in mucosa inflamed because of infection with *Helicobactor pylori* or in histologically normal mucosa. A study carried out in 1992, evaluated GI damage in 713 post mortems conducted on a random series of hospital patients, of whom 249 had taken NSAIDs. Peptic ulcer was found in 20% of the NSAID users compared with 12% in non-NSAID users [61]. In addition to an association with gastric ulceration, NSAIDs are also believed to inhibit epithelial regeneration at the edge of gastric ulcers, thereby delaying ulcer healing [62].

In 1983, Venning published a series of articles in the British Medical Journal on the "identification of adverse reactions to new drugs" [63]. He suggested that the fatal reports related to NSAID-induced GI bleeding indicated that it was the third most important drug-induced cause of death between 1964 and 1980. Independent studies have indicated that the relative risk of ulcer complications for NSAID users is approximately four times higher than non-users [64,65]. Estimates show that 0.7% to 1% of regular NSAID users are hospitalised as a result of upper GI bleeds [66].

Co-prescribing GI protective drugs such as antacids, H_2 blockers, misoprostol and proton pump inhibitors are common procedures in treating mild GI adverse drug reactions due to NSAIDs. However, in cases when the symptoms are severe, further investigations such as endoscopy or gastric biopsy and hospitalisation may be required. These procedures make a significant contribution to the cost of NSAID therapy.

Renal dysfunction is a recognised complication of oral NSAIDs. These drugs may induce fluid and electrolyte disorders and both acute and chronic renal failure [67]. The most common renal adverse effect is haemodynamically mediated, resulting in depression of renal function, which is usually completely reversible within 24 to 72 hours following discontinuation of the drug. Interstitial nephritis is an extremely rare and idiosyncratic event which has been described with many NSAIDs [52,68].

It has been estimated that approximately 5 to 18% of outpatients receiving NSAIDs have renal impairment and the impact on the kidney is the greatest among these patients (usually the elderly) who depend on the synthesis of vasodilatory prostaglandin to maintain renal homeostasis. There is increasing awareness of the difference in the extent of renal damage induced by individual NSAIDs [60]. It is believed that drugs with high renal clearance of active metabolites, such as indomethacin and naproxen, are more toxic to the kidneys [69].

Isolated cases of hepatic damage have been noted with almost all NSAIDs in clinical use. The severity of liver disease has varied from mild asymptomatic elevation of one or more hepatic enzymes to severe hepatocellular injury resulting in death, but these events are generally uncommon. Case reports suggest that NSAIDs may be associated with liver disease, but it appears that the risk is very small [70]. It is believed that greater risk is observed in RA patients and in those who were concomitantly exposed to other potentially hepatotoxic drugs. One study estimated the incidence rate of acute liver injury induced by regular use of NSAIDs to be one per 100 000 prescriptions (equivalent to four per 100 000 users) [71]. These events are generally mild and are usually reversible with reduction in dosage or discontinuation of the drug.

Second to GI toxicity, skin reactions due to NSAIDs are common. Although these reactions (including pruritis and non-specific rashes) are relatively mild in nature, fatal reactions, including erythema multiforme, have been reported. Most cases of dermatological reactions improve when the NSAID is discontinued. Generally, no treatment is required but antihistamines are sometimes prescribed to alleviate itching. It was suggested that drugs with long half-lives, such as piroxicam, are more commonly associated with adverse cutaneous reactions [72].

All NSAIDs have been implicated in adverse events in the CNS, and up to 10% of the regular NSAID users suffer a variety of these symptoms. These include severe headache, dizziness, trouble with thinking, tinnitus and blurred vision. Headache is the most common NSAID-induced CNS side-effect, particularly with patients taking indomethacin [73]. Tinnitus is reported rarely, commonly observed in subjects with high doses of salicylates, e.g. Aspirin, who also experience a reversible sensorineural hearing deficit of up to 30 - 40 decibels across all frequencies. More severe side-effects such as aseptic meningitis, psychosis and cognitive dysfunction have been documented. However, these cases are

extremely rare and have not been reported in the clinical trials or post-marketing studies consulted in this study [74].

Haematological disorders include aplastic anaemia, agranulocytosis, thrombocytopenia and haemolytic anaemia [75]. Agranulocytosis tends to develop primarily in younger patients, often after a few days or weeks of NSAID therapy, but is usually reversible on discontinuation. Phenylbutazone-induced aplastic anaemia was listed as one of the 18 most important adverse reactions by Venning (1983) [63]. This adverse effect occurs more frequently in the elderly and is more likely to prove fatal. Recent studies suggest that indomethacin and diclofenac may cause more haematological toxicity than other NSAIDs [55].

In addition to the above mentioned NSAID-induced drug reactions discussed, other side-events have also been observed with NSAID therapy. These include a variety of disorders such as pulmonary toxicity (commonly observed as bronchospasm), cardiovascular (CV) oedema, enhanced mean arterial blood pressure of hypertensive patients, lethargy, palpitations, amongst others. However, these events are extremely infrequent and have mostly been reported only in individual case reports [76]. Therefore, these secondary events are believed to make little or no contribution towards the economic consequences of NSAID therapy and have not been included in this evaluation.

Selective Serotonin Reuptake Inhibitors

The group of SSRIs including fluoxetine, fluvoxamine, paroxetine and sertraline is one of the most common classes of drugs used in the treatment of depression. Although similar in efficacy to the traditional tricyclic anticholinergics (TCAs), overall, these drugs have been shown to have a superior safety profile, free from anticholinergic, CNS and CV effects [77]. However, no drugs are free of ADRs and events such as nausea, diarrhoea, insomnia, nervousness, agitation and anxiety have been observed with SSRIs [78-80]. Selective serotonin reuptake inhibitors act by inhibition of serotonin reuptake, resulting in increasing amounts of plasma neurotransmitter being available to interact with the receptors. Therefore, most of the adverse events associated with SSRIs are dose related and can be attributed to serotonergic effects. The typical ADRs associated with SSRIs include GI effects, CNS effects and sexual dysfunction.

Compared with the use of NSAIDs, SSRIs are associated with a less substantial ADR profile. Gastrointestinal disturbance are the most frequently reported ADR among patients on SSRIs [81]. Clinical trials have reported GI events such as nausea, vomiting, dyspepsia, abdominal pain, diarrhoea and constipation ranging from 6% to 37%. During the first two years of marketing, gastrointestinal ADRs have been reported between 21.1% (paroxetine) and 38.8% (fluoxetine) of patients in the UK [78]. In a meta-analysis of SSRIs for major depression [79], gastrointestinal ADRs such as nausea and diarrhoea were shown to be more commonly reported – 10.3% (95% CI 7.3% to 13.3%) and 9% (95% CI 4% to 14%), respectively more than those on TCAs. However, when compared with TCAs, a lower rate of constipation was reported (11%; 95% CI 8% to 14%, less than that observed with TCAs).

Between 11% and 26% of patients have reported ADRs to the central nervous system (CNS) including insomnia, somnolence, tremor, dizziness and headache. Other ADRs such as dry mouth and sweating have been observed in 9% to 30%.

Sexual dysfunction is a common characteristic of depression itself, as well as an adverse reaction to antidepression therapy. Therefore, the true incidence of sexual dysfunction attributable to SSRI use is difficult to measure. Studies have reported incidences ranging from 13.5% to 22% based on checklists and spontaneous reporting, respectively. However, systematic enquiry has reported much higher rates of 54% to 65% [82].

Weight gain or weight loss have been reported in approximately 4% of patients on SSRIs. In particular, the weight loss observed with the early short-term clinical trials with fluoxetine have prompted further investigations into fluoxetine as a potential weight loss agent [83]. Although some SSRIs are associated with weight loss at the onset of therapy, weight is often regained after six months and can be followed by additional weight gain with long-term use. Therefore, weight gain has subsequently been shown to be a common ADR of long-term SSRI therapy. Mean weight gains of 6.75 Kg to as much as 10.8 Kg have been observed with sertraline and paroxetine respectively, over a period of six to 12 months in uncontrolled studies [84,85].

Cardiovascular ADRs are uncommon. Symptoms such as palpitation and hypotension, including postural hypotension and tachycardia have been reported in a small proportion of

patients on SSRIs. Collectively, CV events have been reported in 2.6% to 4.1% of patients on SSRIs [78].

Angiotensin Converting Enzyme Inhibitors

ACE inhibitors are widely prescribed as a first line therapy in the management of essential hypertension, particularly in patients with concomitant diabetes, renal disease and congestive heart failure. Their efficacy in reducing both mortality and morbidity associated with hypertension has been shown in many randomised controlled trials.

However, in treatment of hypertension, patients often receive sub-optimal treatment due to poor compliance, intermittent or switched prescriptions. Termination of use disrupts the consistency of treatment. Hypertension is asymptomatic; therefore, patients who are treated with an antihypertensive agent that causes adverse events may perceive a lower quality of life, although blood pressure is controlled. This contributes substantially to patient non-compliance. Non-compliance, in turn results in rebound hypertension and potentially serious CV and renal complications.

Adverse drug reactions (ADRs) may be one reason for changing or stopping drug use, but the proportion of hypertensive patients who change or discontinue treatment because of ADRs is difficult to estimate. A recent pharmacoepidemiology study in Italy showed that physicians (N = 1255) considered the main reason for discontinuation and switching to be inadequate blood pressure control (51.2% of patients) and adverse drug events (34.5%) [86]. However, completed questionnaires from 4612 patients in the same study considered ADRs as the major reason for switching (53.3%) followed by inadequate blood pressure control (34.1%).

Angiotensin converting enzyme inhibitors are generally well tolerated. The most frequently reported adverse effects include headache, cough, dizziness, fatigue and diarrhoea. Adverse events vary among individual drugs within the class. Common side effects include rash (often alleviated with reduced dose), hypotension (first dose, common among elderly) and cough (non-productive, nocturnal and hacking – up to 5% to 15%) [87]. Cough is believed to be a class effect of the ACE inhibitors, occurring in about 25% of patients. The cough is

characterised as dry, non productive, and persistent, and may be disturbing enough to prompt discontinuation of therapy.

Angioedema, often presenting as swelling of the face and neck has also been reported, but in less than 1% of all patients. Although rare, it is potentially life threatening. Leukopenia also occurs rarely, mostly in patients with specific risk factors - severe renal dysfunction or vascular disease [88]. Renal failure is also uncommon, but may occur in patients with bilateral renal artery stenosis or disease associated with high renin activity such as pre-existing congestive heart failure. Uraemia is often observed in those who lack careful renal function monitoring for example in vulnerable patients [88].

3.2.3 Clinical and Economic Consequences of Adverse Drug Reactions

The impact of ADRs on healthcare is difficult to estimate. There is a lack of real patient data; therefore, only extrapolation is possible. By extrapolating the study findings, Lazarou J et al (1998) [43] estimated that over 2.2 million hospitalised patients had serious ADRs and 106 000 had fatal ADRs in the US, making these reactions between the fourth and sixth leading cause of death in 1994. However, this study has been criticised for bias resulting from heterogeneity between the aggregated data and it is believed that the estimated mortality has been much inflated [89].

The direct and indirect costs are difficult to estimate, as data on the consequences, in particular on healthcare resource use of most ADRs are very limited. The costs of incidents where ADRs are probable causes of death or hospital admissions may be identified and measured. Costs may also be estimated based on the description of the nature of ADRs, which gives indication about the severity of the event. However, it is extremely difficult to measure, for example, the medical expenditure or number of days lost from work due to all kinds of ADRs.

The lengths of stay, and subsequently the cost of hospitalisation associated with ADRs have been shown to be substantial [90,91]. In a matched case-control study, Classen et al (1997) [91] matched 1580 patients with one hospital-acquired ADR with 20 197 controls and reported an ADR incident rate of 2.4% during the three-year study period. These events were

associated with an increased length of stay of 1.91 days and an additional cost of US$2262. Similarly, Bates et al (1997) [90] reported an ADR incidence rate of 4.6% in a cohort of 4108 admissions over a six-month period. The additional length of stay and costs associated with ADRs and preventable ADRs were 2.2 days and US$3244, and 4.6 days and US$5857, respectively.

Hospital admissions associated with ADRs are only one aspect of drug related morbidity. A larger proportion of ADRs may never result in hospitalisations, but these events may still lead to substantial health and economic impact in the form of regular visits to GPs, co-prescribing and the use of other social services.

Non-steroidal Anti-inflammatory Drugs

Non-steroidal anti-inflammatory drug therapy is costly. The costs of treating adverse effects add a considerable expense to the cost of the therapy. Adverse drug reactions in NSAID-therapy add considerable burden to the NHS.

Blower et al (1997) [92] attempted to measure the burden of NSAID-related ADRs in the UK in a retrospective analysis of all emergency admissions for upper GI disease, as well as an analysis of the records of all community deaths attributed to upper GI diagnoses, compared with matched controls. The results showed that NSAID users were more likely to require a blood transfusion, a higher volume of transfused blood and to be hospitalised longer than those who are not on NSAIDs. Similar findings were reported by Hawkey et al (1997) [93] when 500 patients, aged over 60 years admitted to hospital with peptic ulcer bleeding over a five-year period were interviewed. In addition, prescribing in 103 practices was also examined. This study reported an average admission rate for bleeding peptic ulcer of 15 per 1000 000 per year. In addition, the authors concluded that the findings were equivalent to one episode of ulcer bleeding in the elderly per 2823 (95% CI 2095 to 8116) prescriptions. In another cohort study of patients over 50 years, based on population data from Tayside [94], 2% of NSAID takers were admitted with GI events compared to 1.4% of non NSAID takers, suggesting that about 0.2% of the over 50s population may be admitted in any one year because of NSAID-related GI events.

In an attempt to address the GI problems associated with NSAID use, the co-prescription of gastroprotective agents such as H_2-receptor antagonists, proton pump inhibitors and misoprostol has become common practice. Among these drugs, misoprostol has been found in clinical trials to reduce the incidence of gastric and duodenal ulcers in patients requiring continuous NSAID therapy. H_2 blockers seem to reduce complications of gastric and duodenal ulcers. In Scotland, Omeprazole was the most costly and the ninth most commonly prescribed drug in the year 2000, at £37 699 000 for over one million prescriptions, lansoprazole was the third most costly at £14 858 000 and ranitidine was the sixth most costly drug at £12 252 000 [95].

In another study, Moore and Phillips (1999) [96]estimated the annual burden of NSAID-related GI ADRs from the perspective of the NHS by conducting a simulation study based on three patterns of NSAID co-prescribing. When the costs for NSAIDs and gastroprotective agents (omeprazole and ranitidine) were included, the cost per patient prescribed an NSAID for an average co-prescription estimate amounted to £40 per year, and to £215 million when the results were extrapolated to the whole of the UK. In addition, the total costs per patient with an NSAID-related bleed were estimated to be £2198, equivalent to an annual cost of £35.5 million in the UK.

Several studies on the real cost of NSAID therapy have been documented. These evaluations not only take into account the cost of the drug but also the cost of treating other factors such as associated GI complications (the 'shadow' cost) [20,21]. De Pouvourville (1992) [20] suggested in his study that the cost of NSAID therapy may be increased by 2.1 to 3.6 fold when the shadow cost of treating GI complications has been taken into account. The economic consequences of the unwanted secondary effects of NSAID therapy can be demonstrated by a simple shadow cost model. The cheapest drug may not be the least expensive in the end.

Selective Serotonin Reuptake Inhibitors

The high costs associated the treatment of depression have increased interest in pharmacoeconomic evaluations of drug treatment, particularly in the 1990s, as the use of SSRIs expanded substantially. Many observational studies have been carried out to

compare differences between SSRIs and TCAs [97-99]. These studies attempted to estimate the costs to the healthcare system based on outcomes such as treatment duration and drug switching. Although SSRIs are generally associated with higher acquisition costs than TCAs, the total healthcare costs are decreased, by the reduction in acquisition costs associated with the use of SSRIs.

Results from short-term studies comparing SSRIs and TCAs suggested that SSRIs are either more cost effective, or that there is no difference in costs. A prospective, randomized trial [97] comparing clinical outcomes and treatment costs for patients who were initially prescribed an SSRI or TCA, showed that the higher cost of fluoxetine therapy was balanced by fewer outpatient and inpatient costs. Patients who were prescribed fluoxetine reported fewer ADRs and lower rates of medication switching and were more likely to reach adequate dosing levels in patients who were prescribed TCAs. The total costs for care over six months were equal in both groups.

Longer term studies, mainly lifetime simulation models, focused more on the impact of maintenance antidepressant therapy and showed more mixed results, but still favoured SSRIs over TCAs. The cost effectiveness of treatments was mainly determined by the costs associated with reduction in relapse rates, and the assumption of lower treatment discontinuation rates [100]. However, comparative studies of individual SSRIs, focusing on the costs associated with adverse drug events, have not been identified. The cost of treating some of these adverse effects has been cited as a major contributor to the overall costs of drug therapy [101]. Adverse effects leading to discontinuation of medication may, in fact, be associated with discomfort and loss of productivity and other indirect costs attributable to treatment failure.

Angiotensin Converting Enzyme Inhibitors

In the US, the total cost of hypertension treatment in 1998 was estimated at $23.3 billion, $7.5 billion of which was the pharmaceutical cost [102]. In Sweden, the total annual cost of treating hypertension in 1992 was approximately 1.6 billion Swedish Crowns (£160m) [103].

Unlike the case of NSAIDs , the literature for cost effectiveness studies on ACE inhibitors in the treatment for hypertension is sparse. Some cost of illness studies have reported on

the economic burden of hypertension to the healthcare system and society as a whole, but few examined the cost effectiveness of drug therapies for the treatment of hypertension.

Only a few studies attempted to evaluate the cost of individual ACE inhibitors for the treatment of hypertension. These studies compared selected ACE inhibitors with drugs from different classes of antihypertensive agents [104-106], Angiotensin I receptor blockers [107]. Others examined the economic and clinical consequences in specific patient groups, in particular, those with type 2 diabetes [108]. The cost implications of drug switching have also been evaluated [109-111].

However, the measure of effectiveness, the cost variables included, and the characteristics of the patient population varied considerably across the studies. This lack of conformity has made it difficult, "if not impossible", to compare the findings and make conclusions about the relative cost effectiveness of different antihypertensive therapies.

SUMMARY

The importance of ADRs is often underestimated. These events are common and in extreme cases, may lead to mortality; while at the opposite end of the scale, these events may incur unnecessary expenses to the NHS. Although the incidence of ADRs and their subsequent impact on costs have been investigated in studies based primarily in hospitals in the US, the implications are clear from the published results that ADRs constitute a widespread problem that causes adverse clinical events and substantial increases in costs.

Therefore, a full economic analysis of drug use must take into account not only the cost of the drug but also the cost of any potential ADR induced by the use of this drug. Despite the wealth of literature on the effect of ADR on an increase length of stay, and with additional hospital admissions, the costs associated with these events in primary care are unknown.

3.3 THE IMPACT OF ECONOMIC INFORMATION ON MEDICAL DECISION MAKING: A PRIMARY CARE PERSPECTIVE

A literature review on the impact of pharmacoeconomic information in influencing primary care prescribing was initially intended. A literature search for studies investigating the influence of economic information in influencing prescribing decisions was conducted. However, extensive trawling of the literature has revealed no studies fulfilling the search criteria. Therefore, a critical review of the impact of economic information, not specific to primary care prescribing, but in overall medical decision making in primary care, was conducted. This review focused on studies that aimed to examine decision makers' perspective on the usefulness, the value and their awareness of economic information; their perceptions about barriers to implementing such information were also examined.

The search strategies (Appendix II) included searching all major electronic databases, the Internet, hand searching of references from relevant literature, author citation search using the Web of Science Database and consultation with other researchers, in the attempt to capture both the mainstream and grey literature in the area. Only articles published in English were retrieved. All the studies meeting the following criteria were included: (1) study participants included medical decision makers in a primary care setting and (2) the aim focused on economic, not cost information.

Despite the volume of research on health economic issues, few published studies concerning the impact of economic information in primary care medical decision making were identified. These studies all focused on primary care decision makers' understanding and perspectives in the role of economic information in medical decision making; therefore, consisted solely of qualitative research such as surveys and focus groups (Table 1). The perspectives of a heterogeneous mix of medical decision makers in different countries were explored including clinicians (primary and secondary care), prescribing advisers, managers and purchasers, both in government and health authorities. Although data relating to primary care decision makers cannot be extracted in isolation, these studies were also included in this review.

The literature has identified and highlighted several influencing factors surrounding the role of economic information in primary care medical decision making. The main findings of these studies are generally in agreement, that there is recognition of the importance of

economic information in decision making, but the current evidence available is not being used sufficiently, due to various barriers relating to relevance and bias.

All the studies identified in the literature search are summarised in Table 1.

3.3.1 Knowledge in Economic Information

There have been some attempts in the literature to assess the level of knowledge in health economics among decision makers through measuring formal training in health economics and use of direct questions regarding self-perception of knowledge. A postal survey (n = 446) conducted in 1997 [112] reported that health economics training primarily consisted of a short course, was modest (37% overall), among prescribing advisers (40%), pharmacists (17%) and directors of public health (86%). The high proportion observed among directors of public health may be explained by the fact that knowledge about health economics was needed as part of their qualifying examinations. Similar results were observed in the European Network on Methodology and Application of Economic Evaluation Techniques (EUROMET) project when decision makers (n = 1022) over nine European countries (including the UK) were surveyed by postal questionnaire, semi-structured interviews, or through focus groups[113]. The study reported, "on average, those who had participated in health economic courses amount to a third", with Norway reported to have the highest training rate of 50%.

The overall lack of training has been reflected in the lack of understanding about economic evaluation techniques. Duthie et al (1999) [114] presented decision makers with different health economic outcome statements on randomly ordered shuffle cards in a focus group study to determine what decision makers view as relevant to their decision making. It was found that a high proportion of the statements relating to traditional health economic outcomes such as incremental ratios, quality adjusted life years and willingness-to pay were not understood, or were viewed as irrelevant. Similar conclusions were drawn from the EUROMET study[113], where the majority of the participants were reported to have poor knowledge of cost benefit, cost effectiveness or cost utility analysis. In a recent focus group study, decision makers from two health authorities (n = 12) were presented with abstracts retrieved from the NHS Economic Evaluation Database (NHS EED) [115] for

discussion. The authors reported that some of the participants experienced difficulties with the economic terminology used in the literature.

3.3.2 The Use of Economic Information

Secondary to evidence of clinical effectiveness, there is a general agreement among decision makers that economic information is an important factor to be taken into account in medical decision making, in particular, when making decisions on adopting new treatments [113,116]. However, studies have generally reported modest use (approximately one third of surveyed participants) of economic information in decision making [113,117]. Contrary to these findings, although no numerical data were presented, it is believed that the focus group study conducted by Hoffmann et al (2002) [115] indicated a higher level of use, stating that "most of the participants" had used economic information previously.

3.3.3 Source of Economic Information

Peer-reviewed clinical journals have been reported to be the most important source of economic information for decision makers [112,113]. The EUROMET study reported that decision makers in the UK viewed secondary sources (e.g. Bandolier [118], effective healthcare bulletins [119], drug and therapeutic bulletins [120]) as the most important source of information. Opinions of colleagues have also been perceived by prescribing advisers and pharmacists to be reliable sources of information[112].

3.3.4 Barriers to the Use of Economic Evaluation

All the studies included in this review investigated barriers to the use of economic evaluation to some extent. Despite the different settings of the studies, with regards to the country in which the studies were undertaken and the type of decision makers consulted, there was a certain pattern to the barriers identified.

Organisational barriers such as the rigidity of the structure of the healthcare system and difficulty in reallocating resources have been highlighted as the major factor associated with

the limited use of economic information in decision making [112-114]. This is not unique to the UK as similar conclusions were drawn from the EUROMET study [113], where "difficulty in moving resources from one sector (budget) to another" has been ranked as the main barrier to the use of economic studies in decision making. Because of this, decision makers felt that there is limited scope in using economic studies in their everyday practice, and that findings from economic studies are of little relevance to their everyday practice. This was echoed by decision makers in the study conducted by Duthie et al [114]. All the participants in the study indicated that financial savings reported in economic studies were only of interest if the savings were "realisable" and resources could be "physically reduced".

Another major barrier discussed was the perceived lack of credibility of economic studies. This was described by 26% of participants in the survey by Ross et al (1995) [117]. Similarly, "studies open to bias because of large number of assumptions" was the second most common barrier reported, described by 56% of decision makers in the Drummond survey [112].

In addition, an equal proportion of participants (26%) raised concerns regarding health economics 'jargon' used in the survey by Ross et al (1995) [117]. It was felt that academic researchers seem to put more emphasis on the rigour of their methods than on communicating the principles involved to decision making. Similar concerns were raised by Duthie et al [114], describing a general mistrust in statements containing health economic jargons and later, by Hoffmann et al [113], who reported that "sponsorship of studies (e.g. by the industry) biases the results" and "economic studies make too many assumptions" as the second and fifth most referred barriers by decision makers.

Decision makers also felt that economic analysis often adopts a long-term perspective. The time horizon adopted in economic studies has often been viewed as impractical and reduces the value of the economic studies [116]. For instance, studies that identified benefits over five to 10 years in exchange for increase spending now; if this were the case, there is a danger of overspending at present. It was felt that faced with pressures to operate within given budgets would mean that investment in a policy for long-term savings may often be impossible.

SUMMARY

Overall, the findings of the studies included in this review are in general agreement with each other. Primary care decision makers such as GPs, medical prescribing advisors and pharmaceutical prescribing advisors generally have a positive interest towards economic information and agreed that economics should be an integral part of medical decision making. However, the knowledge and understanding of health economic principles among decision makers is limited and the extent of actual use of such information in decision making remains unclear. Two key barriers to implementing results of economic studies have been identified: one practical barrier – the difficulty in reallocating resources, and another barrier associated with methodological issues in conducting economic studies.

The impact of any intervention on decision makers' perspectives and behaviour is extremely difficult to measure and the current studies have their own limitations. Several methodologies have been adopted to attempt to measure the level of knowledge of economic issues among primary care decision makers, ranging from examining the level of training in economic issues to presenting and discussing economic studies at face-to-face meetings. In two separate studies, statements relating to economic principles [114] and abstracts of economic studies [113] have been presented to decision makers. Although this gave some indication of the decision makers' understanding on particular health economic issues, their wider understanding of health economics was not explored.

Due to the nature of the research area, these studies have been primarily surveys and qualitative interviews, where responses cannot be validated. Often, in studies of this nature, participants' responses may be more representative of how they believe they should respond instead of what they actually think or practise. This would have particular influence on the measure of use of economic information in practice and is likely to over-estimate the actual use of economic information. In addition, the "use" of economic information has not been defined. It is unknown what exactly was meant when respondents claimed to have "used economic information".

Several barriers to implementing economic information have been identified. However, how real these barriers are is not clear, since there has been no evidence of any attempts by primary care decision makers to actually use an economic evaluation to influence their practice. Methodological issues such as the perspectives adopted, assumptions made in the

economic studies and funding sources have been mentioned in all the studies as one of the barriers to implementing economic information. Over the years, several checklists have been developed to tackle these issues specifically, for the purpose of critical appraisal of economic studies , based on the 10-point checklist developed by Drummond M et al [121]. However, this seems to have had little effect on improving the credibility of economic studies among these decision makers.

Finally, in addition to the reasons discussed above, these studies are also highly susceptible to selection bias. In general, survey respondents and those who consent to participating in interviews are more likely to have particular interest and knowledge in the area. Those who declined to participate may be likely to be representative of those for whom economic information has the least impact.

Therefore, findings of the impact studies are difficult to interpret and should be treated with caution and firm conclusions cannot be drawn. The study population of these studies are generally small, but this probably reflects the difficulty in conducting research and collecting data in this area. Despite the variations in study methodology and study population, it is clear that the themes generated from the individual studies do tend to support each other.

4 STUDY DESIGN AND METHODS

STUDY DESIGN AND METHODS

4.1 INTRODUCTION

This thesis set out to explore the inclusion of ADR data in pharmacoeconomic evaluations. Through discussions with local medical prescribing advisors, three therapeutic areas of interest were selected: NSAIDs for the management of rheumatoid arthritis, SSRIs for the management of depression and ACE inhibitors for the management of hypertension.

An initial pharmacoeconomic study on NSAID therapy (described in Section 4.2), using data from a large record linkage database from Tayside (Scotland) was conducted. Ideally, a similar methodology would be adopted for the other two classes of drugs, however, it was beyond the financial scope of this PhD to purchase the additional data required. Therefore, an alternative data source, based on published randomised controlled trials, was used (Section 4.3).

The second aim of this thesis was to explore the impact of economic information on primary care prescribing. Since there is an absence of literature in this area, no validated tools have been developed. Therefore, three strategies (Section 4.4), based on lessons learnt from studies examining the impact of economic information in other areas of medical decision making were adopted.

4.2 POPULATION-BASED PHARMACOECONOMIC ANALYSIS: AN EXAMPLE WITH NONSTEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDs)

This evaluation is based on clinical data supplied by the record linkage database of MEMO in Tayside (population = 427 786; 1995). This record linkage system contains extensive clinical information from 1 January 1989 on all the people who were registered with a GP and residing in the Tayside Health Board area. Every person is allocated a "CHI (Community Health Index) number" for effective clinical data records linkage. The CHI number start date is either 1 January 1989 (the MEMO start date) or the date on which a

person is subsequently registered with a local GP. This unique patient identifier was recoded into an anonymised sequential number to maintain patient confidentiality.

This linked data set includes details of all dispensed prescriptions within the community and demographic data. Diagnostic data based on International Classification of Disease (ICD 9) and operations based on the Office of Population Censuses and Surveys (OPCS) codes on all the patients who have been admitted to Tayside hospitals, each episode of hospital care generating a form - the Scottish Morbidity Record 1 (SMR 1).

4.2.1 Study Cohort

All the appropriate population data available at the point of study were incorporated into the economic model which covers the recorded data between 1 January 1989 and 31 December 1993.

Individuals less than 50 years old on 1 January 1989 were excluded from the study. Patients' data for six months prior to (recent history) and 12 months after the index date, i.e. the start date of the follow-up period were used. Therefore, those who had died before 30 June 1990, those who have an index date after 31 December 1992 and those who died at any time during the 12 months of follow-up were excluded from the study. However deaths in the year after the end of the study period were linked to an individual's record (Figure 3).

The cohort of patients who received an NSAID prescription during the study period was classed as the 'NSAID' cohort (Figure 4). The indications for NSAID prescriptions are not recorded routinely in this database, however, it is believed that this sub-population mimics NSAID use in the widest sense. A further cohort who met the selection criteria but did not receive any NSAID prescriptions during the study period were categorised as the COMPARATOR cohort. These were unselected, comprising the total population of relevant individuals in Tayside. This group provided a comparable population of Tayside patients for whom there was no prescribed use of NSAIDs throughout the study period. This group provided background rates of events in a local population not on NSAIDs.

Demographic details for all patients were recorded including their age at the start of the study, date of birth, sex, date of death (if after the study period) and postcode. Index dates

for all individuals on NSAIDs were created as the date of the first NSAID prescription dispensed after 1 July 1989 - to ensure at least six months of previous dispensing history prior to this index date being available. Since the individuals in the comparator cohort would not have received a NSAID prescription throughout the entire course of the study period, index dates from the NSAID cohort were used to generate index dates for the comparators. The index dates, in a sequential file of NSAIDs ordered by CHI numbers, were randomised and allocated to the individuals in the comparator file.

The 'NSAID' cohort was further divided into three sub-cohorts based on the records of concomitant prescriptions. These were defined as the prescribing within three days of the index date, of H_2 blockers or omeprazole which generated the 'NSAID and H_2/Omeprazole' sub-cohort, or of misoprostol which generated the 'NSAID and Misoprostol' sub-cohort. The remaining patients formed the 'NSAID Only' sub-cohort. Details of these drugs such as the dispensed date, the exact type and dose of the formulations and the amount of drugs dispensed were recorded.

This evaluation compared the economic consequences of the three NSAID sub-cohorts and the comparator cohort at 45 days, six months and 12 months following the index date, to determine the effects of initial prophylactic concomitant prescribing of misoprostol on later events, compared with concomitant prescribing of H2 blockers or omeprazole, and with no concomitant prescribing. Data on six months of previous medical history up to the index date were consulted to allow any potential confounding factors to be investigated. Details of recorded clinical events included hospitalisations, GI endoscopies, additional co-prescriptions dispensed, and changes in prescriptions at 45 days from the index date, from 45 days to six months and from six months to 12 months. Dispensed prescriptions for the drugs of interest and clinical events (hospital admissions) recorded during these periods were available for future investigations of possible cause and effect relationships.

4.2.2 Clinical Events

These data included records of diagnoses and hospital admissions coded with a gastrointestinal, cardiovascular, rheumatoid and osteoarthritis-diagnosis (ICD/OPCS codes - Appendix III) during each episode of hospital care per patient. For the purpose of effective modelling, it was assumed that each episode of care represents one hospital admission. Although this may over-estimate the admission rate and subsequently the hospitalisation costs for the proportion of patients who received more than one episode of care during individual hospital admissions, this assumption will be tested extensively in a sensitivity analysis.

The lengths of stay (LOS) of these admissions were calculated (discharge date minus admission date plus one day). However, it was believed that there would be a small proportion of patients who may remain in hospital for a long period of time which would exceed the follow-up period, such as those admitted to geriatric units. These patients' LOS would be censored to the length or to the end of the follow-up period (i.e. the maximum LOS in the three time periods would be 45 days, 183 days and 365 days respectively).

Admissions recorded in the six months prior to the index date were defined as a 'prior history of admission'. Admissions within 45 days following the index date, from 45 days to six months and from six months to 12 months were defined as 'events'.

Diagnostic and admission details, in the form of ICD-9 and OPCS codes respectively, of the longest hospital event during each follow-up period were used to indicate possible adverse events associated with the various drug therapies. It was believed that only a small proportion of patients would have more than one hospital admission over the 12 months of the study period. Therefore, the admission with the longest LOS, which represented the most significant cost contribution, would provide a fair indication of the type (GI, CV, rheumatoid or osteoarthritis admissions) and specialty (such as medical, orthopaedics or general surgery) of the other admissions if a patient had more than one admission. All other additional admissions were recorded as counts, i.e. the number of additional admissions and the LOS for all other admissions was also calculated as one aggregated total. The LOS for the longest admission was recorded separately from other admissions.

Details of GI endoscopies carried out were recorded for the whole study population. These were recorded as counts, i.e. the number of GI endoscopies performed. Endoscopies during the six months prior to the index dates were defined as 'previous endoscopies'. Those recorded after the index dates were grouped appropriately to the three time periods according to the date of endoscopy following the index date.

The drug prescriptions in this data set were based on records of the prescription items which were dispensed. One prescription may cover several items consisting of different drug classes. These items were recorded individually in the data set.

The inception drugs (NSAIDs, H_2 blockers, omeprazole and misoprostol) which were recorded as concomitant prescriptions comprised the basic drug therapies. These were identified and recorded in detail, including the type and dose of the formulations and the amount dispensed.

In an attempt to account for all the prescription items dispensed during the three study periods, all dispensed items were identified and recorded as counts, i.e. the number of prescription items dispensed, with the exception of the first and the last items in any period which were recorded in full. This was done to detect changes in drugs the patients were being prescribed. If the first drug recorded differed from the last in any period, then at least one switch was assumed to have taken place (Figure 5). This would also suggest at least one visit to the GP during which the change was made. Records of dispensed items were divided into three categories: NSAIDs, ulcer-healing drugs and all other drugs.

The above data were linked together by the CHI number to provide the raw data for this economic evaluation. Thus, in addition to the demographic details, the linked data set contains all the dispensed prescription item details, records of endoscopies and hospital admissions, and diagnoses for the longest admission of every patient, where appropriate.

All the recorded data from the three follow-up periods were aggregated to create appropriate linked data for the three time spans: from the index date to 45 days, from index date to six months and from index date to 12 months. The total costs associated with the three treatment therapies and the comparator group were calculated separately for the three study periods.

The analysis for all treatment groups was split by sex, and into three age groups, for effective modelling and to allow determination of sex- and age-specific costs. Independent analyses were carried out for males and females, and for patients aged 50 to 59 years, 60 to 74 years and 75 years and over.

4.2.3 Cost Estimates

Based on the assumption that all co-prescriptions were prescribed for events associated with the initial NSAID prescribed, all the drugs were recorded and costed as a clinical event of interest.

The drug costs used in the models were supplied by the Prescriptions Pricing Division (PPD) in place of the commonly used British National Formulary, due to the large number of different formulations covered by the population (approximately 12 000). However, the drug prices listed in the two sources appear to be similar. The actual amount dispensed to the patients was calculated exactly. In addition, the dispensing and container fee (£0.80) for each item which is charged by pharmacists to the NHS for each dispensed item was incorporated in the model. The reference sources for all the unit costs used in the calculations are shown in Appendix IV.

The inception drugs were decoded, identified and costed to generate the basic inception drug therapy costs for each patient.

The costs for the first and last dispensed additional prescription items recorded during each of the study periods were also calculated in a similar manner. For all the other prescriptions (if any), only the number of items dispensed was available. Therefore, an average cost of the first and last dispensed items recorded during each of the study periods was calculated to give an average dispensed prescription item cost which is unique to each individual patient for each study period. The sum of the total costs for drug therapy over one year for each patient was finally calculated by aggregating the inception drug cost, the cost of the first and last prescriptions dispensed and the average cost of all other additional items dispensed during each of the study periods.

It had to be assumed that all the GI endoscopies carried out were day cases since details defining inpatient or day case endoscopies were not available. The cost of all the endoscopic procedures was calculated by multiplying the number of recorded endoscopies per person during the follow-up period by a weighted cost of day case GI endoscopy in Tayside (£208.33). This cost is an average of the various costs of GI endoscopic examinations in all the hospitals in Tayside listed in the Scottish Health Service Costs 1994/5[122] weighted for the number of examinations undertaken in these individual hospitals.

The costs associated with four different types of admission - GI, CV, rheumatoid and osteoarthritis admissions - were not the same and were calculated independently. The cost of hospital admissions is dictated by the specialty group (of the longest admission) and the LOS. A weighted average inpatient cost for each specialty per day was calculated (weighted for the number of admissions recorded in these Tayside hospitals). For each individual patient the appropriate weighted cost is then multiplied by the total number of days in hospital to give the cost of each type of admission.

For the purpose of modelling, it was assumed that each hospital admission was attached to two GP consultations - one prior to admission, one after - and one outpatient consultation following discharge. The sum of these individual costs was added to the cost of the longest hospital admission. Patients with more than one admission had similar costs added to give the total cost of hospitalised events per patient (Figure 6a and 6b).

The total cost of therapy and their 95% confidence intervals (CI) associated with the comparator cohort and the three sub-cohorts was calculated.

Sex and age-specific analyses were performed across the four groups and univariate comparisons (F test) between males and females and between the three age groups were carried out. These costs were aggregated for all individuals in each treatment group. Since some individuals incurred much greater costs than others, an average cost for each member of the individual group was also calculated.

4.2.4 Sensitivity Analysis

Extensive sensitivity analysis was performed on all obvious confounding variables including co-morbidities and mortalities. Patients in the study group who were aspirin takers, who had any prior hospital admissions, prior endoscopies, or prior NSAID prescriptions, were removed from the dataset for re-analysis. These exclusions were dealt with singly and in combination. This is equivalent to the restrictive cohort technique adopted to address confounding factors [123]. In addition, the cost data that were used in the model, including the cost of GP consultations and GI endoscopies, were also tested in the sensitivity analysis.

4.3 MODEL-BASED PHARMACOECONOMIC ANALYSIS: EXAMPLES WITH NONSTEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDs), SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIs) AND ANGIOTENSIN CONVERTING ENZYME (ACE) INHIBITORS

Three pharmacoeconomic analyses were conducted on three of the most widely prescribed classes of drugs in primary care - NSAIDs for the treatment of rheumatoid arthritis, SSRIs for the treatment of depression and ACE inhibitors for the treatment of hypertension. The direct costs associated with the use of all three classes of drug therapies were calculated.

The economic models were based on the key assumption that drugs within each class of drugs were equally effective and the main difference between these drugs was their side effect profile, which dominates patients' preferences and the cost of therapy. The clinical outcomes investigated were all associated ADRs, and the total costs of drug therapy were calculated as 'economic outcomes'. Similar methodologies have previously been adopted in the evaluation of NSAIDs [20,21,124]. The models adopted the perspective of the NHS.

4.3.1 Data Collection

Identical methodologies were adopted for all three pharmacoeconomic evaluations. An extensive literature search was carried out on each individual drug using MEDLINE (1966 to present), BIDS embase (1980 to present) and the Cochrane Trials Register. Search filters published by the SIGN guidelines for randomised controlled trials were combined with keywords on individual drugs and treatment indications (Appendix II). The main searches were restricted to references to randomised controlled trials published in English. Randomised controlled trials of the following comparisons were selected:

- Comparing any of the individual NSAIDs with active or placebo control in the treatment of uncomplicated rheumatoid or osteoarthritis in adults.
- Comparing any of the individual SSRIs with active or placebo control in the treatment of uncomplicated major depression in adults.
- Comparing any of the individual ACE inhibitors with active or placebo control in the treatment of uncomplicated hypertension in adults.

Only double-blind randomised-controlled trials of individual drugs of interest were selected for the meta-analysis. In addition, the trials had to meet the following inclusion criteria:

- Sample size greater than 20 patients – on the basis that this excludes most pre-phase III trials.
- Study duration of at least two weeks – excludes most pre-phase III trials.
- Control group included.
- Reported numerical data on the number of ADRs recorded.

The quality of the selected clinical trials were assessed using the five-point Jadad score [125]. Points were awarded for the description and the appropriateness of randomisation and blinding. For instance, studies that were described as 'randomised and double-blinded' would be awarded two points. If the method of randomisation and blinding were described and believed to be appropriate, an additional two points may be

awarded. However, if the method of randomisation and blinding were inappropriate, negative points should be awarded to the trial. In order to gain the maximum score of five, data (number of patients and reasons) on withdrawal and drop-outs have also to be presented.

4.3.2 Adverse Drug Reactions Data

All the adverse drug reactions data reported in the included trials were collected. Meta-analyses were performed for each individual drug, pooling together all the available side effects data on each individual symptom or event. Average incidence rates, weighted by the sample size of the studies, were calculated for each side effect reported for each individual drug. The 95% confidence interval was also calculated, based on the equation which is normally used to calculated 95% confidence intervals for count tables:

$$\frac{r}{n} \pm 1.96\sqrt{\frac{r(n-r)}{n}}$$

(where r = sum of ADRs reported; n = sum of patients in all the trials)

4.3.3 Management of Adverse Drug Reactions

A list of possible treatment-induced side effects was constructed from the clinical trials. Treatment strategies for each side effect were derived from both the literature and expert opinions. All general practitioners in one of the local healthcare co-operatives (LHCCs) in the Dumfries and Galloway area were invited to participate in providing expert opinion on the management of drug-induced ADRs. Consent to contacting and inviting GPs in this LHCC was given by the LHCC manager, and the author presented the aims, objectives and methodology of the study at a monthly LHCC meeting prior to recruiting GPs. A letter was sent to all the GPs by post (Appendix V), and followed-up with a telephone call. During the period between December 2000 and June 2001, face-to-face, semi-structured interviews were carried out with those who agreed to take part, to determine how these symptoms are generally managed. General practitioners were

asked a series of questions relating to how they would treat the ADR reported in the clinical trials. Each ADR was considered independently. The interviews were based on a clinical scenario that resembles an average patient on NSAIDs, SSRIs or ACE inhibitors. Initially, GPs were asked if they considered the symptom to be drug-related, and if so, what investigations and treatment they would recommend, and for what proportion of the patients. A final consensus on how individual adverse events would be managed, on average, was estimated.

Based on a decision-analytic approach, the treatment strategy was noted and a summary probability of patients who would receive a particular investigation or treatment when suffering from a drug-induced side effect was generated. This was based on the estimated proportion of patients who would receive a particular treatment or investigation despite having the drug changed or stopped. For instance, out of 100 cases of drug-induced constipation, one GP perceived that 80% of the patients would have their drugs changed while 20% would receive a laxative in addition to unchanged treatment. However, another GP would change drugs in 90% of the cases and co-prescribe laxative to 10% of the patients. Therefore, the average estimated probability for the two GPs, of a patient having NSAID stopped would be 85% and the probability of receiving a laxative would be 15%.

4.3.4 Cost Estimates

Direct health service costs for the drugs and the treatment associated adverse effects were calculated. The acquisition drug costs, based on the defined daily dose, for a one-month period, was calculated. The costs associated with managing adverse effects included costs of all GP visits, clinical investigations and additional medical treatment. The unit costs for the investigations and treatment procedures are multiplied by the number of units 'consumed' during the time period of interest. The number of units consumed is the calculated average of the GP treatment patterns, expressed as a probability. The cost for treating a particular side effect with respect to one patient is calculated for each drug. This cost - the 'shadow cost' - was determined by the incorporation of the expected cost for treating all the different side effects experienced for one particular drug, and is dependent on the estimated frequency of occurrence of

the side effect in question. Finally, the total cost of drug therapy, which incorporates the cost of managing associated side effects and the drug acquisition cost, was calculated.

4.3.5 Sensitivity Analysis

Extensive sensitivity analyses were undertaken to test the main assumptions in all the models. Input variables for the economic models including the incidence rates of the ADRs and the unit costs were varied to examine their influence on the model outcomes.

The ADR rate is a major parameter that may significantly influence the outcome of the model. In addition to the sensitivity analysis of varying the ADR rate by 20% above and below that used by the basecase, a scenario-based analysis, based on the 95% confidence intervals was also performed. The 95% confidence intervals for the ADRs that are investigated in the models have been calculated. The upper and lower limit of the confidence interval represents the "best" (lower limit) and the "worse " (upper limit) case scenario associated with the use of individual drugs. It is expected that the ADR rates for some of the events would be extremely low due to their infrequent occurrence. In cases when the values of the counts are low, the quadratic approximation to the confidence intervals tends to have the lower bound below zero. Since in practice, it is impossible to obtain less than 0% for a particular ADR rate, all values in the interval below zero are rejected. All predicted rates of less than 0% (lower limit) for a particular event would be rounded to 0% and interpreted as near 0%.

Scenario-based analysis was carried out by substituting the ADR incidence rates in the basecase with the lower limit and the upper limit of the confidence intervals, representing the "best" and the "worst" case scenarios, respectively.

Unit cost data were also investigated by varying cost data by 20% above and below that used for the basecase.

4.4 THE IMPACT OF PHARMACOECONOIMC INFORMATION ON PRIMARY CARE PRESCIRBING

In an attempt to investigate the potential impact of economic information, three strategies have been adopted:

- Dissemination of the results of the meta-analysis based economic analyses, and examination of prescribing behaviour from routine data sources prior to and after the dissemination exercise.
- A cross-sectional postal and email survey was conducted to gain insight into GPs' views on the usefulness of a variety of economic information and how it related to their everyday practice.
- Qualitative interviews to explore, in depth, the views and current use of economic information among GPs.

4.4.1 Dissemination Exercise

Study Population

Through earlier contacts with GPs while conducting interviews relating to ADRs, it was becoming apparent that the most difficult step in conducting research among GPs is recruitment. Therefore, the same LHCC in the Dumfries and Galloway Health Board area that participated in interviews regarding management of ADRs (as described in section 4.3.3) was also selected for this dissemination exercise. It was hoped that, since this pool of GPs had already demonstrated a previous interest in the area of health economics and were familiar with the objectives of the research work and the author, it would encourage participation in the dissemination exercise.

This LHCC serves nine practices, with 38 GPs. Similar to the previous recruitment, the author attended one of the monthly meetings and presented the aims and methodology of this part of study. During October 2001 to March 2002, those who consented to taking part were later contacted by telephone to arrange a convenient time for meeting. The GPs were visited individually at their practice.

Prescribing Data

Prescribing reports are now regularly produced to enable both cost and quantities of prescribing to be analysed. Scottish Prescribing Analysis (SPA) data were originally designed and generated to aid community pharmacists with reimbursement of prescriptions, but have become an essential tool in prescribing support. Furthermore general practitioners are increasingly using audit to rationalise their prescribing [126].

Scottish Prescribing Analysis (SPA) Level 1 data contain breakdowns of total costs and numbers of items prescribed for major therapeutic categories. Expensive items (those over £100) and drugs of abuse are also included. These data are specific to individual GPs, and comparisons can be made with the averages for the practice, the Health Board and Scotland. Scottish Prescribing Analysis Level 2 data contain a full catalogue of all dispensed items over a period of three months, available on request. Prescribing details include: separate listing of generic and proprietary preparations, dose and formulation of the drug, number of times prescribed, total quantity and cost, average quantity per prescription and cost. SPA Level 2 data was used to measure change in prescribing.

The results of the pharmacoeconomic evaluations were compared against current prescribing data - overall Scottish data and practice-specific data – to assess the cost effectiveness of the prescribing trends. Key messages of the evaluations plus recommendations for change towards more cost-effective prescribing were devised. This was presented to the GPs during a 20-minute meeting with the author. Comparisons in their prescribing prior to and after visits were made using SPA data. In comparison, self-selected controls consisted of those within the LHCC who declined to participate in the study, and therefore received no intervention. Prescribing data from these practices were used as a baseline and compared to the intervention group.

4.4.2 Survey – Quantitative and Qualitative

Two questionnaires were designed and disseminated among GP members of the West of Scotland Primary Care Research and Development Network (WestNet) during the period of January to March 2001. The West of Scotland Primary Care Research and

Development Network is a consortium of 55 general practices, set up to develop and conduct non-commercial research of benefit to general practice.

Questionnaire (I) consisted of five questions, designed to examine the type of economic information currently used by GPs in medical decision-making (Appendix V). Questionnaire (II) consisted of four questions, designed to explore what GPs identify as sources of economic information and their perception on the relevance of the data presented (Appendix V).

A complete list of members and their contact details were obtained from WestNet. All the non-GP members were excluded from the study. Those included were randomised into two groups - questionnaire (I) and questionnaire (II), stratified by their accessibility by email. Each member was either sent the appropriate questionnaire with a personalised covering letter and a pre paid addressed envelope, or emailed the covering letter, with the appropriate questionnaire attached.

4.4.3 Qualitative Interviews

Following consultation with experienced qualitative researchers in the Department of Public Health, a methodology was developed to explore GPs' personal views and opinions about the role and impact of economic information. Due to the recent changes relating to research ethics, ethical approval was sought for carrying out this part of the research. Purposive sampling was used to include ten GPs based on their previous consultation with SIGN and through snowball sampling. It was felt that this group of GPs would have some level of interest and contact with health economic information. Participants were recruited by email, letter and/or telephone contact. During the period between March and June 2004, face to face qualitative interviews, which lasted approximately 45 minutes, were conducted. Although the interviews were semi-structured, an interview guide with a list of main points to be covered was used. Answers to pre-set questions were probed with further discussion and subsidiary questions. All interviews were conducted at the GPs' surgery and were tape-recorded upon consent of the interviewee. Written consent was obtained.

Main points covered included:

- The currently disseminated economic evidence;
- The barriers and facilitators in implementing economic evidence; and
- The role of economic issues in healthcare decision making.

Interviewees were invited to discuss their views and opinions of the decision making process in relation to their own experience. In general, the interviewees were free to guide the interview according to what was felt to be important about decision making in relation to prescribing whilst drawing upon other aspects of healthcare decision making they have experienced.

The method of sequential analysis was adopted [127], where data collected at early stages of the study helped shape ongoing data collection, allowing questions to be refined and negative cases identified. All the collected data was also preserved in text form and indexed to generate or develop analytical categories and theoretical explanations.

The transcriptions of the meeting were compared to the notes taken during the meeting in order to try to fill any blanks in the notes and to obtain a different perspective on the meeting. Following word-for-word transcribing of the interviews, the data were coded to help identify themes and categories. All the data relevant to each category were identified and examined using the method of constant comparison, whereby each item was compared with the rest of the data to establish analytical categories. Multiple themes may emerge from the same section of data. Each theme was examined individually for different views, the frequency of the views that were expressed and how strongly the different views were expressed [127]. Codes were refined and reduced in number by grouping of the data. It was felt that the amount of data collected in this study did not warrant the need of employing traditional software packages designed specially to handle qualitative data (such as ATLAS/Ti) [128]. Therefore, coding and organising of the data were conducted manually. The 'find' function in Microsoft Word was used to identify keywords that were related to the main themes of the study.

5 RESULTS

5 RESULTS

5.1 INTRODUCTION

The results of the thesis are presented chronologically in this chapter. For ease of reading, all the tables and figures relating to the results are placed at the end of the thesis.

In accordance to the first aim of the thesis, section 5.2 presents the results of the economic model based on population data. The clinical data recorded in the database is described (section 5.2.1 and 5.2.2), followed by the cost (section 5.2.3). Results of the sensitivity analysis are presented in section 5.3.4. Tables containing detailed breakdown of the data are presented in the Appendix VII.

Section 5.3 presents the results of the three meta-analysis based economic analyses. The results of the literature review of randomised controlled trials for each of the three classes of drugs are presented in section 5.3.1. Relevant data on adverse drug reactions were aggregated and are presented in section 5.3.2. The clinical management pattern was determined (section 5.3.3). Finally, the calculation of costs and the sensitivity analysis are presented in section 5.3.4 and 5.3.5.

In accordance with the second aim of the thesis, the results of the impact study are presented in section 5.4. The findings of the dissemination exercise are reported in 5.4.1. This is followed by results of the GP survey (section 5.4.2). The findings of the qualitative interviews are presented in 5.4.3.

5.2 POPULATION BASED PHARMACOECONOMIC ANALYSIS: AN EXAMPLE WITH NONSTEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDs)

5.2.1 Study Population - Demographics

The study population comprised 98 887 people (42 648 male and 56 239 female), divided into four subgroups for effective modelling:

- Comparator cohort (N = 47 350)
- NSAID only sub-cohort (N = 49 212)
- NSAID and misoprostol sub-cohort (N = 212)
- NSAID and H_2 blocker or omeprazole sub-cohort (N = 2113)

Demographic details and clinical history of the patients from the MEMO population database are shown in Table 2. The age distributions of the patients in the four treatment groups are similar, predominantly between the age of 60 and 74 years. However, both the NSAID only and the misoprostol sub-cohorts have a higher percentage of elderly patients over 75 years (approximately 20% and 24% respectively) compared with the H2 sub-cohort (19%) and the comparator cohort (17%). It is evident from the data that female patients have a higher probability of receiving NSAIDs compared to male patients. Therefore, economic analyses were conducted in sex and age specific groups.

Overall, 4% (N = 3994) of the study population had a history of a GI diagnosis in the six months prior to the index date. These patients were almost as likely to be NSAID users (52%) as non-NSAID users (50%). The proportion of patients who had a previous history of GI diagnoses was similar in the NSAID only sub-cohort (3%) to the comparator cohort (4%). However, patients with a prior GI diagnosis were four times and six times more likely to be prescribed concomitant prescriptions of misoprostol (13%) and H_2/omeprazole (18%) respectively.

Twice as many GI endoscopies (N = 8052) as GI diagnoses (N = 3994) were recorded in the six months prior to the index date. Approximately 7% and 8% of the patients had previous endoscopies in the NSAID only sub-cohort and the comparator cohort respectively.

Patients with prior endoscopies were over four times more likely to receive concomitant H_2/omeprazole (32%) and three times more likely to receive concomitant misoprostol (20%) than NSAIDs alone.

Patients with a previous history of CV diagnosis were 39% more likely to be NSAID users than those without a prior CV diagnosis. Only a relatively small proportion of patients (6%) from the comparator group had a previous history of CV diagnoses, which is unlike the other treatment sub-cohorts (ranging from 12% observed in the NSAID only sub-cohort to 21% in the H_2/omeprazole sub-cohort). A similar trend was noted for a prior history which included a diagnosis of RA/SLE, and OA.

Based on the details of the inception NSAIDs, it is apparent that, irrespective of the different treatment groups, ibuprofen, diclofenac sodium and naproxen are the more commonly prescribed NSAIDs in Tayside (Table 2). The data also show a preference for ranitidine among all H_2 blockers prescribed by GPs in Tayside, which was given to 81% of the patients in the H_2/omeprazole sub-cohort.

Mortality within a year after the study period has been recorded. The highest crude mortality rate has been observed among those who were on H_2/omeprazole (16.4%). Lower but similar rates were found among NSAID takers (13.7%) and those who were given misoprostol (13.2%). The differences were reduced after adjusting for age and sex, as might be expected given the mean age of the cohorts, but the trends were unchanged.

5.2.2 Clinical Events

When comparing the three age groups, the highest endoscopy rate is observed in the 60 to 74 years age group. Unsurprisingly, those aged above 75 years were substantially less likely to receive endoscopies than younger patients in both the comparator and the NSAID cohort. This pattern is consistent throughout the three study periods (Figure 7).

Endoscopies were required more often in NSAID patients than in those who were non-users of NSAIDs. Patients deemed to require GI protection and given concomitant H_2 blockers or omeprazole have a higher probability of receiving endoscopic investigations (6%) compared to those on NSAIDs alone (2%). Over the 12-month period, the relative risk was

3.67. The relative risk among patients deemed to need GI protection and prescribed misoprostol was only 1.21 relative to those on NSAIDs alone.

There were no endoscopies recorded in the misoprostol sub-cohort during the first 45 days of the study period. The proportion of patients in the NSAID only sub-cohort who received endoscopies within the initial 45 days (0.2%) is the same as that observed in the comparator cohort (Table 3). A substantial increase (up to four fold in the NSAID only sub-cohort) in endoscopies is observed in all groups at six months following the index date. The high rates observed in the H_2 sub-cohort remained consistent throughout the follow-up period (5.7% compared with 1.9% in the misoprostol sub-cohort, 1.6% in NSAID only sub-cohort and 1.2% in the comparator cohort). In addition, female patients who are on NSAIDs, regardless of the sub-cohort (NSAID only, NSAID with concomitant misoprostol or NSAID with concomitant H_2 blocker/omeprazole) have been shown to be more likely to have undergone endoscopic examinations. A larger number of endoscopic events were observed in females in these three sub-cohorts at all time periods (Table 3). This was most apparent among the H_2/omeprazole sub-cohort where an approximately four-fold difference was observed in the first 45 days. However, this may be by chance as few events were actually recorded.

Records of dispensed prescriptions were high in the NSAID cohort, ranging from 35.3% in the NSAID only sub-cohort at 45 days, to as much as 93.4% in the NSAID and H_2 sub-cohort in 12 months. Over the period of 12 months, patients on NSAIDs alone received 3.3 times more prescriptions than non-users. Those on H_2/omeprazole received 25% more prescriptions compared with those on NSAIDs alone, but those on misoprostol received only 9% more. Records of any dispensed prescriptions for only 8.7% (45 days) to 22.8% (12 months) of the comparator cohort were formed. Similar to that observed with the endoscopic examinations, there is a consistent trend among the population that, irrespective of drug therapy, patients in the 60 to 74 years age group and females have a higher probability of being prescribed drugs (Table 4). There was no age trend amongst the patients in the comparator cohort. However, a clear increase in prescriptions per patient with increasing age among NSAID users was observed. A similar trend was present, but less pronounced among the H_2/omeprazole sub-cohort.

The highest proportion of patients receiving prescriptions was observed with the H_2 sub-cohort (ranging from 1.13 times greater than that of misoprostol to 6.7 times greater than

that of the comparator cohort at 45 days). A consistent increase in patients receiving prescriptions has also been noted over time, the amount of increase mirroring the above trends - an increment of 39.4% was observed in the NSAID only sub-cohort from 45 days to 12 months of follow-up compared to 34.4% increase in the H_2/omepazole sub-cohort, 29.2% in the misoprostol sub-cohort and 14.1% in the comparator cohort.

All the patients who were admitted due to any diagnosis over the three observation periods are shown in Table 5. The H_2/omeprazole sub-cohort has the highest hospital admission rate for almost all combinations of admission diagnosis and study periods. Hospitalisations of a CV-cause are the most common cause of admission in this population, followed by GI-cause, OA-cause and RA-cause respectively.

Admissions of a GI-cause have been observed in all groups. Patients on NSAIDs alone (1.1%) were 1.5 times more likely to be admitted for a GI event than non-users (0.7%). Those on NSAIDs and H_2/omeprazole were twice as likely to be admitted for GI events compared with those on NSAIDs alone. However, only one GI admission has been recorded from the misoprostol sub-cohort throughout the follow-up periods. This resulted in a GI admission rate lower than that of the comparator cohort at one year (0.5% compared with 0.7%).

Cardiovascular events were the most common cause for hospital admissions irrespective of study groups and study periods. Over the 12-month period, there were 3.4 times as many patients admitted due to a CV event among all NSAID users (N = 2250) than non-users (N = 658). Cardiovascular admission rates ranged from 0.2% at 45 days to 1.4% at one year observed in the comparator cohort, and 1.7% at 45 days to 7.6% at one year observed in the H_2 sub-cohort.

Patients admitted due to a RA-cause were rare in non-NSAID users (0.03%). Rheumatoid arthritis admissions were more common among NSAID takers - 0.2% recorded in the NSAID only sub-cohort, 0.5% recorded in the NSAID and misoprostol sub-cohort, and 0.6% recorded in the NSAID and H_2/omeprazole sub-cohort. Similarly, the OA admission rate was low among non-NSAID users (0.2%) when compared with NSAID users (1.3%). Admissions for OA ranged from 0.2% observed in the comparator cohort to 2.4% observed in the misoprostol sub-cohort at one year. Females dominate both OA and RA admissions

across the comparator and the NSAID cohorts. (In the whole database 56.9% were female Table 2).

Details for the longest hospital admission were recorded for each patient in the study population. The mean LOS for the longest admission and other admissions vary among treatment groups and different diagnoses (Table 6). For instance, the mean LOS due to the longest GI admission in the first 45 days of the study period range from 5.57 days in the comparator cohort to 34.00 days in the misoprostol sub-cohort. The number of hospital admissions can be deduced from table 6 by adding the number of cases of the longest hospital admission and the sum of counts for additional admissions. For instance, in the case of the misoprostol sub-cohort, only a few cases of hospital admissions were recorded over the 12-month period - four GI admissions (one recorded as the longest admission plus three additional admission counts), 23 CV admissions (13 recorded as the longest admission plus 10 additional admission counts), one RA admission (one longest admission and no additional admission counts) and eight OA admissions (five longest admissions recorded plus three additional admission counts). This may be, in part, due to the small sample size of this study group. Therefore, these results are difficult to interpret and may not reflect the true pattern in clinical practice.

On average, patients with one admission are likely to have one to two additional admissions, irrespective of treatment groups and admission causes. However, no additional admissions of any causes were recorded among the misoprostol sub-cohort over the six-month period. Over the first 45 days of the study, no additional RA and OA admissions were recorded in the comparator and H_2 blocker sub-cohort respectively.

The mean additional admission counts were calculated in a similar manner to that of the mean LOS as described above. For instance, the mean number of additional GI admissions during a 12-month period for the few patients in the NSAID only sub-cohort with any admission is 3.24 (total number of admissions divided by the number of individuals concerned; for example 327 admissions for 101 individuals). Similar GI mean additional admission counts were recorded in all the NSAID sub-cohorts.

Over a period of 12 months, the longest mean LOS among NSAID users (ranged from 13.3 days among the H_2/omeprazole users to 34 days among misoprostol users), were longer than non-NSAID users (12 days). Gastroprotective agents (H_2 blockers, omeprazole and

misoprostol) appeared to have no effect on GI LOS. The mean LOS of the longest CV admission was shorter for patients in both the NSAID only (16 days) and NSAID and H_2/omeprazole sub-cohort (15 days), relative to the comparator cohort (25 days). The misoprostol sub-cohort was associated with the longest mean LOS at 31 days. The longest mean LOS of both the comparator cohort (37 days) and NSAID only sub-cohort (25 days) was observed in RA admissions. Osteoarthritis admissions were also the cause of the longest mean LOS in the NSAID only (23 days) and H_2/omeprazole sub-cohort (24 days).

5.2.3 Cost Estimates

Weighted average costs for inpatient admissions and outpatient visits were calculated by individual specialty (Appendix IV, Table 34 and 35). Separate data on admission costs to specialties such as nephrology, cardiology, anaesthetics and haematology were not available. These were costed as medical cases at £188.48 per case per day of stay. The average LOS and the cost per case per day vary significantly among the various specialities. Geriatric long stay has the longest average LOS at a cost of £96.25 per case per day. Although A&E has the shortest average LOS (0.8 days), it has incurred the highest cost amongst all the specialties at £1480 per case per day. The recorded hospital admissions in the dataset were dominated by medical cases.

All the additional drugs and hospital interventions were costed and incorporated into the economic model to calculate the shadow cost of the drug therapies i.e. the cost of interventions for events associated with the drug therapy. This cost is added subsequently to the costs of the initial NSAID prescriptions to provide the total cost of the therapy. The individual costs which were incorporated in the three study-period models are shown in Appendix IV. The costs of the additional drugs (NSAIDs, ulcer-healing drugs and other drugs) dispensed to the patients, the GP consultation costs, the costs contributed by all the hospital events (longest admission and other admissions due to GI, CV, RA or OA-causes) and the cost of GI endoscopies, all contribute to the shadow cost.

The composition of the total costs for the three separate study periods is shown in Figures 8 to 10. The trends of individual cost composition are similar across the different groups and the different time periods. Endoscopies and GI admissions were not the most cost dominant variables, but admission due to CV related events was consistently the most dominant cost

variable. The individual total cost compositions for all the time periods and sub-cohorts are shown in Figure 11. Although it is a repetition of the data displayed in Figures 8 to 10, it allows comparisons across the time periods and study groups to be made readily.

The estimated average cost per patient for each treatment group is shown in Table 7. The basic inception drug cost for the H_2/omeprazole sub-cohort was substantially higher than the basic NSAID drug cost (3.4 times) and the basic misoprostol drug cost (1.7 times). At 45 days, the shadow cost associated with the NSAID only sub-cohort was greater than that of the comparator cohort (£44.19 and £13.35 respectively). The H_2/omeprazole sub-cohort was associated with the highest shadow cost (£104.06) indicating a relatively high level of clinical events subsequent to the initial prescription. There was a smaller increase in the misoprostol sub-cohort (£75.56). When the basic drug costs were incorporated, the ranking of the total costs of the treatment groups remained the same. The difference between the shadow and total costs represented the cost of all drugs dispensed per patient of each cohort averaged across all.

However, when the study period was extended to six months, a substantial increase (four times) in associated shadow cost was observed for the NSAID group (£179.01 compared with £44.19). This is roughly in line with the four-fold increase in the time covered (six months compared with 45 days). A similar escalation in cost was also observed in the misoprostol group (shadow costs: £356.50 and £99.90 respectively). However, an even greater difference was noted when the study period is one year. H_2 therapy remained the most expensive throughout the three observation periods (£144.79 at 45 days, £458.93 at six months and £937.76 at one year).

Similar patterns are observed when males and females are analysed independently (Table 8). The average shadow cost for females is greater than that of males in both the comparator and the misoprostol therapy groups. When misoprostol therapy is compared with NSAID only and H_2 therapy, potential savings were observed among males - 3% at 45 days to 7.4% at one year when compared with NSAID therapy and 55% at one year to 77.2% at six months when compared with H_2 blocker therapy. However, misoprostol therapy does not produce savings among females.

Age specific total costs are shown in Table 9. Misoprostol therapy remained cheaper than H_2/Omeprazole therapy, with the exception of all time periods for those above 75 years old.

A saving was also observed at six months when comparing misoprostol therapy with NSAID therapy among those aged 60 to 74. More detailed breakdown of sex and age-specific costs are shown in Appendix VII (Tables 36 to 38).

There is a consistent trend of substantial savings in total costs being achieved when comparing misoprostol prophylaxis to H_2/omeprazole therapy at all ages and time periods (13.4% to 31%), the only exception being females above the age of 75 years. These potential savings are shown in Tables 10 to 12. From a NHS perspective, potential savings of £34 400 to £266 513, according to time period, may be achieved if all the Tayside patients in the H_2/omeprazole sub-cohort had their prescriptions replaced by misoprostol. However, the results also show that misoprostol therapy failed to provide a saving for female H_2 blocker takers, especially those above the age of 75 years. For male NSAID takers, misoprostol therapy has shown to generate potential savings of 5.3% at 45 days and 33.8% at six months.

5.2.4 Sensitivity Analysis

Extensive sensitivity analysis has been carried out to test the assumptions made when developing the economic model. The basic model has assumed that each episode of care recorded in the database is representative of an individual hospital admission. Therefore, the economic consequence of the alternative assumption was investigated (Appendix VIII, Tables 39 to 41) - that multiple episodes of care recorded for each patient, were from one single hospital admission. The resultant costs were marginally lower than those from the base case, but there were no effects on the results of the basic model (Table 13).

The much lower history of CV diagnosis observed in the comparator cohort compared with the other treatment groups suggested a selection bias. It was initially suspected that this was due to patients who were prescribed aspirin in the treatment groups. Aspirin may be prescribed for prevention of CV disease, which would explain the high rates of previous history of CV diagnosis in the NSAID treatment cohorts. Therefore, as part of the sensitivity analysis, patients who were receiving aspirin were removed from the study. The results showed an expected reduction in the average shadow cost but no change was observed in the overall ranking of the treatment groups.

Other factors which may influence the final results were also examined (Appendix VIII, Tables 42 to 44). Patients who had a prior history of GI and CV diagnoses, patients who had prior GI endoscopic examinations, those who had received NSAID prescriptions, and those who died in the year after the study period – termed 'survivors' - were excluded from the analyses independently. Analysis was also carried out by eliminating the above risk factors simultaneously. Only patients with 'no risk factors' were included in the analysis. No consistent changes were observed in the overall ranking of the drugs (Table 14) .

Sensitivity analysis was also carried out by varying the cost data. Other published GP consultation costs were also used to test the robustness of the results. The costs of £4.77 and £8.38 have been selected for a low and high cost scenario respectively (Table 15). In addition, the endoscopy cost has also been investigated by increasing and reducing the cost of endoscopy by 50% independently. The results remained consistent when these alternative costs were used in the modelling, and the actual overall effect was small. The greatest change in cost was found when the cost of GP consultations was estimated at £4.77. This only resulted in a modest change in the total costs in all groups - 2% in the comparator cohort and the NSAID and misoprostol sub-cohort, and 3% in the NSAID only and the NSAID and H2/omeprazole sub-cohorts.

The overall effects of varying individual clinical factors and costs on the shadow costs of the different therapies are shown in Figures 12 to 14. The absolute differences between the base case costs and each sensitivity analysis are shown. The left hand part of the graph shows costs in groups with various risk factors. These costs tend to be higher than the base case. The rankings of the four groups changed little, but the absolute differences in costs varied markedly - mostly because of small numbers of the affected individuals. Patients on misoprostol with a prior GI admission seemed particularly at risk and were expensive, but the numbers were small (N = 27).

The right hand part of the graph shows similar findings for the groups with high risk factors excluded. The size of the groups are much larger, variation is much less.

5.3 MODEL-BASED PHARMACOECONOMIC ANALYSIS: EXAMPLES WITH NONSTEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDs), SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIs) AND ANGIOTENSIN CONVERTING ENZYME (ACE) INHIBITORS

5.3.1 Data Collection

Despite a large number of clinical trials being identified by the searches, only a small proportion of the resulting references fulfilled the inclusion criteria for the meta-analyses (Figure 15). The is particularly the case with NSAIDs as most of the clinical trials were conducted ten to 30 years ago (clinical trials dated as far back as 1972 were included in the analysis), before quality guidance for conducting good clinical trials was established. Although most well conducted clinical trials recorded and described drug-induced side effects, only a small proportion of the trials contained detailed reports of incidence rates of side effects of interest to the study. As a result, the final number of clinical trials included in the analyses was small.

The search filters used in the literature search focused on sensitivity instead of specificity. Therefore, the number of references identified by the search differs significantly from the number of studies included in the analysis. In all, over 9000 trials were identified from the databases for NSAIDs, SSRIs and ACE inhibitors. These included comparative trials of any of these drugs against a placebo or active control. The majority of the trials were small, phase III, double-blind, randomised controlled trials of short duration – four to six weeks. A total of only 69 trials met the selection criteria and contributed usable data to the three meta-analyses.

Non-Steroidal Anti-Inflammatory Drugs

Over 3000 studies were identified by the search through the databases. Studies that did not fulfil the inclusion criteria, including those evaluating biological inflammatory indicators for arthritis, the use of NSAIDs for indications other than RA or osteoarthritis, and absence of recorded frequencies of individual adverse events, were excluded. These studies

included clinical trials that did not compare individual NSAIDs, those that failed to provide detailed figures of individual adverse drugs reactions, trials that reported serious GI adverse events only as opposed to all adverse drug reactions.

Fifteen studies evaluated RA patients, eight studied OA patients and one study included both RA and OA patients. In total, 24 studies were included in the meta-analyses of NSAIDs-induced adverse events [129-152] (Table 16). The mean study period was 10 weeks (range two to 51 weeks). Eight studies reported efficacy and tolerability of indomethacin, a further six on naproxen, assessment of ibuprofen and ketoprofen were all reported in four studies; there were three on piroxicam and tolmetin, two on sulindac, fenoprofen, and one on diclofenac. Although it was possible to extract numerical adverse drugs reactions (ADR) data from these trials, the methods used for recording these events are not always known (52.4%). Only two trials (9.5%) reported the use of checklists, while 11 trials (52.3%) depended on indirect questioning to obtain ADR data. No trials gave detailed definitions of each ADR. The qualities of the studies were generally poor, with a Jadad score of less than three. The median Jadad score for the NSAID trials was two.

Selective Serotonin Reuptake Inhibitors

Clinical studies on SSRIs have been dominated by comparative studies between SSRIs and TCAs as a class of drug. Generally, data were presented in aggregated format for the drug class instead of individual drugs, focusing on the differences in efficacy and safety between SSRIs and TCAs. The search for studies on SSRIs produced 21 randomised controlled trials with usable data on all SSRIs [153-173] (Table 17). The mean duration of study was nine weeks (range four to 76 weeks). Nine studies reported data on fluoxetine, seven on fluvoxamine, four on paroxetine and a further four on sertraline. Although five studies were found to report detailed ADR rates associated with citalopram, they were excluded from the analysis due to insufficient sample sizes ($N < 20$).

Clinical trials on SSRIs were performed more recently (1983 onwards) and were of better quality than those on NSAIDs. Only one study had a Jadad score of less than three and the median Jadad score for all the studies was three. Various methods of ADR recording were used. Thirty-eight percent of the trials did not specify the method used to collect ADR data, while checklists were the most frequent method, used by 33.3% of the trials.

Angiotensin Converting Enzyme Inhibitors

The meta-analysis on ACE inhibitors adverse events was based on data from 24 trials [174-197] (Table 18). The mean duration of the studies was 11 weeks (range four to 51 weeks). Ten were trials on enalapril, six on linsinopril, three each on captopril and ramipril. Data on trandolapril, moexipril and perindapril were only based on one randomised controlled trial. Although one trial was identified with ADR rates for fosinopril, the sample size was too small to be included in the analysis.

The clinical trials for ACE inhibitors were conducted more recently than those for NSAIDs and SSRIs. The Jadad score for the clinical trials ranged from two to five (maximum score), with a median score of three. Methods of ADR recording included open (12.5%), direct and indirect questioning (8.3%), spontaneous reporting (33.3%) and the use of checklists (4%). However, 16.7% of the trials did not specify the method of ADR recording.

5.3.2 Adverse Drugs Reactions Data

The ADR profile for NSAIDs, SSRIs and ACE inhibitors are presented in Tables 19, 20 and 21 respectively. The total number of events reported, the weighted number of events and the weighted percentage of events (weighted according to the sample size of the group) associated with each individual symptom were calculated for each drug.

Non-Steroidal Anti-Inflammatory Drugs

A meta-analysis of 1987 patients on eight NSAIDs was conducted (Table 19). Large variations in event rates have been observed among individual NSAIDs. In particular, fenoprofen appeared to be the least well tolerated of all the NSAIDs in the analysis. It was shown to have the highest rate for abdominal pain, constipation, confusion, headache, tinnitus, visual disturbance, rash/pruritis and oedema.

Gastrointestinal symptoms such as abdominal pain, dyspepsia and nausea and vomiting have dominated the ADR profile irrespective of some variation in ADR rates among individual drugs. Most of the GI events reported are minor symptoms. The highest incidence of GI events has been observed with fenoprofen. Many of the GI events such as abdominal pain, constipation, diarrhoea, dyspepsia and nausea and vomiting have been reported consistently by all NSAIDS. Although less commonly reported, serious events such as peptic ulcer has been reported by 0.03% of patients in trials of ibuprofen.

Many non-gastrointestinal ADRs have also been reported in the clinical studies. Dizziness and vertigo, and headache have been reported by patients on all the individual NSAIDs. In particular, headache has been reported by 15.2% of those on fenoprofen, 11.1% of those on diclofenac, 6.0% of those on sulindac, 2.8% of those on indomethacin, and less than 2% of those on the remaining NSAIDs. Patients have reported high incidences of rash or pruritis, up to 30.8% on fenoprofen. One case of anaemia has been reported by patients on indomethacin during the clinical trials. A serious complication, such as anaemia, was only recorded by one patient in the indomethacin group.

Selective Serotonin Reuptake Inhibitors

An aggregated total of 779 patients was included in the meta-analysis of SSRIs-induced adverse events (Table 20). There were 194 patients in the fluoxetine group, 183 in the sertraline group, 132 in the fluvoxamine group, and 270 in the paroxetine group. The ADR profiles between individual SSRIs vary considerably. Sertraline appeared to have the worst toxicity profile among all the SSRIs evaluated. This is most apparent in drug-related decreased libido (14.2% compared with 0.1% among fluoxetine patients, 0.9% among fluvoxamine patients and 3.5% among paroxetine patients). The most common ADRs reported by patients on SSRIs included nausea and vomiting, ranging from 10.4% among those on fluvoxamine to 25.8% among sertraline takers, dry mouth, ranging from 2.2% among those on fluoxetine to 21.6% of sertraline patients, and drowsiness, reported by 1.5% of fluoxetine patients to 23.5% of paroxetine patients.

Many side effects referable to the central nervous systems such as dizziness, constipation, fatigue and headache are also prominent with SSRIs. Both fluoxetine and fluvoxamine

appeared to be better tolerated than paroxetine and sertraline. Adverse events incidence rates for fluoxetine and fluvoxamine are generally lower than those of sertraline and paroxetine.

Angiotensin Converting Enzyme Inhibitors

Data on 2211 patients on ACE inhibitors were used to calculate weighted average incidence rates for reported ADRs (Table 21). In general, with the exception of perindapril, ADR incidence rates for ACE inhibitors were low, thus they all appeared to be well tolerated. The ADR rates recorded in patients taking perindapril were much higher than all the other ACE inhibitors being assessed irrespective of individual symptoms. However, this was only based on one study.

The most common ADR reported was headache – 0.7% among those on enalapril to 25.5% among those on perindapril. Cough, which is a well-documented adverse event induced by ACE inhibitors, was observed among 3.3% to 31.9% of patients who were on lisinopril and perindapril respectively. No serious adverse drug reactions have been reported by the published clinical trials.

5.3.3 Management of Adverse Drugs Reactions

The local LHCC that participated in our study consisted of 38 GPs in nine practices. Following recruitment via post and telephone follow-up, only nine GPs agreed to take part in the interview. Semi-structured, face-to-face interviews were conducted to determine the possible treatment strategies and outcomes associated with the adverse events reported in the clinical trials. When presented with the list of ADRs associated with NSAIDs, SSRIs and ACE inhibitors, all GPs recognised the events as symptoms of possible drug-induced adverse events. However, symptoms such as "eyelid soreness", "malaise", "shoulder ache" and "taste impairment" would be unlikely to result in patients seeking consultations with their GPs, and were not included in the analysis.

Estimates of the following parameters were made by the GPs, based on their personal experience in dealing with patients who were on any of the three classes of drugs in general practice:

- the proportion of patients who would have their drugs stopped or changed when experiencing side-effects,
- those who would receive a particular investigation and/or treatment (dependent on the estimated rate of recovery),
- those who would fail to improve and require hospitalisation, and
- the total number of GP or outpatient visits involved.

Analysis of the GP interviews has provided a summary of the average probability of a GP performing a particular investigation or allocating any specific treatment to counteract the adverse drug reactions induced by a course of drug therapy. The results are shown in Figure 16a – d in the form of decision trees. When dealing with drug-induced events, it was believed that on average, two GP visits would be involved for the purpose of diagnosis, investigations and treatment. Often, patients would be recommended to stop the drug or switch to a therapeutically equivalent drug, possibly of the same class, in the expectation that the ADR would diminish without further management. This has been the preferred choice with all GPs when confronted with suspected drug-induced side effects. However, there are instances when further investigations and co-prescribing of additional drug treatment would be necessary, such as endoscopies and co-prescribing of ulcer-healing drugs in the case of peptic ulcers. This is most prominent among GI complications.

5.3.4 Cost Estimates

Drug costs vary considerably among drugs of the same class. The calculations for the cost of drugs were based on the assumption that where possible, the formulations of the lowest purchasing costs would be prescribed, and generic formulations would be preferred to proprietary formulations. It was also assumed that the defined daily dose (DDD) would be prescribed. Ranges of costs representing the lowest and the highest DDD are presented in Table 19. All the drug costs and defined daily doses were taken from the British National Formulary (BNF). The higher the DDD, the higher the drug acquisition costs, with the exception of ketoprofen. The maximum DDD of ketoprofen incurs lower costs than when

the minimum DDD is prescribed. This is due to potential savings from larger pack size of the drugs. The 100 mg formulation for ketoprofen has a lower cost than the 50 mg formulation.

For consistency purposes, all three classes of drugs were modelled for the same duration of treatment. The average length of all the clinical trials (in all three classes of drugs) used in the meta-analysis was approximately 10 weeks; therefore, the costs of drugs were calculated for a duration of 10 weeks.

Amongst NSAIDs, piroxicam and indomethacin have the lowest acquisition costs - £3.54 to £11.44 and £3.57 to £5.60 respectively, over a 10-week period, while ketoprofen is associated with the highest cost - £22.12 to £22.45 over 10 weeks. There is at least a six-fold increase in cost when comparing the costs of piroxicam with ketoprofen.

This is also observed among SSRIs, where drug acquisition costs range from £18.01 to £54.04 for fluoxetine, to £41.44 to £125.81 for paroxetine, a three-fold increase in cost. This large difference in costs may be partially explained by the lack of generic versions available for paroxetine (Seroxat ®) and sertraline (Lustral ®), the two more expensive preparations.

ACE inhibitors are relatively new drugs, only captopril and enalapril are available in generic forms. The drug acquisition costs in this class of drugs ranged between £5.75 to £10.51 for captopril and £24.06 to £69.49 for Perindopril, representing as much as a three-fold increase in costs.

Unit costs used to calculate the costs for managing individual adverse events are shown in Appendix IV. The direct medical costs related to the management of individual adverse events were calculated. The calculation of these costs has taken into account the resource utilisation and the costs of input variables such as GP consultations, prescriptions, clinical investigations (such as GI endoscopies for suspected ulcers and blood tests for anaemia), any outpatient hospital visits and possible hospitalisation in the more serious cases.

The least costly adverse events were those associated with the central nervous system including symptoms such as headache, dizziness and tinnitus (Table 23). The results of the GP interviews suggested that only minor cases of these events have been seen and would

only require one GP visit and no co-prescription, at a cost of £8.50. However, more serious adverse events, such as peptic ulcers, incur much greater costs (£308.41) due to further investigations, referrals and co-prescriptions. These costs were applied to the weighted probabilities (Tables 19 to 21), calculated from the meta-analysis and are shown in Tables 24 to 26. The sum of these costs is the estimated cost of managing all associated adverse drugs reactions – i.e. the shadow costs. The shadow costs for each individual drug per patient and per 1000 patients are presented in the tables.

The results of the cost analyses are shown in Table 27. The drug acquisition costs, the shadow costs (costs of managing adverse drug reactions) and the total costs of therapies per 1000 patients are presented. Irrespective of individual drugs, the total costs of drug therapies increased substantially when the shadow costs are taken into account.

In the case of NSAIDs, the cost of drug therapy increased between 12.3% (ketoprofen) and 59% (diclofenac sodium) when the cost of managing ADRs was taken into account. The most significant increase was observed in both fenoprofen (£19 860 to £43 204 per 1000 patients) and diclofenac sodium (£5850 to £14 288 per 1000 patients), when the total cost of therapy rose by over two fold when the shadow costs were taken into account.

The cost of SSRIs therapy increased by approximately 25% (fluoxetine and fluvoxamine) to 42% (sertraline) when shadow costs were included in the total cost of therapy.

The cost of ACE inhibitors therapy increased by 4% (enalapril and lisinopril) to 54% (perindopril) folds when shadow costs were taken into account. The costs associated with managing enalapril and lisinopril associated ADRs were low - £357 and £626 per 1000 patients over 10 weeks, respectively – and have little impact on the final cost of drug therapy.

Table 27 also shows the relative ranking of the drugs according to their costs. The original ranking represented the ranking of drugs according to their acquisition costs alone. For NSAIDs, piroxicam is the cheapest to purchase, followed by indomethacin, ibuprofen, diclofenac, naproxen, sulindac, fenoprofen and ketoprofen. However, when the shadow costs for these drug therapies were taken into account, the final ranking of the drugs, according to the total costs of therapy, changed. Indomethacin became the therapy with the lowest cost, followed by piroxicam. Naproxen previously ranked fifth, became the third

cheapest drug to use. Fenoprofen became the most costly drug therapy, in place of ketoprofen.

If NSAID prescribing decisions were based on the acquisition costs, piroxicam would be the preferred choice. However, when shadow costs were taken into account, indomethacin became less costly, a potential saving of £1131.85 (£6651.58 with piroxicam minus £5519.73 with indomethacin) in 1000 patients over 10 weeks may be achieved.

A similar finding was observed with SSRIs. Although the ranking of fluoxetine and fluvoxamine remained unchanged when the shadow costs were taken into account, the ranking of sertraline and paroxetine switches between placed third and fourth. If SSRI prescribing decisions were based on the acquisition costs, sertraline (£40 500 per 1000 patients) would be a cheaper alternative to paroxetine (£41 440 per 1000 patients). However, when shadow costs were taken into account, paroxetine became more cost effective, a potential saving of £7063.14 in 1000 patients over 10 weeks may be achieved.

In the case of the ACE inhibitors. Moexipril became more costly than trandolapril when the shadow costs were taken into account, and a potential saving of £320.34 (£27 155.43 with moexipril minus £26 835.09 with trandolapril) in 1000 patients over 10 weeks may be achieved.

5.3.5 Sensitivity Analysis

The input values on costs and probabilities of ADRs used in the model above were tested in the sensitivity analysis. Both the unit costs and the probabilities of developing an ADR were inflated and reduced by 20%, singly and combined. Scenario analysis based on the extremes of the 95% confidence intervals was also conducted. The resultant effect on the three models are shown in Figure 17, 18 and 19. Overall, the results are robust and the ranking of the drugs all the three models remained unchanged. Increasing and reducing the costs and probabilities resulted in corresponding increase and reduction in the total cost of drug therapies.

5.4 THE IMPACT OF PHARMACOECONOMIC INFORMATION ON PRESCRIBING IN PRIMARY CARE

5.4.1 Dissemination Exercise

Recruitment took place during one of the monthly LHCC meetings when seven GPs from five different practices were present. During the meeting, all seven GPs showed interest in the study and also agreed to encourage colleagues from the same practice to participate. However, only five GPs participated in the study. Two GPs were from the same practice, while others were from different practices. The main reason for non-participation was "lack of time".

Prescribing Data

The national prescribing trends for NSAIDs, SSRIs and ACE inhibitors evaluated in the previous sections are shown in table 28. There is no indication of any particular pattern, in relation to purchasing cost and relative cost effectiveness, in prescribing of any of the three classes of drugs.

Overall, there is a general decrease in NSAID prescribing. This may reflect the increase in the use of cyclo-oxygenase II (COX-II) inhibitors, replacing the traditional NSAIDs. The results from the economic analysis favoured the use of piroxicam and indomethacin. However, the national prescribing trend showed that these drugs were not particularly favoured by GPs. Diclofenac, ibuprofen and naproxen – ranked 3, 4 and 5 in the economic analysis –were the top three NSAIDs prescribed in Scotland. The drugs shown to be less cost effective – ketoprofen, sulindac and fenoprofen – were the least prescribed drugs.

Selective serotonin re-uptake inhibitors prescribing appeared to be generally in agreement to the results of the economic analysis, with the exception of fluvoxamine. Although fluvoxamine was the second most costly drug to purchase and the second most cost-effective drug to use in comparison to other three SSRIs evaluated, it appeared to be the least preferred choice among GPs. While increase in prescribing was recorded for all other SSRIs, an 11.71% reduction in fluvoxamine prescribing was observed.

The less favourable ACE inhibitors, ranked 5, 6 and 7 according to the results of the economic analysis, were prescribed in smaller volumes than those ranked 2, 3 and 4. However, the least costly and the most cost effective ACE inhibitor – captopril, was not the most commonly prescribed ACE inhibitor.

The prescribing trend of the LHCC in the study was in agreement with national prescribing. The change in national prescribing over a 12-month period differed from those recorded in the LHCC in this study. This is not unexpected given the sample size for this study is small. Two drugs that were included in the economic analyses – fenoprofen and moexipril – were not used by the LHCC.

Overall, there was a reduction in NSAID prescribing in both groups. The only exception was observed with diclofenac. A moderate increase (1.02%) was observed in the study group compared with a 5.27% reduction recorded in the control group over a six-month period (table 29). However, this difference was not statistically significant. The only difference in the change of prescribing was observed with ketoprofen. A larger reduction in prescribing was recorded in the control group (29.01%) when compared with the study group (17.23%).

Increases in fluoxetine, sertraline and paroxetine prescribing were observed in both groups over the six-month period. However, none of the differences were of sustainable significance. Similar to that observed with the national prescribing data, there was a reduction in fluvoxamine prescribing, but the differences between the study group were not statistically significant.

The only statistically significant difference in the change in prescribing among the ACE inhibitors was observed with trandolapril. The prescribing of trandolapril was reduced by 8.79% compared with 0.12% in the control group.

This dissemination exercise appeared to have no obvious effect on prescribing. Neither a significant increase in the more cost effective drugs, nor a significant reduction in the less cost effective drugs was observed in the study group. The significantly large reduction of trandolapril prescribing when compared with the control group may be a positive result,

however, it is almost certain that this observation could be explained by the small number of prescriptions recorded.

5.4.2 Survey – Quantitative and Qualitative

A total of 53 members and 17 affiliated members were identified by the WestNet database. Four non-GP members (pharmacist, optometrist, clinical auditor and dentist) were excluded from the survey. All the eligible GPs (n = 66) were divided into two groups - email group, i.e. those with a contact email addresses (n = 33) and postal group, i.e. those without contact email addresses (n = 33). However, email was undeliverable to five members - three from questionnaire (I) group and two from questionnaire (II) group.

Response Rates

A total of 27 GPs returned the questionnaires, an overall response rate of 44%. Table 30 gives a detailed breakdown of the response rate by each group. Higher response rates were observed with the postal group when compared with the email group and with questionnaire (I) when compared to (II). However, none of the differences between groups were significant.

Questionnaire (I) - Economic Information Used in Medical Decision-Making

All respondents indicated they believe that economic information comparing cost and effectiveness of treatments has influenced their medical decision-making. The majority of the respondents (n = 9; 69%) reported that such a decision was made as recently as one month previously or less, while 15% (n = 2) reported such decisions made one to six months ago and another 15% (n = 2), over six months ago.

Both published and verbal economic information produced by local authorities (Health Boards, PCGs, Prescribing Medical Advisors [PPAs] and Medical Prescribing Advisors [MPAs]) were the most commonly used by GPs, followed by information generated by the pharmaceutical industry (table 31). However, only 13% (n = 2) and 20% (n = 3) have

used conferences, seminars, and journal articles as economic information sources respectively. A slight preference to published information was noted.

All respondents (n = 15) uniformly reported changes in prescribing as their recent economic-information-influenced medical decision. Change in proton pump inhibitors prescribing was described by 33% (n = 5), statin prescribing in 20% (n = 3), and 13% (n = 2) described changes in the prescribing of non-steroidal anti-inflammatory drugs.

Four respondents described circumstances when economic information had failed to influence their decision-making. 50% (n = 2) felt it was 'impossible to implement these findings into practice', while one respondent disagreed with the results of the information presented. One respondent described the reason to be due to the 'cost of time in implementing changes not being reimbursed'.

Questionnaire (II) - Sources and Relevance of Economic Information

All respondents believed that economic information should be incorporated in healthcare decision-making. They were all, with the exception of one (n = 11; 92%), able to describe the various sources of economic information they had used (table 32). The most common source was the Scottish Prescribing Analysis (SPA) data - used by 83% of the respondents (n = 10), 80% (n = 8) of whom found the material relevant to their everyday practice. This was followed by the literature produced by the pharmaceutical industry, which was used by 75% of the respondents (n = 9), but only 20% (n = 2) found the material relevant to practice. Fifty-eight percent (n = 7) recognised medical prescribing advisors and pharmaceutical prescribing advisors as a source of economic information, while 62% (n = 5) regarded the information as relevant.

However, 80% (n = 8), 73% (n = 8) and 67% (n = 8) of the respondents did not regard the British Journal of General Practice, locally produced newsletters and prescribing formularies, and the General Practice Administration System for Scotland (GPASS) feedback as an economic information source.

Higher proportions of respondents preferred published material compared with verbally presented material (table 33). In particular, locally specific information and summarised

information in leaflet format were favoured by 54% (n = 6) respondents.

5.4.3 Qualitative Interviews

Fifty letters of invitation were sent to GPs by post and followed up by telephone, only four agreed to be interviewed. Another four GPs were recruited through snowball sampling. All of the eight GPs participated in the interviews were from different practices. None of the GPs interviewed had any previous training. One of the GPs interviewed was relatively non-communicative giving brief and often mono-syllabic answers and was excluded from the formal analysis.

The Use of Current Evidence

All the GPs interviewed were able to describe the most recent economic information they have encountered. However, at the onset, the majority of the interviewees described the reviewing of Scottish Prescribing Analysis data.

> *"I had economic information coming from the prescribing centre in Edinburgh. They would send out regular analysis on prescribing costs, etc.; and it drew attention to your placing in terms of your individual practice, your locality and nationally." (GP 2)*

> *"I look at level 2 reports, detail breakdown of the prescribing quarter and analysis of prescribing; and also look at the information the prescribing bureau send us on drugs and cost analysis." (GP 3)*

Subsequently during the interview, the term "economic information" was defined as "information relating to both costs and benefits" and the question was repeated. Although peer-reviewed medical journals, including the Lancet and the British Medical Journal, were the most commonly cited source of recent economic information, none of the interviewees were able to recall details of the information they had read. Some of the

GPs interviewed described economic information presented to them by pharmaceutical drug representatives, however, they showed much scepticism towards the quality and the validity of the information presented to them. One interviewee recalled economic information that was discussed in a regular newsletter disseminated by the British Heart Foundation. While all the interviewees described the information as of interest to varying degrees, none had made or changed decisions in practice based on this information.

> *"...but she was telling me about the additional benefit adding that into statin therapy. And if you double the statin dose, compare that to the cost of adding this additional drug, you get this benefit and that. What the cost benefit was, I can't remember... That's probably the most often source I see it from. But that's the source I tend to ignore." (GP 5)*

> *"I think there was something recently in promotional literature concerning the use of statins... there were some explanation, rationale to statin in a much more broader population context and its effect on the reduction on ischaemic heart disease and stroke." (GP 7)*

Despite defining economic information as information relating to both costs and benefits, most GPs interviewed did not differentiate between economic evidence and cost data. All the GPs interviewed stressed that they bear cost issues in mind when prescribing; five interviewees described "paying attention" to the costs of drugs that are displayed with the GPASS system that they use. However, one GP described the use of a GPASS-integrated online formulary produced by the local medicines management team that takes into account the relative cost effectiveness of drugs.

> *"If I felt it did not compromise the treatment in any way, then I would certainly use the generic brand of drug; if I felt there was an issue in relation to the efficacy of the medicine, and that's what the patient needed and that was important, then take precedence. But other than that, I would go for generic or the cheapest." (GP 1)*

> *"...the cost of the drugs comes on the screen with the GPASS and I do have a look at that" (GP 4)*

"Recently, I had a look at CV drugs because my prescribing cost for CV drugs are above the national average. So, I looked at level 2 data and try to analysis why this was..." (GP 2)

"I suppose when you have two drugs and there is nothing to choose between them, previously you would have looked at the cost; now with the formulary, you get first choice and second choice... The formulary takes into account the cost of buying the drugs and the associated costs." (GP 7)

Two interviewees indicated that they were satisfied with the way economic information is presented in the literature. However, all the GPs interviewed, including these two, said they were unfamiliar with most of the economic principals presented to them. All the interviewees recognised terms such as "direct and indirect costs", "cost effectiveness", "cost benefit" and "quality of life adjusted years"; however, only a small proportion recognised the terms "marginal cost" and "incremental cost effectiveness".

In addition to the commonly used economic jargon, the concept of "shadow costs" – taking into consideration the cost of managing adverse drug reactions was discussed. Overall, the interviewees described this to be "interesting" and "relevant". However, most believed that such information is purely academic and would not have significant impact on their prescribing decisions.

"It would be (of interest) if you put it in a form that is clear, that will be good information to know." (GP 4)

"...it's probably more of academic interest than anything... it is not going to influence prescribing unless it is a side effect that is very common...
...So if you treat 100 patients and 2% get a side effect and they will be more expensive, forget it. If you can show that 90% will get the side effect, therefore, 90% of the time more expensive, so that's worth considering." (GP 5)

Some GPs felt that they are already taking into account such considerations when prescribing.

> *"Perhaps subconsciously, this shows an influencing factor in your choice... although you know this other product is slightly more expensive than another, if from your experience, patients seem to tolerate it better, come back less often, feel it's more efficacious... Therefore, you wouldn't necessarily be selecting based on the ways you have been suggesting, the product that was more expensive... But from your perspective is a better product for that individual patient for a combination of all the reasons that I have mentioned, so although, there was economics involved, they were indirect economics, of the kind you mentioned, but I don't particularly remember analysing it in the way you have presented...*
> *...I do wonder a lot of GPs with experience possibly do the same thing, but not think in those terms. These products work well, patients takes them, like them. I know it's slightly more expensive that product B, but for these reasons, I think, it's worth the expense." (GP 1)*

> *"That process you've described is exactly what (the formulary) has done to decide the first choice for (drug) use... It's not something that I do personally. It's been done for me." (GP 7)*

The Barriers and Facilitators in Implementing Economic Evidence

All the interviewees uniformly stated lack of time to be the major barrier to implementing economic evidence. It is also clear that the recent introduction of the new GP contract has taken priority in the thoughts of most GPs.

> *"We don't really have the time... a lot of people come in and give you chapters and verse on the studies, where to find them and what they show and you tend to just accept that –well ok." (GP 4)*

> *"Time is the key barrier. We don't have time to do much more than what we're already doing." (GP 5)*

"...Again, it's finding the time to read many of these articles..." (GP 6)

"Frankly, we have the new contract, where is there time to put it in? There is so much in general practice at the moment." (GP 7)

"...especially with the new contract coming into place, I don't think GPs will have time to think about much else" (GP 1)

Some GPs interviewed regard health economics as an academic discipline and lacks practical applications.

"I suppose GPs traditionally, again in a non-critical way, don't see themselves as academics. Therefore, they're practical people getting on with their day-to-day job of "real" medicine." (GP 2)

"They're (economic studies) often are involved in hospital trials rather than general practice trials and hospital trials are a different environment to general practice. And you feel the conditions and the controlling factors are quite different to the people coming into general practice in the daily surgery. Although it might recommend a particular product for hypertension or whatever, you did feel it didn't necessarily provide the information in the setting that you were familiar with. So, it wasn't necessarily, you couldn't extrapolate it directly." (GP 6)

None of the GPs were able suggest facilitators that may help implement economic information in their practice. There were suggestions about improving the presentation of the findings in a more precise manner. However, it was also pointed out that although this may increase the likelihood that such information may be read, none of the GPs believe that the information will be absorbed and used in clinical practice. This may, in part be due to their perspective on the role of economic issues in health care decision making as a whole, which is presented below.

<u>The Role of Economic Issues in Healthcare Decision Making</u>

Overall, the participants believed that it is important to have a general awareness of health economic issues, however, they don't believe that such information has a role at a practice level. All the GPs interviewed believed that the use of economic information should be carried out either nationally or at the least, by the local trusts.

> *"I think these decisions should not be taken at a general practice level...*
> *...these information should be filtered through either regional or national level... you can't have decisions made at practice level. You'll then have undoubted result in one practice doing one thing and another practice doing another, and then you have an inequality." (GP 7)*

> *"And I think it is reasonable that GPs as gatekeepers to these services that cost money have responsibility and awareness... I don't think there's a way round for GPs; I think they have to have information like that. Whether they use it or not it's up to them but I think they need to have the information of cost, because otherwise, you would loose sight within a few years absolutely of relative costs." (GP 1)*

> *"Well, I think... trusts or nationally. We're in the sharp end here – we have 10 minutes with the patients, and patients may come with 10 problems each, so there's really no time to think about economics in the wider sense. But if we have some sort of feedback from the trusts or nationally, in a simple form, it might be interesting." (GP 3)*

> *"...it would have to done at a national level, probably medicines committee of the NHS, centrally, that would have to do that. But some sort of body like that." (GP 5)*

Overall, all the GPs interviewed have regularly come across health economic information and feel that they should be kept informed. However, the difficulty they expressed in recalling the information has indicated the lack of impact the information has had. Time and applicability has been found to be the key barrier to implementing the findings of economic studies. However, the view that the implementation of economic information should be at a national or a trust level has represented an indirect barrier to their using of such information.

6 DISCUSSION

6 DISCUSSION

6.1 INTRODUCTION

The discussion of this thesis follows the same order as the work described in previous chapters. The discussion on the results of the thesis starts with the findings of the population based economic analysis in section 6.2. This is followed by discussion on the findings from the meta-analysis based economic analyses of NSAIDs, SSRIs and ACE inhibitors (section 6.3). The findings of the dissemination exercise, the survey and the qualitative interviews follow in section 6.4.

6.2 POPULATION BASED ECONOMIC ANALYSIS

The cost of drug therapy cannot be represented solely by its purchasing cost. The population based pharmacoeconomic evaluation of NSAID therapy (section 5.2), by calculating its complete cost, including that of unintended adverse events, is made from a NHS perspective.

The strength of using population data in cost analyses has been demonstrated by this study. Detailed recording of epidemiological data, such as those recorded by MEMO, provide a clear view of drug use in real clinical practice. These data are particularly valuable when investigating unintended adverse effects and subsequently their costs for individual drugs. In contrast, clinical trials would not be able to provide accurate data for this type of costing exercise due to issues surrounding the transferability of appropriate prescribing decisions into real practice and the methods adopted to record adverse drug reactions. In addition, the number of subjects in clinical trials are several orders of magnitude smaller than those in the population-based study described here. However, this population dataset has one major limitation, in that the absence of indication for prescribing makes these studies particularly vulnerable to confounding by indication.

Sensitivity analysis has shown that the results obtained from this study are robust. Taking a NHS perspective, misoprostol therapy concurrent with NSAID treatment has been shown to produce significant savings in a Tayside population compared with H_2 blockers or

omeprazole therapy. In comparison to NSAID only therapy, modest savings may also be made on males who are over 75 years old, but not females in any age group.

From a NHS perspective, a disproportionate increase in costs is observed in those who were prescribed any GI protective such as H_2 blockers, omeprazole or misoprostol, concurrently with NSAIDs. This is likely to be due to confounding by indication in groups perceived by GPs to have higher risks who were co-prescribed ulcer-healing drugs. Patients with GI symptoms, or more ill are more likely to be given GI protective agents by their GPs. Therefore, there is an inherent bias against both the sub-cohorts receiving GI protectives. This study has attempted to remove all possible bias in the sensitivity analysis, by using very strict subject selection. All the patients that are potential confounders, those who may be 'more ill' were removed from the dataset for reanalysis. All the patients with prior GI events and endoscopies were excluded. These patients are perceived to be at high risk of GI events and may be prescribed different patterns of drugs from those who were at low risk. All the patients who were prescribed aspirin were also excluded from the sensitivity analysis. These patients may be receiving prophylactic aspirin in the prevention of peripheral CV disease. In addition, patients with prior history of CV events were also excluded. These patients may be at high risk of developing CV events, thus perceived to be 'more ill' may be also prescribed different patterns of drugs. Finally, those who died within the 12 months post-study period were also excluded as they may also indicate increased severity of illness. These factors were excluded alone and in combination in the various analyses performed in the sensitivity analysis to replicate the principles of the 'restrictive cohort design' [123]..

Despite the attempts at removing all potential biases from the study, the findings of this study are most probably due to uncontrollable confounding factors that are unmeasured or cannot be measured. The baseline risk in the two groups given NSAID and GI protectives were high demonstrating that these patients were not comparable with regards to GI and CV risks. There are other recognised techniques to deal with confounding issues such as propensity scores [198]. However, these analytical techniques are only useful for reducing confounding that has been measured and would add little value to the findings of this study.

For each individual, the clinical and cost impact of the non-GI related events – shown in particular, by the additional prescriptions, GP consultations and CV admissions – was shown to be significantly elevated. The costs of these events accounted for the excess over

the comparator group of £166 in the NSAID only group, and £577 in the two groups prescribed NSAID and GI protective combined. It was found that 78% of the incremental cost (total cost of the two NSAID and GI protective groups compared with the comparator group) was attributable to CV admissions and prescriptions in the NSAID and GI protective (H_2 blockers, omeprazole or misoprostol) patients. The unexpected finding was that GI admissions and endoscopies accounted for only 8% of incremental costs. The high incidence of CV events, seen in particular among those on GI protectives, is associated with a high background rate of prior CV admissions. This is not unusual in a Scottish population. An association between NSAIDs usage and increased CV events has been documented in some studies - prior history of CV disease has been shown to be one of the risk factors for serious upper GI complications [199]. NSAIDs elevate blood pressure in hypertensives, and to a lesser extent, normotensive individuals [76,200-203], which may also have contributed to the increased CV events observed. There is additional evidence in the literature about the association between biochemical evidence of chronic inflammation and increased CV risks [204]. However, it seems unlikely that these factors could explain the difference between the two NSAID groups. Removing pure aspirin takers from the analyses (suspected to have been prescribed for prophylaxis of CV events) had little effect on the results.

From a cost perspective, the most striking feature of the study is the exceptionally high cost of individuals in the groups taking NSAIDs and any GI protective (such as H_2 blockers or proton pump inhibitors) or misoprostol – these costs were 135% more than the NSAID only group. Further investigation into this sub-cohort of individuals who receive concomitant prescriptions of GI protective agents seems useful. Although the groups co-prescribed misoprostol and GI protectives have a higher mean age, a greater proportion of females, a higher mortality rate and a greater proportion of individuals with prior endoscopies and admissions, these findings do not explain the differences. Excluding all patients with evidence of prior co-morbidity would be expected to help to adjust for 'confounding by indication', i.e. the groups prescribed GI protective or misoprostol are more expensive merely because these patients are already at risk from co-morbidities (and already more expensive to the NHS) and were more likely to be prescribed GI protective drugs or misoprostol. The incremental cost of the groups prescribed GI protective drugs or misoprostol were unaffected by this analysis. Therefore, factors such as sex, age, prior admissions, and prior use of ulcer healing drugs, did not appear to be responsible for the additional cost observed among the GI protective and misoprostol takers. The residual

explanation may be that the profile of this group of individuals includes more illness - additional to the restricted list of GI, CV, RA and OA events recorded in this study - explaining their greater utilisation of healthcare resources. The use of GI protective drugs and misoprostol may possibly be related to other clinical factors, not measured here.

There are several recently developed population databases which record reasons for prescribing (e.g. General Practice Research Database [31], MediPlus [32] and Continuous Morbidity Recording [34]). These databases record activities in GP practices and are able to provide indications for prescribing. However, it is uncertain whether data from these databases would be able to provide a clear explanation for the additional costs incurred in these patients.

6.3 MODEL-BASED PHARMACOECONMIC ANALYSIS: EXAMPLES WITH NSAIDs, SSRIs AND ACE INHIBITORS

The literature review of the large amount of randomised controlled trials of the various drug therapies has resulted in only a few relevant studies suitable for inclusion in the meta-analysis (24 on NSAIDs, 21 on SSRIs and 24 on ACE inhibitors). This is not unusual in meta-analysis, when strict inclusion criteria have to be applied in order to aggregate data from similar studies to calculate a weighted average rate. Unlike most meta-analyses, where efficacy data are evaluated, this study is particularly problematic because of the focus on ADR data. Although the lack of good quality clinical trials (mostly due to time-factor, especially in the case of NSAIDs) were in part responsible for the resultant lack of data, the method of ADR reporting in many trials may have contributed to the problem. The initial result of the literature search has identified many randomised controlled trials with reports on associated ADRs. However, on reviewing the actual papers, it was apparent that ADRs are often secondary or tertiary outcome measures and data presented are often incomplete or unextractable. Graphical display of data or aggregated ADR data according to major organs or biological systems is common. Although these studies may have recorded reliable drug-induced ADR data, reviewers are unable to extract data for meta-analysis and are forced to exclude many studies from the analysis.

The pharmacoeconomic analyses of NSAIDs, SSRIs and ACE inhibitors have successfully demonstrated that local economic analysis using local cost and resource data can be easily performed. The results of the studies have proved the importance of taking drug-induced ADRs into account when conducting pharmacoeconomic analyses. These adverse clinical events may add significantly to the total cost of therapy. In the case of NSAIDs, a 12% (ketoprofen) to 59% (diclofenac sodium) increase in cost was observed (table 31). In the more severe cases, inclusion of the shadow costs changed the ranking of the drugs. Although a change in ranking was not observed among SSRIs, the incremental costs attributed by the shadow costs ranged from 24% with fluvoxamine to 42% with sertraline.

Economic evaluations in drug therapies are generally used to calculate the incremental cost-effectiveness ratio of two interventions. This ratio provides a standard comparison for the cost effectiveness of drugs, based on the difference in cost and clinical efficacy of the drugs being compared. However, in cases where the drug therapies being compared are of similar efficacy, as in the case of many drug treatments for chronic diseases such as RA, depression and hypertension, the measure of effectiveness is based on improved tolerability. This is often seen in economic evaluations of NSAIDs, where drug-induced GI toxicity is frequently used as a measure of clinical effectiveness. Similar methodology is used in comparing SSRIs with TCAs, when reduced suicide rates have been used for the same purpose. In addition, these studies are predominantly based in hospital settings.

Based on this methodology, pharmacoeconomic analyses were carried out to compare the real costs of NSAID, SSRI and ACE inhibitor drug therapies, taking into account their complete adverse drug reactions profile. This study attempted to widen this approach to incorporate all the drug-associated adverse events reported in the medical literature. In contrast to hospital-based publications, this study attempts to assess the real cost of drug therapies in a general practice setting.

The study limitations associated with the economic analyses are inherent in any cost-effectiveness analysis when definitive data do not exist on the probability of some or all of the outcomes examined. For instance, randomised controlled trials are designed to test the efficacy of drugs and may not provide an appropriate answer to effectiveness and safety. The objective of economic evaluation is to generate policy-relevant data to inform decision-makers about the incremental costs and outcomes of the drugs that can be expected in routine clinical practice. It is often felt that clinical experiments, such as randomised

controlled trials, may not serve economic analysis well as they do not reflect practice in 'real life'. In addition, there is concern regarding generalising trial results to clinical populations that are not studied in the trial but covered by a decision makers' drug plan (e.g. specific age groups), and to geographical settings and health care systems different from those studied. However, until such data are readily available, there is little alternative to the current methodologies. There is current encouragement and guidance to add economic data to trials [205].

The literature searches on randomised controlled trials were conducted systematically. Although they were not formal systematic reviews, the process was in line with the common guidance for carrying out a systematic review [206]. An appropriate search strategy of the literature was developed, clinical trials inclusion and exclusion criteria were defined and followed, ADR data were extracted systematically and the quality of the clinical trials was assessed. In the case of a systematic review, the literature search would be more intense and at least two reviewers would be required to review the clinical trials and extract the data to eliminate personal bias [206]. However, this was not practicable for this study.

Some heterogeneity may have existed between the trials selected for meta-analysis. For instance, the trials covered a range of drug dosages within the three classes of drugs. Adverse drug reactions are often dose-related effects and may potentially influence the findings of this study. However, it is believed that the dosages of the drugs covered in the clinical trials included in the meta-analysis were within the BNF recommended therapeutic range for their indication, therefore, it is unlikely that this would have significantly influenced the results.

The results of the literature review have highlighted the need to improve adverse events data reporting in clinical trials. The method of gathering adverse drugs event data and number of adverse events reported are often unclear or not reported. The introduction of validation tools to assess clinical trial quality, such as the Jadad score, has helped to improve the quality of clinical trials substantially over the years. However, these quality assessments have focused on issues relating to randomisation, blinding and withdrawal. Given the importance of the potential toxicity profile, it is worth considering introducing the measure of adverse clinical events into the quality assessment of clinical trials. Although the adverse clinical data used to populate the economic models were based on randomised controlled trials, the pooled probabilities of individual adverse events are

robust, and generally agree with those reported in post-marketing surveillance reports. In addition to improving the quality of adverse events reporting in clinical trials, it is also important to report the complete range of adverse events. In the case of NSAIDs, many clinical trials have focused solely on the associated GI events. Other adverse events such as those related to the central nervous system (such as dizziness, headache, insomnia) may be of lower clinical risk, these events add substantially to the cost of the drug therapy and should not be ignored in pharmacoeconomic models.

This study, unlike the population model described in the previous section, was based on data from randomised controlled trials. Although randomised controlled trials are the gold standard for examining the efficacy of drugs, they are not designed to measure the ADR profile of drugs. In addition, clinical trials are often limited by sample size and time. In order to fully appreciate drugs' toxicity profile, observations of a large sample over longer periods of time is required. The true ADR rates associated with these drugs may be underestimated by clinical trials. On the other hand, the proportion of patients who actually seek medical help as a result of experiencing these ADRs is unknown. This study is based on the assumption that all the patients who experience these ADRs would seek medical management. This may over-estimate the true costs associated with these drug therapies. However, this study is a comparative analysis and the drugs are ranked relative to each other; there is no evidence to suggest particular bias in any of the drugs studied. .

The most difficult measurement in economic evaluations is the measuring of resource utilisation. Record linkage is a potential solution to this problem. Relevant measures include data on prescriptions, the number of GP consultations, referrals, outpatient visits, clinical procedures and diagnostic tests. Ideally, these data would be collected from patients' case notes. This is possible in situations in which resources used in a hospital setting are measured. Here one would expect definitive diagnoses and treatments to be recorded in a relatively standard manner, but often are not. This is even more rarely the case in the primary care setting. Many databases are beginning to record events and resource utilisation in primary care in a standardised format. However, to date, there is no readily available database to enable formal economic evaluations to be undertaken.

The MEMO database that was used in the population study is a database with such potential. However, without linkage between prescriptions and indications, the value of the MEMO data in primary care research is limited. The great strength of the MEMO data lies

in the estimates it provides of the incidence of hospitalisation giving the ability to calculate the costs associated with them. Its weakness, in common with all observational data, is that it provides no reliable internal estimate of efficacy due to the inevitable, but unknown extent of confounding by pre-existing risk factors.

Having explored the various available databases without success, a more traditional method of seeking expert opinions on resource utilisation was used in the economic analyses. The difficulty of recruiting GPs for research has been highlighted in all areas of primary care research. General practitioners are constantly under pressure from their trust and political issues which affect their daily practice, in particular working within their new contract; in addition, the 'researchability' of this group of healthcare professionals are reaching saturation point due to the large amount of academic and commercial research carried out in primary care. Therefore, it is unsurprising that only a small sample of GPs was successfully recruited for the economic study.

A further problem with determining resource utilisation data from expert opinion is the method of surveying itself. General practitioners respond to questions posed at these interviews based on their own personal perspective and clinical experience. As a result, a subjective perspective of management strategies and resource used is obtained. A more effective method is to adopt the Delphi technique, an approach used for establishing and developing consensus [207]. It is usually based on experts being sent a self-completion questionnaire, analysing the responses, feeding back a summary of the group's view and asking respondents to re-evaluate their own views given the results. If a substantial amount of disagreement remains a further round of feedback may ensue. However, due to time and financial restraints, it was felt that revisiting and re-interviewing the participated GPs would not be feasible in this study.

This thesis recruited GPs who have no special interest in the drugs being evaluated and the conditions they are indicated for. It is believed that a sample selected in this manner would represent average GP behaviour in primary care. Although the GPs in this study were not representative due to the small sample size, this could be the case if a large sample size can be achieved and if GPs were selected at random. An alternative approach is to create an expert panel with healthcare professionals who have special interest and knowledge in the area being investigated. This is the current approach adopted by the HTBS when conducting economic evaluations [208]. However, there is controversy surrounding this

approach. Creating an expert panel would overcome the problems related to recruitment and commitment, but such panels are unlikely to be representative of average clinical behaviour.

The meta-analysis based economic analyses have attempted to measure and compare all the indirect costs associated with NSAIDs, SSRIs and ACE inhibitors. Based on the measure of primary clinical outcomes such as pain reduction and mobility scores associated with arthritis, the Hamilton Rate Scale for Depression (HRSD) and the Clinical Global Impression (CGI) associated with major depression and the measure of blood pressure in hypertension, the literature has shown that there are no statistically significant differences in the efficacy of the individual preparations within these three classes of drugs. This was evident from the studies included in the meta-analysis. All the included studies that made comparisons between the drug being investigated and an active comparator reported no statistically significant difference in the measured outcomes. As a result, a therapeutic class effect may be speculated. In particular, the class effect of ACE inhibitors have been widely discussed in the literature [209].

Therefore, the measure of secondary clinical outcomes associated with ADRs should be considered, but these are extremely difficult to measure. Adverse drug reactions are symptoms arising from drug therapy, and all the morbidity that may be associated with these events is limited and usually reversible on stopping or switching of drugs. Measures of health loss such as disability adjusted life years (DALYs) and quality of adjusted life years (QALYs) have been designed to measure health loss based on the assumption of permanent change and would not be applicable for morbidities associated with ADRs.

One way of addressing non-permanent health loss associated with ADRs may be the measuring of utilities from the patients' perspective. Cost benefit analysis may be carried out to determine whether the benefits of preventing certain ADRs during drug treatment therapy outweigh costs from a societal perspective. The contingent valuation method [210,211] may be used to measure willingness to pay for a reduction of certain ADR symptoms associated with individual drugs. This would potentially provide an estimate of the 'value' of preventing or reducing certain drug-associated ADRs from a societal perspective. However, this would require assessment at the level of individual patients which was beyond the scope of this thesis.

6.4 THE IMPACT OF PHARMACOECONOIMC INFORMATION ON PRIMARY CARE PRESCIRBING

The impact study was an exploratory exercise to assess any change in prescribing pattern by GPs as a result of disseminating pharmacoeconomic information.

Implementation of research findings has been recognised as a major hurdle in public health research. The implementation of the various strategies on improving clinical and cost effectiveness of primary care prescribing has been met with similar difficulties. A recent study [119] of the methods that have been adopted to promote the uptake of research findings suggested that it was possible to identify strategies that were more, or less effective. Strategies such as postal distribution of materials or didactic educational sessions were found to be largely ineffective. Local consensus conferences, the use of opinion leaders or audit and feedback were of variable effectiveness, and strategies such as interactive educational workshops, reminder systems, educational outreach and multifaceted interventions were suggested to be largely effective. In the case of influencing prescribing, the conclusions from implementation studies on different methods of changing prescribing behaviour in primary care are generally in agreement with those described in the review. The key to successful implementation of evidence in prescribing, and probably all other areas of healthcare is to conduct multifaceted, but tailored interventions.

None of the strategies described in the literature, such as dissemination of printed material, educational outreach and feedback, are novel approaches to dissemination. These are all methods that have been adopted by the pharmaceutical industry in promoting the use of their products. Dissemination of printed material via simple advertising in journals and postal marketing literature and outreach visits by medical representatives are routine activities within the pharmaceutical industry. This is probably an indication of the potential benefit of these strategies.

The impact study on pharmacoeconomic information on prescribing has failed to promote significant changes in prescribing patterns. There is no strong evidence in the literature to support or refute any particular interventions for changing prescribing in primary care. There is much diversity in the methodology and the quality of the implementation studies. Therefore, the transferability of the results from these studies is questionable, and it is

impossible to draw any firm conclusions about the effectiveness of the various interventions. The reported success of various interventions at influencing primary care prescribing, based on both clinical and economic material, is unclear.

Generally studies that have shown positive results were those that involved GPs who hoped to implement change in their clinical practice irrespective of the type of intervention in the first place, thus willingness to participate. This has contributed to over-estimation of the impact of many interventions. In addition, confounding factors are extremely difficult to measure. Since it is impossible to create a controlled environment, factors that may play a role in influencing prescribing may not be identified or adjusted for. This is not always clear whether the observed effects are genuine effects as a result of the intervention.

Due to the nature of this type of research, the majority of these studies are often focused on a small group and tend to have a limited follow-up period. Results of these studies are often interpreted as ineffective, however, size limitations meant that it is often difficult to demonstrate a positive effect, which does not equate to deducing there is no effect. Even in cases where positive effects were observed, there is no evidence to suggest such effects will be sustained over time.

In a discussion paper on implementing evidence in general practice, Wensing M et al (1998) [212] summarised the challenge ahead. "*Not all interventions to induce change achieve the intended results. Change is a stepwise process, in which several barriers have to be removed. For change to be successful it is necessary for the target group of clinicians to have the knowledge, skills and motivation needed to adopt a practice. In addition, it is that practical and organisational conditions make the new behaviour possible and that colleagues, patients and others accept it. Interventions to induce change should focus on the removal of these barriers, support the process of change, and consolidate the new practice.*" There is no "magic bullet" to achieve change.

Salisbury C et al (1999) [213] conducted a study to attempt to understand the barriers and facilitators to implementation, and to study the characteristics of those who successfully implement evidence-based change, using prescribing as a model. Three key areas of change in prescribing were audited, and amalgamated to give an "implementation score" per practice. Wide variations were noted between practices' implementation scores. An innovative approach among GPs and fundholding status were the only factors shown to

have significant relationship with prescribing changes. Use of clinical protocols, disease registers, or computers was not associated with high implementation scores, nor was the GP's age. It was also found that GPs feel that there is an information overload. It was felt that analysis at a practice level may be realistic, as patients' treatment may reflect decisions made by several different GPs as well as practice policy, but may mask the influence of characteristics such as the GP's age.

The most important factor in implementation is to recognise and understand the barriers that influence effectiveness. For instance, educational outreach as a strategy for changing prescribing behaviour has been the most extensively researched area in this field. Many American studies have suggested these interventions to be effective, and in some cases, even cost saving, but the UK studies have reported mixed findings. One uniform conclusion may be drawn from these studies - untargeted educational outreach is ineffective. However, how these interventions should be targeted, remains unclear.

Another important factor in influencing behaviour and effectiveness is the acceptability of the intervention to the intended audience. The willingness to change and improve prescribing behaviour in both clinical and economic terms is crucial to the success of these studies.

Finally, many small but important factors come into play during decision making. It is important to identify these factors and understand their interplay. For instance, the style of data presentation has significant influence of the acceptability of evidence. In one study, Elting LS et al showed that clinical investigators' decisions could be affected by factors unrelated to the actual data [214]. The study showed that the accuracy of decisions was affected by the type of data display and by positive or negative framing of the data. Their principle conclusions were that the mean times to make decisions were similar for each display and professional group. The formats preferred by doctors were not the ones that led to optimal decision making. Pie charts and bar graphs were inferior to tables and icon displays. Icon displays and negatively framed data in tables led to superior decisions, but icons were not liked.

The measure of effectiveness of interventions influencing prescribing is dependent on the available prescribing data. Prescribing data differ in quality and ease of data extraction.

There is growing pressure to make effective use of prescribing data in order to inform policy and to ensure equitable distribution of resources.

Prescribing Analysis and Costs (PACT) data is the main source of prescribing data in England (from Prescribing Prescriptions Authority). These data are universal, comprehensive and accurate. Indicators based on PACT data could be used fairly easily for financial management of the drug bill. However, these data are not linked to patients or their diagnoses and it is difficult to use them to assess quality or cost-effectiveness. There are many limitations. The PACT data are based on costs. The cost included on data was the net ingredient cost (NIC) – i.e. the Drug Tariff price, not including dispensing fees, container costs and VAT. The number of items prescribed (indication of frequency of prescribing) is described, but not the item size, which is particularly important in repeat prescribing. There is no individual patient data although various prescribing measures weighted to registered populations are included in PPA reports.

The advent of electronic PACT data has already had a considerable impact on prescribing analysis [215]. Further developments are taking place centring on electronic data interchange (EDI) which, unlike PACT, will be patient-based and comprise complete medication profiles with information on prescription quantities, frequencies, and duration. Various scenarios are being considered, involving transmission of electronic prescription records directly from GPs to pharmacies or indirectly via the PPA; the PPA would also receive electronic dispensing records from pharmacies. These records will contain a patient identifier code that will enable, for example, comparison of drugs prescribed and dispensed. A further step might involve using EDI to evaluate expert systems such as PRODIGY (Prescribing Rationally with Decision support In General practice studY) [216], which are currently being developed to provide on screen advice to GPs on treatment options. Other sources of prescribing data include EPACT, epact.net, community.net and the prescribing toolkit (a stand alone information system which currently contained information on potential savings from generic substitution, a specialist drugs catalogue and various prescribing indicators).

The situation in Scotland is not that dissimilar. Basic prescribing statistics have been available to Health Boards and GPs in Scotland since 1954 based on prescriptions dispensed in a single month and supplied as an analysis three times each year. The Pharmacy Practice Division (PPD) was set up originally as the *Prescription Pricing*

Division to process GPs' prescriptions and pay community pharmacists and dispensing doctors. Following computerisation at PPD (commenced in 1987) a project was set up to develop a comprehensive database on GPs' prescribing which would enable speedy publications of more meaningful prescribing statistics to GPs and enable them to assess and develop their prescribing practice. The result of the project was the paper-based Scottish Prescribing Analysis (SPA). From April 1990 SPA level 1 has been sent quarterly to all GPs and health boards, containing basic information that gives feedback on prescribing frequency and cost compared with health board average. SPA level 2 is a very detailed catalogue of all prescribing over a three-month period supplied by PPD on request.

It was recognised that paper-based information was of limited value to prescribing advisers and that access to computerised databases would be necessary. As a result, the Scottish Office funded PPD to develop, with input from prescribing advisers, a computer-based information system (Prescribing Information System for Scotland PRISMS), which holds detailed information on prescribing down to the root drugs (but not individual formulations), at GP, practice, health board and national level. It distinguishes between generic and proprietary prescribing on an 'intention to prescribe' basis. PRISMS has been available since 1993 and has proven to be an invaluable tool for analysing and monitoring trends in prescribing. A pilot project – the Computerised Prescribing Information for Practices (CPiP) has been set up to examine the feasibility of providing similar information on computer to interested practices and the preliminary feedback from GPs has been favourable. In addition, the PPD also provide regular reports on generic prescribing, monographs on new drugs and information tracking the prescribing of newly launched drugs.

It has been argued that prescribing analysis should not focus solely on readily available measures (e.g. number of items prescribed or total costs). Other factors influencing prescribing such as volume, patient demographics and morbidity, are susceptible to should be taken into account to avoid misinterpretation of unadjusted 'raw' data [217,218]. More sophisticated measurements of prescribing - prescribing indicators have been developed. This study has not been able to adopt any prescribing indicators in the analysis of the prescribing data.

The limited dissemination of economic information in this study has failed to show any impact on prescribing. However, this may be in part due to the limited design of the

dissemination exercise. Firstly, research in primary care, in particular among GPs are extremely difficult to conduct due to lack of time and research fatigue. This study had attempted to address this issue by targeting an LHCC that is familiar to the researcher has shown interest in the research area. The majority of the ground work such as meeting the group and introducing the concept of the research was conducted during their regular LHCC meetings in order to limit the taking up of the GPs' free time. However, recruitment remained relatively unsuccessful and ultimately, this study suffered from a lack of adequate sample size.

Secondly, although the drugs evaluated were recommended by local prescribing advisers, these drugs may not be an individual GP's priority. Individual GPs within the same locality may have different patient mix, the drugs evaluated may not be commonly prescribed by all.

Thirdly, there are many factors involved in prescribing decisions. The dissemination exercise has failed to adjust for external influences such as visits from pharmaceutical industry representatives and other sources of prescribing information. These may play a significant role in GPs' prescribing behaviour.

Finally, the study duration may have been insufficient to measure any real change in prescribing. Promoting changes in any form of behaviour will take time to implement. The dissemination exercise was conducted over a period of six months which is not sufficient to examine prescribing trends.

A GP perspective on economic information has not been explored previously. It is unclear what type of materials are being recognised and interpreted as economic information. The relevance and the extent of use of the wide variety of economic information being presented are also unknown.

Despite the small sample size and low response rate, this survey has provided some preliminary indication about GPs' perceptions and their use of economic information in medical decision-making.

Although questionnaire (I) was designed to record recent activities - using economic information in decision-making, while questionnaire (II) examined perceptions of

economic information, the results were comparable. Both questionnaires showed the SPA data being recognised and used by most respondents as a source of economic information. The SPA data (level 1) consist of a breakdown of total costs and the number of items dispensed for major therapeutic areas. These are sent automatically to GPs, comparing their own average values with those of other practices, the Health Board and Scotland as a whole. However, such data contain solely cost information on prescribing are not strictly an economic information source, they give no indication of the real quality of the prescribing taken place. Therefore, it is beneficial to consider including reliable economic information such as cost-effectiveness data, with the feedback information.

The results have also showed that published materials are used in preference to information from verbal presentations. In particular, locally specific evaluations and summary leaflets of studies were favoured by 54%. However, 73% did not regard locally produced newsletters and prescribing formularies as economic sources. This may be an indication that locally produced newsletters and formularies lack adequate economic information that GPs find useful. The need for precise and summarised information, produced locally, has been highlighted.

Since the launch of the Scottish Office's primary care communications initiative in April 1997, 99% of the practices in Scotland were computer-connected by the year 2000 [219]. However, a recent survey of internet connectivity and use in Lothian [220] reported that 43% of their respondents spend no time using email. Therefore, it is not surprising that our survey has shown that email communications from GPs are still scarce and often unreliable.

It is clear that GPs recognise that economic information should be incorporated in medical decision-making. However, the task of incorporating economic into practice is a challenging one. Although all of our respondents in questionnaire (I) have indicated that economic information has previously influenced their medical decision-making, four described situations where such information had failed to influence their decision-making. This suggests that some economic information can only be applied in certain circumstances, and despite the effort and the cost spent on compiling and presenting such economic evidence, there is still wide variation in their usefulness and quality.

The results of the survey have confirmed the difficulties of getting economics into

practice. This revelation may not be novel, but it is important as it suggests that the message, and the information, is not getting through to GPs. Despite the time and money spent on compiling and synthesising the evidence, and the prominent position GPs still occupy in the rationing process, especially after the creation of LHCCs, there is little evidence on effective use of economic information. Although these GPs are not representative of all GPs in the UK, the results of this study are likely to be an underestimation of the prevalence of poor understanding and implementation of economic information in primary care.

The qualitative research had set out to interview a sample size of ten GPs, however, only eight could be interviewed during the given time of the study. Given the introduction of the new GP contract, the political turbulence and sense of "survey fatigue" known to characterise GPs, this is not surprising. There is also an inherent selection bias in this type of research. Several GPs added hostile comments to justify their non-participation, which may suggest that the non-participants may have been a more negative or hostile group. Therefore, the findings of this study may represent the overall GP perspective in economic matters in a less negative picture than actually obtains in practice.

There is a "healthy" awareness relating to health economics among all the GPs interviewed. Often, despite the incomplete understanding about the economic information they were exposed to, there is still evidence of interest, which was reflected through their reading and partial recalling of relevant information.

Similar to the findings in the current literature (reported in Section 3.3), the lack of time and the lack of practical applications have been described as the key barriers to implementing economic information. However, the barriers that have been identified are not unique to health economics. Similar findings have been reporting in implementing changes in other aspects of medical decision making and practice based on other sources of information. There is much similarity to the situation and responses at the time of introduction of evidence-based medicine in clinical practice. Many health professionals are still getting to terms with some of the evidence-based medicine principals such as "relative risk reduction" and "numbers needed to treat". Promoting changes in practice take time, as has been evident with the case of evidence-based medicine over the years.

Overall, the GPs interviewed were unable to suggest a facilitating factor that may help

improve the use of economic information in practice. This may be explained by the feeling that economic issues should not be considered at a practice level. All the GPs interviewed believed that economic information should be considered at a higher level – nationally through the NHS, or locally through the health board. This information should be "filtered" and incorporated in their guidance through guidelines and formularies. This should be viewed as a positive finding; although GPs do not feel they should personally digest and use economic information, they are demonstrating receptiveness and willingness to use guidance produced for them that has incorporated economic thinking.

Finally, this qualitative study has helped to explain the findings of the dissemination exercise in Section 5.4.2. While GPs found such information of interest to their practice, they are reluctant to implement change. Overall, there is a strict adherence to prescribing formularies, although there is prescribing out with the recommendations of the formularies, it was felt that this has to be justified. Despite being purchasers themselves, it is becoming evident that GPs are implementers of other's decisions.

Does health economics work? Does it not work? The answer is far from black and white. The lack of "use" described by GPs may be disappointing, however, in an indirect manner, GPs are taking into account of health economics in their decision making. In terms of prescribing, GPs are aware of the costs of the drugs and would always "choose the generic version or the cheaper alternative" if they feel that their patient care is not compromised. This reflects decisions based upon both the costs and the benefits; GPs might not use the terms that health economists' use, but they appear to be taking economics into account all the time.

6.4 CONCLUSIONS

Pharmacoeconomic information in healthcare is becoming an important component of the process of medical decision-making. This has been highlighted by the introduction of groups such as NICE and HTBS in the UK. Despite the volume of literature produced, there is still much confusion regarding the understanding, application and transferability of this information to clinical (patient) decision making.

This thesis has investigated the effect of incorporating ADRs in economic analyses of drug therapies including NSAIDs, for the management of rheumatoid arthritis, SSRIs in the treatment of depression and ACE inhibitors in the management of hypertension.

Adverse drug reactions add a considerable clinical and economic burden to the NHS. The economic studies included in this thesis have demonstrated the importance of adopting a wider perspective in considering cost effectiveness rather than costs alone. The population based economic analysis has demonstrated that the shadow costs associated with NSAID takers are substantial. Population databases such as the MEMO database are invaluable in reflecting 'real life' clinical practice. However, similar to all observational data, the interpretation of these data is limited by confounding issues. This study has attempted to address this by conducting sensitivity analyses based on the restrictive cohort technique, which did not alter the main conclusions. In the absence of prescribing indications, it is difficult to determine whether the recorded events and subsequently the costs are solely attributed to the drug therapy. Therefore, the MEMO database, at its current format may not be an appropriate data source for this type of economic analysis. Economic studies in other disease areas where the primary clinical outcomes of interest are focused primarily on the number of deaths prevented, number of hospital admissions prevented or the duration of hospital stay reduced may find the MEMO database an appropriate source of data.

In the meta-analysis based economic analysis, the substantial costs due to management of drug-induced ADRs have been revealed. This was particularly prominent among NSAIDs, where as much as a 59% increase in costs associated with treatment of ADRs was observed with diclofenac sodium. In cases where clinical effectiveness is not compromised and costs may be one of the influencing factors, it is important not to be dependent on acquisition costs alone. A higher purchasing cost may result in cost savings in the long term if a broader perspective is adopted - as found for NSAIDs including naproxen, ketoprofen and trandolapril in this study, SSRIs including sertraline and paroxetine and ACE inhibitors including lisinopril and moexipril. The meta-analysis based economic analyses allow comparisons to be drawn between the costing of three classes of drugs. When the shadow costs were incorporated, the impact on NSAID costs were more substantial than that observed with SSRIs and ACE inhibitors. This may be explained by the more prevalent ADR profile associated with NSAID use. In particular, NSAID use is associated with GI events, some of which are extremely costly to manage. In contrast to NSAID therapy, SSRIs and ACE inhibitors were associated with ADRs that are less costly to manage.

However, all three classes of drugs have demonstrated a change in ranking when taking into account shadow costs. This reflects the importance of adopting a wider perspective and taking the associated costs of managing ADRs when considering the cost effectiveness of drugs.

This thesis demonstrated that producing pharmacoeconomic evaluations based on local ADR management data is possible. This study has pooled together ADR incidence data from the literature, disease management strategies and resource utilisation from expert opinions locally, and local costs and prescribing data. However, recent developments in population databases such as GPASS and CMR could eventually lead to a much more effective means of carrying out such research. Currently, CMR produces and disseminates regular reports on GP workload, prescribing and disease prevalence. It provides a potentially ideal setting for inclusion of not solely cost, but also limited economic information.

The course of researching this thesis has provided many opportunities for communicating with GPs. Within the small sample of GPs who were involved in this research, through face-to-face interviews for the purpose of extracting ADR management profile and the discussion of the pharmacoeconomic results during dissemination, a general consensus that echoes the research findings on GPs' perspective on economic matters was observed. Many of them were aware of the importance of pharmacoeconomic information and often recall studies published by major journals or information presented to them from industry medical representatives. However, there was a general feel of uncertainty on how these results should be understood or applied to their everyday practice. Their perspective on this research was generally positive and supportive. This is supported by the findings of the impact study and the qualitative interviews.

The interpretation and implementation of economic information, with regards to prescribing are increasingly being conducted at a national or a local level by the health boards and PCTs. As a result, GP prescribing decisions have become limited and implementing economic information at a practice level is not feasible.

RECOMMENDATIONS

Adverse Drug Reactions and Economic Evaluations

It is clear that ADRs add considerable clinical and economic burden to the NHS. Although different drugs are associated with different ADR profile, and some drugs may only be associated with mild, symptomatic ADRs that may not result in hospitalisation or death, at the minimum, they may still cause inconvenience to the patients and incur an element of cost. Adverse events should be taken into account when conducting economic studies.

When conducting such studies, clinical events, resource utilisation and cost are taken into account. Electronic record linkage has the potential to produce efficient and powerful economic evaluations based on real patient data. The lack of reliable data, especially about resource utilisation, has resulted in the reliance on expert opinions in economic modelling. This has often been criticised as one of the limitations of economic evaluations. The development of electronic record linkage such as MEMO and CMR may result in the possibility of conducting more powerful economic models for the NHS, based on local data. The scope of this should be explored.

Incorporating Economic Information in Clinical Guidance Literature

There is general acceptance among GPs that economic information is a factor when making decisions about prescribing. Despite having purchasing power, GPs are implementers of others' decision making. There is confidence among GPs that clinical guidance such as those produced by NICE and HTBS, clinical guidelines such as SIGN guidelines and local prescribing formularies provide the best evidence on clinical management and prescribing issues. Economic information should become and remain an integral part of these sources. There is much ongoing research in developing frameworks for incorporating cost effectiveness in evidence-based clinical guidelines [221]. Recently NICE has called for tender to develop methodology in incorporating economic evidence in guidelines. However, there is to date no formal framework for introducing the cost consequences of ADRs in economic analyses.

There is also a general agreement among GPs that they should not be sheltered from economic evidence themselves. Therefore, there is still a need to improve the current presentation of economic evidence to a more applicable form.

Currently, economic studies have focused on evaluation of new drugs and health care technologies. However, the bulk of the drugs prescribed on a daily basis are established drugs and economic information on these preparations are rare. Therefore, more research into the economic consequences of the more established therapies are needed.

TABLES

Table 1 **Studies exploring the role and impact of economic evidence in decision making in primary care.**

AUTHOR	STUDY TYPE	PARTICIPANTS	METHODS	KEY FINDINGS
Ross J (1995) [117]; Australia	Survey	Decision makers - senior managers in government (n = 34)	Structured interviews containing a mixture of open and closed questions. Points covered: participants' characteristics, programme/policy characteristics, use of economic evaluation, if used how cost and benefits are measured, other factors and barriers.	High level of awareness of economic evaluation among the group and that some (38%) had used it in decision making. However, there is not often time to consider economic evaluations when making decisions. Other limiting factors include availability of data and lack of expertise. Participants recommended that researchers should be more responsive to the needs of the decision makers using them.
Drummond M et al (1997) [112]; UK	Survey	Prescribing advisors (n = 178), hospital directors (n = 202), directors of public health (n = 66)	A questionnaire was developed following a focus group meeting, covering four main themes: knowledge, importance, barriers and awareness	The use of economic studies was limited. The major barriers were inflexibilities in healthcare budgets and concerns relating to methodological issues.
Walley T et al (1997) [116]; UK	Survey	Prescribing advisors in the UK (n = 178)	A questionnaire was developed following a focus group meeting, covering four main themes: knowledge, importance, barriers and awareness.	Economic issues were rated to be less important than clinical issues, but were considered at most meetings between prescribing advisors and GPs. While they wish to consider true cost effectiveness, they often feel obliged to consider drug acquisition costs and risk of budgetary overspends. The perceived inflexibility of the system and the lack of credibility of evaluations were major barriers.
Duthie T et al (1999) [114]; UK	Survey	Heterogeneous mix of decision makers (n = 34)	Duo interviews (semi-structured) - participants were grouped in pairs to encourage quality discussion.	A large proportion of statements relating to traditional health economics principals (e.g. incremental ratios, QALYs) were not understood or considered irrelevant.
Ginsbury ME et al (2000) [122]; US	Survey	Randomly selected physicians (n = 512)	Questionnaire containing 30 close-ended questions.	Most physicians regard cost effectiveness as important and appropriate in clinical practice. However, they varied considerably in terms of how such information should be implemented.

Table 1 (cont) Studies exploring the role and impact of economic evidence in decision making in primary care.

Motheral BR et al (2000) [123]; US	Survey	Pharmacists and physicians (n = 409)	Three questionnaires: (1) use and importance of economic information, (2) sources of economic information used and (3) internal research activities and barriers to the use of economic information.	Half the respondents reported to consider economic information for most or every decision, but 62% indicated that only occasionally did this result in action or change. Peer-reviewed journals were identified as the key source of information.
Hoffmann C et al (2000) [113]; Europe	Survey	Decision makers in nine European countries (n = 1041).	Survey by postal questionnaires, semi-structured interviews and focus group discussions. Questions include issues about the extent of knowledge on economic evaluations, the actual and potential use of study results as well as barriers and incentives of the use of studies.	Despite positive attitude, knowledge about formal methodology is rather limited. Economic studies are not widely used in decision making. Institutional problems and credibility of the studies were viewed as major barriers. Training and better explanations of the practical relevance of economic studies is needed.
Hoffmann C et al (2002) [115]; UK	Focus group	Decision makers from two UK health authorities who had demonstrated interest in health economics and willing to participate (n = 12).	Focus group with convenience sampling. Four meetings (two at each HA) conducted: (1) current knowledge and use of economic information, (2) usefulness of NHS EED abstracts.	The value of economic studies was generally recognised, but methodological improvement was viewed to be necessary to increase the reliability of the studies.

The study cohort described in Walley et al (1997) was a sub-cohort of those examined by Drummond M et al (1997). Walley et al reported detailed findings of the prescribing advisor sub-cohort. QALYs – quality adjusted life years; HA – health authorities; NHS EED – National Health Service Economic Evaluation Database

Table 2 **Demographics and characteristics of the study population**

	COMPARATOR	%	NSAID ONLY	%	NSAID & MISOPROSTOL	%	NSAID & H^2*	%
Total (N)	47350	100	49212	100	212	100	2113	100
Age (years)								
50 to 59	18259	38.56	16509	33.55	57	26.89	594	28.11
60 to 74	20959	44.26	22913	46.56	103	48.58	1115	52.77
75+	8132	17.17	9790	19.89	52	24.53	404	19.12
Mean Age (years)	*64 years*		*65 years*		*67 years*		*66 years*	
Sex								
Male	21918	46.29	19801	40.24	62	29.25	867	41.03
Female	25432	53.71	29411	59.76	150	70.75	1246	58.97
History of GI Diagnosis								
Yes	2012	4.25	1582	3.21	27	12.74	373	17.65
No	45338		47630		185		1740	
History of Endoscopy								
Yes	3458	7.30	3872	7.87	42	19.81	680	32.18
No	43892		45340		170		1433	
History of CV Diagnosis								
Yes	2835	5.99	6069	12.33	29	13.68	448	21.20
No	44515		43143		183		1665	
History of RA/SLE Diagnosis								
Yes	44	0.09	187	0.38	3	1.42	30	1.42
No	47306		49025		209		2083	
History of OA Diagnosis								
Yes	531	1.12	1483	3.01	12	5.66	97	4.59
No	46819		47729		200		2016	
NSAID Prescriptions								
Acemetacin			9	0.02	0	0.00	0	0.00
Azapropazone			1077	2.19	9	4.25	56	2.65
Diclofenac Sodium			6321	12.84	33	15.57	341	16.14
Diflunisal			437	0.89	0	0.00	14	0.66
Etodolac			121	0.25	2	0.94	7	0.33
Fenbufen			876	1.78	3	1.42	54	2.56
Fenoprofen			44	0.09	0	0.00	3	0.14
Flurbiprofen			785	1.60	4	1.89	38	1.80
Ibuprofen			12512	25.42	34	16.04	334	15.81
Indomethacin			1814	3.69	7	3.30	59	2.79
Ketoprofen			1074	2.18	8	3.77	51	2.41
Mefenamic Acid			4026	8.18	2	0.94	146	6.91
Nabumetone			628	1.28	4	1.89	47	2.22
Naproxen			7469	15.18	79	37.26	275	13.01
Naproxen Combination Pack					30	14.15		
Piroxicam			3079	6.26	16	7.55	165	7.81
Sulindac			139	0.28	0	0.00	11	0.52
Tenoxicam			384	0.78	3	1.42	26	1.23
Tiaprofenic Acid			252	0.51	0	0.00	9	0.43
Tolectin			5	0.01	0	0.00	2	0.09
Concomitant use of H_2								
Cimetidine							338	16.00
Ranitidine							1703	80.60
Nizatidine							14	0.66
Famotidine							41	1.94
Concomitant use of Omeprazole - Losec							17	0.80
Concomitant use of Misoprostol - Cytotec					182	85.85		
Concomitant use of Aspirin			8160	16.58	8	3.77	475	22.48
Death After Study Period to 1994								
crude rates (observed)	5269	11.13	6767	13.75	28	13.21	346	16.37
adjusted for sex and age +		11.13		12.61		11.25		14.92

* **H_2 blockers/omeprazole**

+ **Mortality rates were adjusted by the direct method to the comparator cohort distribution.**

Table 3 Gastrointestinal endoscopies recorded in the three follow-up periods

	Comparator (n = 47 350)			NSAID Only (n = 49 212)			NSAID & Misoprostol (n = 212)			NSAID & H_2 blocker/Omeprazole (n = 2113)		
	Male	Female	% (Both Sexes)	Male	Female	% (Both Sexes)	Male	Female	% (Both Sexes)	Male	Female	% (Both Sexes)
45 days												
50 to 59 years	14	19	0.07%	12	21	0.07%	0	0	0.00%	2	5	0.33%
60 to 74 years	18	23	0.09%	15	21	0.07%	0	0	0.00%	1	7	0.38%
75+ years	1	7	0.02%	4	7	0.02%	0	0	0.00%	0	2	0.09%
sub-total	33	49		31	49		0	0		3	14	
% of each sex	0.15%	0.19%		0.16%	0.17%		0.00%	0.00%		0.35%	1.12%	
Total		**82**	**0.17%**		**80**	**0.16%**		**0**	**0.00%**		**17**	**0.80%**
Six months												
50 to 59 years	57	49	0.22%	47	81	0.26%	0	0	0.00%	9	12	0.99%
60 to 74 years	69	65	0.28%	74	110	0.37%	0	1	0.47%	9	19	1.33%
75+ years	10	27	0.08%	22	51	0.15%	0	0	0.00%	3	5	0.38%
sub-total	136	141		143	242		0	1		21	36	
% of each sex	0.62%	0.55%		0.72%	0.82%		0.00%	0.67%		2.42%	2.89%	
Total		**277**	**0.59%**		**385**	**0.78%**		**1**	**0.47%**		**57**	**2.70%**
12 months												
50 to 59 years	110	102	0.45%	105	138	0.49%	1	0	0.47%	15	24	1.85%
60 to 74 years	129	143	0.57%	153	234	0.79%	0	3	1.42%	27	42	3.27%
75+ years	25	45	0.15%	40	100	0.28%	0	0	0.00%	6	7	0.62%
sub-total	264	290		298	472		1	3		48	73	
% of each sex	1.20%	1.14%		1.50%	1.60%		1.61%	2.00%		5.54%	5.86%	
Total		**554**	**1.17%**		**770**	**1.56%**		**4**	**1.89%**		**121**	**5.73%**

Table 4 Prescription items recorded in the three follow-up periods

	Comparator (n = 47 350)			NSAID Only (n = 49 212)			NSAID & Misoprostol (n = 212)			NSAID & H_2 blocker/Omeprazole (n = 2113)		
	Male	Female	% (Both Sexes)	Male	Female	% (Both Sexes)	Male	Female	% (Both Sexes)	Male	Female	% (Both Sexes)
45 days												
50 to 59 years	594	801	2.95%	1967	2894	9.88%	10	16	12.26%	119	194	14.81%
60 to 74 years	863	1051	4.04%	3439	4948	17.04%	14	39	25.00%	266	384	30.76%
75+ years	268	561	1.75%	1188	2910	8.33%	5	27	15.09%	75	208	13.39%
sub-total	1725	2413		6594	10752		29	82		460	786	
% of each sex	7.87	9.49%		33.30%	36.56%		46.77%	54.67%		53.06%	63.08%	
Total		**4138**	**8.74%**		**17346**	**35.25%**		**111**	**52.36%**		**1246**	**58.97%**
Six months												
50 to 59 years	1200	1722	6.17%	3721	5558	18.86%	17	24	19.34%	210	302	24.23%
60 to 74 years	1549	1869	7.22%	6264	8783	30.58%	21	54	35.38%	442	559	47.37%
75+ years	414	950	2.88%	2182	4892	14.37%	6	33	18.40%	110	268	17.89%
sub-total	3163	4541		12167	19233		44	111		762	1129	
% of each sex	14.43%	17.86%		61.45%	65.39%		70.97%	74.00%		87.89%	90.61%	
Total		**7704**	**16.27%**		**31400**	**63.81%**		**155**	**73.11%**		**1891**	**89.49%**
12 months												
50 to 59 years	1742	2395	8.74%	4652	6768	23.21%	20	25	21.23%	232	310	25.65%
60 to 74 years	2157	2658	10.17%	7195	10211	35.37%	23	63	40.57%	459	583	49.31%
75+ years	610	1248	3.92%	2420	5485	16.06%	6	36	19.81%	115	274	18.41%
sub-total	4509	6301		14267	22464		49	124		806	1167	
% of each sex	20.57%	24.78%		72.05%	76.38%		79.03%	82.67%		92.96%	93.66%	
Total		**10810**	**22.83%**		**36731**	**74.64%**		**173**	**81.60%**		**1973**	**93.37%**

Table 5 Hospitalised patients recorded

		GI ADMISSIONS										CV ADMISSIONS									
		50 to 59 years			60 to 74 years			75+ years				50 to 59 years			60 to 74 years			75+ years			
	N	F	M	Total	F	M	Total	F	M	Total	Incidence	F	M	Total	F	M	Total	F	M	Total	Incidence
45 days																					
Comparator	47350	7	7	**14**	13	13	**26**	5	2	**7**	**0.10%**	1	22	**23**	9	16	**25**	35	8	**43**	**0.19%**
NSAID	49212	7	9	**16**	25	18	**43**	23	10	**33**	**0.19%**	23	52	**75**	86	119	**205**	69	28	**97**	**0.77%**
Misoprostol	212	0	0	**0**	0	0	**0**	1	0	**1**	**0.47%**	0	0	**0**	1	0	**1**	1	0	**1**	**0.94%**
H_2 blocker/Omeprazole	2113	3	1	**4**	0	4	**4**	1	0	**1**	**0.43%**	3	8	**11**	5	13	**18**	4	3	**7**	**1.70%**
Six months																					
Comparator	47350	21	26	**47**	45	37	**82**	19	12	**31**	**0.34%**	13	58	**71**	47	64	**111**	97	48	**145**	**0.69%**
NSAID	49212	24	33	**57**	80	51	**131**	72	23	**95**	**0.58%**	73	171	**244**	240	334	**574**	226	105	**331**	**2.33%**
Misoprostol	212	0	0	**0**	0	0	**0**	1	0	**1**	**0.47%**	0	0	**0**	1	0	**1**	3	0	**3**	**1.89%**
H_2 blocker/Omeprazole	2113	5	4	**9**	6	9	**15**	8	1	**9**	**1.56%**	6	16	**22**	21	32	**53**	14	5	**19**	**4.45%**
12 months																					
Comparator	47350	41	56	**97**	95	72	**167**	52	32	**84**	**0.73%**	36	114	**150**	98	135	**233**	176	99	**275**	**1.39%**
NSAID	49212	58	62	**120**	153	98	**251**	142	44	**186**	**1.13%**	158	310	**468**	418	585	**1003**	401	205	**606**	**4.22%**
Misoprostol	212	0	0	**0**	0	0	**0**	1	0	**1**	**0.47%**	0	1	**1**	4	1	**5**	7	0	**7**	**6.13%**
H_2 blocker/Omeprazole	2113	12	6	**18**	11	15	**26**	11	2	**13**	**2.70%**	11	25	**36**	36	50	**86**	28	10	**38**	**7.57%**

		RA ADMISSIONS										OA ADMISSIONS									
		50 to 59 years			60 to 74 years			75+ years				50 to 59 years			60 to 74 years			75+ years			
	N	F	M	Total	F	M	Total	F	M	Total	Incidence	F	M	Total	F	M	Total	F	M	Total	Incidence
45 days																					
Comparator	47350	0	0	**0**	1	1	**2**	0	0	**0**	**0.00%**	0	1	**1**	4	2	**6**	9	1	**10**	**0.04%**
NSAID	49212	2	3	**5**	7	0	**7**	2	0	**2**	**0.03%**	5	6	**11**	15	17	**32**	26	4	**30**	**0.15%**
Misoprostol	212	0	0	**0**	0	0	**0**	0	0	**0**	**0.00%**	0	0	**0**	0	0	**0**	0	0	**0**	**0.00%**
H_2 blocker/Omeprazole	2113	1	0	**1**	0	1	**1**	0	0	**0**	**0.09%**	2	0	**2**	2	1	**3**	2	0	**2**	**0.33%**
Six months																					
Comparator	47350	0	0	**0**	2	1	**3**	5	0	**5**	**0.02%**	3	6	**9**	8	9	**17**	24	4	**28**	**0.11%**
NSAID	49212	8	7	**15**	25	2	**27**	13	1	**14**	**0.11%**	21	29	**50**	72	58	**130**	99	20	**119**	**0.61%**
Misoprostol	212	0	0	**0**	0	0	**0**	0	0	**0**	**0.00%**	0	0	**0**	0	0	**0**	0	0	**0**	**0.00%**
H_2 blocker/Omeprazole	2113	1	0	**1**	4	2	**6**	1	0	**1**	**0.38%**	4	2	**6**	5	4	**9**	8	0	**8**	**1.09%**
12 months																					
Comparator	47350	1	0	**1**	3	2	**5**	6	0	**6**	**0.03%**	4	13	**17**	16	14	**30**	38	9	**47**	**0.20%**
NSAID	49212	17	11	**28**	49	8	**57**	28	3	**31**	**0.24%**	53	52	**105**	172	124	**296**	192	47	**239**	**1.30%**
Misoprostol	212	0	0	**0**	1	0	**1**	0	0	**0**	**0.47%**	0	1	**1**	2	0	**2**	2	0	**2**	**2.36%**
H_2 blocker/Omeprazole	2113	3	0	**3**	6	2	**8**	2	0	**2**	**0.62%**	6	3	**9**	13	8	**21**	12	0	**12**	**1.99%**

F = females; M = males

Table 6 Details of hospital events recorded in three follow-up periods

	longest admission mean los (days)	minimum los (days)	maximum los (days)	sum los (days)	no. of cases N	additional admissions mean los (days)	minimum los (days)	maximum los (days)	sum los (days)	additional admissions mean counts	minimum counts	maximum counts	sum counts	no. of cases N	average admissions per person
GASTROINTESTINAL EVENTS															
comparator	5.57	1	45	262	47	2.80	1	8	14	1.00	1	1	5	5	1.11
comparator	7.20	1	77	1152	160	6.11	6	18	165	2.41	2	3	65	27	1.41
comparator	11.85	1	365	4704	397	8.71	1	37	592	3.59	3	12	244	68	1.61
nsaid	11.05	1	45	1017	92	6.71	2	15	94	3.33	1	3	20	14	1.22
nsaid	10.15	1	183	2872	283	10.37	1	22	425	2.27	2	3	93	41	1.33
nsaid	14.84	1	365	12257	826	8.81	1	95	890	3.24	3	5	327	101	1.40
misoprostol	34.00	1	34	34	1	0.00	0	0	0	0.00	0	0	0	0	1.00
misoprostol	34.00	1	34	34	1	0.00	0	0	0	0.00	0	0	0	0	1.00
misoprostol	34.00	1	34	34	1	15.00	1	15	15	3.00	1	1	3	1	4.00
h2 blocker/omeprazole	8.33	1	26	75	9	2.00	2	2	2	1.00	1	1	1	1	1.11
h2 blocker/omeprazole	12.73	1	183	420	33	4.75	1	1	19	2.25	1	1	9	4	1.27
h2 blocker/omeprazole	13.29	1	183	1010	57	9.29	1	18	65	3.14	3	4	22	7	1.29
CARDIOVASCULAR EVENTS															
comparator	16.48	1	45	1500	91	6.14	1	21	135	1.32	1	4	29	22	1.32
comparator	22.85	1	183	7472	327	12.56	1	76	1093	2.31	2	6	201	87	1.61
comparator	24.96	1	365	16421	658	19.77	1	259	3539	3.51	3	9	628	179	1.95
nsaid	10.58	1	45	3987	377	5.53	1	26	531	1.39	1	5	133	96	1.35
nsaid	14.17	1	183	16280	1149	12.56	1	87	1093	10.30	2	7	896	87	1.78
nsaid	15.93	1	365	33092	2077	14.20	1	245	10322	3.62	3	17	2635	727	2.27
misoprostol	20.50	7	34	41	2	0.00	0	0	0	0.00	0	0	0	0	1.00
misoprostol	36.50	7	88	146	4	0.00	0	0	0	0.00	0	0	0	0	1.00
misoprostol	30.92	2	163	402	13	11.67	2	30	35	3.33	3	4	10	3	1.77
h2 blocker/omeprazole	9.36	1	45	337	36	4.92	2	9	64	1.54	1	3	20	13	1.56
h2 blocker/omeprazole	11.90	1	183	1119	94	9.87	1	31	375	2.53	2	6	96	38	2.02
h2 blocker/omeprazole	15.34	1	365	2454	160	17.52	1	72	946	4.15	3	18	224	54	2.40
RHEUMATOID ARTHRITIS EVENTS															
comparator	13.50	13	14	27	2	0.00	0	0	0	0.00	0	0	0	0	1.00
comparator	49.25	7	183	394	8	16.00	3	29	32	2.00	1	1	4	2	1.50
comparator	37.17	2	183	446	12	68.25	1	212	273	3.25	3	4	13	4	2.08
nsaid	13.64	3	27	191	14	4.00	4	4	4	1.00	1	1	1	1	1.07
nsaid	18.84	1	183	1055	56	17.80	2	66	178	2.20	2	3	22	10	1.39
nsaid	24.76	1	365	2872	116	51.79	3	249	725	3.21	3	4	45	14	1.39
misoprostol	0.00	0	0	0	0	0.00	0	0	0	0.00	0	0	0	0	0.00
misoprostol	0.00	0	0	0	0	0.00	0	0	0	0.00	0	0	0	0	0.00
misoprostol	5.00	1	5	5	1	0.00	0	0	0	0.00	0	0	0	0	1.00
h2 blocker/omeprazole	5.00	2	8	10	2	0.00	0	0	0	0.00	0	0	0	0	1.00
h2 blocker/omeprazole	12.50	1	46	100	8	3.50	2	5	7	2.00	1	1	4	2	1.50
h2 blocker/omeprazole	14.85	1	46	193	13	20.25	2	48	81	4.00	3	7	16	4	2.23
OSTEOARTHRITIS EVENTS															
comparator	22.06	1	45	375	17	16.00	8	24	32	1.00	1	1	2	2	1.12
comparator	30.13	1	183	1627	54	32.00	4	53	128	2.00	1	1	8	4	1.15
comparator	33.52	1	365	3184	95	35.00	2	145	210	3.00	1	1	18	6	1.19
nsaid	18.71	1	45	1366	73	8.00	2	12	32	1.25	1	2	5	4	1.07
nsaid	23.46	1	183	7016	299	17.44	1	57	471	2.07	2	3	56	27	1.19
nsaid	23.02	1	282	14735	640	35.58	1	236	2206	3.13	3	6	194	62	1.30
misoprostol	0.00	0	0	0	0	0.00	0	0	0	0.00	0	0	0	0	0.00
misoprostol	0.00	0	0	0	0	0.00	0	0	0	0.00	0	0	0	0	0.00
misoprostol	25.20	15	38	126	5	2.00	1	2	2	3.00	1	1	3	1	1.60
h2 blocker/omeprazole	23.57	3	42	165	7	0.00	0	0	0	0.00	0	0	0	0	1.00
h2 blocker/omeprazole	23.00	3	47	529	23	8.67	2	16	26	9.00	2	3	27	3	2.17
h2 blocker/omeprazole	23.55	1	58	989	42	27.00	11	43	108	3.25	3	4	13	4	1.31

EVENTS OBSERVED IN THE FIRST 45 DAYS. EVENTS OBSERVED SIX MONTHS FOLLOWING THE INDEX DATE. EVENTS OBSERVED 12 MONTHS FOLLOWING THE INDEX DATE.

Table 7 **Calculated shadow and total costs (£) per individual**

	N	Inception Drug Costs	Period 1 (0 to 45 days)	Period 2 (0 to six months)	Period 3 (0 to12 months)
Comparator	47350	£0.00			
shadow costs			£13.35	£59.63	£141.51
total costs			£13.35	£59.63	£141.51
95% CI			*(£11.44 to £15.27)*	*(£53.82 to £65.45)*	*(£126.58 to £156.43)*
NSAID Only	49212	£7.51			
shadow costs			£44.19	£179.01	£386.93
total costs			£51.70	£186.52	£394.44
95% CI			*(£47.38 to £56.03)*	*(£176.71 to £196.32)*	*(£374.79 to £414.09)*
NSAID & Misoprostol	212	£24.34			
shadow costs			£75.56	£332.16	£787.29
total costs			£99.90	£356.50	£811.63
95% CI			*(£22.75 to £177.05)*	*(£40.26 to £672.73)*	*(£403.93 to £1219.32)*
NSAID & H_2 Blocker/Omeprazole	2113	£40.73			
shadow costs			£104.06	£418.20	£897.03
total costs			£144.79	£458.93	£937.76
95% CI			*(£119.71 to £169.87)*	*(£403.64 to £514.22)*	*(£805.01 to £1070.51)*

* *F test probabilities:* *p = 0.00 (45 days)* *p = 0.00 (six months)* *p = 0.00 (12 months)*

Table 8 **Sex-specific total costs per individual (95% CI)**

	N	Total Costs (£)		
		45 Days	**Six Months**	**12 Months**
FEMALE				
Comparator	25432	£14.71 *(£11.79 to £17.63)*	£64.71 *(£55.91 to £73.52)*	£148.97 *(£128.78 to £169.16)*
NSAID Only	29411	£48.37 *(£43.97 to £52.77)*	£184.20 *(£171.88 to £196.52)*	£393.86 *(£368.82 to £418.91)*
NSAID & Misoprostol	150	£119.02 *(£9.83 to £228.20)*	£451.89 *(£4.52 to £899.26)*	£971.56 *(£406.27 to £1536.86)*
NSAID & H_2 blocker/Omeprazole	1246	£135.30 *(£104.25 to £166.35)*	£438.94 *(£269.13 to £508.75)*	£934.25 *(£733.22 to £1135.29)*
MALE				
Comparator	21918	£11.78 *(£9.41 to £14.15)*	£53.74 *(£46.42 to £61.06)*	£132.85 *(£110.70 to £154.99)*
NSAID Only	19801	£56.66 *(£48.12 to £65.19)*	£189.96 *(£173.87 to £206.05)*	£395.30 *(£363.65 to £426.44)*
NSAID & Misoprostol	62	£53.64 *(£43.70 to £63.58)*	£125.70 *(£95.19 to £156.22)*	£424.66 *(£150.50 to £698.84)*
NSAID & H_2 blocker/Omeprazole	867	£158.43 *(£116.60 to £200.26)*	£487.65 *(£397.57 to £577.73)*	£942.81 *(£796.72 to £1088.89)*
* *F test probabilities*	*Comparator*	*p = 0.13 (45 days)*	*p = 0.06 (6 months)*	*p = 0.29 (12 months)*
	NSAID	*p = 0.06 (45 days)*	*p = 0.57 (6 months)*	*p = 0.94 (12 months)*
	Misoprostol	*p = 0.45 (45 days)*	*p = 0.36 (6 months)*	*p = 0.23 (12 months)*
	H_2/Omeprazole	*p = 0.37 (45 days)*	*p = 0.40 (6 months)*	*p = 0.95 (12 months)*

Table 9 **Age-specific total costs per individual (95% CI)**

	N	Total Costs (£)		
		45 Days	Six Months	12 Months
50 to 59 years				
Comparator	18259	£7.45	£32.08	£76.79
		(£6.02 to £8.88)	*(£26.90 to £37.26)*	*(£60.60 to £92.98)*
NSAID Only	16509	£35.30	£108.77	£226.03
		(£27.31 to £43.30)	*(£97.66 to £119.88)*	*(£207.98 to £244.07)*
NSAID & Misoprostol	57	£50.32	£122.60	£370.26
		(£40.55 to £60.09)	*(£88.59 ti £156.61)*	*(£97.70 to £642.82)*
NSAID & H_2 Blocker/Omeprazole	594	£133.38	£358.26	£683.18
		(£94.84 to £171.92)	*(£293.44 to £423.09)*	*(£578.87 to £787.50)*
60 to 74 years				
Comparator	20959	£11.42	£51.10	£120.35
		(£8.97 to £13.85)	*(£44.42 to £57.77)*	*(£102.59 to £138.10)*
NSAID Only	22913	£55.10	£189.41	£384.54
		(£49.27 to £60.93)	*(£175.48 to £203.33)*	*(£361.64 to £407.43)*
NSAID & Misoprostol	103	£67.32	£156.48	£466.97
		(£40.56 to £94.08)	*(£118.95 to £194.01)*	*(305.58 to £628.37)*
NSAID & H_2 Blocker/Omeprazole	1115	£149.96	£486.93	£942.35
		(£113.11 to £186.81)	*(£399.02 to £574.83)*	*(£812.10 to £1072.59)*
75+ years				
Comparator	8132	£31.60	£143.51	£341.35
		(£23.00 to £40.22)	*(£116.83 to £170.19)*	*(£277.22 to £405.48)*
NSAID Only	9790	£71.41	£310.87	£701.61
		(£61.17 to £81.64)	*(£279.14 to £342.58)*	*(£624.77 to £778.46)*
NSAID & Misoprostol	52	£218.77	£1,009.06	£1,978.09
		(£0 to £534.46)	*(£0 to £2312.02)*	*(£375.18 to £3580.99)*
NSAID & H_2 Blocker/Omeprazole	404	£147.31	£529.67	£1,299.41
		(£86.46 to £208.16)	*(£404.40 to £654.92)*	*(£725.21 to £1873.61)*

* *F test probabilities*	*Comparator*	*p = 0.00 (45 days)*	*p = 0.00 (6 months)*	*p = 0.00 (12 months)*
	NSAID	*p = 0.00 (45 days)*	*p = 0.00 (6 months)*	*p = 0.00 (12 months)*
	Misoprostol	*p = 0.22 (45 days)*	*p = 0.07 (6 months)*	*p = 0.00 (12 months)*
	H_2/Omeprazole	*p = 0.85 (45 days)*	*p = 0.07 (6 months)*	*p = 0.01 (12 months)*

Table 10 Comparisons between the two NSAID and gastroprotectives sub-cohorts (45 Days)

	N	% Greater than NSAID Only	N	% Less than H_2 blocker/Omeprazole	Tayside Savings (£)
Base Case	49212	93.23%	2113	31.00%	£34,399.64
Sex and Age-Specific					
Female					
50 to 59 years	9324	91.08%	339	60.68%	£26,886.09
60 to 74 years	13319	51.62%	623	42.98%	£33,374.11
75+ years	6768	218.76%	284	-57.00%	-£26,576.72
Total	29411	146.06%	1246	12.03%	£20,284.88
Male					
50 to 59 years	7185	5.67%	255	64.34%	£22,465.50
60 to 74 years	9594	-13.89%	492	68.54%	£61,381.92
75+ years	3022	9.53%	120	48.77%	£6,286.80
Total	19801	-5.33%	867	66.14%	£90,852.93
Sensitivity Analysis					
Non-aspirin Takers	41554	117.12%	1683	22.13%	£48,285.61
No Prior GI Admissions	47630	106.11%	1740	20.23%	£45,830.03
No Prior CV Admissions	43143	32.88%	1665	52.27%	£105,439.79
No Prior RA Admissions	49025	96.43%	2083	30.78%	£92,919.09
No Prior OA Admissions	47729	106.76%	2016	25.99%	£71,128.71
No Prior Endoscopies	45340	122.92%	1433	22.30%	£45,224.62
Survivors	42445	141.38%	1767	24.41%	£60,063.69
No Risk Factors *	30513	60.20%	764	35.45%	£22,726.25

** Excluded aspirin takers, those with prior GI, CV, RA or OA admissions, prior endoscopies and those died during the study.*

% indicates the percentage of shadow costs greater than the NSAID Only and less than NSAID & H2 blocker/Omeprazole sub-cohort.

Table 11 Comparisons between the two NSAID and gastroprotectives sub-cohorts (six months)

	N	% Greater than NSAID Only	N	% Less than H2 blocker/Omeprazole	Tayside Savings (£)
Base Case	49212	91.13%	2113	22.32%	£216,434.59
Sex and Age-Specific					
Female					
50 to 59 years	9324	48.68%	339	59.00%	£66,328.74
60 to 74 years	13319	-4.03%	623	61.55%	£158,983.37
75+ years	6768	251.71%	284	-131.20%	-£170,956.64
Total	29411	145.33%	1246	-2.95%	£16,135.70
Male					
50 to 59 years	7185	-20.59%	255	73.53%	£73,809.75
60 to 74 years	9594	-33.00%	492	74.32%	£211,520.64
75+ years	3022	-52.85%	120	60.09%	£22,713.60
Total	19801	-33.83%	867	74.22%	£313,810.65
Sensitivity Analysis					
Non-aspirin Takers	41554	120.38%	1683	9.30%	£62,341.18
No Prior GI Admissions	47630	16.36%	1740	49.47%	£352,159.82
No Prior CV Admissions	43143	96.54%	1665	18.00%	£109,907.65
No Prior RA Admissions	49025	94.53%	2083	21.74%	£205,713.96
No Prior OA Admissions	47729	112.18%	2016	18.12%	£163,524.01
No Prior Endoscopies	45340	129.97%	1433	6.54%	£40,844.37
Survivors	42445	157.79%	1767	4.68%	£33,177.72
No Risk Factors *	30513	0.85%	764	59.12%	£112,097.82

** Excluded aspirin takers, those with prior GI, CV, RA or OA admissions, prior endoscopies and those died during the study.*

% indicates the percentage of shadow costs greater than the NSAID Only and less than NSAID & H2 blocker/Omeprazole sub-cohort.

Table 12 Comparisons between the two NSAID and gastroprotectives sub-cohorts (12 months)

	N	% Greater than NSAID Only	N	% Less than H_2 blocker/omeprazole	Tayside Savings (£)
Base Case	49212	105.77%	2113	13.41%	£266,512.69
Sex and Age-Specific					
Female					
50 to 59 years	9324	44.16%	339	54.14%	£115,632.90
60 to 74 years	13319	35.79%	623	40.81%	£202,524.84
75+ years	6768	219.25%	284	-50.12%	-£227,631.68
Total	29411	146.68%	1246	-3.99%	-£46,488.26
Male					
50 to 59 years	7185	85.97%	255	36.05%	£69,298.80
60 to 74 years	9594	4.24%	492	59.64%	£330,673.20
75+ years	3022	-48.73%	120	65.63%	£46,446.00
Total	19801	6.96%	867	54.96%	£449,236.05
Sensitivity Analysis					
Non-aspirin Takers	41554	135.80%	1683	1.31%	£18,312.55
No Prior GI Admissions	47630	65.86%	1740	27.80%	£420,345.55
No Prior CV Admissions	43143	87.33%	1665	20.19%	£255,151.26
No Prior RH Admissions	49025	110.50%	2083	12.71%	£246,639.49
No Prior OS Admissions	47729	126.20%	2016	8.90%	£165,073.51
No Prior Endoscopies	45340	148.30%	1433	-5.29%	-£66,884.42
Survivors	42445	139.38%	1767	6.51%	£86,662.34
No Risk Factors *	30513	37.44%	764	36.26%	£123,475.77

** Excluded aspirin takers, those with prior GI, CV, RA or OA admissions, prior endoscopies and those died during the study.*

% indicates the percentage of shadow costs greater than the NSAID Only and less than NSAID & H_2 blocker/omeprazole sub-cohort.

Table 13 Sensitivity analysis - base case versus one admission (multiple episodes of care representing one individual admission)

	Cost of Inception Drugs	Cost of All Event Rx *	Cost of GP Consultations	Cost of Endoscopy	Cost of GI admissions	Cost of CV admissions	Cost of RA admissions	Cost of OA admissions	Shadow Costs	Total Costs
45 Days										
Comparator										
base case	£0.00	£3.18	£1.36	£0.40	£1.32	£5.28	£0.11	£1.70	£13.35	£13.35
one admission	£0.00	£3.18	£1.36	£0.40	£1.31	£5.24	£0.11	£1.69	£13.29	£13.29
NSAID										
base case	£7.51	£7.34	£5.61	£0.34	£4.39	£19.40	£0.84	£6.37	£44.29	£51.80
one admission	£7.51	£7.34	£5.51	£0.34	£4.35	£19.24	£0.84	£6.36	£43.98	£51.49
Misoprostol										
base case	£24.34	£18.74	£11.62	£0.00	£19.36	£25.84	£0.00	£0.00	£75.56	£99.90
one admission	£24.34	£18.74	£11.62	£0.00	£19.36	£25.84	£0.00	£0.00	£75.56	£99.90
H_2 blocker/omeprazole										
base case	£40.73	£24.92	£12.27	£1.77	£7.26	£36.32	£0.95	£20.58	£104.07	£144.80
one admission	£40.73	£24.92	£12.27	£1.77	£7.23	£35.70	£0.95	£20.58	£103.42	£144.15
Six Months										
Comparator										
base case	£0.00	£14.59	£4.25	£1.46	£5.63	£26.63	£1.03	£6.04	£59.63	£59.63
one admission	£0.00	£14.59	£4.25	£1.46	£5.49	£26.41	£1.02	£6.02	£59.24	£59.24
NSAID										
base case	£7.51	£37.52	£18.91	£1.82	£11.92	£72.31	£4.11	£32.41	£179.00	£186.51
one admission	£7.51	£37.52	£18.91	£1.82	£11.71	£71.30	£4.09	£32.34	£177.69	£185.20
Misoprostol										
base case	£24.34	£78.94	£30.11	£1.97	£27.53	£193.61	£0.00	£0.00	£332.16	£356.50
one admission	£24.34	£78.94	£30.11	£1.97	£27.06	£192.97	£0.00	£0.00	£331.05	£355.39
H_2 blocker/omeprazole										
base case	£40.73	£144.69	£41.74	£6.70	£31.70	£121.46	£9.05	£62.85	£418.19	£458.92
one admission	£40.73	£144.69	£41.74	£6.70	£31.26	£118.85	£8.95	£62.62	£414.81	£455.54
12 Months										
Comparator										
base case	£0.00	£33.88	£8.10	£3.00	£17.33	£65.68	£1.35	£12.16	£141.50	£141.50
one admission	£0.00	£33.88	£8.10	£3.00	£18.89	£64.96	£1.34	£12.10	£142.27	£142.27
NSAID										
base case	£7.51	£83.47	£33.89	£3.83	£26.68	£156.08	£12.81	£70.17	£386.93	£394.44
one admission	£7.51	£83.47	£33.89	£3.83	£26.07	£153.31	£12.74	£69.84	£383.15	£390.66
Misoprostol										
base case	£24.34	£181.79	£49.11	£6.88	£45.01	£361.06	£4.71	£138.72	£787.28	£811.62
one admission	£24.34	£181.79	£49.11	£6.88	£43.95	£358.12	£4.71	£138.47	£783.03	£807.37
H_2 blocker/omeprazole										
base case	£40.73	£312.61	£72.25	£14.99	£49.70	£309.49	£18.16	£119.83	£897.03	£937.76
one admission	£40.73	£312.61	£72.25	£14.99	£48.33	£303.40	£17.73	£119.18	£888.49	£929.22

** Rx = prescription items.*

Table 14 **Sensitivity analysis - excluding various clinical risk factors**

		45 Days		Six Months		One Year	
	N	Shadow Costs	Total Costs	Shadow Costs	Total Costs	Shadow Costs	Total Costs
Base Case							
comparator	47350	£13.35	£13.35	£59.63	£59.63	£141.51	£141.51
NSAID	49212	£44.19	£51.70	£179.01	£186.52	£386.93	£394.44
misoprostol	212	£75.56	£99.90	£332.16	£356.50	£787.29	£911.63
H_2 blocker/omeprazole	2113	£104.06	£144.79	£418.20	£458.93	£897.03	£937.76
Non-aspirin Takers							
comparator	47350	£16.03	£16.03	£59.63	£59.63	£141.51	£141.51
NSAID	41554	£44.47	£52.95	£155.40	£163.88	£339.62	£348.10
misoprostol	206	£93.12	£117.62	£336.65	£361.15	£796.31	£820.81
H_2 blocker/omeprazole	1683	£110.54	£152.35	£356.38	£398.20	£789.87	£831.69
No Prior History of GI Diagnosis							
comparator	45338	£13.46	£13.46	£52.49	£52.49	£127.40	£127.40
NSAID	47630	£48.99	£56.50	£170.15	£177.66	£370.79	£378.30
misoprostol	185	£95.39	£119.45	£182.65	£206.71	£603.38	£627.44
H_2 blocker/omeprazole	1740	£112.61	£152.80	£369.29	£409.48	£828.83	£869.02
No Prior History of CV Diagnosis							
comparator	44515	£12.99	£12.99	£47.81	£47.81	£111.14	£111.14
NSAID	43143	£41.78	£49.59	£145.20	£153.02	£315.56	£323.38
misoprostol	183	£49.04	£72.80	£276.97	£300.73	£582.01	£605.78
H_2 blocker/omeprazole	1665	£102.24	£143.34	£325.64	£366.74	£717.92	£759.02
No Prior History of GI Endoscopy							
comparator	43892	£12.38	£12.38	£49.07	£49.07	£119.97	£119.97
NSAID	45340	£47.58	£55.08	£169.58	£177.08	£366.35	£373.85
misoprostol	170	£101.68	£125.92	£382.55	£406.79	£904.04	£928.29
H_2 blocker/omeprazole	1433	£124.44	£162.95	£397.23	£435.75	£843.10	£881.61
No Prior NSAID Prescriptions							
comparator	47350	£16.03	£16.03	£59.63	£59.63	£141.51	£141.51
NSAID	37871	£48.15	£55.14	£149.93	£156.92	£321.82	£328.82
misoprostol	193	£95.47	£119.70	£350.13	£374.36	£811.03	£835.27
H_2 blocker/omeprazole	1452	£114.60	£154.70	£389.70	£429.81	£774.15	£814.26
No Risk Factors *							
comparator	40612	£7.84	£7.84	£36.01	£36.01	£87.30	£87.30
NSAID	27635	£29.05	£36.82	£99.72	£107.50	£216.67	£224.44
misoprostol	116	£32.94	£56.02	£87.87	£110.95	£390.29	£413.37
H_2 blocker/omeprazole	610	£45.17	£83.32	£194.49	£232.64	£396.09	£434.24
Survivors							
comparator	42081	£12.41	£12.41	£38.85	£38.85	£87.57	£87.57
NSAID	42445	£42.23	£49.78	£140.70	£148.25	£286.92	£294.47
misoprostol	184	£96.91	£121.38	£357.70	£382.18	£680.43	£704.90
H_2 blocker/omeprazole	1767	£121.11	£161.91	£360.15	£400.95	£713.14	£753.94
Survivors with no risk factors							
comparator	36721	£6.33	£6.33	£25.57	£25.57	£59.14	£59.14
NSAID	25332	£25.61	£33.35	£86.09	£93.83	£172.65	£180.39
misoprostol	105	£32.41	£55.77	£76.36	£99.72	£219.93	£243.28
H_2 blocker/omeprazole	548	£43.95	£81.86	£160.09	£197.99	£350.75	£388.66

* *Excluded aspirin takers, those with prior GI, CV, RA or OA admissios, prior endoscopies and those who died during the study.*

Table 15 **Sensitivity analysis - varying costs**

	N	45 Days		Six Months		12 Months	
		Shadow Costs	Total Costs	Shadow Costs	Total Costs	Shadow Costs	Total Costs
Low GP Cost (£4.77)							
Comparator	47350	£12.83	£12.83	£57.98	£57.98	£138.33	£138.33
NSAID Only	49212	£42.08	£49.59	£171.74	£179.25	£373.84	£381.35
NSAID & Misoprostol	212	£71.19	£95.53	£320.86	£345.20	£768.37	£792.71
NSAID & H_2 blocker/omeprazole	2113	£99.34	£140.07	£402.16	£442.89	£869.19	£909.91
Low Endoscopy Cost (£208.33 x 0.5)							
Comparator	47350	£12.83	£12.83	£58.90	£58.90	£140.01	£140.01
NSAID Only	49212	£45.24	£52.75	£178.10	£185.61	£385.01	£392.52
NSAID & Misoprostol	212	£75.56	£99.90	£331.18	£355.51	£783.85	£808.19
NSAID & H_2 blocker/omeprazole	2113	£103.18	£143.91	£414.85	£455.58	£889.54	£930.27
Base Case							
Comparator	47350	*£13.35*	*£13.35*	*£59.63*	*£59.63*	*£141.51*	*£141.51*
NSAID Only	49212	*£44.19*	*£51.70*	*£179.01*	*£186.52*	*£386.93*	*£394.44*
NSAID & Misoprostol	212	*£75.56*	*£99.90*	*£332.16*	*£356.50*	*£787.29*	*£811.63*
NSAID & H_2 blocker/omeprazole	2113	*£104.06*	*£144.79*	*£418.20*	*£458.93*	*£897.03*	*£937.76*
High Endoscopy Cost (£208.33 x 1.5)							
Comparator	47350	£13.24	£13.24	£60.37	£60.37	£143.00	£143.00
NSAID Only	49212	£45.58	£53.09	£179.92	£187.43	£388.84	£396.35
NSAID & Misoprostol	212	£75.56	£99.90	£333.14	£357.48	£790.73	£815.07
NSAID & H_2 blocker/omeprazole	2113	£104.95	£145.68	£421.55	£462.28	£904.53	£945.26
High GP Cost (£8.38)							
Comparator	47350	£13.51	£13.51	£60.12	£60.12	£142.44	£142.44
NSAID Only	49212	£44.81	£52.32	£181.14	£188.65	£390.78	£398.29
NSAID & Misoprostol	212	£76.85	£101.18	£335.48	£359.82	£792.85	£817.18
NSAID & H_2 blocker/omeprazole	2113	£105.45	£146.18	£422.91	£463.64	£905.22	£945.95

Table 16 NSAID trials included in the meta-analysis

Year	Author	Indication	Duration	N	Drugs Included in the Study	Method of ADR Recording	Jadad Score
1982	Abe T	RA	6 weeks	164	Piroxicam 10-20 mg; indomethacin 75 mg	Unspecified	2
1982	Abruzzo JL et al	OA	12 weeks	114	Piroxicam 20 mg; aspirin 2.6-3.9 g	Indirect questions	2
1977	Aylward M et al	RA	6 weeks	44	Tolmetin 1.6 g, alclofenac 4 g	Spontaneous reporting	3
1986	Bellamy N et al	OA	6 weeks	57	Piroxicam 10-20 mg, isoxicam 100-200 mg	Unspecified	3
1983	Berry H et al	OA	2 weeks	24	Naproxen 750 mg, antrafenine 450-900 mg, placebo	Indirect questions	3
1978	Bijlsma A	RA	6 months	36	Diclofenac 75-125 mg, indomethacin 75-125 mg	Unspecified	2
1975	Blechman WJ et al	RA	51 weeks	885	Ibuprofen 3-6 g, aspirin 800-1600 mg	Indirect questions	4
1975	Bowers DE et al	RA	16 weeks	80	Naproxen 250-750 mg, aspirin 0.8-4.8 g	Questionnaire	4
1977	Brewis IDL	RA	2 weeks	30	Indomethacin 100 mg, flurbiprofen 240 mg, placebo	Indirect questions	2
1976	Brooke JW	OA	12 weeks	30	Fenoprofen 200-600 mg, aspirin 325-975 mg, placebo	Daily checklist	2
1986	Brown BL et al	OA	6 weeks	148	Sulindac 300 mg, flurbiprofen 100 mg	Unspecified	3
1977	Cardoe N et al	RA	4 weeks	24	Tolmetin 1600 mg, phenylbutazone 400 mg	Spontaneous reporting	3
1978	Castles JJ et al	RA	20 weeks	132	Naproxen 500 mg, indomethacin 100 mg, aspirin 3.6 g, placebo	Indirect questions	2
1979	Daymond TJ et al	RA	4 weeks	41	Ibuprofen 1200 mg, tiaprofenic acid 600 mg	Unspecified	4
1973	Fries JF et al	RA	6 weeks	30	Fenoprofen 1.6-2.4 g, aspirin 4.0-6.0 g, placebo	"Queried"	3
1972	Gyory AN et a	RA/OA	2 weeks	88	Ketoprofen 100 mg, indomethacin	Indirect questions	4
1976	Kirchheiner B et al	RA	2 weeks	30	Ketoprofen, indomethacin	Unspecified	1
1977	Kruger HH	RA	2 weeks	30	Indomethacin 150 mg, flurbiprofen 300 mg	'Enquired for' at each visit	2
1981	Liyanage SP et al	OA	4 weeks	30	Naproxen 750 mg, sulindac 400 mg	Indirect questions	2
1977	McMillen JI	RA	12 weeks	104	Ibuprofen 1600 mg, tolmetin 1200 mg	Unspecified	3
1973	Mills SB et al	RA	2 weeks	35	Ketoprofen 150 mg, ibuprofen 1200 mg	Indirect questions	2
1987	Vasey FB et al	RA	6 months	367	Naproxen 500 mg, nabumetone 1500 mg	Unspecified	4
1987	Vetter G	OA	4 weeks	36	Indomethacin 150 mg, SAMe 1200 mg	Unspecified	2
1978	Woolheim FA et al	OA	4 weeks	30	Ketoprofen 200 mg, naproxen 750 mg	Checklist	2

Table 17 SSRI trials included in the meta-analysis

Year	Author	Country	Duration	N	Drugs Included in the Study	Method of ADR Recording	Jadad Score
1994	Ansseau M et al	Belgium	6 weeks	190	Milnacipran 100 mg, fluoxetine 20 mg	Checklist and spontaneous reporting	3
1995	Bennie EH et al	UK	6 weeks	308	Sertraline 50-100 mg, fluoxetine 20-40 mg	Spontaneous reporting	3
1994	Bersani G et al	Italy	8 weeks	68	Sertraline 50-100 mg, amitriptyline 50-150 mg	Unspecified	3
1988	Byerley WF et al	US	6 weeks	103	Fluoxetine 20-80 mg, imipramine 75-300 mg	Unspecified	4
1996	Claghorn JL et al	US	6 weeks	138	Fluvoxamine 50-150 mg, imipramine 80-240 mg, placebo	Indirect questions	3
1991	Dunbar GC et al	US	6 weeks	717	Paroxetine 20-50 mg, imipramine 80-275 mg, placebo	COSTART	3
1991	Fabre LF et al	US	5 weeks	205	Nortriptyline 43 mg, fluoxetine 17.4 mg	Unspecified	3
1985	Feighner JP	US	5 weeks	44	Fluoxetine 55 mg, amitriptyline 159 mg	Unspecified	3
1995	Geretsegger C et al	Australia	6 weeks	91	Paroxetine 20-30 mg, amitriptyline 50-150 mg	Checklist	3
1983	Guelfi JD et al	France	4 weeks	158	Fluvoxamine 300 mg, imipramine 200 mg	Checklist	3
1983	Itil TM et al	US	4 weeks	69	Fluvoxamine 101 mg, imipramine 127 mg	DOTES/TWIS	2
1998	Keller MB et al	US	76 weeks	169	Sertraline 200 mg, placebo	Unspecified	3
1997	Kiev A et al	US	7 weeks	60	Fluvoxamine 50-150 mg, paroxetine 20-50 mg	Spontaneous reporting	4
1987	Lapierre YD	Canada	6 weeks	63	Fluvoxamine 50-300 mg, imipramine 50-300 mg, placebo	DOTES/TWIS	3
1988	Muijen M et al	UK	6 weeks	81	Fluoxetine 20-80 mg, mianserin 20-80 mg, placebo	Unspecified	3
1991	Noguera R et al	Spain	6 weeks	120	Fluoxetine 20-40 mg, chlorimipramine 100 mg	Unspecified	3
1984	Norton KRW et al	UK	4 weeks	91	Fluvoxamine 132.8 mg, imipramine 153.3 mg, placebo	DOTES/TWIS	3
1989	Perry PJ et al	US	6 weeks	40	Fluoxetine 21-50 mg, trazodone 241-357 mg	Adverse events form	3
1989	Rickels K et al	US	6 weeks	111	Paroxetine 10 mg, placebo	Recorded in open-ended fashion	3
1990	Reimherr FW et al	US	8 weeks	448	Sertraline 104 mg, amitriptyline 145 mg, placebo	Unspecified	3
1987	Young JPR et al	UK	6 weeks	64	Fluoxetine 40-80 mg, amitriptyline 50-150 mg	Adverse events form	3

Table 18 ACE inhibitor trials included in the meta-analysis

Year	Author	Country	Duration	N	Drugs Included in the Study	Method of ADR Recording	Jadad Score
1991	Beevers DG et al	UK	8 weeks	144	Lisinopril 10-40 mg, atenolol 50-100 mg, placebo	Open questioning	3
1987	Bolzano K et al	Austria	12 weeks	490	Lisinopril 20-80 mg, atenolol 50-200 mg	Unspecified	3
1994	Chrysant SG et al	US	12 weeks	505	Lisinopril 10 mg, HCTZ 12.5 mg, lisinopril 10 mg/HCTZ 12.5 mg, placebo	"Questioned"	2
1998	Cushman WC et al	US	12 weeks	891	Enalapril 5 mg, diltiazem ER 120-180 mg, enalapril 5 mg/diltiazem ER 120-180 mg, placebo	Indirect questions	3
1984	EHSG	UK	12 weeks	54	Enalapril 5-20 mg, propranolol 40-120 mg	Open questioning	2
1990	Ferme I et al	France	4 weeks	96	Enalapril 20 mg, diltiazem SR 300 mg, enalapril 20 mg/diltiazem SR 300 mg	Unspecified	3
1994	Fernandez M et al	Mexico	8 weeks	67	Fosinopril 20 mg, HCTZ 12.5 mg, fosinopril 20 mg/HCTZ 12.5 mg, placebo	Spontaneous reporting	3
1995	Gradman AH et al	US	8 weeks	576	Enalapril 20 mg, losartan 10-150 mg, placebo	Observed and reported	3
1997	Gradman AH et al	US	8 weeks	707	Enalapril 5-20 mg, felodipine 2.5-10 mg, enalapril 5-20 mg/felodipine 2.5-10 mg, placebo	Spontaneous reporting	2
1990	Grunfeld J-P et al	France	8 weeks	186	Enalapril 20 mg, spironolactone 15 mg/altizid 25 mg	Spontaneous reporting	3
1993	Lacourcciere Y et al	Canada	8 weeks	43	Captopril 25-50 mg, amlodipine 5-10 mg	Indirect questions	3
1988	Mehta J et al	US	12 weeks	26	Lisinopril 20-80 mg, lisinopril/ 20-80 mgHCTZ 12.5-50 mg	"Interviewed"	3
1998	Meserli F et al	US	6 weeks	631	Trandolapril 4 mg, verapamil SR 20 mg, trandolapril 4 mg/verapamil SR 20 mg, placebo	Unspecified	3
1992	Morgan	Australia	12 weeks	190	Perindopril 2 mg, atenolol 25 mg	Direct questioning and spontaneous reporting	2
1987	Morlin C et al	Sweden	12 weeks	136	Lisinopril 20-80 mg, nifedipine 40-80 mg	Unspecified	3
1991	Mroczek WJ et al	US	4 weeks	159	Enalapril 5-20 mg, ramipril 2.5-10 mg	"Questioned"	2
1995	Nicaise J et al	Belgium	8 weeks	100	Captopril 12.5-25 mg, diltiazem SR 200-300 mg	Observed and reported	3

Table 18 (cont) **ACE inhibitor trials included in the meta-analysis**

Year	Author	Country	Duration	N	Drugs Included in the Study	Method of ADR Recording	Jadad Score
1995	Prisant L et al	US	12 weeks	218	Enalapril 5-20 mg, amlodipine 2.5-10 mg, bisoprolol 2.5-10 mg/HCTZ 6.25 mg	Spontaneous reporting	5
1996	Stimpel M et al	Germany	12 weeks	159	Captopril 25 mg, moexipril 7.5 mg	Open questioning	2
1995	Thijs L et al	Belgium	4 weeks	611	Ramipril 5 mg, piretanide 6 mg, ramipril 5 mg/piretanied 6 mg	Spontaneous reporting	3
1991	TOMHS	US	12 months	902	Enalapril 5 mg, acebutolol 400 mg, amlodipine 5 mg, chlorthalidone 15 mg, doxazosin 2 mg, placebo	Checklist	4
1991	Vasmant D et al	France	8 weeks	205	Ramipril 2.5-5 mg, placebo	Spontaneous reporting	2
1991	Verkaaik R et al	The Netherlands	8 weeks	44	Enalapril 20-40 mg, nitredipine 20-40 mg	Open questioning and spontaneous reporting	4
1987	Zachariah PK et al	US	8 weeks	179	Lisinopril 40-80 mg, metoprolol 100-200 mg	Unspecified	3

Table 19 Adverse drug reactions data extracted from NSAID trials

	Ibuprofen (N = 560)			Naproxen (N = 548)			Piroxicam (N = 138)			Sulindac (N = 85)		
		Weighted			Weighted			Weighted			Weighted	
	N	N	%	N	N	%	N	N	%	N	N	%
Abdominal Pain	36	24.02	4.29%	32	6.41	1.17%	14	4.90	3.55%	4	3.29	3.88%
Anorexia	7	4.07	0.73%	3	0.29	0.05%	2	0.81	0.59%	2	1.65	1.94%
Constipation	6	3.97	0.71%	34	6.37	1.16%	3	1.22	0.88%	8	4.65	5.47%
Diarrhoea	9	4.94	0.88%	14	3.65	0.67%	5	1.77	1.28%	5	4.12	4.84%
Peptic Ulcer	2	0.19	0.03%	-	-	-	-	-	-	-	-	-
Dyspepsia	28	14.98	2.67%	30	4.10	0.75%	2	0.77	0.56%	3	1.18	1.38%
Flatulence	1	0.09	0.02%	4	0.66	0.12%	-	-	-	-	-	-
GI Haemorrhage	-	-	-	-	-	-	-	-	-	-	-	-
Nausea/Vomiting	44	26.71	4.77%	45	9.64	1.76%	3	1.00	0.72%	6	4.29	5.05%
Oral Ulcers	-	-	-	9	2.73	0.50%	3	1.00	0.72%	1	0.18	0.21%
Fatigue	3	0.28	0.05%	2	0.24	0.04%	8	2.96	2.15%	2	1.65	1.94%
Confusion	-	-	-	-	-	-	-	-	-	-	-	-
Depression	6	3.25	0.58%	10	2.08	0.38%	-	-	-	1	0.82	0.97%
Dizziness/Vertigo	16	11.14	1.99%	14	3.21	0.59%	4	1.21	0.88%	8	5.94	6.99%
Drowsiness	1	0.06	0.01%	4	0.31	0.06%	2	0.42	0.30%	-	-	-
Dry Mouth	-	-	-	-	-	-	1	0.21	0.15%	-	-	-
Headache	28	10.69	1.91%	39	7.55	1.38%	1	0.41	0.29%	7	5.12	6.02%
Nervousness /Irritability	5	3.22	0.58%	4	0.83	0.15%	-	-	-	-	-	-
Sleep/Restlessness	1	0.06	0.01%	3	0.47	0.09%	-	-	-	-	-	-
Nightmares	-	-	-	-	-	-	-	-	-	-	-	-
Tinnitus	13	10.17	1.82%	17	3.01	0.55%	3	1.17	0.85%	2	1.65	1.94%
Visual Disturbance	-	-	-	-	-	-	-	-	-	-	-	-
Flu-Like Symptoms	-	-	-	5	0.33	0.06%	2	0.62	0.45%	-	-	-
Rash/Pruritis	30	19.23	3.43%	50	7.50	1.37%	8	2.99	2.16%	3	2.47	2.91%
Oedema	2	0.19	0.03%	8	1.66	0.30%	10	3.04	2.20%	-	-	-
Anaemia	-	-	-	-	-	-	-	-	-	-	-	-

Table 19 (cont) **Adverse drug reactions data extracted from NSAID trials**

	Fenoprofen (N = 57)			Ketoprofen (N = 186)			Indomethacin (N = 395)			Diclofenac (N = 18)	
		Weighted			Weighted			Weighted			
	N	N	%	N	N	%	N	N	%	N	%
Abdominal Pain	22	11.37	19.94%	18	3.65	1.96%	29	4.16	1.05%	-	-
Anorexia	-	-	-	2	0.31	0.17%	7	1.19	0.30%	-	-
Constipation	6	3.16	5.54%	4	0.97	0.52%	7	1.25	0.32%	-	-
Diarrhoea	-	-	-	6	2.03	1.09%	16	3.64	0.92%	1	5.56%
Peptic Ulcer	-	-	-	-	-	-	-	-	-	-	-
Dyspepsia	-	-	-	18	5.28	2.84%	18	1.86	0.47%	-	-
Flatulence	-	-	-	-	-	-	-	-	-	-	-
GI Haemorrhage	-	-	-	-	-	-	1	0.05	0.01%	-	-
Nausea/Vomiting	11	5.53	9.70%	17	4.13	2.22%	51	6.79	1.72%	3	16.67%
Oral Ulcers	-	-	-	7	2.52	1.35%	5	0.93	0.24%	-	-
Fatigue	-	-	-	4	1.38	0.74%	10	1.47	0.37%	-	-
Confusion	6	3.16	5.54%	-	-	-	-	-	-		
Depression	-	-	-	6	2.04	1.10%	4	0.84	0.21%	-	-
Dizziness/Vertigo	6	3.16	5.54%	3	0.81	0.43%	31	5.18	1.31%	2	11.11%
Drowsiness	6	3.16	0.29%	-	-	-	3	0.17	0.04%	-	-
Dry Mouth	-	-	-	1	0.15	0.08%	1	0.08	0.02%	-	-
Headache	17	8.68	15.24%	8	1.27	0.68%	62	10.93	2.77%	2	11.11%
Nervousness/ Irritability	6	3.16	5.54%	-	-	-	1	0.29	0.07%	-	-
Sleep/Restlessness	-	-	-	-	-	-	1	0.29	0.07%	-	-
Nightmares	-	-	-	-	-	-	1	0.05	0.01%	-	-
Tinnitus	26	13.26	23.27%	2	0.30	0.16%	8	1.67	0.42%	-	-
Visual Disturbance	12	6.32	11.08%	1	0.15	0.08%	-	-	-	-	-
Flu-Like Symptoms	-	-	-	-	-	-	3	0.35	0.09%	-	-
Rash/Pruritis	35	17.53	30.75%	15	3.70	1.99%	18	3.81	0.96%	-	-
Oedema	12	6.32	11.08%	-	-	-	3	0.72	0.18%	-	-
Anaemia	-	-	-	-	-	-	1	0.08	0.02%	-	-

Table 20 Adverse drug reactions data extracted from SSRI trials

		Fluoxetine (N = 194)			Sertraline (N = 183)		
		N	Weighted N	Weighted %	N	Weighted N	Weighted %
CNS	Anxiety	27	8.60	4.43%	18	14.66	8.01%
	Blurred Vision	14	3.37	1.74%	16	13.03	7.12%
	Confusion	4	0.52	0.27%	-	-	-
	Depersonalized Syndrome	-	-	-	-	-	-
	Dizziness/Syncope	12	3.33	1.72%	26	18.66	10.19%
	Drowsiness	17	2.80	1.45%	29	23.61	12.90%
	Dry Mouth	16	4.31	2.22%	57	39.50	21.58%
	Dysmenorrhoea	-	-	-	-	-	-
	Fatigue	8	1.21	0.62%	13	10.58	5.78%
	Headache	23	4.98	2.57%	24	19.54	10.68%
	Insomnia	16	4.66	2.40%	26	21.17	11.57%
	Palpitation	-	-	-	-	-	-
	Paraesthesia	-	-	-	-	-	-
	Sweating	1	0.11	0.06%	11	8.96	4.89%
	Taste Perversion	-	-	-	4	3.26	1.78%
	Tinnitus	-	-	-	-	-	-
	Tremor	18	4.17	2.15%	24	19.54	10.68%
GI							
	Anorexia	-	-	-	6	4.89	2.67%
	Constipation	9	2.64	1.36%	21	14.58	7.97%
	Decreased Appetite	2	0.27	0.14%	-	-	-
	Diarrhoea	7	1.88	0.97%	35	28.50	15.57%
	Flatulence	1	0.11	0.06%	-	-	-
	Dyspepsia	1	0.11	0.06%	23	12.44	6.80%
	Nausea/Vomiting	52	13.87	7.15%	58	47.22	25.81%
	Weight Gain, Excessive	3	1.44	0.74%	-	-	-
	Weight Loss, Excessive	8	3.47	1.79%	-	-	-
CV							
	Hypotension	3	1.44	0.74%	-	-	-
	Tachycardia-Palpitations	7	3.36	1.73%	7	5.70	3.11%
	Vasodilation	-	-	-	-	-	-
Skin							
	Dermatites/Allergy	19	4.48	2.31%	18	14.66	8.01%
Flu Symptoms							
	Flu-Like Symptoms	5	0.54	0.28%	-	-	-
Urinary Problems							
	Urinary Problems	4	1.92	0.99%	2	1.63	0.89%
Sexual Problems							
	Abnormal Ejaculation	-	-	-	-	-	-
	Decreased Libido	1	0.11	0.06%	32	26.05	14.24%
	Impotence	-	-	-	-	-	-

Table 20 (cont) Adverse drug reactions data extracted from SSRI trials

	Fluvoxamine (N = 132)			Paroxetine (N = 270)		
	N	Weighted N	Weighted %	N	Weighted N	Weighted %
CNS						
Anxiety	31	8.74	6.62%	6	0.67	0.25%
Blurred Vision	-	-	-	12	10.67	3.95%
Confusion	-	-	-	-	-	-
Depersonalized Syndrome	2	0.45	0.34%	4	0.44	0.16%
Drowsiness	39	10.64	8.06%	82	63.56	23.54%
Dry Mouth	43	10.82	8.20%	64	48.33	17.90%
Dysmenorrhoea	2	0.71	0.54%	3	0.33	0.12%
Headache	32	9.20	6.97%	12	1.33	0.49%
Insomnia	23	5.26	3.98%	9	1.00	0.37%
Palpitation	1	0.23	0.17%	4	0.44	0.16%
Paraesthesia	-	-	-	12	10.67	3.95%
Sweating	20	5.09	3.86%	29	23.44	8.68%
Taste Perversion	-	-	-	5	4.44	1.65%
Tinnitus	-	-	-	2	1.78	0.66%
Tremor	22	5.52	4.18%	27	21.67	8.02%
GI						
Anorexia	28	7.32	5.54%	-	-	-
Constipation	19	5.30	4.01%	40	34.00	12.59%
Decreased Appetite	-	-	-	19	16.89	6.26%
Diarrhoea	26	7.25	5.49%	14	1.56	0.58%
Flatulence	1	0.23	0.17%	4	0.44	0.16%
Dyspepsia	9	2.69	2.04%	7	0.78	0.29%
Nausea/Vomiting	54	13.77	10.43%	78	60.78	22.51%
Weight Gain, Excessive	-	-	-	-	-	-
Weight Loss, Excessive	-	-	-	-	-	-
CV						
Hypotension	-	-	-	-	-	-
Tachycardia-Palpitations	-	-	-	9	8.00	2.96%
Vasodilation	5	1.46	1.11%	5	4.44	1.65%
Skin						
Dermatites/Allergy	15	3.69	2.79%	2	0.22	0.08%
Flu Symptoms						
Flu-Like Symptoms	20	7.12	5.39%	-	-	-
Urinary Problems						
Urinary Problems	-	-	-	17	15.11	5.60%
Sexual Problems						
Abnormal Ejaculation	5	1.39	1.06%	15	12.56	4.65%
Decreased Libido	5	1.14	0.86%	14	9.33	3.46%
Impotence	3	0.68	0.52%	2	0.22	0.08%

Table 21 Adverse drug reactions data extracted from ACE inhibitor trials

	Lisinopril (N = 653)			Enalapril (N = 699)			Trandolapril (N = 159)	
		Weighted			Weighted			
	N	N	%	N	N	%	N	%
CNS								
Asthenia/Fatigue	25	6.37	0.98%	18	2.13	0.30%	5	3.14%
Ataxia				2	0.27	0.04%		
Depression				1	0.10	0.01%		
Dizziness/ Vertigo/Syncope	28	7.85	1.20%	21	2.58	0.37%	4	2.52%
Dryness Of Mouth								
Headache	39	11.03	1.69%	41	4.81	0.69%	17	10.69%
Insomnia				2	0.13	0.02%		
Nervousness								
Paresthesia	3	0.34	0.05%	1	0.13	0.02%		
Somnolence /Tiredness	2	0.36	0.06%	3	0.18	0.03%		
Ageusia/Taste Impairment				1	0.13	0.02%		
Tinnitus								
Visual Disturbance				1	0.02	0.00%		
GI								
Abdominal Pain							5	3.14%
Anorexia				1	0.13	0.02%		
Constipation				1	0.04	0.01%	1	0.63%
Diarrhoea	6	0.91	0.14%	6	0.68	0.10%	5	3.14%
Dyspepsia				2	0.20	0.03%		
Nausea & Vomiting	9	3.43	0.52%	8	0.79	0.11%	5	3.14%
CV								
Oedema	1	0.14	0.02%	13	1.96	0.28%	4	2.52%
Palpitations /Breathlessness				12	1.00	0.14%		
Postural Hypotension				8	0.98	0.14%		
Flu Symptom	36			36	4.84	0.69%	25	15.72%
Skin Rash	9	2.67	0.41%	5	0.31	0.04%	5	3.14%
Impotence				3	0.19	0.03%		

Table 21 (cont) **Adverse drug reactions data extracted from ACE inhibitor trials**

	Ramipril (N = 397)			Captopril (N = 104)			Moexipril (N = 105)		Perindapril (N = 94)	
		Weighted			Weighted					
	N	N	%	N	N	%	N	%	N	%
CNS										
Asthenia/Fatigue	5	1.15	0.29%	7	3.63	3.49%	11	10.48%	24	25.53%
Ataxia										
Depression	4	2.11	0.53%	1	0.48	0.46%				
Dizziness/ Vertigo/Syncope	17	7.79	1.96%	8	4.12	3.96%	8	7.62%	25	26.60%
Dryness Of Mouth									16	17.02%
Headache	20	8.98	2.26%	10	5.12	4.92%	13	12.38%	24	25.53%
Insomnia	6	3.16	0.80%	1	0.48	0.46%			27	28.72%
Nervousness				3	1.56	1.50%	4	3.81%		
Paresthesia Somnolence /Tiredness	9	4.74	1.19%	3	1.56	1.50%	1	0.95%		
Ageusia/Taste ImpairmEnt				1	0.48	0.46%				
Tinnitus				1	0.48	0.46%			8	8.51%
Visual Disturbance										
GI										
Abdominal Pain	2	0.54	0.14%							
Anorexia										
Constipation										
Diarrhoea	1	0.27	0.07%				6	5.71%	14	14.89%
Dyspepsia										
Nausea & Vomiting	4	1.85	0.47%						20	21.28%
CV										
Oedema				5	2.56	2.46%	12	11.43%		
Palpitations/ Breathlessness	4	2.11	0.53%	3	1.56	1.50%	2	1.90%		
Postural Hypotension									16	17.02%
Flu Symptom	11	5.79	1.46%	17	8.75	8.41%				
Skin Rash				1	0.48	0.46%			14	14.89%
Impotence	7	3.69	0.93%						3	3.19%

Table 22 Drug costs

	Defined Daily Dose (DDD)		Cost	
	Minimum	Maximum	Minimum DDD	Maximum DDD
NSAIDs				
Ibuprofen	1 200 mg	2 400 mg	£5.58	£11.17
Naproxen	500 mg	1 000 mg	£7.85	£15.10
Piroxicam	10 mg	30 mg	£3.54	£11.44
Sulindac	200 mg	400 mg	£18.63	£32.50
Fenoprofen (Fenopron ®)	900 mg	2 400 mg	£19.85	£51.21
Ketoprofen	100 mg	200 mg	£22.45	£22.12
Indomethacin	50 mg	200 mg	£3.57	£5.60
Diclofenac Sodium	75 mg	150 mg	£5.85	£9.28
SSRIs				
Fluoxetine	20 mg	60 mg	£18.01	£54.04
Sertraline (Lustral ®)	50 mg	200 mg	£40.50	£132.55
Fluvoxamine	100 mg	300 mg	£38.71	£116.13
Paroxetine (Seroxat ®)	20 mg	50 mg	£41.44	£125.81
ACE Inhibitors				
Captopril	25 mg	100 mg	£5.75	£10.51
Cilazapril (Vascace ®)	1 mg	5 mg	£16.15	£35.70
Enalapril Maleate	5 mg	40 mg	£9.40	£30.60
Fosinopril (Staril ®)	10 mg	40 mg	£30.10	£65.00
Imidapril Hydrochloride (Tanatril ®)	5 mg	20 mg	£14.13	£19.18
Lisinopril (Zestril ®)	2.5 mg	40 mg	£15.65	£54.85
Moexipril (Perdix ®)	7.5 mg	30 mg	£20.30	£70.20
Perindopril (Coversyl ®)	2 mg	8 mg	£24.06	£69.49
Quinapril (Accupro ®)	10 mg	80 mg	£17.93	£48.75
Ramipril (Tritace ®)	1.25 mg	10 mg	£13.25	£32.50
Trandolapril ®)	0.5 mg	4 mg	£20.45	£61.40

Table 23 Calculated cost of managing clinical adverse events

Adverse Drug Events	Cost (£)
Dyspepsia	£ 30.89
Suspected peptic ulcer	£ 33.02
Abdominal pain	£ 21.88
Nausea and vomiting	£ 33.55
Constipation	£ 22.22
Diarrhoea	£ 17.24
Peptic ulcers	£ 308.41
Rash or Pruritis	£ 20.24
Insomnia	£ 18.14
Other CNS symptoms	£ 8.50
Oedema	£ 23.74
Anaemia	£ 91.87

Table 24 The cost of managing adverse drug reactions in NSAID therapies

		Fenoprofen (N = 57)		Diclofenac (N = 18)		Sulindac (N = 85)		Ibuprofen (N = 560)		Ketoprofen (N = 186)		Piroxicam (N = 138)		Naproxen (N = 548)		Indomethacin (N = 395)	
	Cost	Weighted %	Cost	%	Cost	Weighted %	Cost	Weighted %	Cost	Weighted %	Cost	Weighted %	Cost	Weighted %	Cost	Weighted %	Cost
Abdominal Pain	**£21.88**	19.94%	£4.36	-		3.88%	£0.85	4.29%	£0.94	1.96%	£0.43	3.55%	£0.78	1.17%	£0.26	1.05%	£0.23
Anorexia	**£8.50**	-		-		1.94%	£0.16	0.73%	£0.06	0.17%	£0.01	0.59%	£0.05	0.05%	£0.00	0.30%	£0.03
Constipation	**£22.22**	5.54%	£1.23	-		5.47%	£1.21	0.71%	£0.16	0.52%	£0.12	0.88%	£0.20	1.16%	£0.26	0.32%	£0.07
Diarrhoea	**£17.24**	-		5.56%	£0.96	4.84%	£0.84	0.88%	£0.15	1.09%	£0.19	1.28%	£0.22	0.67%	£0.11	0.92%	£0.16
Peptic Ulcer	**£308.41**	-		-		-		0.03%	£0.10	-		-		-		-	
Dyspepsia	**£30.89**	-		-		1.38%	£0.43	2.67%	£0.83	2.84%	£0.88	0.56%	£0.17	0.75%	£0.23	0.47%	£0.15
Flatulence	**£8.50**	-		-		-		0.02%	£0.00	-		-		0.12%	£0.01	-	
Nausea/Vomiting	**£33.55**	9.70%	£3.25	16.67%	£5.59	5.05%	£1.69	4.77%	£1.60	2.22%	£0.74	0.72%	£0.24	1.76%	£0.59	1.72%	£0.58
Oral Ulcers	**£8.50**	-		-		0.21%	£0.02	-		1.35%	£0.11	0.72%	£0.06	0.50%	£0.04	0.24%	£0.02
Fatigue	**£8.50**	-		-		1.94%	£0.16	0.05%	£0.00	0.74%	£0.06	2.15%	£0.18	0.04%	£0.00	0.37%	£0.03
Confusion	**£8.50**	5.54%	£0.47			-		-		-		-		-		-	
Depression	**£8.50**	-		-		0.97%	£0.08	0.58%	£0.05	1.10%	£0.09	-		0.38%	£0.03	0.21%	£0.02
Dizziness/Vertigo	**£8.50**	5.54%	£0.47	11.11%	£0.94	6.99%	£0.59	1.99%	£0.17	0.43%	£0.04	0.88%	£0.07	0.59%	£0.05	1.31%	£0.11
Drowsiness	**£8.50**	0.29%	£0.02	-		-		0.01%	£0.00	-		0.30%	£0.03	0.06%	£0.00	0.04%	£0.00
Dry Mouth	**£8.50**	-		-		-		-		0.08%	£0.01	0.15%	£0.01	-		0.02%	£0.00
Headache	**£8.50**	15.24%	£1.30	11.11%	£0.94	6.02%	£0.51	1.91%	£0.16	0.68%	£0.06	0.29%	£0.02	1.38%	£0.12	2.77%	£0.24
Nervousness/ Irritability	**£8.50**	5.54%	£0.47	-		-		0.58%	£0.05	-		-		0.15%	£0.01	0.07%	£0.01
Insomnia	**£18.14**	-		-		-		0.01%	£0.00	-		-		0.09%	£0.02	0.08%	£0.02
Tinnitus	**£8.50**	23.27%	£1.98	-		1.94%	£0.16	1.82%	£0.15	0.16%	£0.01	0.85%	£0.07	0.55%	£0.05	0.42%	£0.04
Visual Disturbance	**£8.50**	11.08%	£0.94	-		-		-		0.08%	£0.01	-		-		-	
Flu-Like Symptoms	**£8.50**	-		-		-		-		-		0.45%	£0.04	0.06%	£0.01	0.09%	£0.01
Rash/Pruritis	**£20.24**	30.75%	£6.22	-		2.91%	£0.59	3.43%	£0.70	1.99%	£0.40	2.16%	£0.44	1.37%	£0.28	0.96%	£0.20
Oedema	**£23.74**	11.08%	£2.63	-		-		0.03%	£0.01	-		2.20%	£0.52	0.30%	£0.07	0.18%	£0.04
Anaemia	**£91.87**	-		-		-		-		-		-		-		0.02%	£0.02

Table 25 The cost of managing adverse drug reactions in SSRI therapies

			Sertraline (N = 183)		Paroxetine (N = 270)		Fluvoxamine (N = 132)		Fluoxetine (N = 194)	
		Unit Costs	Weighted %	Cost	Weighted %	Cost	Weighted %	Cost	Weighted %	Cost
CNS	Anxiety	£8.50	8.01%	£0.68	0.25%	£0.02	6.62%	£0.56	4.43%	£0.38
	Blurred Vision	£8.50	7.12%	£0.61	3.95%	£0.34	-		1.74%	£0.15
	Confusion	£8.50	-		-		-		0.27%	£0.02
	Depersonalized Syndrome	£8.50	-		0.16%	£0.01	0.34%	£0.03	-	
	Dizziness/Syncope	£8.50	10.19%	£0.87	14.40%	£1.22	4.19%	£0.36	1.72%	£0.15
	Drowsiness	£8.50	12.90%	£1.10	23.54%	£2.00	8.06%	£0.69	1.45%	£0.12
	Dry Mouth	£8.50	21.58%	£1.83	17.90%	£1.52	8.20%	£0.70	2.22%	£0.19
	Dysmenorrhoea	£8.50	-		0.12%	£0.01	0.54%	£0.05	-	
	Fatigue	£8.50	5.78%	£0.49	15.43%	£1.31	1.50%	£0.13	0.62%	£0.05
	Headache	£8.50	10.68%	£0.91	0.49%	£0.04	6.97%	£0.59	2.57%	£0.22
	Insomnia	£18.14	11.57%	£2.10	0.37%	£0.07	3.98%	£0.72	2.40%	£0.44
	Palpitation	£8.50	-		0.16%	£0.01	0.17%	£0.01	-	
	Paraesthesia	£8.50	-		3.95%	£0.34	-		-	
	Sweating	£8.50	4.89%	£0.42	8.68%	£0.74	3.86%	£0.33	0.06%	£0.00
	Taste Perversion	£8.50	1.78%	£0.15	1.65%	£0.14	-		-	
	Tinnitus	£8.50	-		0.66%	£0.06	-		-	
	Tremor	£8.50	10.68%	£0.91	8.02%	£0.68	4.18%	£0.36	2.15%	£0.18
GI	Anorexia	£8.50	2.67%	£0.23	6.26%	£0.53	5.54%	£0.47	0.14%	£0.01
	Constipation	£22.22	7.97%	£1.77	12.59%	£2.80	4.01%	£0.89	1.36%	£0.30
	Diarrhoea	£17.24	15.57%	£2.68	0.58%	£0.10	5.49%	£0.95	0.97%	£0.17
	Flatulence	£8.50	-		0.16%	£0.01	0.17%	£0.01	0.06%	£0.00
	Dyspepsia	£30.89	6.80%	£2.10	0.29%	£0.09	2.04%	£0.63	0.06%	£0.02
	Nausea/Vomiting	£33.55	25.81%	£8.66	22.51%	£7.55	10.43%	£3.50	7.15%	£2.40
	Weight Gain, Excessive	£17.00	-		-		-		0.74%	£0.13
	Weight Loss, Excessive	£17.00	-		-		-		1.79%	£0.30
CV	Hypotension	£8.50	-		-		-		0.74%	£0.06
	Tachycardia-Palpitations	£8.50	3.11%	£0.26	2.96%	£0.25	-		1.73%	£0.15
	Vasodilation	£8.50	-		1.65%	£0.14	1.11%	£0.09	-	
Skin	Dermatites/Allergy	£20.24	8.01%	£1.62	0.08%	£0.02	2.79%	£0.57	2.31%	£0.47
Flu Symptoms										
	Flu-Like Symptoms	£8.50	-		-		5.39%	£0.46	0.28%	£0.02
Urinary Problems										
	Urinary Problems	£8.50	0.89%	£0.08	5.60%	£0.48	-		0.99%	£0.08
Sexual Problems										
	Abnormal Ejaculation	£17.00	-		4.65%	£0.79	1.06%	£0.18	-	
	Decreased Libido	£17.00	14.24%	£2.42	3.46%	£0.59	0.86%	£0.15	0.06%	£0.01
	Impotence	£17.00	-		0.08%	£0.01	0.52%	£0.09	-	

Table 26 The cost of managing adverse drug reactions in ACE inhibitor therapies

-	-	Perindapril (N = 94)		Moexipril (N = 105)		Trandolapril (N = 159)		Captopril (N = 104)		Ramipril (N = 397)		Lisinopril (N = 653)		Enalapril (N = 699)	
	Unit Cost	%	Cost	%	Cost	%	Cost	Weighted %	Cost	Weighted %	Cost	Weighted %	Cost	Weighted %	Cost
CNS															
Asthenia/Fatigue	**£8.50**	25.53%	£2.17	10.48%	£0.89	3.14%	£0.27	3.49%	£0.30	0.29%	£0.02	0.98%	£0.08	0.30%	£0.03
Ataxia	**£8.50**													0.04%	£0.00
Depression	**£8.50**							0.46%	£0.04	0.53%	£0.05			0.01%	£0.00
Dizziness/Vertigo/Syncope	**£8.50**	26.60%	£2.26	7.62%	£0.65	2.52%	£0.21	3.96%	£0.34	1.96%	£0.17	1.20%	£0.10	0.37%	£0.03
Dryness Of Mouth	**£8.50**	17.02%	£1.45												
Headache	**£8.50**	25.53%	£2.17	12.38%	£1.05	10.69%	£0.91	4.92%	£0.42	2.26%	£0.19	1.69%	£0.14	0.69%	£0.06
Insomnia	**£18.14**	28.72%	£5.21					0.46%	£0.08	0.80%	£0.14			0.02%	£0.00
Nervousness	**£8.50**			3.81%	£0.32			1.50%	£0.13						
Paresthesia	**£8.50**											0.05%	£0.00	0.02%	£0.00
Somnolence/Tiredness	**£8.50**			0.95%	£0.08			1.50%	£0.13	1.19%	£0.10	0.06%	£0.00	0.03%	£0.00
Ageusia/Taste Impairmnt	**£8.50**							0.46%	£0.04					0.02%	£0.00
Tinnitus	**£8.50**	8.51%	£0.72					0.46%	£0.04						
Visual Disturbance	**£8.50**													0.00%	£0.00
GI															
Abdominal Pain	**£21.88**					3.14%	£0.69			0.14%	£0.03				
Anorexia	**£8.50**													0.02%	£0.00
Constipation	**£22.22**					0.63%	£0.14							0.01%	£0.00
Diarrhoea	**£17.24**	14.89%	£2.57	5.71%	£0.99	3.14%	£0.54			0.07%	£0.01	0.14%	£0.02	0.10%	£0.02
Dyspepsia	**£30.89**													0.03%	£0.01
Nausea & Vomiting	**£33.55**	21.28%	£7.14			3.14%	£1.06			0.47%	£0.16	0.52%	£0.18	0.11%	£0.04
CV															
Oedema	**£23.74**			11.43%	£2.71	2.52%	£0.60	2.46%	£0.58			0.02%	£0.00	0.28%	£0.07
Palpitations/Breathlessness	**£8.50**			1.90%	£0.16			1.50%	£0.13	0.53%	£0.05			0.14%	£0.01
Postural Hypotension	**£8.50**	17.02%	£1.45											0.14%	£0.01
Flu Symptom	**£8.50**					15.72%	£1.34	8.41%	£0.72	1.46%	£0.12			0.69%	£0.06
Skin Rash	**£20.24**	14.89%	£3.01			3.14%	£0.64	0.46%	£0.09			0.41%	£0.08	0.04%	£0.01
Impotence	**£17.00**	3.19%	£0.54							0.93%	£0.16			0.03%	£0.00
Cost per Patient			£28.69		£6.86		£6.39		£3.03		£1.20		£0.63		£0.36
Cost per 1 000 Patients			£28,691.49		£6,855.43		£6,385.09		£3,027.72		£1,199.17		£625.58		£357.35

Table 27 **Total costs of the three drug therapies**

	Minimum DDD	Drug Costs	Shadow Costs	Total Costs	*Original Ranking*	*Final Ranking*
NSAIDs						
Ibuprofen	£5.58	£5,580.00	£5,133.63	£10,713.63	*3*	*4*
Naproxen	£7.85	£7,850.00	£2,144.27	£9,994.27	*5*	*3*
Piroxicam	£3.54	£3,540.00	£3,111.58	£6,651.58	*1*	*2*
Sulindac	£18.63	£18,630.00	£7,308.74	£25,938.74	*6*	*7*
Fenoprofen (Fenopron ®)	£19.85	£19,850.00	£23,353.56	£43,203.56	*7*	*8*
Ketoprofen	£22.45	£22,450.00	£3,164.71	£25,614.71	*8*	*6*
Indomethacin	£3.57	£3,570.00	£1,949.73	£5,519.73	*2*	*1*
Diclofenac Sodium	£5.85	£5,850.00	£8,438.23	£14,288.23	*4*	*5*
SSRIs						
Fluoxetine	£18.01	£18,010.00	£6,026.56	£24,036.56	*1*	*1*
Sertraline (Lustral ®)	£40.50	£40,500.00	£29,878.45	£70,378.45	*3*	*4*
Fluvoxamine	£38.71	£38,710.00	£12,500.68	£51,210.68	*2*	*2*
Paroxetine (Seroxat ®)	£41.44	£41,440.00	£21,875.31	£63,315.31	*4*	*3*
ACE Inhibitors						
Captopril	£5.75	£5,750.00	£3,027.72	£8,777.72	*1*	*1*
Enalapril Maleate	£9.40	£9,400.00	£357.35	£9,757.35	*2*	*2*
Lisinopril (Zestril ®)	£15.65	£15,650.00	£625.58	£16,275.58	*4*	*4*
Moexipril (Perdix ®)	£20.30	£20,300.00	£6,855.43	£27,155.43	*5*	*6*
Perindopril (Coversyl ®)	£24.06	£24,060.00	£28,691.49	£52,751.49	*7*	*7*
Ramipril (Tritace ®)	£13.25	£13,250.00	£1,199.17	£14,449.17	*3*	*3*
Trandolapril ®)	£20.45	£20,450.00	£6,385.09	£26,835.09	*6*	*5*

Table 28 National prescribing trends (Scotland)

	No of Items Prescribed		
	2001	2002	Difference in Prescribing
NSAIDs			
Ibuprofen	603 438	576 681	-4.43%
Naproxen	174 258	156 350	-10.28%
Piroxicam	37 578	37 809	0.61%
Sulindac	3743	3216	-14.08%
Fenoprofen	1048	860	-17.94%
Ketoprofen	18 593	9274	-50.12%
Indomethacin	58 550	51 389	-12.23%
Diclofenac	639 938	626 941	-2.03%
SSRIs			
Fluoxetine	463 076	500 390	8.06%
Sertraline	195 388	210 468	7.72%
Fluvoxamine	4073	3596	-11.71%
Paroxetine	456 232	468 847	2.77%
ACE Inhibitors			
Captopril	105 781	89 992	-15.78%
Enalapril	387 311	388 295	0.25%
Lisinopril	543 257	599 070	10.27%
Moexipril	131	73	-44.27%
Perindopril	113 748	135 479	19.12%
Ramipril	219 472	369630	68.42%
Trandolapril	18 025	17 381	-3.57%

Table 29 Study prescribing trends over six months

	Study Group Prescribing (n = 5 GPs)	Control Group Prescribing (n = 33 GPs)	P values
NSAIDs			
Ibuprofen	-2.48%	-3.96%	0.55
Naproxen	-3.51%	-9.59%	0.08
Piroxicam	-2.90%	-2.97%	0.98
Sulindac	-31.58%	-27.78%	0.56
Fenoprofen	Not Prescribed	Not Prescribed	N/A
Ketoprofen	-17.23%	-29.01%	*0.05
Indomethacin	-2.63%	-8.51%	0.07
Diclofenac	1.02%	-5.27%	0.08
SSRIs			
Fluoxetine	9.78%	9.62%	0.97
Sertraline	10.85%	13.61%	0.96
Fluvoxamine	-20.31%	-28.92%	0.92
Paroxetine	5.48%	7.34%	0.59
ACE Inhibitors			
Captopril	-18.17%	-29.4%	0.06
Enalapril	4.65%	0.44%	0.06
Lisinopril	8.58%	10.47%	0.65
Moexipril	Not Prescribed	Not Prescribed	N/A
Perindopril	10.45%	17.00%	0.12%
Ramipril	5.3%	2.25%	0.26
Trandolapril	-8.79%	-0.12%	*0.00

**statistical significance*

Table 30 **Survey response rates (number returned/number sent)**

	Questionnaire(I)	Questionnaire (II)	Total
Email	6/13 (46%)	4/15 (27%)	10/28 (36%)
Postal	9/17 (53%)	8/16 (50%)	17/33 (51%)
Total	15/30 (50%)	12/31 (39%)	

Table 31 **Economic information influencing decision-making**

	'Yes' N (%)
Published Information	
Local Health Board/PCG/PPAs/MPAs	12 (80%)
Articles in Journals	3 (20%)
Industry Literature	5 (33%)
Others	2 (13%)
Verbally Presented Information	
Meetings with Representatives from Local Health Board/PCG/PPAs/MPAs	6 (40%)
Conferences and Seminars	2 (13%)
Pharmaceutical Industry Representatives	5 (33%)
Others	2 (13%)

Missing Data n=0

Table 32 Sources of economic information used (numbers found the material relevant)

	Yes	No	(Sometimes)	Don't Know	Missing
SPA Prescribing Feedback	10 (8)	2 (0)	(2)	0 (0)	0 (2)
Industry Literature	9 (2)	2 (2)	(4)	1 (2)	0 (2)
MPAs and PPAs	7 (5)	3 (0)	(2)	2 (1)	0 (4)
British Medical Journal	6 (4)	5 (0)	(2)	0 (0)	1 (6)
Industry Representatives	6 (1)	5 (2)	(2)	1 (2)	0 (5)
GPASS Feedback	4 (2)	8 (0)	(2)	0 (1)	0 (7)
Local Newsletter	* 3 (3)	8 (1)	(1)	0 (1)	1 (6)
Other Journals	** 3 (2)	3 (0)	(2)	0 (0)	6 (8)
British Journal of General Practice	2 (1)	8 (0)	(2)	0 (0)	2 (9)
Local Prescribing Formulary	2 (1)	8 (0)	(1)	1 (2)	1 (8)

**Newsletters generated from the Local Healthcare Co-operatives, Glasgow Prescriber*

***Prescriber, Journal of Health Economics, Bandolier, Durgs & Therapeutics Bulletin*

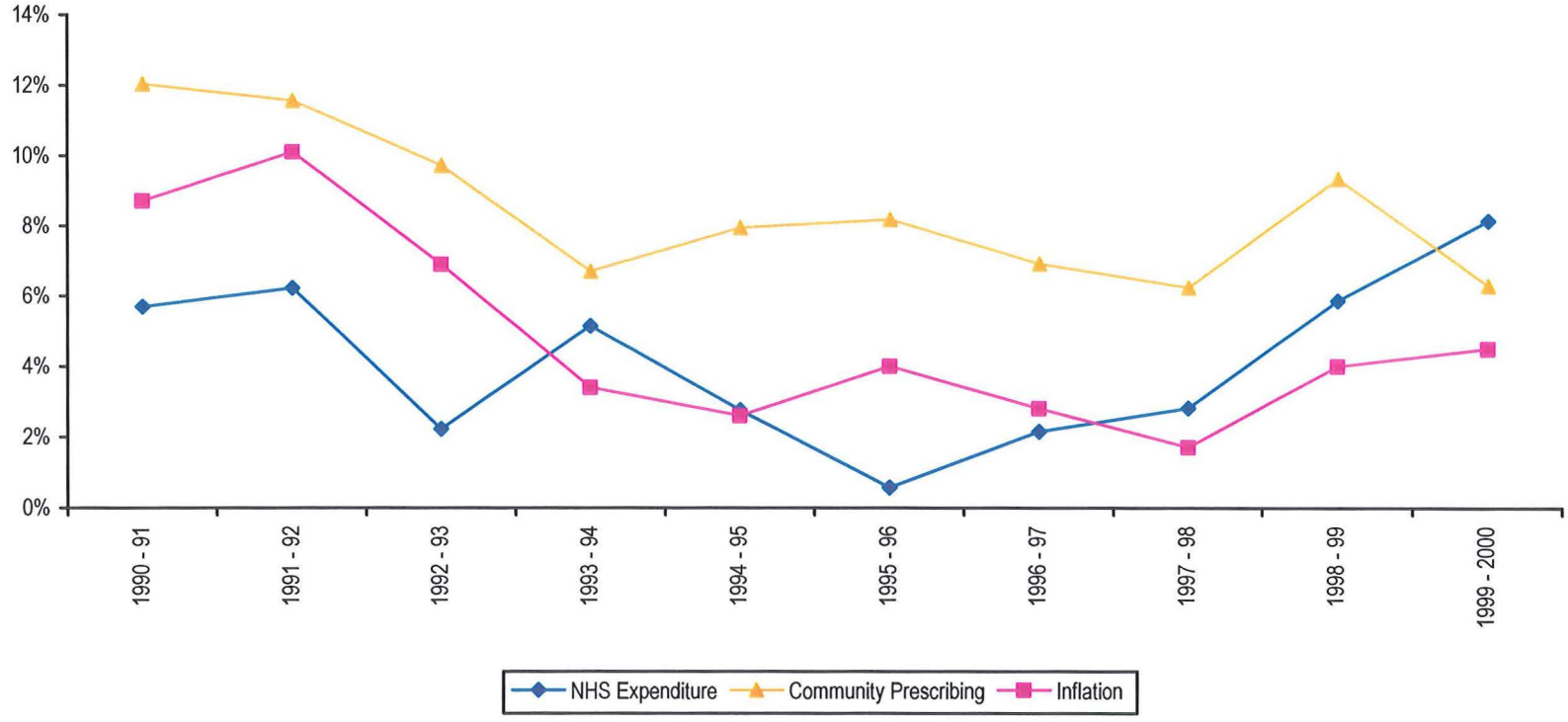
Table 33 Preferred methods of presenting economic data

	N (%)
Locally specific evaluations and studies	6 (54%)
Summary of evaluations and studies published in leaflet format	6 (54%)
Evaluations and studies published in literature	5 (45%)
Simple recommendations presented in leaflet format	5 (45%)
Summary of evaluations and studies presented verbally at a meeting	3 (27%)
Simple recommendations presented verbally at a meeting	1 (9%)

Missing Data n=1

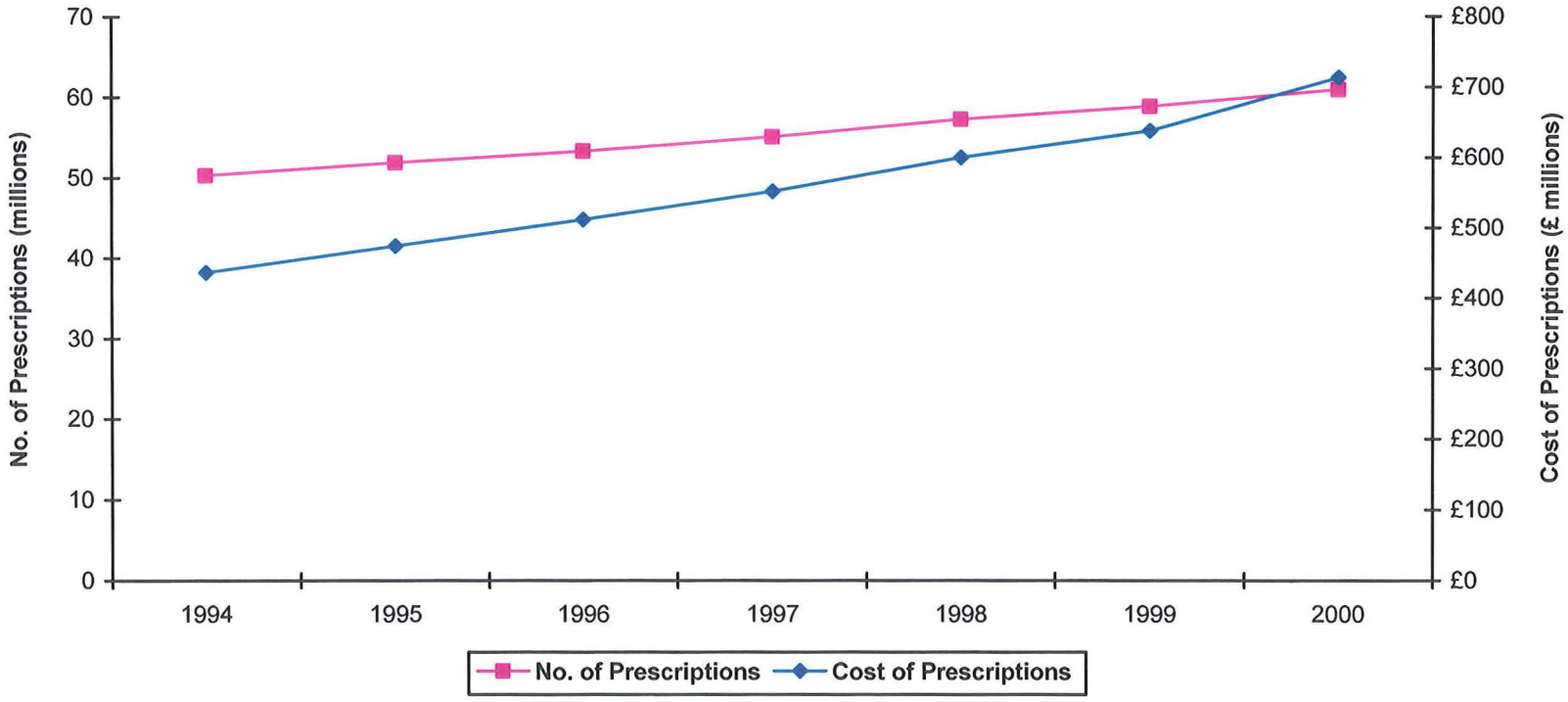
FIGURES

Figure 1 The annual percentage increase in expenditure for NHS as a whole and community prescribing, compared with hospital and community health services pay and price inflation



Data on NHS expenditure and community prescribing were obtained from Information Statistics Division for Scotland. Inflation data were obtained from the Scottish Executive through personal communications.

Figure 2 The increase of prescribing volume and cost over time (1994 to 2000)



Data were obtained from the Information Statistics Division for Scotland

Figure 3 Study population from the Medicines Monitoring Unit (MEMO) database

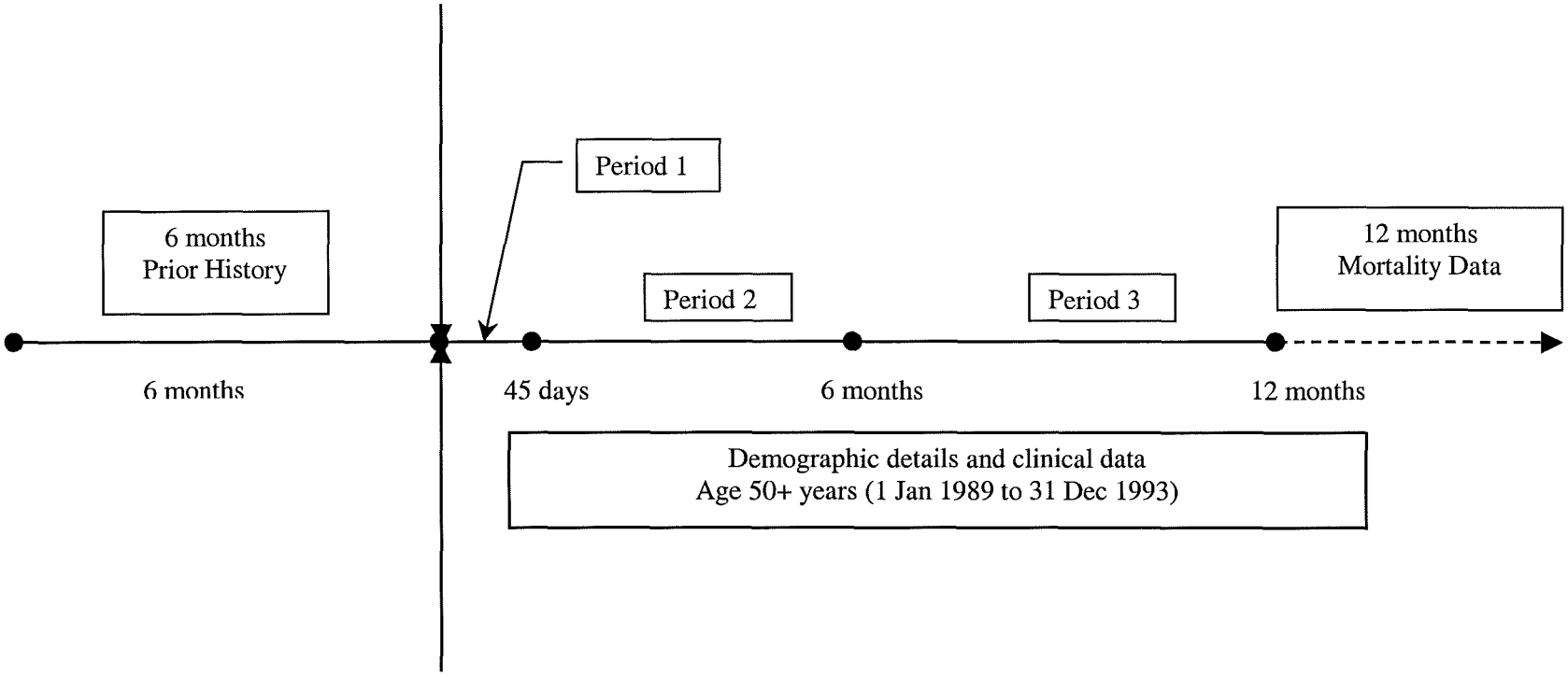
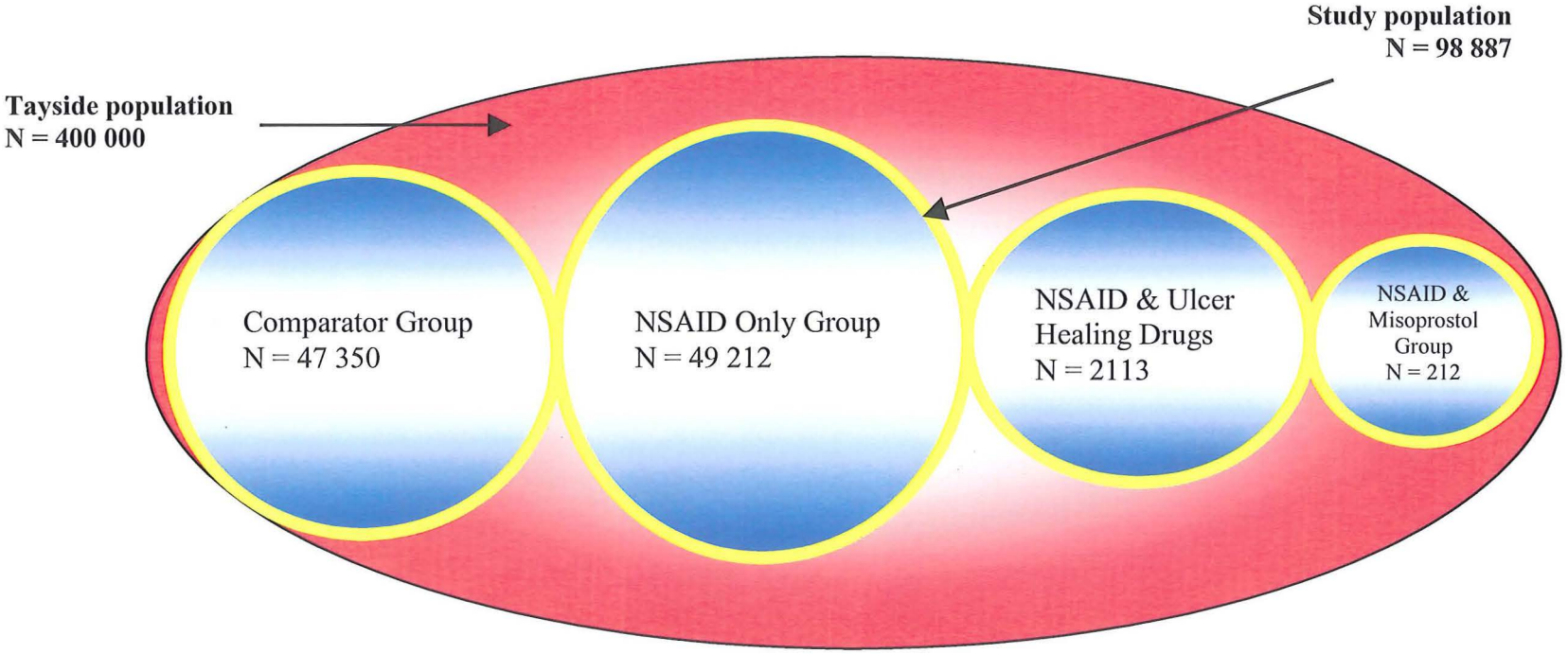


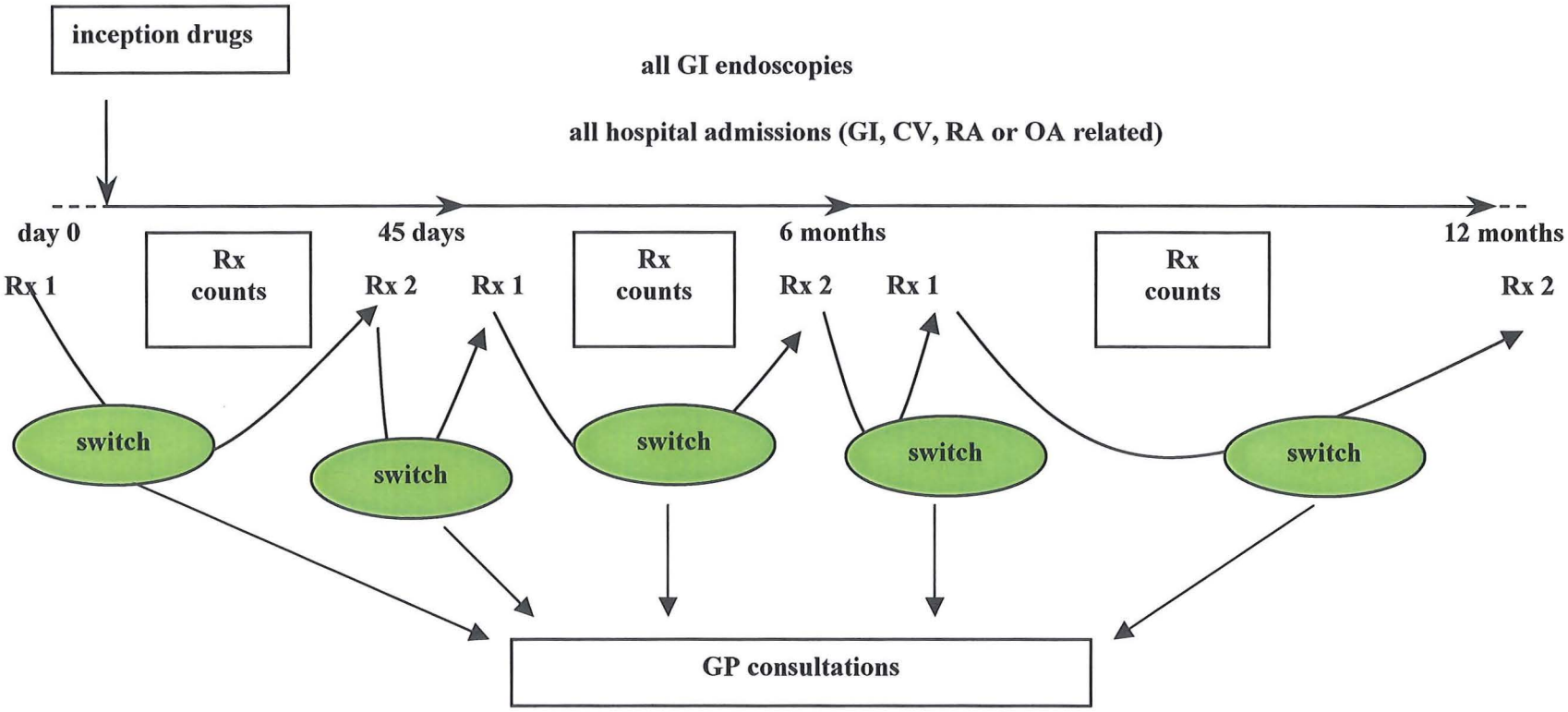
Figure drawn to scale

Figure 4 The population study – study cohort *(not drawn to scale)*



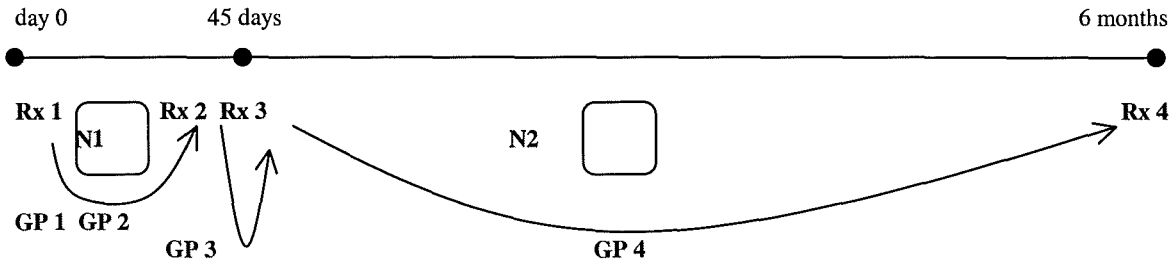
- **All living individuals residing in the Tayside health board area during the period: 1 January 89 to 31 December 93.**
- **Registered with a GP.**
- **Individuals less than 50 years old on 1 Jan 89 were excluded.**

Figure 5 Cost composition of the population study



Rx 1 = first prescription *Rx 2 = last prescription*
Rx counts = total number of additional prescriptions recorded
switch represents a change in prescriptions

Figure 6a The contribution of drug prescriptions and GP consultation costs (example for 45 days and for six months)



Rx 1 = First prescription recorded at inception
Rx 2 = Last prescription recorded during the 45-day period
Rx 3 = First prescription recorded at the onset of the 45 days to 6 months period
Rx 4 = Last prescription recorded at the 45 days to 6 months period

N1 = number of additional prescriptions recorded from 0 to 45 days
N2 = number of additional prescriptions recorded from 45 days to 6 months

GP 1-4 = visits to GPs (for change in prescriptions)

COSTS OF DRUG PRESCRIPTIONS

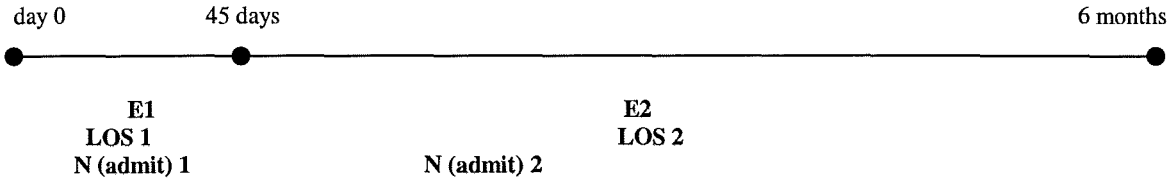
Cost of all prescriptions at 45 days:
Rx 1 + Rx 2 + 1/2(Rx 1 + Rx 2) x N1
Cost of all prescriptions at 6 months:
Rx 1 + Rx 2 + 1/2(Rx 1 + Rx 2) x N1 + Rx 3 + Rx 4 + 1/2(Rx 3 + Rx 4) x N2

COSTS OF GP CONSULTATIONS

Based on the assumption that prescription switches have taken place:
At 45 days, total cost of GP consultations = £7.56 x 2
At 6 months, total cost of GP consultations = £7.56 x 4

Figure drawn to scale

Figure 6b The contribution of endoscopy and hospital admission costs and costs to total cost (example for 45 days and for six months)



E1 = number of endoscopies recorded at 45 days
E2 = number of endoscopies recorded at 45 days to six months

LOS 1 = length of stay of the longest admission at 45 days
LOS 2 = length of stay of the longest admission from 45 days to six months

N (admit) 1 = number of other admissions at 45 days
N (admit) 2 = number of other admissions from 45 days to six months

COSTS OF GASTROINTESTINAL ENDOSCOPIES

Cost of all endoscopies at 45 days: £208.33 x E1
Cost of all endoscopies at six months: £208.33 x (E1 + E2)

COSTS OF HOSPITAL ADMISSIONS

Cost of hospital admissions at 45 days:
(LOS 1 x specialty cost + 2 x GP visits + 1 x outpatient visit) + [Σ length of stay of additional admissions x specialty cost + 2 x N (admit) 1 x GP visits + N (admit) 1 x outpatient visits]
Cost of hospital admissions at six months:
(LOS 1 x specialty cost + 2 x GP visits + 1 x outpatient visit) + [Σ length of stay of additional admissions x specialty cost + 2 x N (admit) 1 x GP visits + N (admit) 1 x outpatient visits]
+
(LOS 2 x specialty cost + 2 x GP visits + 1 x outpatient visit) + [Σ length of stay of additional admissions x specialty cost + 2 x N (admit) 2 x GP visits + N (admit) 2 x outpatient visits]

Figure drawn to scale

Figure 7 Trend of gastrointestinal endoscopies recorded by the three study periods

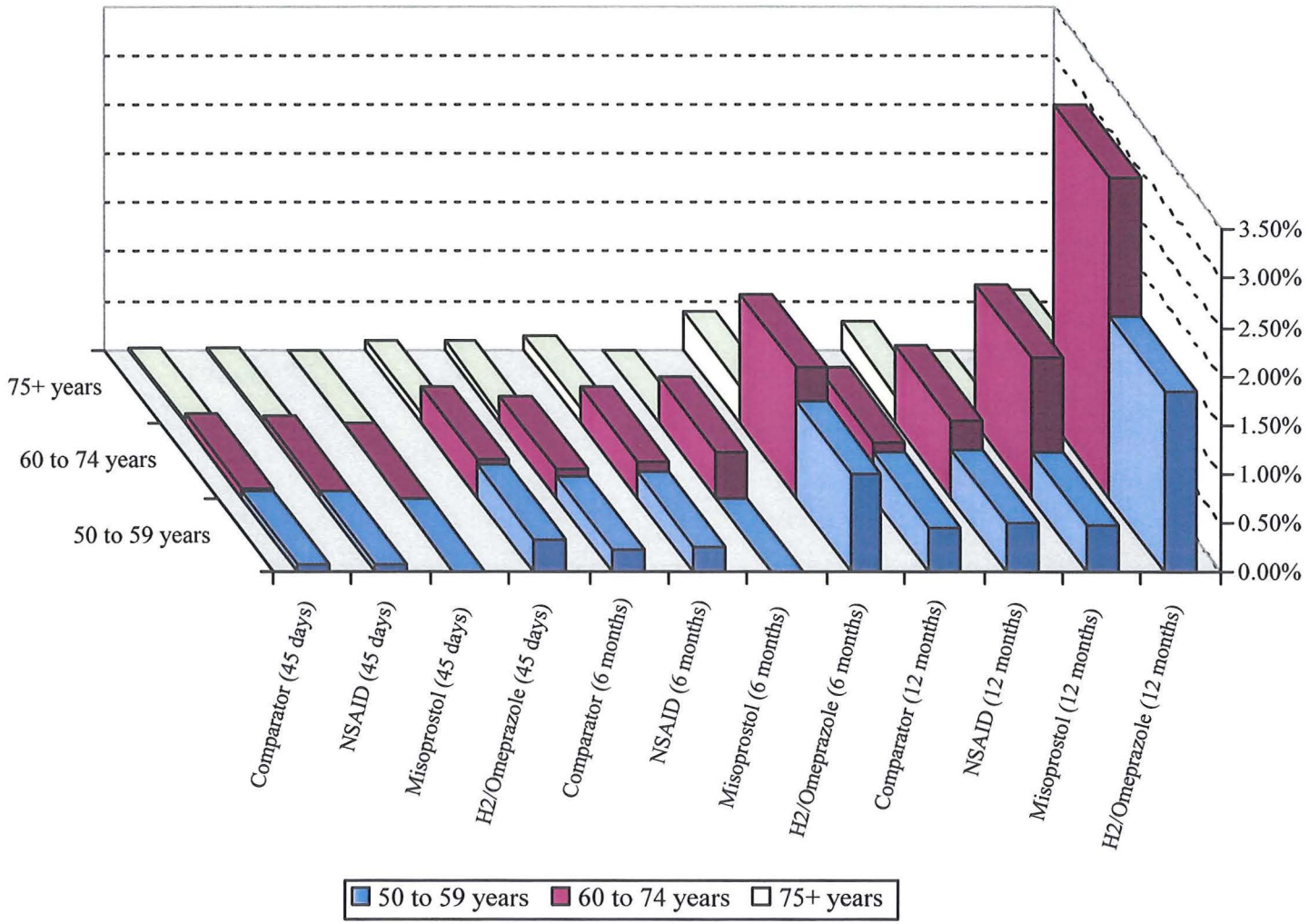


Figure 8 Composition of total costs for the 45-day follow-up period

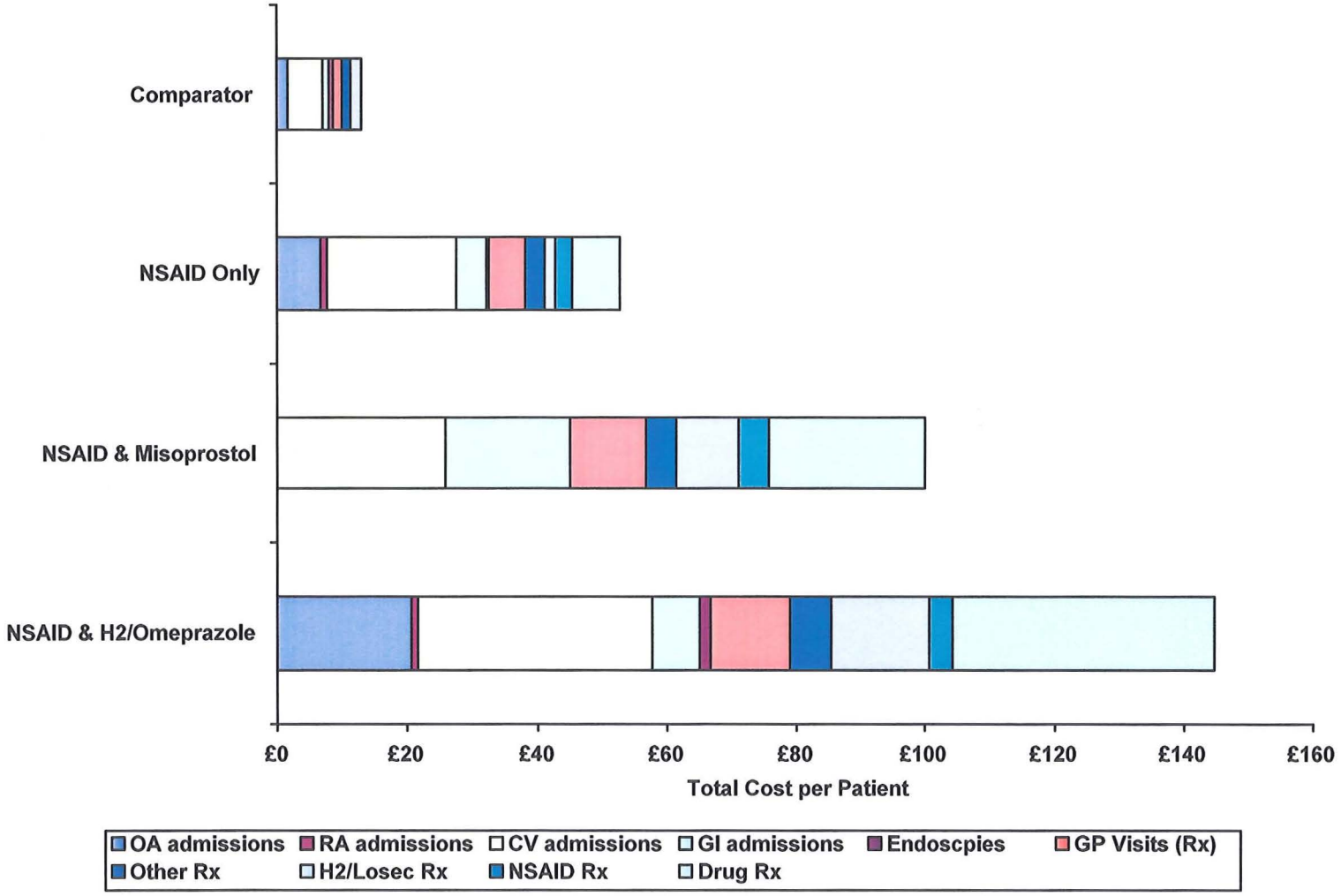


Figure 9 Composition of total costs for the six-month follow-up period

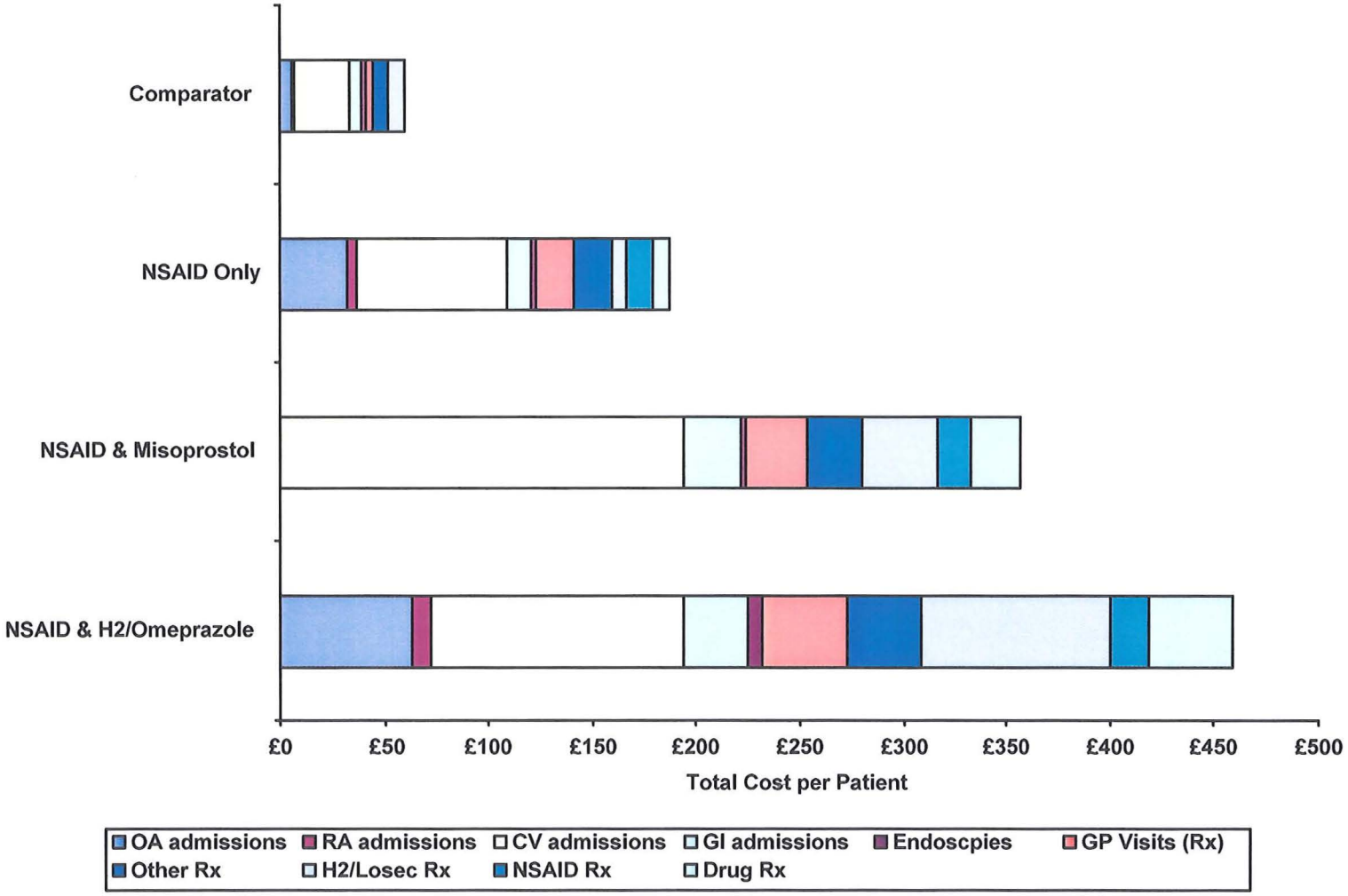


Figure 10 Composition of total costs for the 12-month follow-up period

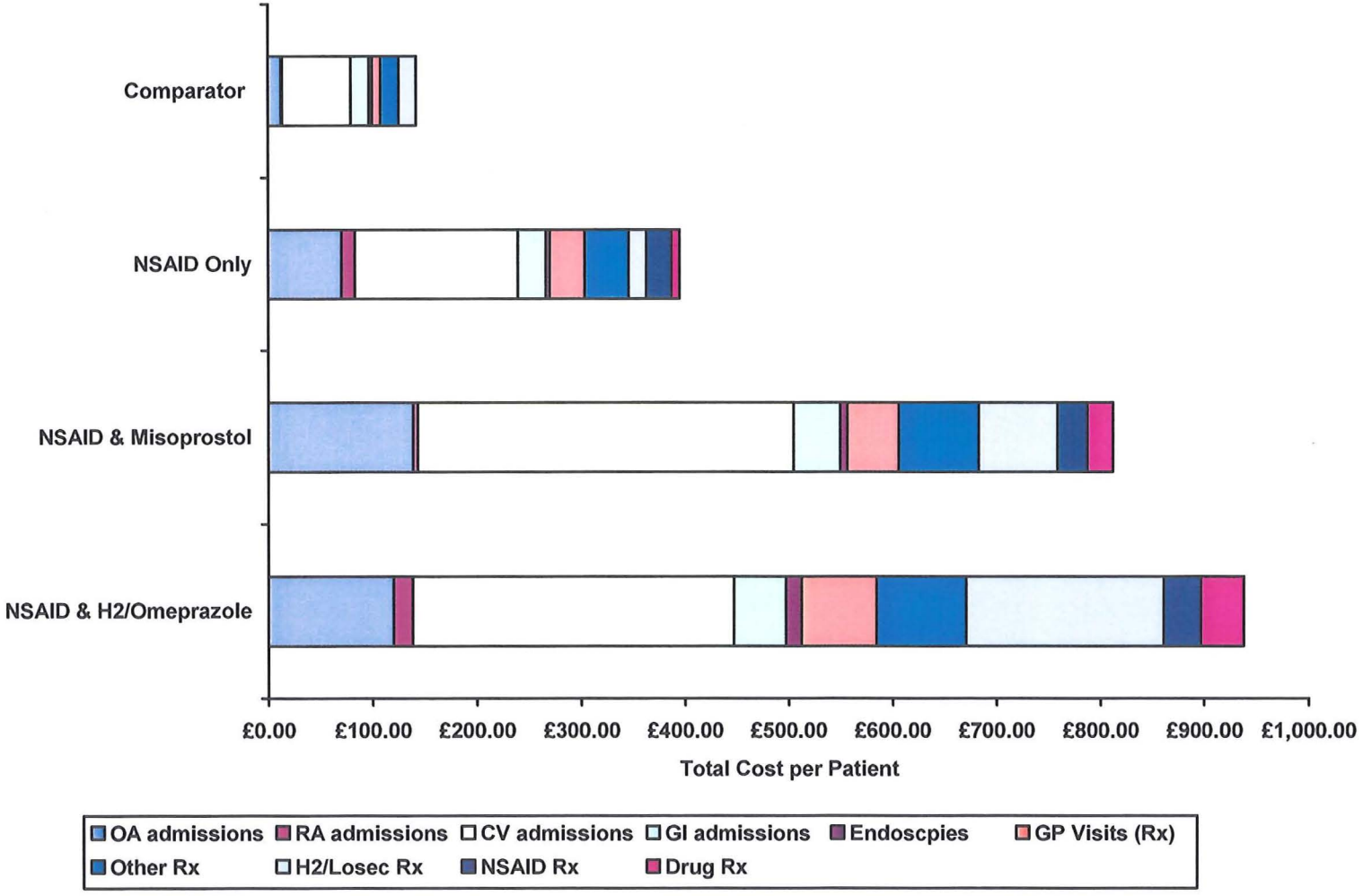


Figure 11 Total costs composition showing increase in total costs over all study periods

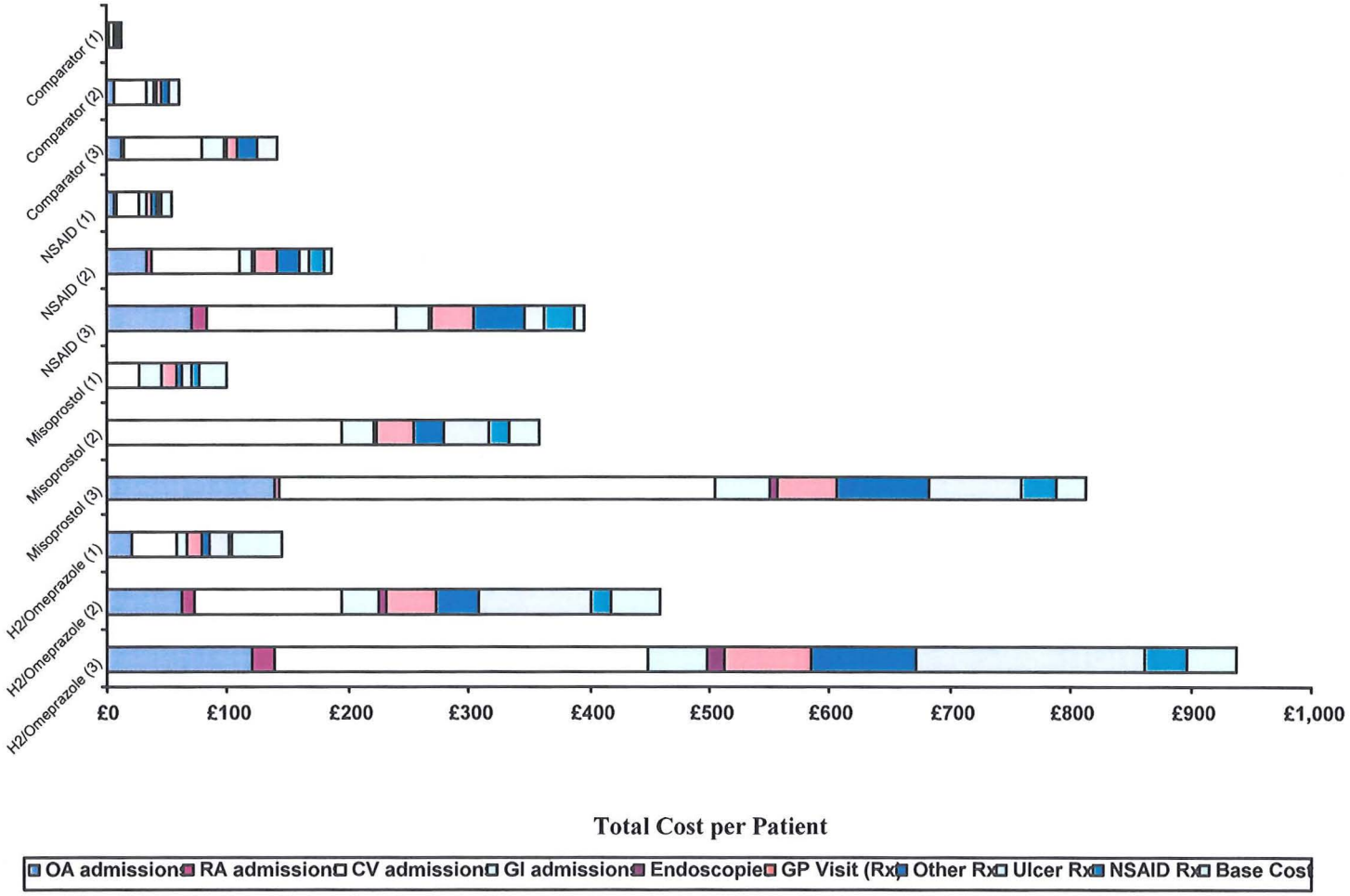


Figure 12 Sensitivity analysis on 45 days follow-up period

Figure 13 Sensitivity analysis on six months follow-up period

Figure 14 Sensitivity analysis on 12 months follow-up period

Figure 15 Studies selected for meta-analysis

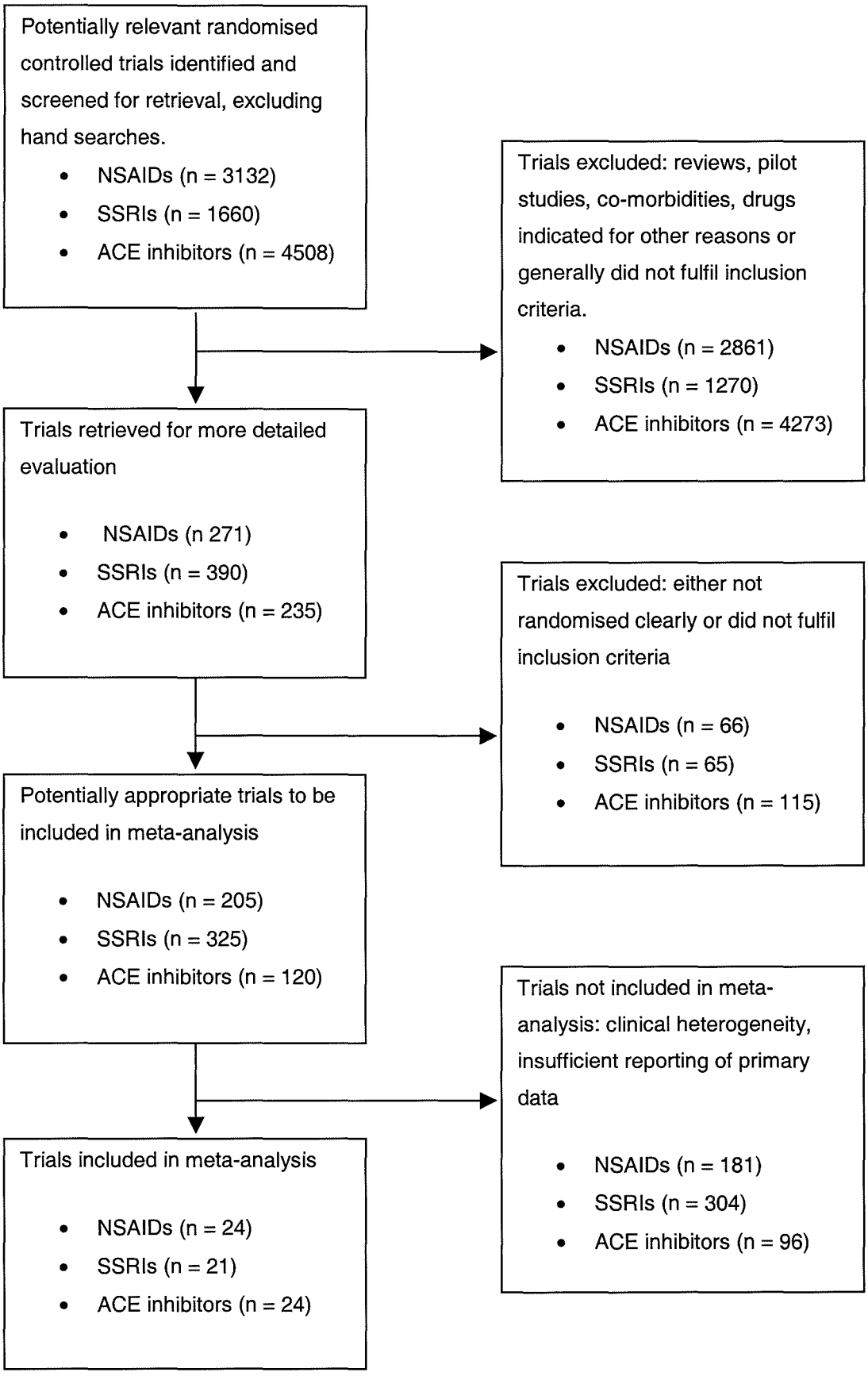
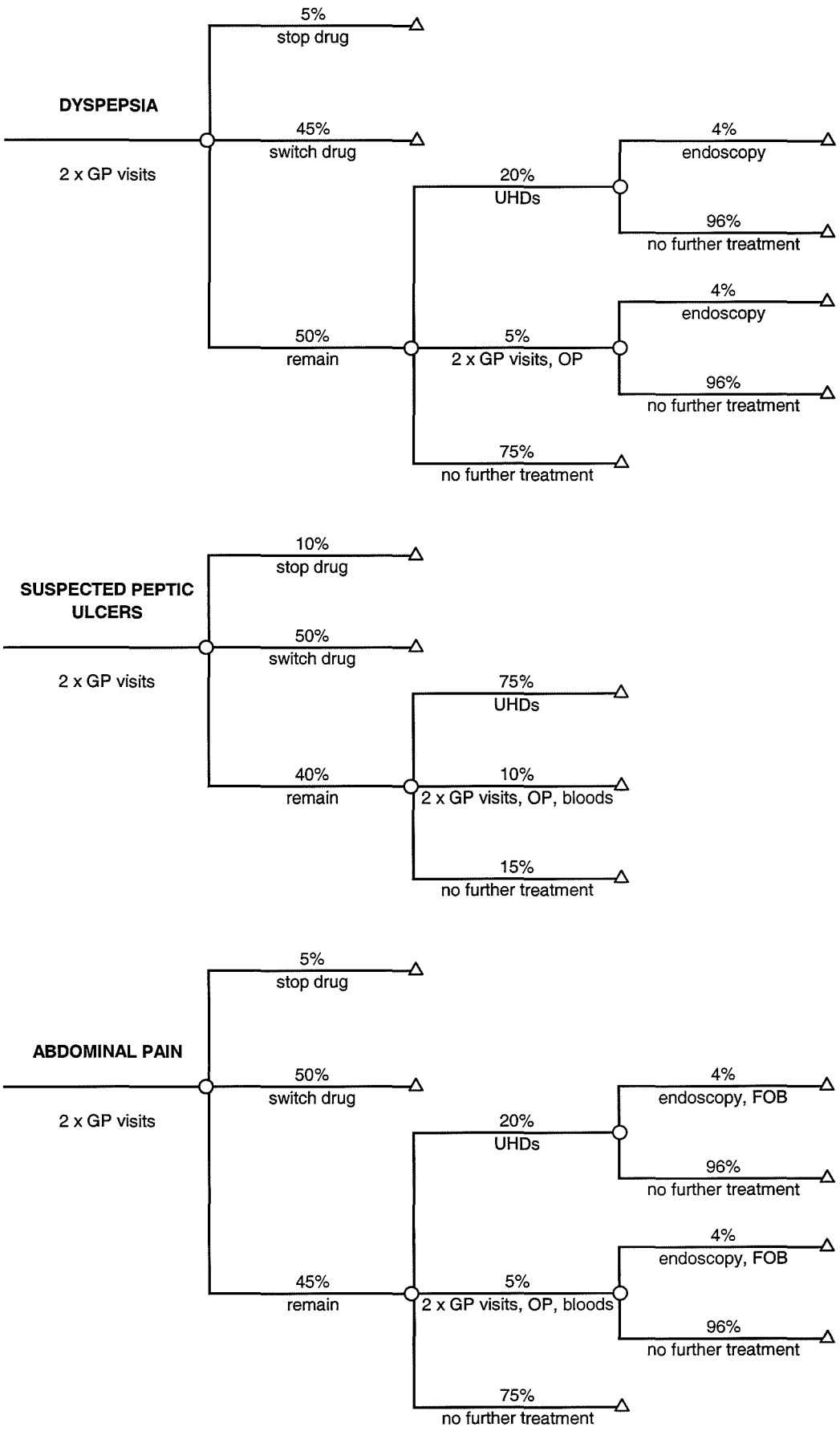
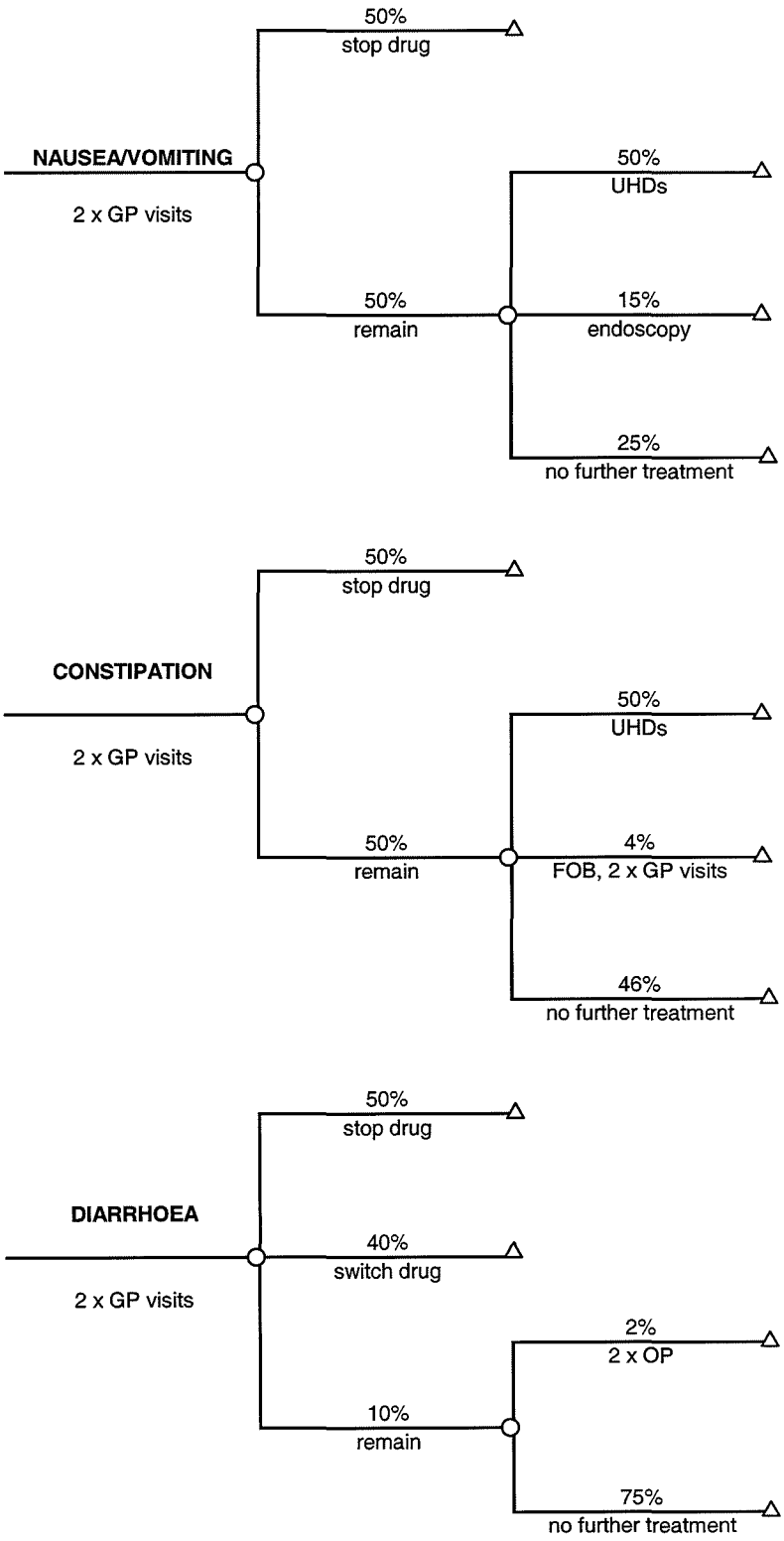


Figure 16a The Management of Adverse Events



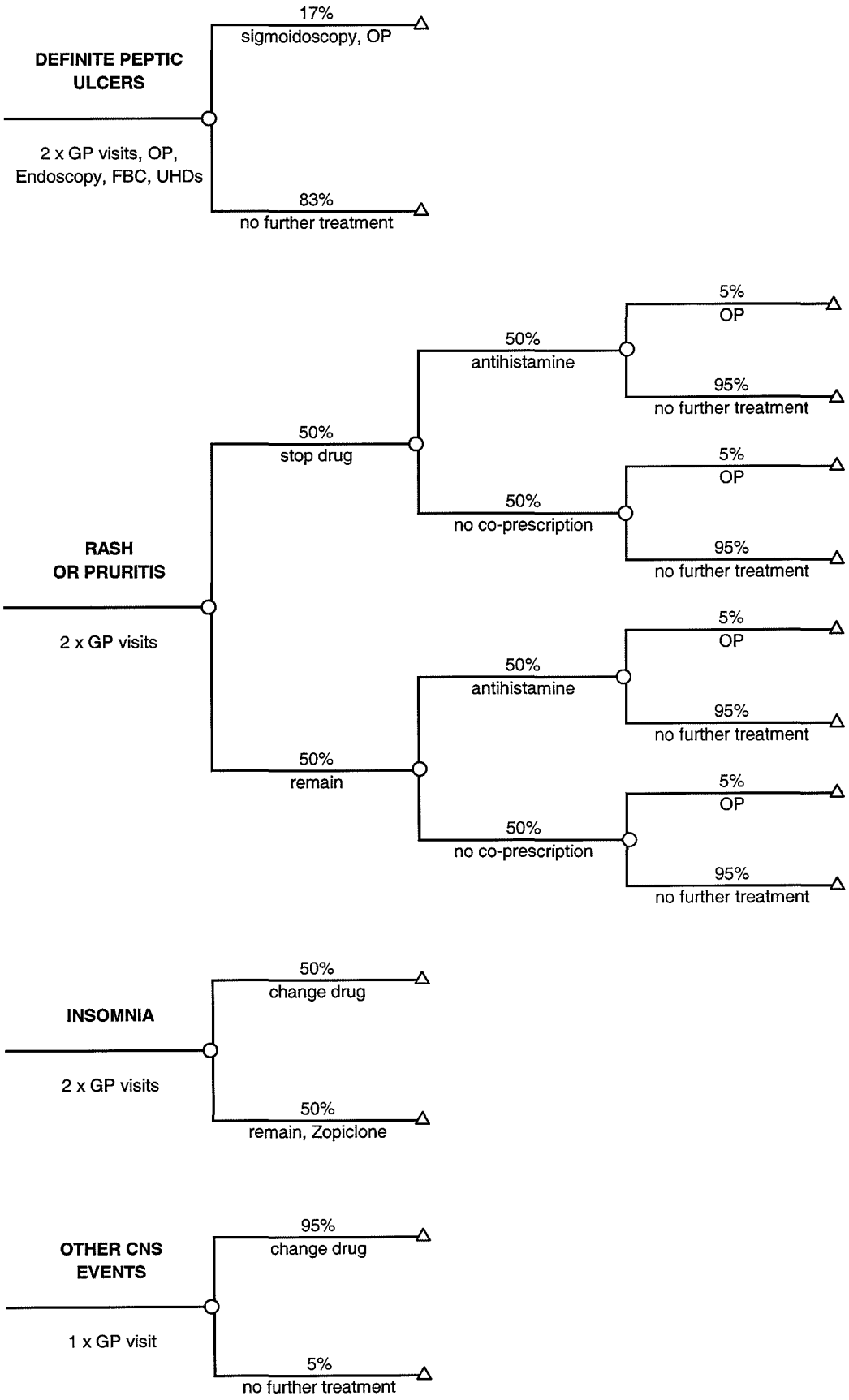
UHDs – ulcer healing drugs; OP – outpatient visits, FOB – fecal occult blood

Figure 16b The Management of Adverse Events



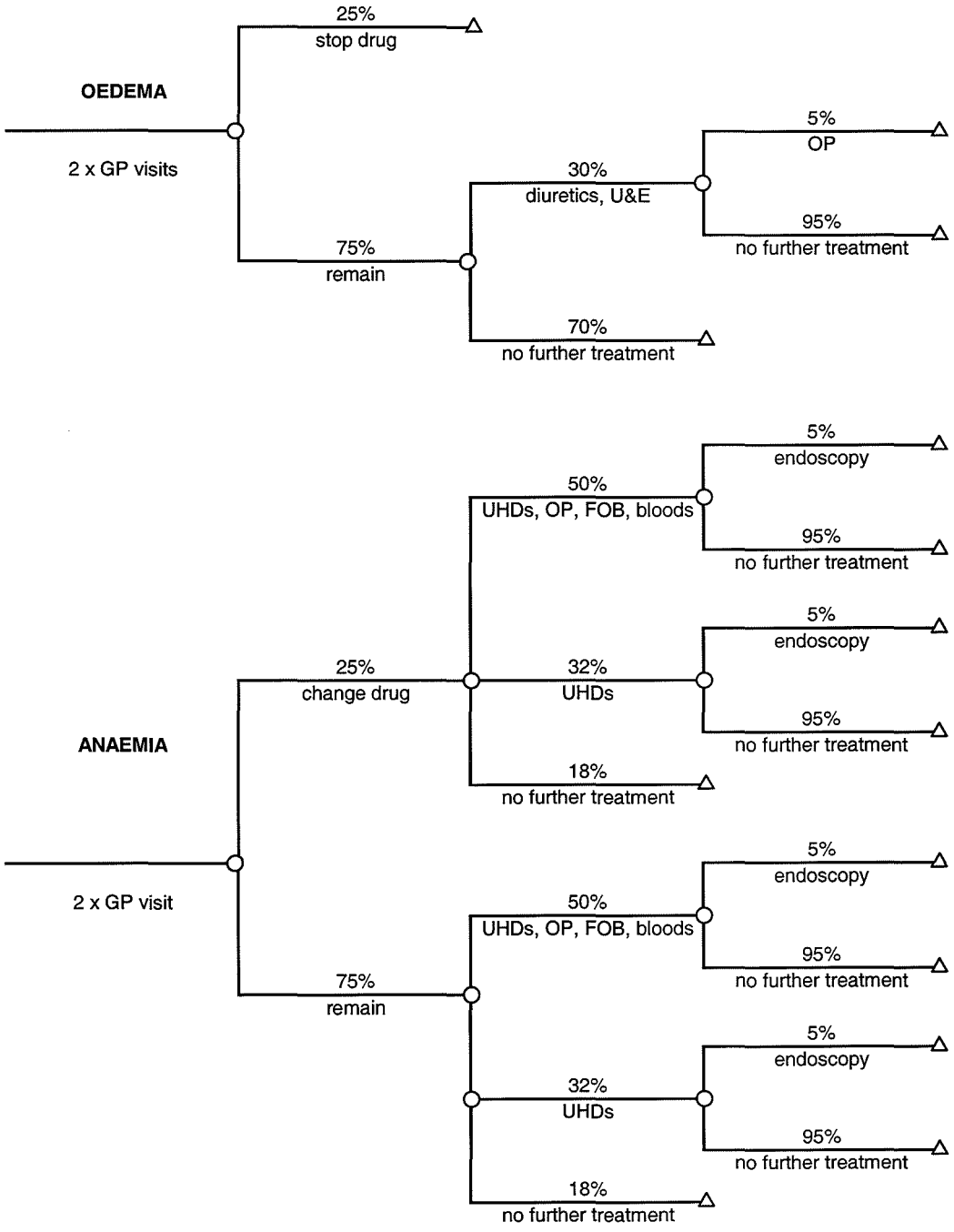
UHDs – ulcer healing drugs; OP – outpatient visits, FOB – fecal occult blood

Figure 16c The Management of Adverse Events



UHDs – ulcer healing drugs; OP – outpatient visits, FOB – fecal occult blood

Figure 16d The Management of Adverse Events



UHDs – ulcer healing drugs; OP – outpatient visits, FOB – fecal occult blood

Figure 17 **Sensitivity Analysis – NSAID Study**

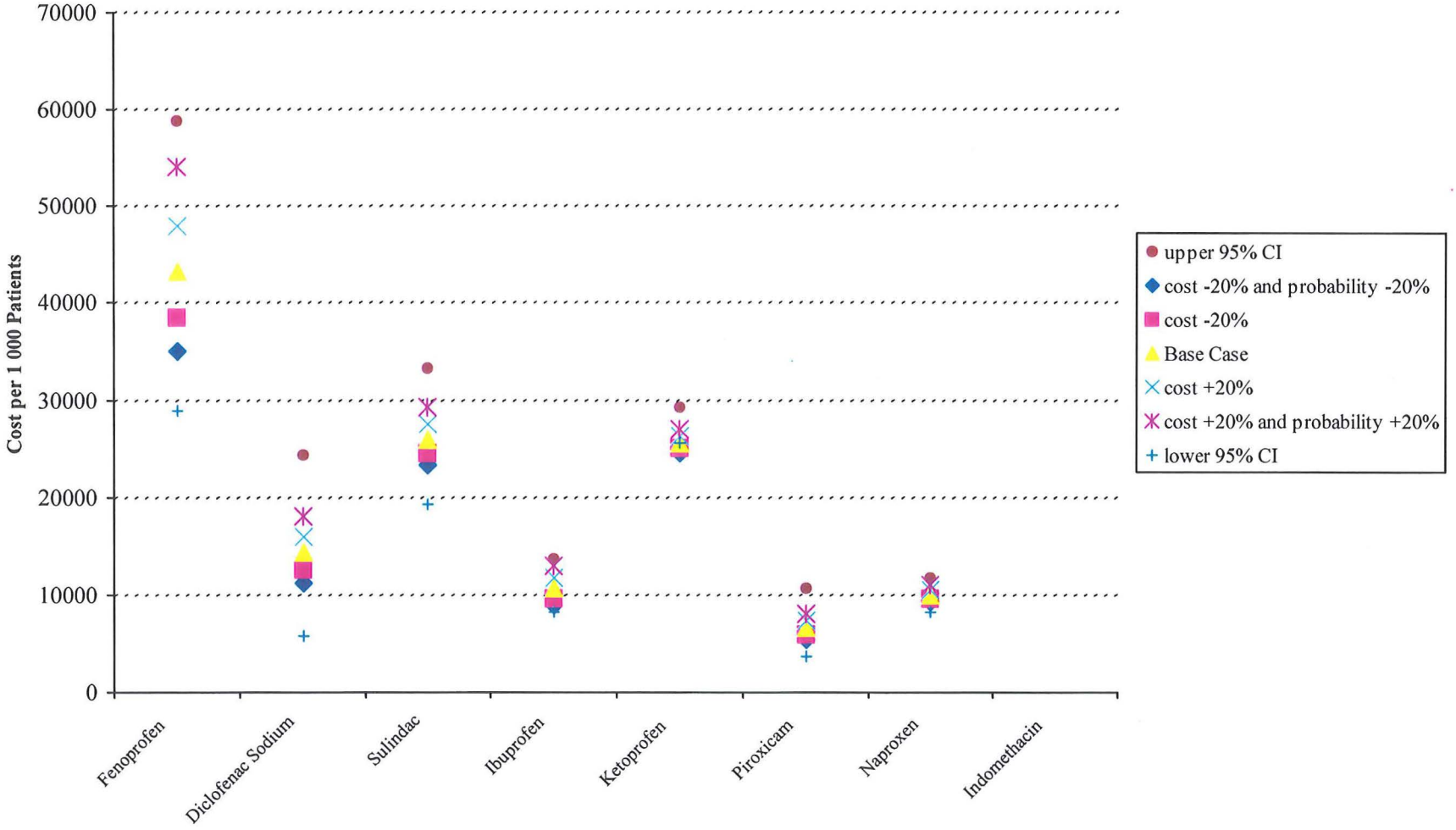


Figure 18 **Sensitivity Analysis – SSRI Study**

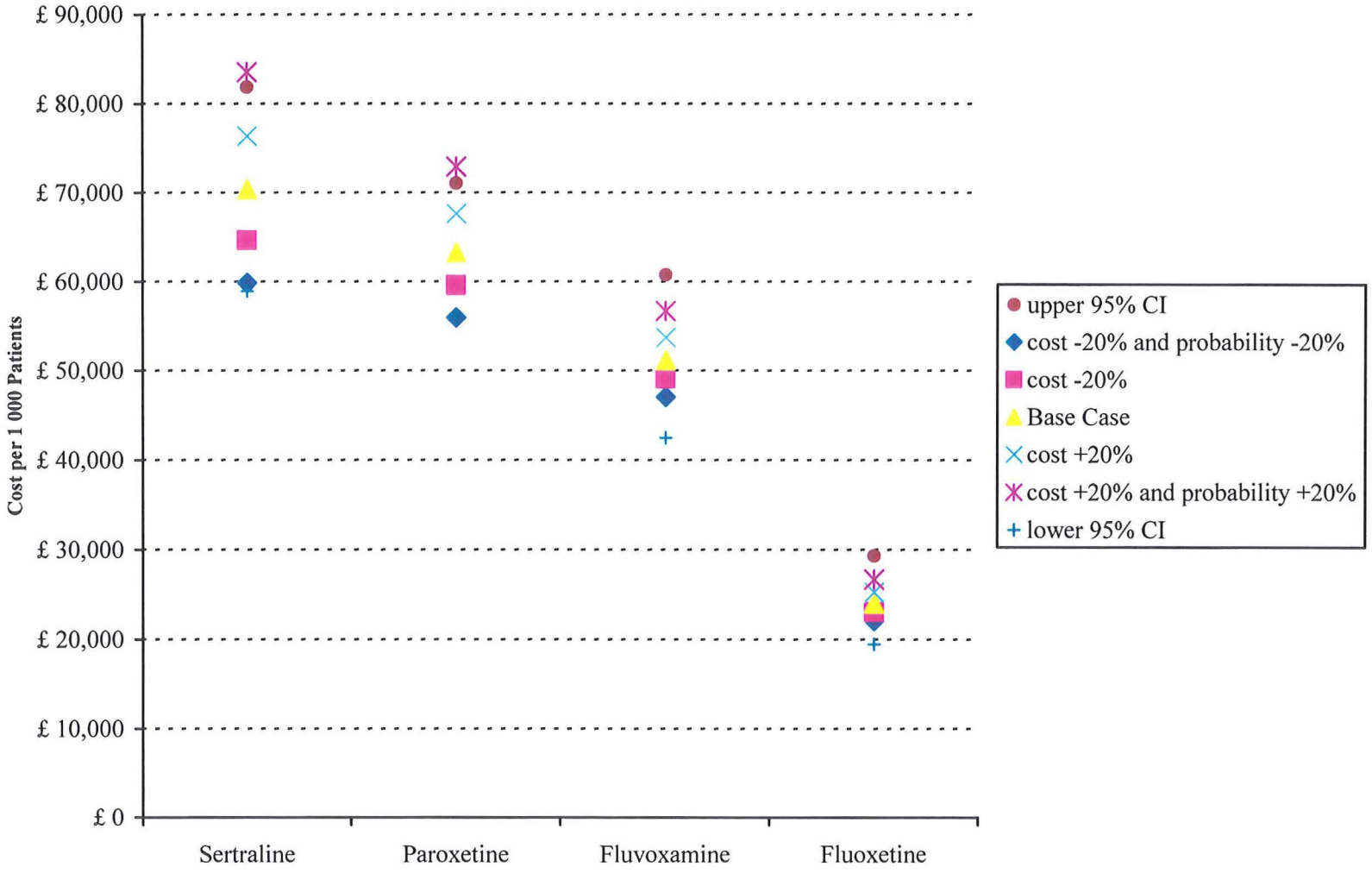
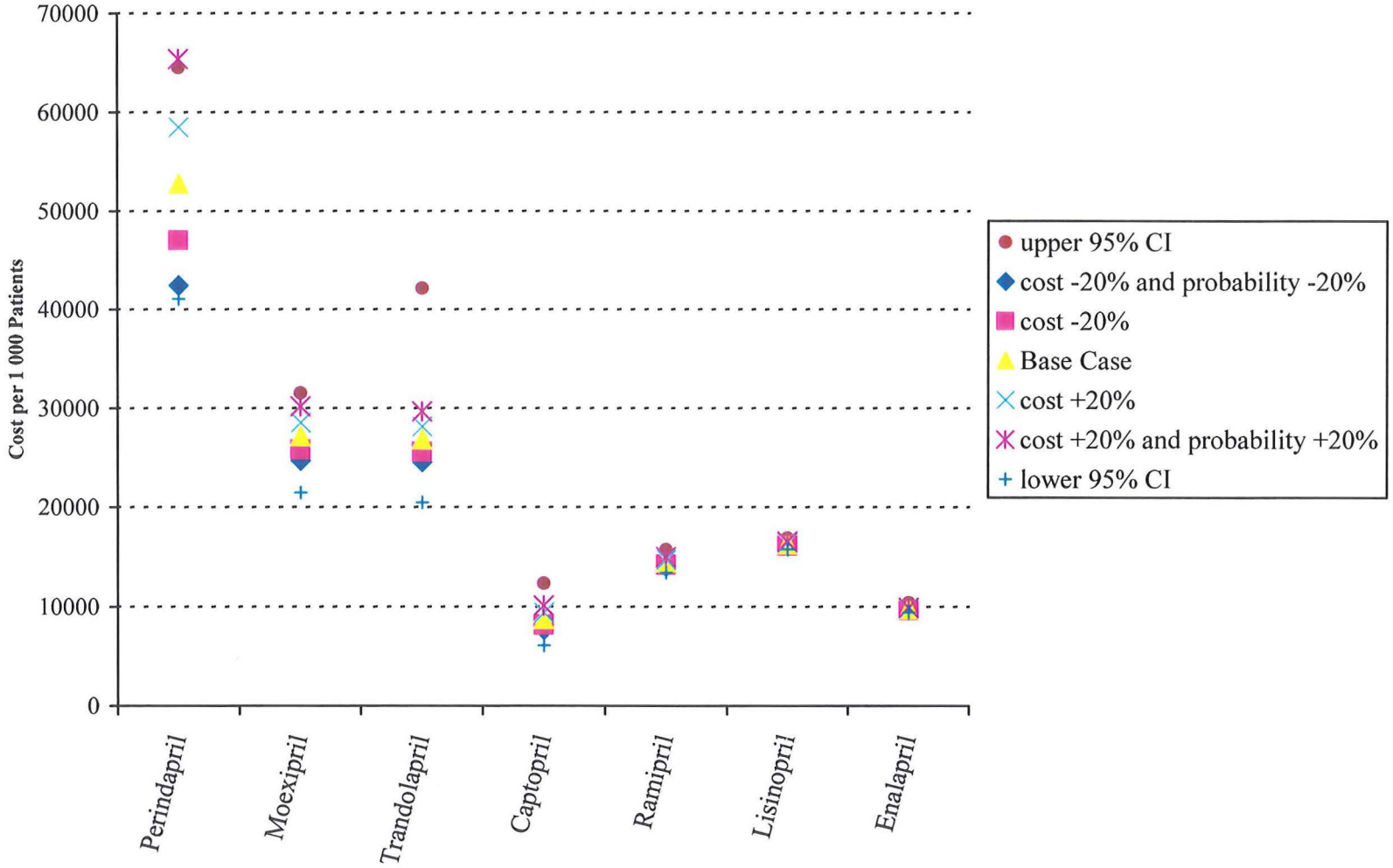


Figure 19 **Sensitivity Analysis – ACE Inhibitor Study**



APPENDICES

APPENDIX I

COST CONTAINMENT STRATEGIES

Cost Containment Strategies

The need to control escalating NHS prescribing expenditure has long been recognised (Figure 20). Early evidence dated back to 1911, when prescribing policies included a national formulary, a list of prescribable products, the use of regional medical officers to visit high cost prescribers, and an incentive scheme designed to encourage GPs to control their prescribing costs. The latter scheme was called the "floating sixpence" which offered a financial reward to GPs who spent less than the allocated budget per patient. This scheme was abolished in 1920 because it was felt that patients were not getting the drugs they needed [222].

Prescription charges were first imposed by the government in 1951 when they used the legislation to bring in a one-shilling (five pence) charge per prescription. The charges have remained (except between 1965 and 1968) and risen progressively since 1979, from £0.45 to the present value of £6.20 per item. However, approximately five out of six prescriptions are exempt from charges under the exemption scheme. Of all the items prescribed, almost half were issued to those over 60 years old (one of the categories eligible for exemption). Between the years 1969 and 1992, there was a 3.2% fall in paid-for prescriptions following a 10% increase in the charge. The 1992 increase in the charge from £3.75 to £4.25 brought in £17.3 million of extra revenue and cut the 55 million prescriptions not exempt from charge by 2.3 million. Although, the increases in prescription charge seemed to have an impact on the consumption of prescribed drugs, there is concern about the adverse effect on compliance for some patients requiring chronic treatment. If those deterred from using prescription drugs ended up being treated for more serious conditions, the cost of that treatment could erode the savings [223]. Other strategies on unit cost reduction such as retail networks and manufacturer contracting were introduced in the 1970s. However, these schemes were designed solely to reduce drug acquisition costs.

Over the years the government introduced several initiatives to improve prescribing. At a national level, strategies included educational publications, improving prescribing data and prescribing advice to GPs. Locally, Health Boards began to introduce measures to control the growth of local drug costs, in an attempt to promote rational prescribing. Prescribing advisers were employed to do this, this is discussed later.

Drug Formularies

Drug formularies introduced in the 1980s formed the cornerstone of strategies aimed at influencing the range of pharmaceutical preparations available for prescription. They were originally designed to control the introduction of new therapies in hospitals. Subsequently, this concept has been developed in primary care by using practice-based formularies to promote rational and quality prescribing, and to limit costs. These vary from a simple list of pharmaceuticals with no prescribing information to a comprehensive prescribing guide which is usually agreed through the local Drugs and Therapeutics Committees. In 1985, the government introduced the 'selected list', which barred GPs from prescribing certain drugs in their proprietary state. However, this measure has had little impact on cost and, in some instances was counter-productive as relatively cheap proprietary products were replaced with more expensive alternatives [5]. However, a recent review [224] concluded that acquisition cost was the prime influencer of formulary decisions, rather than overall benefits and costs in healthcare. By 1990 the Department of Health recommended development and ownership, and voluntary implementation of local practice formularies.

Although it has been possible to demonstrate that formularies have an impact on prescribing habits, it is very difficult to extrapolate this into real savings because of the number of influencing variables, particularly the increase in numbers of patients treated. There is little evidence to show whether formularies reduced cost, improved care or both. A recent search to locate systematic reviews, reviews, or randomised trials looking at the effect of formulary restriction on benefits and costs, was rather fruitless [225]. One open-label, randomised trial of two formulary systems was found [226]. Prescribers were randomised into either a restricted thyroxine dose (five doses) formulary or an unrestricted one where more dose strengths (ten doses) were available. Treatment efficacy was assessed by thyroid function tests, prescriptions were analysed and their cost calculated. The study concluded that simplifying the doses of thyroxine available to prescribers did not adversely affect patients or increase costs. In another study, Avery AJ et al demonstrated the effect of a formulary to produce positive changes in prescribing towards greater compliance over time [227]. Ten practices in Lincolnshire developed a formulary for NSAIDs, to help GPs to prescribe from a narrower range of drugs. Prescribing analyses and cost (PACT) data from intervention practices and matched controls were analysed to determine whether changes had occurred.

The results showed significant differences in the reduction of mean number of different drugs used (focused on three main NSAIDs) and an increase in prescribing NSAIDs in their defined daily doses.

In 1996, Hill-Smith conducted a controlled trial comparing prescribing by 50 GPs (from 11 practices) who participated in creating a district drug formulary, with other GPs in south Bedfordshire [228]. The proportion of prescription items listed in the formulary rose significantly in three therapeutic groups: cardiovascular (by 7-12% above control), musculoskeletal (by 1-11%) and obstetrics and gynaecology (by 6-9%). The number of items prescribed per prescribing unit fell significantly in three therapeutic groups: musculoskeletal (by 1-7% below control), nervous (by 7-12%) and nutrition and blood (by 15-21%). It was suggested that estimated savings of up to £150 000 (£3 000 per doctor per year) were achieved, but this was not based on any formal calculations or economic analysis. One American study did provide empirical evidence about the influence of hospital formulary restrictions [229]. They found that across-the-board restrictions did not result in cost savings, although savings may be realised for particular drug categories. The observations from these studies could neither prove nor disprove the effect of formularies on overall benefit and cost savings to the NHS.

The concept of outcomes or disease management, which originated in North America in the late 1990s, brought in the introduction of disease management guidelines and shared protocols between primary and secondary healthcare sectors. Unlike formularies, clinical guidelines contain guidance on how drugs should be used. Prescribers were given clinical scenarios and then taken through the treatment of the clinical situation step by step – diagnosis, treatment, monitoring and discharge policy. The focus is the disease and its optimum cost effective management, rather than on the drug acquisition costs alone. It was believed that such programs would ensure higher and more consistent standards of care, and that treatment and support were received in the most appropriate setting.

In Scotland, the Scottish Intercollegiate Guidelines Network (SIGN) was formed in 1993, to improve the quality of healthcare by reducing variation in practice and outcome by developing and disseminating national clinical guidelines based on current evidence. Improvements in the quality of care resulted by complying to SIGN guidelines have been

apparent [230], but there is still no evidence, to date, about their impact on costs. In recent years, guidelines produced by SIGN are beginning to introduce evidence on resource utilisation and cost effectiveness.

Deregulation of Pharmaceuticals

In the early 1980s, deregulation of pharmaceuticals was introduced in the hope of helping to strengthen the role of community pharmacists and to create savings in the NHS prescribing budget. The first radical deregulation occurred in 1983, when the legal classification of loperamide was changed from prescriptions-only-medicine (POM) to pharmacy medicine (P). This was followed by a wide range of drugs that were previously POMs, subsequently deregulated to be available for sale from community pharmacists. In 1994, cimetidine became the first H_2 blocker to become available over-the-counter (OTC). By the beginning of 1997, the UK and Germany each had 67 switched products, which was the highest in Europe. This number continued to increase over the following years.

Newly deregulated pharmaceuticals are widely purchased. However, it is unclear whether this increase in commercial sales translates into NHS savings. A clear reduction in prescriptions for aciclovir was observed since its deregulation. In addition, early economic analyses were able to demonstrate significant savings to the NHS through the deregulation of loperamide and hydrocortisone [231]. These reductions in prescriptions and costs were not apparent in all deregulated drugs, as demonstrated by the case with H_2 blockers. Since deregulation, the number of prescriptions for H_2 blockers and proton pump inhibitors continued to rise. This may be in part due to patients who previously self-medicated themselves for chronic dyspepsia with antacids, found H_2 blockers to be effective but expensive, and subsequently seeking long-term supply through prescriptions.

Prescribing Advisers

In addition to organisational reforms, it was apparent that prescribing support at a local level is extremely important. At a local level, Health Boards were becoming increasingly

active in providing prescribing support, promoting high quality and cost-effective drug use, and in improving pharmaceutical care of patients. Practices, especially fundholders, have sought extra prescribing advice or pharmaceutical expertise and have employed staff from a variety of pharmaceutical backgrounds to assist. Initially Medical Prescribing Advisers (MPAs) were introduced, and later Pharmaceutical Prescribing Advisers (PPAs) were created to supplement the role of MPAs.

Subsequent to the 1990 White Paper 'Improving Prescribing', Prescribing Advisers were employed by local Health Boards in attempt to control prescribing costs in primary care. Their role included provision and interpretation of information on prescribing matters mainly to GPs, Health Boards, regional office and secondary care. Their methods of managing GP prescribing involved working with hospitals to ensure appropriate shared care and provide primary care oriented input into local Drugs and Therapeutics committees. They also introduced programmes to reduce patients' demand for prescriptions, and promoted cost-effective prescribing among GPs via education, feedback and possible manipulation of financial incentives. In addition, the Scottish Association of Medical Prescribing Advisers (SAMPA) – their professional group, met regularly to share ideas and offer mutual support and training. The group also meets Scottish Office personnel two to three times a year to discuss national prescribing issues.

Prescribing advisers have been visiting GPs to offer prescribing support since the early 1990s. During their visits, they presented GPs with prescribing data including feedback on practices' prescribing and making comparisons with their peers, offering suggestions for rationalisation. Prescribing Bulletins, containing therapeutic articles written from a local perspective, were disseminated on a regular basis. Later, they became increasingly involved in production and implementation of formularies and guidelines. Prescribing advisers have been successful in promoting good quality evidence based, cost-effective prescribing, while reducing the expenditure on drugs in general practice without depriving patients of essential medications. In Glasgow alone, the result was the transformation of a budget £3.4m overspend in 1992 to £1.3m below budget in 1998. GPs also recognise them as a useful source of independent information and advice about prescribing matters [232].

Many factors hampered prescribing advisers in their attempts to alter local prescribing patterns and behaviour. For instance, prescribing advisers work to counter generously financed and well organised marketing from pharmaceutical industry. However, the number of pharmaceutical company representatives still outnumber prescribing advisers (8000 vs. 200 in 1997), with a promotional expenditure of £250 million a year, while the Department of Health now spent £4 million a year on advising GPs on prescribing [233]. Industry representatives are extremely well trained in communication and presentation skills, but lack credibility among GPs. Although prescribing advisers have high credibility with GPs, they do not have the benefit of the extensive training in interviewing, influencing, and the persuasion skills that industry representatives receive. While fulfilling their other duties, the lack of time to make repeat visits to the same practice regularly reduces their effectiveness. Other factors include local hospitals' prescribing policies and patient demands, which significantly affect attempts made by advisers to change local prescribing behaviour.

The majority of prescribing advisers now sit within Public Health Directorates and the remainder within Primary Care Directorates. Recent reforms in primary care, the introduction of PCTs, together with central and local policy directives (such as National Service Frameworks and Clinical Governance) have provided prescribing advisers with the opportunity to grow their activities beyond their more traditional boundaries. The focus of the work of prescribing advisers is changing. They are likely to become more involved in providing strategic direction, devising local policies and acting as PCT prescribing co-ordinators.

Until recently, medical and pharmaceutical advisers provided the mainstay of formal prescribing advice and support to GPs at a local level. However, there is still a need for greater local support of the prescribing process beyond that able to be provided by Health Boards. Therefore, many locally led initiatives have begun to look at additional models of providing prescribing support. These initiatives have considered the role of various healthcare professionals in the prescribing process.

Drugs and Therapeutics Committees (DTCs)

In 1994, all Health Boards were instructed to establish joint prescribing committees – Area Drugs and Therapeutics Committees, Purchasing Prescribing Committees or Therapeutics Committees – for the development of local prescribing strategies. Prescribing advisers and other healthcare professionals worked together in attempts to resolve issues surrounding the responsibilities for prescribing high cost therapies and the need to plan for therapeutic development. They work closely with local Drugs and Therapeutics Committees, especially in the management of entry of new drugs, and to improve prescribing across the primary-secondary care interface.

Local Research Ethics Committees were instructed to standardise procedures used to review research applications, including local evaluations of new pharmaceutical products. At the Health Board level, introduction of new interventions would require review by Drugs and Therapeutics Committees. Evidence for efficacy and safety would be reviewed, often without taking into account cost effectiveness and the financial implications of the decision for the trust or the Health Board as a whole. However, even if a request was refused, consultants may ask GPs to prescribe the therapy, thereby circumventing the Drugs and Therapeutics Committees and shifting the cost to primary care.

Indicative Prescribing Scheme (IPS) and GP Fundholding

Prescribing in primary care had been viewed as too unpredictable to impose a cash limit system, and until the NHS reforms in 1991 no attempt had been made to impose a ceiling on the total primary care drugs bill. A range of measures has been adopted to encourage prescribers to take costs as well as effectiveness of drugs into account. These have ranged from exhortation of GPs not to waste resources, through provision of prescribing information (the PACT scheme) and the setting of indicative prescribing targets, to provision of financial incentives to achieve savings within GP fundholding.

Indicative Prescribing Scheme (IPS) and GP fundholding made more subtle alterations to prescribing habits. The emphasis of IPS was on improving prescribing through enhanced

information, education and reasoned persuasion. General practitioners were given more discretion but a financial rigour, which was perceived to be absent previously. The scheme, in particular amongst fundholders, led to some cost containment of expenditure without any apparent disadvantage to patients. However, these effects seemed to be less for later waves and early gains made were not sustained over time.

The Fundholding Scheme stemmed from a blueprint for the 'internal market' drawn up by Alain Enthoven, a health management specialist at Stanford University. In theory, under this scheme, health authorities would be able to buy and sell services from each other and the private sector instead of providing the full range of services themselves. In 1984, as part of the government's review, two health economists – Alan Maynard and Nick Bosanquet – suggested that GPs should be given control of their own budgets to buy hospital services. They believed that this would help in directing funds towards hospitals and specialists who did most to meet patients' needs, as interpreted by their GPs. However, at the time, the idea was dismissed on the grounds that GPs lacked the skills to administer such budgets.

Following the publication of the White Paper "Working for Patients" in 1991, GP prescribing budgets were established as one of a number of measures to exert pressure on expenditure on drugs within the NHS – indicative prescribing or cash-limited budgets for fundholders. On 1 April 1991, as part of the NHS reform, GP fundholding was introduced.

Each year, the Treasury approves the cash resources for the primary care bill in Scotland based on the estimated expenditure submitted by the Scottish Office. The money was held centrally by the Management Executive and a notional sum – representing the expected cost of prescribed drugs and appliances – is allocated to each Health Board. In turn, this is divided amongst practices as Target Budgets (initially termed Indicative Prescribing Amounts) set by each Health Board's prescribing advisers. Larger practices could choose to have an overall practice budget with which to buy treatment for their patients - 'fundholding practices'. However, a GP could still overspend his target budget in order to prescribe necessary interventions.

The original Target Budgets were based on previous patterns of prescribing expenditure. However, as prescribing advisers became more familiar with their practices, weighted capitation – based on the age/sex profile of practice lists, morbidity in the locality, and the degree of socio-economic deprivation – was introduced to set budgets which closely reflected the predicted health needs of the patients. Similarly, the Management Executive introduced a simple needs based element into their prescribing budget setting methodology for Health Boards. A working group, the Prescribing Allocation Review Group, has been commissioned by the Scottish Office to examine the current pattern of prescribing costs at Health Board level with a view to recommending a budget setting methodology which would more closely reflect the varying needs of the population in different Health Board areas. These figures were intended as benchmarks. Practices and Health Boards were expected to contain prescribing costs within their allocated amounts unless they had to exceed their amount for justifiable clinical need. The prescribing budget became part of the allocated sum for fundholding and the fundholder was expected to live within the prescribing budget.

In addition, each GP and Health Board received a monthly budget schedule prepared by the Pharmacy Practice Division (PPD) to enable the performance against Target Budgets to be monitored. Similarly, each GP in England and Wales received a monthly expenditure statement, a monthly 'Merec Bulletin' (provides information on an area of therapeutics) and a three-monthly PACT standard report (summary of prescribing data for the practice over the past quarter).

This had been the strongest move yet, to shift emphasis from secondary to primary care. Under the voluntary fundholding scheme, GPs were given responsibilities to buy non-urgent treatments for their patients and placed budgetary responsibility firmly on GPs. Any savings achieved by a practice within its total budget could be reinvested at the practice's discretion. As purchasers, however, GPs increasingly recognise that they are responsible for the whole care of the patient and the optimal use of the drug budget. This has made some fundholders re-evaluate their role in accepting recommendations of hospital consultants. They began to question the appropriateness of some proposed treatment options when the health gain may be small.

Over the years, increasing numbers of practices joined the scheme, and by 1997/98, 60% of the population was covered by fundholding GPs.

Early studies showed positive effects of fundholding on prescribing costs. Baines et al [233] found a clear consensus that fundholding practices achieved one-off reductions in their prescribing costs relative to non-fundholders, releasing savings for use elsewhere. Brandlow & Coulter (1993) [234] compared prescribing and cost information (prescribing costs, number of items prescribed, the proportion of generics) of 15 practices (fundholding vs non-fundholding, dispensing vs non-dispensing, use of formularies and protocols) over two six-month periods. They showed that fundholders seemed to curb increasing prescribing costs. Similar results were seen in a study by Wilson et al (1995) who analysed growth in prescribing costs as measured by the percentage increase in annual net ingredient cost per prescribing unit of virtually all practices (412 in total) in the former Mersey Region between April 1990 to March 1994. Their results suggested that in comparison growth in prescribing costs of fundholders tended to be substantially lower in the early period, but had subsequently returning to a growth rate similar to that of non-fundholders [235]. Thus the GP fundholding scheme appeared to have controlled costs in the short-term only.

Later studies in England and Wales have concluded that fundholding did not contribute to any great extent to the observed variation in prescribing behaviour between practices but that fundholders have contained their prescribing costs more effectively than non-fundholders [235,236]. This may be because GPs who become fundholders have different attributes to those who do not. It was suggested that financial incentives can bring about changes and motivate GPs in both fundholding and non-fundholding, but there is doubt about how long the effects persist. Initial savings can be from increased generics use and other strategies that are relatively easy to implement, but sustained improvement requires a more fundamental change in attitudes and a commitment to cost-effective prescribing.

The Indicative Prescribing Scheme (IPS) stressed cost containment, and made little allowance for the consideration of the quality of appropriateness of prescribing. Overall, the IPS has generally failed to control the increasing drug expenditure due to unrealistic targets and the absence of an incentive or penalty to encourage compliance. Fundholding has been shown to reduce the rates of rising drug costs in participating practices. However,

the overall evidence of their success in restraining the rise in prescribing costs was inconclusive. Often many studies targeted selected practices and only looked at short-term outcomes. Prescribing budgets for fundholders and indicative prescribing amounts for non-fundholding practices, especially in the early years, were often set arbitrarily. In some cases disproportionately large budgets were given to fundholders, which inevitably meant that they could more easily under-spend than others. Fundholding was eventually abolished in March 1999. However, GPs retained their role in buying treatment through 'locality purchasing', whereby groups of practices in an area make decisions about purchasing.

Primary Care Trusts (PCTs) and Local Healthcare Co-operatives (LHCCs)

In April 1999, cash-limited unified budgets were introduced and called Joint Investment Funds. These were expected to tackle costs at the primary-secondary care interface, by transferring resources to match changes in clinical practice. Under this new scheme, overspending in prescribing would be managed within the overall primary care budget, resulting in a reduction in resources available for hospital and community services. Conversely, more rational and effective prescribing of high cost drugs should allow resources to be "freed up" and redirected to areas of unmet clinical needs, or to areas seen as national or local priorities.

Primary Care Trusts were introduced to offer new ways for GPs in the same area, regardless of whether previously fundholding or not, to work with each other and other health professionals to plan the way in which care should be provided. These trusts receive a budget to manage purchasing of hospital services, prescriptions and employ staff. The total number of trusts was reduced and most Health Boards now have one primary care trust and one acute trust. The responsibility for primary care was moved from being a Health Board function to become a PCT function, which include services for primary care and all other community-based healthcare. PCTs will typically include community hospitals and mental health services, as well as networks of local healthcare co-operatives (LHCCs). Local healthcare co-operatives are voluntary groupings of GPs and primary care professionals, accountable to PCTs, and members are accountable for their use of resources and quality of care.

Currently, there are 79 LHCCs across Scotland, covering 952 practices in all mainland areas, except West Lothian [237]. The size of the LHCCs vary widely, patient populations range from 4 000 to 172 000 patients, the number of practices covered by each LHCC ranges from two to 31, and the number of GPs ranges from eight to 115.

Local healthcare co-operatives are positioned to have major impact on improving the quality and cost-effectiveness of prescribing, and significant work is being done. Eighty-eight percent of the LHCCs in the survey have dedicated pharmacist input, varying from one session per week in 25% of the LHCCs to 30 sessions per week in one LHCC. Seventy-five percent (n=44) of LHCCs are involved in specific prescribing projects, while 32% (n=19) use a formulary. The average prescribing budget, based on data from 26 LHCCs, is 38% (ranging from 23% to 68%) of the total devolved budget.

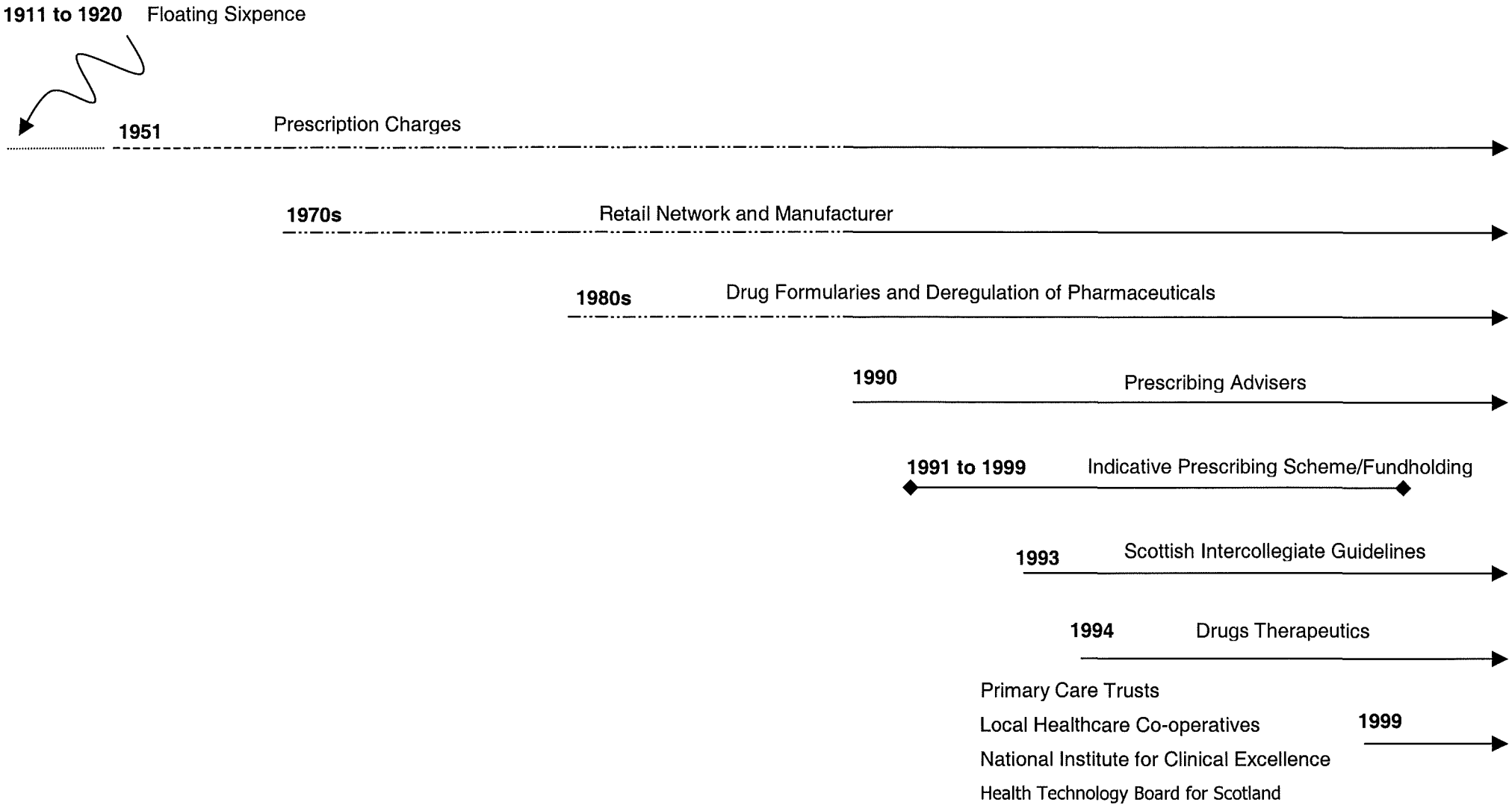
Primary Care Trusts (PCTs) and LHCCs were designed to encourage the development of joint working between GPs and pharmacists on prescribing, medicines management and direct patient care services. Often each locality has a small team of GPs with a full-time general manager, a core management team and a multi-disciplinary board, such as a pharmacist for prescribing advice, which determines policy and direction.

Summary

The continuing rise in the prescribing expenditure is an ongoing challenge for the NHS. Over the years, a confusion of policies including cost containment and reallocation of budgets have been introduced. Various approaches to cost containment have been introduced and adopted throughout the years, ranging from the "stick" approach (e.g. restricted list) to the "carrot" approach (e.g. incentives with a prescribing message on them). However, there is often a lack of rigorous evidence because interventions were implemented as part of a strategic decision rather than on a formally evaluated basis. In addition, most of these methods appear only to have short-term benefits. Cost containment strategies could only generate a finite amount of savings, which would reach a plateau in

the long term. In order to achieve cost effectiveness in healthcare, a wider perspective needs to be adopted.

Figure 20 Strategies Adopted to Control Prescribing



APPENDIX II

LITERATURE SEARCH STRATEGIES

LITERTURE REVIEW – THE IMPACT OF ECONOMIC INFORMATION OF PRIMARY CARE DECISION MAKING

The following search strategy was used to search Medline, EMBASE and Cinahl for relevant studies.

1. Economic$ in ti ab
2. Cost$ in ti ab
3. (Primary adj3 care) in ti ab
4. (General adj3 practice$) in ti ab
5. (General adj3 practitioner$) in ti ab
6. Impact$ in ti ab
7. Influen$ in ti ab
8. Chang$ in ti ab
9. Attitude$ in ti ab
10. Deci$ in ti ab
11. Or/1-10

LITERTURE REVIEW – META-ANALYSIS

The search filters recommended by the SIGN guidelines were used to retrieve randomised controlled trials in Medline, EMBASE and Cinahl. Keywords for the individual drugs were combined with the appropriate filters to retrieve relevant studies.

Medline

12. Randomized controlled trials/
13. Randomized controlled trial.pt.
14. Random allocation/
15. Double blind method/
16. Single blind method/
17. Clinical trial.pt.
18. Exp clinical trials/
19. or/1-7
20. (clinc$ adj trial$).tw.
21. ((sigl$ or doubl$ or treb$ or trip$) adj (blind$3 or mask$3)).tw.
22. Placebos/
23. Placebo$.tw.
24. Randomly allocated.tw.
25. (allocated adj2 random).tw.
26. or/9-14
27. 8 or 15
28. Case report.tw.
29. Letter.pt.
30. Historical article.pt.
31. Review of reported cases.pt.
32. Review, multicase.pt.
33. or/17-21
34. 16 not 22

EMBASE

1. Clinical trial/
2. Randomized controlled trial/
3. Randomization/
4. Single blind procedure/
5. Double blind procedure/
6. Crossover procedure/
7. Placeb/
8. Randomi?ed controlled trial$.tw.
9. Rct.tw.
10. Random allocation.tw.
11. Randomly allocated.tw.
12. Allocated randomly.
13. (allocated adj2 random).tw.
14. Single blind$.tw.
15. Double blind.tw.
16. ((treble or triple) adj (blind$)).tw.
17. Placebo$.tw.
18. Prospective study/
19. Or/1-18
20. Case study/
21. Case report.tw.
22. Abstract report/
23. Letter/
24. Or/20-23
25. 19 not 24

Cinahl

1. Exp clinical trials/
2. Clinical trial.pt.
3. (clinc$ adj trial$).tw.
4. (singl$ or doubl$ or trebl$ or tripl$) adj (blind$3 or mask$)).tw.
5. Randomi?ed control$ trial$.tw.
6. Random assignment/
7. Random$ allocat$.tw.
8. Placebo$.tw.
9. Placebos/
10. Quantitative studies/
11. Allocat$ random$.tw.
12. Or/1-11

APPENDIX III

DIAGNOSTIC (ICD-9) AND OPERATIONAL (OPCS) CODES OF CLINICAL EVENTS OF INTEREST

Gastrointestinal Events

208 leukaemia of unspecified cell type
530 disease of oesophagus
531 gastric ulcer
532 duodenal ulcer
533 peptic ulcer, site unspecified
534 gastrojeujunel ulcer
535 gastritis and duodenitis
536 disorder of function of stomach
578 gastrointestinal haemorrhage
787 symptoms involving digestive systems

Cardiovascular Events

401 to 405 Hypertensive Disease
- 401 essential hypertension
- 402 hypertensive heart disease
- 403 hypertensive renal disease
- 404 hypertensive heart and renal disease
- 405 secondary hypertension

410 acute myocardial infarction
411 to 414 Ischaemic Heart Disease
- 411 other acute and subacute form of ischaemic heart disease
- 412 old myocardial infarction
- 413 angina pectoris
- 414 other forms of chronic ischaemic heart disease

415 acute pulmonary heart disease
416 chronic pulmonary heart disease
425 cardiomyopathy
426 conduction disorders
427 cardiac dysrhythmias

428 heart failure

429 ill-defined descriptions and complications of heart disease

440 atherosclerosis

441 aortic aneurysm

Rheumatoid Arthritis

710 diffuse diseases of connective tissue

714 rheumatoid arthritis and other inflammatory polyarthropathies

Osteoarthritis

715 osteoarthrosis and allied disorders

W37 total prosthetic replacement of hip joint using cement

W38 total prosthetic replacement of hip joint not using cement

W39 other total prosthetic replacement of hip joint

W40 total prosthetic replacement of knee joint using cement

W41 total prosthetic replacement of knee joint not using cement

W42 other total prosthetic replacement of knee joint

W43 total prosthetic replacement of other joint using cement

W44 total prosthetic replacement of other joint not using cement

W45 other total prosthetic replacement of other joint

APPENDIX IV

UNIT COSTS USED IN THE ANALYSIS

The following unit costs were used in the non-population model.

Resources	1993 Values	1995 Values	2000 Values
GP Visit		£ 6.90	£ 8.50
Investigations			
ESR	£ 3.00		£ 4.02
FBC	£ 3.00		£ 4.02
WBC	£ 5.00		£ 6.70
WBC diff	£ 7.00		£ 9.38
Ferritin	£ 12.00		£ 16.08
Marrow	£ 70.00		£ 93.81
Bloods	£ 23.00		£ 30.82
LFT	£ 11.00		£ 14.74
U&E	£ 7.00		£ 9.38
Glucose	£ 3.00		£ 4.02
Amylase	£ 3.00		£ 4.02
Renal Biopsy	£ 60.00		£ 80.41
Gastric Biopsy	£ 58.00		£ 77.73
Creatinine	£ 4.00		£ 5.36
Immunoglobin	£ 15.00		£ 20.10
XR abdo	£ 21.00		£ 28.14
XR chest	£ 12.00		£ 16.08
IVP	£ 80.00		£ 107.21
Barium meal	£ 34.00		£ 45.56
Barium enema	£ 41.00		£ 54.94
Upper endoscopy	£ 119.00		£ 159.47
Sigmoidoscopy	£ 50.00		£ 67.01
ECG	£ 6.00		£ 8.04
Faeces OB	£ 11.00		£ 14.74
Faeces Culture	£ 10.00		£ 13.40

GP consultation cost was taken from the following study and inflated to present value.
Graham B & McGregor K. What does a GP consultation cost? BJGP 1997; 47:170-172

All investigative costs were taken from a previous study and inflated to present value.
Knill-Jones RP. An economic evaluation of Arthrotec in the treatment of arthritis. Br J Med Econ 1992;5:51-58

Table 34 Tayside Weighted Average Inpatient Costs by Specialty

Inpatients Acute Specialties	Code	LOS * (days)	Cost/Case (£)	Number of Discharges	Cost/Case per Day (£)
General Surgery	1	5.7	1451	1725	
		3.7	926	3770	
		4.6	1049	1793	
Weighted Values		*4.39*	*1080.52*	*7288*	*245.86*
Orthopaedics	2	7.1	1794	3116	
		8.1	2336	1843	
		8.2	1951	1279	
		30.5	12038	158	
Weighted Values		*8.19*	*2234.63*	*6396*	*272.98*
ENT	3	*2.9*	*907*	*2803*	*312.76*
Ophthalmology	4	*2.9*	*892*	*1909*	*307.59*
Urology	5	4.1	1222	2112	
		4.1	1198	383	
Weighted Values		*4.10*	*1218.32*	*2495*	*297.15*
Neurosurgery	6	*7.6*	*2787*	*842*	*366.71*
Cardiothoracic Surgery	7	-	-	-	
Plastic Surgery & Burns	8	4.8	1405	1751	
		2.4	938	16	
Weighted Values		*4.78*	*1400.77*	*1767*	*293.15*
Oral Surgery & Medicine	12	1.8	1008	666	
		1.1	681	364	
Weighted Values		*1.55*	*892.44*	*1030*	*574.79*
Medical	16	5.2	1085	12014	
		6.9	1219	972	
		5.5	813	4422	
		5.4	955	3067	
Weighted Values		*5.38*	*1013.14*	*20475*	*188.48*
Neurology	19	*8.3*	*2468*	*474*	*297.35*
Dermatology	23	*13.2*	*2050*	*562*	*155.30*
Rehab Medicine	26	-	-	-	
Respiratory Med	28	*8.8*	*1136*	*2895*	*129.09*
Communicable Disease	31	*7.7*	*2768*	*1361*	*359.48*
Radiotherapy	34	*10.8*	*1586*	*1006*	*146.85*
Spinal Paralysis	38	-	-	-	
Surgical Paediatrics	39	*1.9*	*683*	*397*	*359.47*
Medical Paediatrics	40	2.9	1024	2728	
		2.8	822	1081	
Weighted Values		*2.87*	*966.67*	*3809*	*336.63*
Gynaecology	42	3.6	870	1725	
		3.1	994	1076	
		1.8	250	4	
Weighted Values		*3.41*	*916.68*	*2805*	*269.17*
Baby Special/Intensive	46	16	7279	341	
		9.4	3677	195	
Weighted Values		*13.60*	*5968.57*	*536*	*438.90*

Inpatients Acute Specialties	Code	LOS * (days)	Cost/Case (£)	Number of Discharges	Cost/Case per Day (£)
Intensive Therapy Unit	48	6.6	10611	270	
		1.5	1221	1015	
Weighted Values		*2.57*	*3194.00*	*1285*	*1242.03*
A&E	49	*0.8*	*1184*	*766*	*1480.00*
Geriatric Assess	50	15.3	1945	494	
		21.5	2331	930	
		28	3276	652	
		44.5	4745	368	
		25.3	3438	815	
Weighted Values		*25.41*	*3010.97*	*3259*	*118.50*
General Practice	73	21.2	2363	281	
		18.9	2038	104	
		10.6	1223	422	
		14.4	1390	326	
		24.1	2527	148	
		17.7	1927	289	
		13.1	1434	175	
		16.3	1623	265	
		17.7	2674	86	
Weighted Values		*16.18*	*1759.12*	*2096*	*108.74*
Acute Other	98	14.4	2738	409	
		14.4	3345	200	
		14.4	2633	409	
Weighted Values		*14.40*	*2815.07*	*1018*	*195.49*
				Cost per inpatient week	
Geriatric Long Stay	51		466	21	
			589	19	
			736	389	
			820	110	
			579	203	
			666	52	
			580	61	
			517	40	
			547	20	
			535	11	
			678	7	
			850	6	
			689	18	
Weighted Values			*673.75*	*957*	*96.25*
Young Chronic Sick	52		*1243*	*130*	*177.57*
Costed as Medical Cases:					
Nephrology	24				*188.48*
Cardiology	17				*188.48*
Anaesthetics	41				*188.48*
Haematology	62				*188.48*

* *LOS = length of stay in hospital*

Table 35 Tayside Weighted Average Outpatient Costs by Specialty

Outpatients Specialties	*Code*	*Total Attendance*	*Cost per Attendance (£)*
General Surgery	**1**	18400	175
		2308	37
		736	20
		673	43
		8446	23
		386	93
		1003	46
		589	42
		580	29
		170	47
		183	77
		173	110
	Weighted Values	*33647*	*110.20*
Orthopaedics	**2**	26200	35
		2171	31
		73	27
		681	37
		11019	35
		5438	55
		1280	42
		378	42
		46	65
		37	27
		39	51
		43	116
	Weighted Values	*47405*	*37.48*
ENT	**3**	15660	47
		1496	40
		246	37
		625	42
		4116	27
		1053	45
		566	51
		268	30
		246	28
		138	36
	Weighted Values	*24414*	*115.52*
Ophthalmology	**4**	24935	34
		1790	32
		1132	42
		9894	22
		369	65
		489	31
	Weighted Values	*38609*	*31.32*
Urology	**5**	5379	112
		18	278
		274	47
		499	80
	Weighted Values	*6170*	*107.01*
Neurosurgery	**6**	3472	43
		111	117
	Weighted Values	*3583*	*45.29*
Plastic Surgery & Burns	**8**	11646	20
		529	30
	Weighted Values	*12175*	*20.43*
Oral Surgery & Medicine	**12**	650	108
		4435	45
		309	178
	Weighted Values	*5394*	*274.38*
Medical	**16**	53933	35
		6459	53
		3111	47
		621	19
		597	65
		15029	49
		1391	92
		810	60
		378	79
		252	44
		253	40
		128	63
		138	36
		3	333
	Weighted Values	*83103*	*40.97*
Neurology	**19**	5031	41
		249	36
		976	49
Weighted Cost		*6256*	*42.05*
Dermatology	**23**	28962	33
		1319	31
		632	28
		4408	32
		520	50
		707	44
Weighted Cost		*36548*	*33.18*
Rehab Medicine	**26**	*As Medical Outpatients*	
Respiratory Medicine	**28**	441	39
		297	54
		1230	45
		645	42
		7415	53
	Weighted Values	*10028*	*50.73*
Communicable Disease	**31**	*1521*	*93*
Radiotherapy	**34**	6724	52
		1333	26
	Weighted Values	*8057*	*47.70*
Spinal Paralysis	**38**	*As Medical Outpatients*	
Surgical Paedicatrics	**39**	*1137*	*206*
Medical Paediatrics	**40**	6676	78
		438	39
		161	43
		3247	120
		146	55
		1742	46
	Weighted Values	*12410*	*82.40*
Gynaecology	**42**	12782	41
		793	32
		192	31
		417	41
		3346	71
		482	60
		311	51
		93	43
		109	28
		38	79
	Weighted Values	*18563*	*46.59*
Baby Care Intensive	**46**	*896*	*35*
A&E	**49**	4844	57
		46801	34
		3041	20
		2497	24
		25687	37
		5446	61
		4475	21
		1372	24
		1576	34
		1441	37
		696	45
		2165	26
		8	125
	Weighted Values	*100049*	*35.91*
Geriatric Assessment	**50**	535	82
		687	95
		1409	45
		489	27
	Weighted Values	*3120*	*59.53*
General Practice	**73**	*As Medical Outpatients*	
Acute Other	**98**	974	49
		1106	45
		389	98
		6742	128
	Weighted Values	*9211*	*108.41*

APPENDIX V

CORRESPONDANCES AND QUESTIONNAIRES

From: Olivia Wu
Direct line: 0141 330 3296

Dr R P Knill-Jones
Direct line: 0141 330 5010

UNIVERSITY
of
GLASGOW

[Date]

Dear

Pharmacoeconomic Evaluations of Adverse Drug Reactions

We are conducting research on the impact of pharmacoeconomic information on GP prescribing. Part of our research involves conducting economic evaluations on three classes of drugs - NSAIDs, ACE inhibitors and SSRIs. This involves modelling the additional costs to the NHS of treating most side effects, onto the basic drug dispensing cost. This calculation of the total costs of prescriptions leads to a more accurate comparative evaluation of the 'real' costs of prescribing different NSAIDs.

In order to calculate the costs of treating side effects, we need to establish a general treatment model from GPs. This activity involves a half-hour interview asking about the actions GPs would take, and investigations/follow-up initiated, given a series of complications which could arise in a patient on one of the three classes of drugs mentioned above. No special interest or expertise in the particular drugs or economic evaluations is needed. We have had experience in doing this successfully on several occasions in the past.

This study is independent of any pharmaceutical sponsorship for good academic reasons. We would be most grateful if you could help.

Yours sincerely

Olivia Wu
Research Student

Dr Robin Knill-Jones
Senior Lecturer in Epidemiology
Honorary Consultant in Public Health

Department of Public Health, University of Glasgow
1 Lilybank Gardens, Glasgow G12 8RZ
Tel: +44 141 330 4039 Fax: +44 141 330 5018

From: Olivia Wu and Dr Robin Knill-Jones
Direct line: 0141 330 3296/5010

Dr Philip Wilson
WestNet
4 Lancaster Cresent
Glasgow G12 0RR

UNIVERSITY
of
GLASGOW

[Date]

Dear

Exploratory Survey among WestNet Members

We have noted the large increase in economic data about health care. These range from simple recommendations on cost issues to purposefully designed economic evaluations. Many GPs are concerned about the increasing dominance of economic issues in major decisions about clinical care, and feel their opinions on economic matters have not been heard. However, it is unclear whether this information has any impact on everyday clinical practice in a primary care setting.

We are conducting a short exploratory survey among WestNet members to look into this. This survey would allow us to gain valuable insight into your views on the usefulness of a variety of economic information in relation to your everyday practice. We believe the results of this survey would provide a sense of direction to future research in this area.

From personal experience, we know that there is very little spare time in a GP's day. We have restricted this survey to a very short questionnaire which is enclosed. We would be most grateful if you could take some time to complete this and return it in the reply-paid envelope provided.

Yours sincerely

Olivia Wu
Research Student

Dr Robin Knill-Jones
Senior Lecturer in Epidemiology
Honorary Consultant in Public Health

pp Dr Philip Wilson

Enc

Section of Public Health and Health Policy
Division of Community Based Sciences, University of Glasgow
1 Lilybank Gardens, Glasgow G12 8RZ
Tel: +44 141 330 4039 Fax: +44 141 330 5018

Please mark 'x' or type, where appropriate, within the brackets provided.

1. Has economic information comparing cost and effectiveness of treatments ever influenced your decision-making?
   [ ] Yes (please proceed to fill in questions 2 to 4)
   [ ] No (please go straight to question 5)
   [ ] Don't Know (thank you for your time, your questionnaire ends here)

2. If yes, when was the last time economic information has influenced your decision-making?
   [ ]

3. What was the source of this information (pick all relevant options)?
   Published information:
   [ ] from local Health Board/PCG/PPAs/MPAs
   [ ] articles in journals
   [ ] from pharmaceutical industry
   [ ] others, please specify
   Verbally presented information:
   [ ] from individual meetings with representatives from local Health Board/PCG/PPAs/MPAs
   [ ] from conferences and seminars
   [ ] from pharmaceutical industry representatives
   [ ] others, please specify

4. What was the decision made?
   [ ]

5. Why has economic information failed to influence your decision-making (pick all relevant options)?
   [ ] I never receive any economic information.
   [ ] I do not receive economic information relevant to my decision-making.
   [ ] It is not possible to implement the economic information into my everyday practice.
   [ ] I do not agree with the results of the information presented.
   [ ] Other reasons, please specify.

Please return the completed questionnaire in the reply-paid envelope provided.

Thank you very much for your time. If you have any questions regarding this survey, please contact:

Olivia Wu or Dr Robin Knill-Jones
Department of Public Health
University of Glasgow
Tel: 0141 330 3296/5010 Fax: 0141 330 5018
Email: 9406070w@clinmed.gla.ac.uk or
R.P.Knill-Jones@udcf.gla.ac.uk

Dr Philip Wilson
WestNet, 4 Lancaster Crescent
Glasgow G12 0RR
Tel: 0141 211 1690 Fax: 0141 211 1667
Email: p.wilson@clinmed.gla.ac.uk

1 **Please mark 'x' or type, where appropriate, within the brackets provided.**

	Have you ever used this as a source of economic information? By economic information, we mean information comparing the costs and benefits of different kinds of health care. (Y = yes N = no DK = don't know)	If yes, do you find this information of relevance to your everyday practice? (Y = yes N = no S = sometimes DK = don't know)
MPAs and/or PPAs	Y[ ] N[ ] DK[ ]	Y[ ] N[ ] S[ ] DK[ ]
Prescribing Feedback (SPA)	Y[ ] N[ ] DK[ ]	Y[ ] N[ ] S[ ] DK[ ]
Prescribing Feedback (GPASS)	Y[ ] N[ ] DK[ ]	Y[ ] N[ ] S[ ] DK[ ]
Locally Produced Newsletters, please specify [ ]	Y[ ] N[ ] DK[ ]	Y[ ] N[ ] S[ ] DK[ ]
Local Prescribing Formulary	Y[ ] N[ ] DK[ ]	Y[ ] N[ ] S[ ] DK[ ]
Pharmaceutical Industry Literature	Y[ ] N[ ] DK[ ]	Y[ ] N[ ] S[ ] DK[ ]
Pharmaceutical Industry Representatives	Y[ ] N[ ] DK[ ]	Y[ ] N[ ] S[ ] DK[ ]
British Medical Journal	Y[ ] N[ ] DK[ ]	Y[ ] N[ ] S[ ] DK[ ]
British Journal of General Practice	Y[ ] N[ ] DK[ ]	Y[ ] N[ ] S[ ] DK[ ]
Other Journals, please specify [ ]	Y[ ] N[ ] DK[ ]	Y[ ] N[ ] S[ ] DK[ ]

2 If there are sources of economic information that you find relevant and are not on the list above, please specify.

[ ]

3 How do you think economic information should be presented to you (pick all relevant options)?

[ ] evaluations and studies published in literature

[ ] summary of evaluations and studies presented in a leaflet format

[ ] summary of evaluations and studies presented verbally at a meeting

[ ] simple recommendations presented in a leaflet format

[ ] simple recommendations presented verbally at a meeting

[ ] locally specific evaluations and studies

4 Do you think economic information should be used in health care decision-making?

[ ] Yes

[ ] No

Please return the completed questionnaire in the reply-paid envelope provided.

Thank you very much for your time. If you have any questions regarding this survey, please contact:

Olivia Wu or Dr Robin Knill-Jones
Department of Public Health, University of Glasgow.
Tel: 0141 330 3296/5010 Fax: 0141 330 5018
Email: 9406070w@clinmed.gla.ac.uk or
R.P.Knill-Jones@udcf.gla.ac.uk

Dr Philip Wilson
WestNet, 4 Lancaster Crescent
Tel: 0141 211 1690 Fax: 0141 211 1667
Email: p.wilson@clinmed.gla.ac.uk

From: Olivia Wu and Dr Robin Knill-Jones
Direct line: 0141 330 3296/5010

[Date]

UNIVERSITY
of
GLASGOW

Dear

The Use of Economic Evidence in Primary Care

We have noted the large increase in economic data about health care. These range from simple recommendations on cost issues to purposefully designed economic evaluations. Many GPs are concerned about the increasing dominance of economic issues in major decisions about clinical care, and feel their opinions on economic matters have not been heard.

We are conducting an exploratory survey to look into this. This survey would allow us to gain valuable insight into your views on the role of economic information in relation to your everyday practice. We believe the results of this survey would provide information that will help the design of useful and comprehensible economic evidence for GPs and tackle 'information overload'.

Your participation in this would be voluntary and should you agree to be involved, you may withdraw at any point without prejudice. If you consent to take part, then we will need to undertake one semi-structured interview with you. This will last no longer than 45 minutes and, with your permission, will be audio-recorded. These interviews will be transcribed and your replies will be treated as confidential. We will also ensure that none of your responses can be directly attributed to you.

As a general guide, the interview will cover your views on the use of economic evidence in clinical decision making. However, no special knowledge on economics is required. If you require further information or wish to discuss this in more detail, please do not hesitate to contact us.

Yours sincerely

Olivia Wu
Research Assistant

Dr Robin Knill-Jones
Reader in Epidemiology
Honorary Consultant in Public Health

Section of Public Health and Health Policy
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APPENDIX VI

BREAKDOWN OF COSTS – POPULATION MODEL

Table 36 All the Costs (£) Incorporated in the Economic Modelling of the Tayside Population Based on 45 Days Observations (from the Index date)

	N	Base Cost Drug Rx	Additional NSIAD RX	Additional Ulcer Rx	Additional Other Rx	Event Cost All Rx	GP Visit (Rx) Costs	Cost of Endoscopies	Cost of GI admissions	Cost of CV admissions	Cost of RH admissions	Cost of OS admissions	Cost of all admissions	Hidden Costs	Shadow Costs
COMPARATOR															
Female															
50 to 59yrs	8640			1.39	1.50	2.89	1.28	0.51	0.70	0.64	0.00	0.00	1.34	6.02	6.02
60 to 74yrs	11380			1.88	1.26	3.14	1.51	0.44	1.21	1.99	0.22	0.96	4.38	9.47	9.47
75+yrs	5410			2.17	2.02	4.19	1.86	0.27	2.04	23.34	0.00	7.93	33.31	39.62	39.62
sub-total of all female	25432			1.77	1.50	3.28	1.50	0.43	1.21	6.07	0.10	2.12	9.50	14.71	14.71
Male															
50 to 59yrs	9617			1.48	0.85	2.33	0.86	0.37	0.79	3.93	0.00	0.46	5.18	8.74	8.74
60 to 74yrs	9579			2.36	1.30	3.67	1.42	0.48	2.18	3.89	0.28	1.81	8.17	13.73	13.73
75+yrs	2722			2.20	1.39	3.59	1.56	0.08	1.13	7.59	0.00	1.72	10.44	15.67	15.67
sub-total of all male	21918			1.96	1.12	3.07	1.19	0.38	1.44	4.37	0.12	1.21	7.14	11.78	11.78
Total Comparator Cohort	47350			1.86	1.32	3.18	1.36	0.40	1.32	5.28	0.11	1.70	8.41	13.35	13.35
NSAID ONLY															
Female															
50 to 59yrs	9324	8.05	2.47	1.49	2.83	6.79	4.46	0.49	0.94	4.07	0.30	1.81	7.11	18.85	26.90
60 to 74yrs	13319	7.71	2.92	1.85	3.16	7.93	6.01	0.33	4.87	13.57	1.89	4.57	24.90	39.17	46.88
75+yrs	6768	7.55	3.30	1.75	3.67	8.72	7.44	0.22	9.19	30.39	0.96	16.39	56.93	73.30	80.86
sub-total of all female	29411	7.78	2.87	1.71	3.17	7.75	5.85	0.35	4.62	14.43	1.17	6.42	26.63	40.58	48.37
Male															
50 to 59yrs	7185	7.46	2.04	1.42	1.97	5.43	3.76	0.35	2.62	23.97	0.99	1.64	29.21	38.75	46.21
60 to 74yrs	9594	6.98	2.49	1.75	3.21	7.45	5.51	0.33	3.60	31.97	0.00	10.67	46.24	59.53	66.50
75+yrs	3022	6.69	2.80	1.42	3.29	7.51	6.31	0.28	8.96	17.03	0.00	3.46	29.45	43.55	50.24
sub-total of all male	19801	7.11	2.37	1.58	2.77	6.73	5.00	0.33	4.06	26.78	0.36	6.29	37.50	49.55	56.66
Total NSAID Only Sub-Cohort	49212	7.51	2.67	1.66	3.01	7.34	5.51	0.34	4.39	19.40	0.84	6.37	31.00	44.19	51.70
NSAID & MISOPROSTOL															
Female															
50 to 59yrs	33	23.37	5.01	9.66	3.31	17.98	10.05	0.00	0.00	0.00	0.00	0.00	0.00	28.03	51.40
60 to 74yrs	75	25.14	3.07	8.79	4.82	16.68	10.92	0.00	0.00	18.34	0.00	0.00	18.34	45.94	71.08
75+yrs	42	22.17	8.58	11.07	5.05	24.70	15.47	0.00	97.71	97.71	0.00	0.00	195.41	235.58	257.75
sub-total of all female	150	23.92	5.04	9.62	4.55	19.21	12.01	0.00	27.36	36.53	0.00	0.00	63.89	95.10	119.02
Male															
50 to 59yrs	24	26.17	4.05	8.30	2.13	14.48	8.18	0.00	0.00	0.00	0.00	0.00	0.00	22.66	48.83
60 to 74yrs	28	25.04	2.33	11.95	5.85	20.14	12.09	0.00	0.00	0.00	0.00	0.00	0.00	32.22	57.26
75+yrs	10	24.20	3.09	9.83	5.05	17.96	12.86	0.00	0.00	0.00	0.00	0.00	0.00	30.82	55.03
sub-total of all male	62	25.34	3.12	10.20	4.28	17.60	10.70	0.00	0.00	0.00	0.00	0.00	0.00	28.30	53.64
Total NSAID & Misoprostol Sub-Cohort	212	24.34	4.48	9.79	4.47	18.74	11.62	0.00	19.36	25.84	0.00	0.00	45.20	75.56	99.90
NSAID & H2/OMEPRAZOLE															
Female															
50 to 59yrs	339	42.32	3.87	14.88	5.16	23.90	11.02	3.07	5.68	12.34	4.61	27.76	50.39	88.39	130.71
60 to 74yrs	623	40.89	3.64	16.30	6.76	26.70	12.71	2.34	0.00	24.74	0.00	17.26	42.00	83.76	124.65
75+yrs	284	41.08	5.40	18.15	6.34	29.89	17.38	1.47	4.44	24.51	0.00	45.41	74.36	123.09	164.17
sub-total of all female	1246	41.32	4.10	16.33	6.23	26.67	13.32	2.34	2.56	21.32	1.26	26.53	51.66	93.98	135.30
Male															
50 to 59yrs	255	40.28	2.66	13.22	4.17	20.05	9.32	1.63	4.65	60.99	0.00	0.00	65.65	96.65	136.93
60 to 74yrs	492	40.37	3.14	13.48	6.56	23.17	11.01	0.85	22.28	62.27	0.88	21.19	106.62	141.65	182.02
75+yrs	120	37.00	2.98	14.44	6.89	24.31	12.81	0.00	0.00	33.30	0.00	0.00	33.30	70.42	107.42
sub-total of all male	867	39.88	2.98	13.54	5.90	22.41	10.76	0.96	14.01	57.88	0.50	12.03	84.42	118.55	158.43
Total NSAID & H2/Omeprazole Sub-Cohort	2113	40.73	3.64	15.18	6.10	24.92	12.27	1.77	7.26	36.32	0.95	20.58	65.10	104.06	144.79

Table 37 All the Costs (£) Incorporated in the Economic Modelling of the Tayside Population Based on Six Months Observations (from the index date)

	N	Base Cost Drug Rx	Event Costs NSAID Rx	Event Costs H2/Losec Rx	Event Costs Other Rx	Event Costs All Rx	Costs of GP Visits (Rx)	Cost of Endoscopies	Cost of all GI admissions	Cost of all CV admissions	Cost of all RH admissions	Cost of all OS admissions	Cost of all admissions	Hidden Costs	Shadow Costs
COMPARATOR															
Female															
50 to 59yrs	8640			6.49	7.90	14.39	4.40	1.30	1.78	3.27	0.00	1.85	6.89	26.98	26.98
60 to 74yrs	11380			8.18	6.69	14.87	4.59	1.52	8.45	16.83	0.45	3.00	28.73	49.71	49.71
75+yrs	5410			9.27	8.77	18.04	5.49	1.16	7.08	92.33	7.53	24.94	131.88	156.57	156.57
sub-total of all female	25432			7.83	7.55	15.38	4.72	1.37	5.89	28.28	1.80	7.28	43.25	64.71	64.71
Male															
50 to 59yrs	9617			6.72	4.12	10.84	2.85	1.45	3.05	16.20	0.00	2.28	21.53	36.67	36.67
60 to 74yrs	9579			9.54	6.67	16.21	4.37	1.81	6.46	17.94	0.28	5.67	30.36	52.75	52.75
75+yrs	2722			8.14	6.65	14.79	4.42	1.15	9.42	78.72	0.00	9.05	97.20	117.55	117.55
sub-total of all male	21918			8.13	5.55	13.68	3.71	1.57	5.33	24.73	0.12	4.60	34.79	53.74	53.74
Total Comparator Cohort	47350			7.97	6.62	14.59	4.25	1.46	5.63	26.63	1.03	6.04	39.33	59.63	59.63
NSAID ONLY															
Female															
50 to 59yrs	9324	8.05	11.16	6.18	16.22	33.56	15.52	2.08	2.73	15.45	2.78	11.28	32.25	83.40	91.45
60 to 74yrs	13319	7.71	13.92	8.44	17.73	40.08	20.38	1.91	11.92	49.15	9.08	25.90	96.04	158.41	166.13
75+yrs	6768	7.55	16.32	8.47	20.59	45.37	24.88	1.79	30.03	141.98	5.38	90.56	267.96	339.99	347.54
sub-total of all female	29411	7.78	13.59	7.73	17.91	39.23	19.87	1.93	13.17	59.82	6.23	36.15	115.38	176.42	184.20
Male															
50 to 59yrs	7185	7.46	8.57	6.31	12.50	27.37	12.76	1.51	6.53	60.12	1.65	13.84	82.15	123.79	131.25
60 to 74yrs	9594	6.98	11.88	8.20	18.28	38.35	19.36	1.74	9.60	114.45	0.54	30.71	155.30	214.75	221.72
75+yrs	3022	6.69	14.27	7.32	20.77	42.36	22.81	1.65	19.88	89.08	0.61	45.64	155.21	222.03	228.73
sub-total of all male	19801	7.11	11.04	7.38	16.56	34.98	17.49	1.64	10.05	90.87	0.96	26.87	128.74	182.86	189.96
Total NSAID Only Sub-Cohort	49212	7.51	12.57	7.59	17.36	37.52	18.91	1.82	11.92	72.31	4.11	32.41	120.76	179.01	186.52
NSAID & MISOPROSTOL															
Female															
50 to 59yrs	33	23.37	12.64	27.76	43.48	83.88	28.72	0.00	0.00	0.00	0.00	0.00	0.00	112.61	135.97
60 to 74yrs	75	25.14	14.82	41.06	23.56	79.44	30.96	5.56	0.00	18.34	0.00	0.00	18.34	134.30	159.44
75+yrs	42	22.17	21.17	36.73	24.30	82.20	34.49	0.00	138.98	944.50	0.00	0.00	1083.48	1200.17	1222.34
sub-total of all female	150	23.92	16.12	36.92	28.15	81.19	31.46	2.78	38.92	273.63	0.00	0.00	312.54	427.97	451.89
Male															
50 to 59yrs	24	26.17	15.34	28.05	12.66	56.04	22.00	0.00	0.00	0.00	0.00	0.00	0.00	78.05	104.22
60 to 74yrs	28	25.04	12.14	47.78	31.44	91.36	32.16	0.00	0.00	0.00	0.00	0.00	0.00	123.52	148.56
75+yrs	10	24.20	16.62	34.93	13.83	65.38	23.70	0.00	0.00	0.00	0.00	0.00	0.00	89.08	113.28
sub-total of all male	62	25.34	14.10	38.07	21.33	73.50	26.86	0.00	0.00	0.00	0.00	0.00	0.00	100.36	125.70
Total NSAID & Misoprostol Sub-Cohort	212	24.34	15.53	37.26	26.15	78.94	30.11	1.97	27.53	193.61	0.00	0.00	221.14	332.16	356.50
NSAID & H2/OMEPRAZOLE															
Female															
50 to 59yrs	339	42.32	20.09	90.27	28.25	138.61	38.90	7.37	18.62	28.25	4.61	52.94	104.43	289.31	331.63
60 to 74yrs	623	40.89	18.96	94.00	36.05	149.01	42.63	7.02	11.17	97.35	12.68	53.88	175.07	373.74	414.63
75+yrs	284	41.08	25.49	104.11	38.46	168.06	52.01	6.60	33.04	134.07	14.80	170.72	352.63	579.30	620.38
sub-total of all female	1246	41.32	20.75	95.29	34.48	150.52	43.76	7.02	18.18	86.92	10.97	80.26	196.32	397.62	438.94
Male															
50 to 59yrs	255	40.28	13.25	75.54	25.34	114.13	33.05	7.35	13.36	151.89	0.00	33.60	198.85	353.39	393.67
60 to 74yrs	492	40.37	15.25	90.20	40.65	146.10	40.43	5.93	81.54	203.74	11.11	49.25	345.65	538.10	578.48
75+yrs	120	37.00	16.11	87.48	39.73	143.33	44.68	5.21	6.75	78.01	0.00	0.00	84.76	277.98	314.98
sub-total of all male	867	39.88	14.78	85.51	36.02	136.31	38.85	6.25	51.14	171.09	6.30	37.83	266.36	447.77	487.65
Total NSAID & H2/Omeprazole Sub-Cohort	2113	40.73	18.30	91.28	35.11	144.69	41.74	6.70	31.70	121.46	9.05	62.85	225.06	418.20	458.93

Table 38 All the Costs (£) Incorporated in the Economic Modelling of the Tayside Population Based on 12 Months (from the index date)

	N	Base Cost Drug Rx	Event Costs NSAID Rx	Event Costs H2/Losec Rx	Event Costs Other Rx	Event Costs All Rx	Costs of GP Visits (Rx)	Costs of all Endoscpies	Costs of all GI admissions	Costs of all CV admissions	Costs of all RH admissions	Costs of all OS admissions	Costs of all admissions	Hidden Costs	Shadow Costs
COMPARATOR															
Female															
50 to 59yrs	8640		0.00	13.23	19.74	32.97	8.58	2.75	5.98	8.75	0.57	1.95	17.25	61.55	61.55
60 to 74yrs	11380		0.00	17.48	17.36	34.83	8.81	3.33	17.48	46.41	1.13	8.28	73.30	120.28	120.28
75+yrs	5410		0.00	18.99	22.75	41.74	9.95	2.12	25.42	212.36	7.66	49.74	295.18	348.99	348.99
sub-total of all female	25432		0.00	16.35	19.31	35.67	8.97	2.88	15.26	68.92	2.33	14.95	101.45	148.97	148.97
Male															
50 to 59yrs	9617		0.00	13.89	10.39	24.29	5.52	2.82	19.60	31.22	0.00	7.04	57.86	90.49	90.49
60 to 74yrs	9579		0.00	19.89	17.72	37.61	8.29	3.57	16.26	45.98	0.52	8.21	70.97	120.43	120.43
75+yrs	2722		0.00	16.91	21.11	38.01	8.34	2.76	32.38	226.51	0.00	18.17	277.06	326.17	326.17
sub-total of all male	21918		0.00	16.89	14.93	31.81	7.08	3.14	19.73	61.92	0.23	8.94	90.81	132.85	132.85
Total Comparator Cohort	47350		0.00	16.60	17.28	33.88	8.10	3.00	17.33	65.68	1.35	12.16	96.53	141.51	141.51
NSAID ONLY															
Female															
50 to 59yrs	9324	8.05	21.72	14.02	39.35	75.10	28.30	3.66	7.04	41.29	10.71	26.32	85.36	192.42	200.47
60 to 74yrs	13319	7.71	27.18	18.90	42.14	88.22	36.46	4.19	21.55	106.38	14.70	68.03	210.67	339.54	347.25
75+yrs	6768	7.55	31.91	18.76	45.63	96.29	43.33	3.76	82.26	313.35	17.19	188.30	601.09	744.47	752.02
sub-total of all female	29411	7.78	26.54	17.32	42.06	85.92	35.46	3.92	30.92	133.37	14.01	82.48	260.78	386.08	393.86
Male															
50 to 59yrs	7185	7.46	16.50	14.16	31.87	62.53	23.21	3.65	14.44	120.43	2.72	24.75	162.34	251.73	259.19
60 to 74yrs	9594	6.98	23.45	18.23	46.53	88.20	34.91	3.84	16.71	224.22	1.44	59.99	302.36	429.32	436.30
75+yrs	3022	6.69	28.02	15.78	50.53	94.33	40.77	3.24	46.22	245.56	61.25	90.66	443.68	582.03	588.72
sub-total of all male	19801	7.11	21.63	16.38	41.82	79.82	31.56	3.68	20.39	189.82	11.03	51.89	273.12	388.19	395.30
Total NSAID Only Sub-Cohort	49212	7.51	24.56	16.94	41.96	83.47	33.89	3.83	26.68	156.08	12.81	70.17	265.75	386.93	394.44
NSAID & MISOPROSTOL															
Female															
50 to 59yrs	33	23.37	24.75	52.68	143.66	221.10	44.52	0.00	0.00	0.00	0.00	0.00	0.00	265.62	288.99
60 to 74yrs	75	25.14	30.80	91.23	68.93	190.96	52.54	16.67	0.00	56.57	13.31	116.33	186.22	446.38	471.52
75+yrs	42	22.17	31.20	64.28	49.58	145.07	52.06	0.00	227.18	1607.34	0.00	346.98	2181.50	2378.64	2400.81
sub-total of all female	150	23.92	29.58	75.21	79.95	184.74	50.64	8.33	63.61	478.34	6.66	155.32	703.93	947.64	971.56
Male															
50 to 59yrs	24	26.17	28.29	57.45	42.38	128.11	39.49	8.68	0.00	24.94	0.00	254.62	279.56	455.84	482.01
60 to 74yrs	28	25.04	23.34	96.12	107.54	227.00	52.95	0.00	0.00	149.82	0.00	0.00	149.82	429.76	454.80
75+yrs	10	24.20	31.27	75.05	33.55	139.87	38.59	0.00	0.00	0.00	0.00	0.00	0.00	178.46	202.66
sub-total of all male	62	25.34	26.53	77.75	70.38	174.67	45.42	3.36	0.00	77.31	0.00	98.56	175.87	399.32	424.66
Total NSAID & Misoprostol Sub-Cohort	212	24.34	28.69	75.95	77.15	181.79	49.11	6.88	45.01	361.06	4.71	138.72	549.50	787.29	811.63
NSAID & H2/OMEPRAZOLE															
Female															
50 to 59yrs	339	42.32	39.29	184.48	74.80	298.57	67.80	15.36	35.87	52.17	14.01	103.98	206.04	587.77	630.09
60 to 74yrs	623	40.89	37.32	194.05	89.85	321.22	73.38	17.05	21.06	195.32	23.92	103.75	344.06	755.71	796.60
75+yrs	284	41.08	46.42	211.11	84.65	342.18	86.60	9.54	44.63	766.53	31.75	276.98	1119.89	1558.21	1599.29
sub-total of all female	1246	41.32	39.93	195.33	84.57	319.83	74.88	14.88	30.46	286.57	23.01	143.30	483.34	892.93	934.25
Male															
50 to 59yrs	255	40.28	29.30	165.42	67.39	262.11	59.36	15.52	31.27	280.17	0.00	65.06	376.49	713.49	753.77
60 to 74yrs	492	40.37	30.00	192.37	100.22	322.60	70.93	16.09	116.04	423.11	19.72	118.03	676.91	1086.53	1126.90
75+yrs	120	37.00	31.33	188.51	84.10	303.94	77.80	10.42	16.59	143.96	0.00	0.00	160.55	552.71	589.71
sub-total of all male	867	39.88	29.98	183.91	88.33	302.22	68.48	15.14	77.34	342.43	11.19	86.11	517.08	902.93	942.81
NSAID & H2/Omeprazole Sub-Cohort	2113	40.73	35.85	190.65	86.11	312.61	72.25	14.99	49.70	309.49	18.16	119.83	497.19	897.03	937.76

APPENDIX VII

SENSITIVITY ANALYSIS – POPULATION MODEL

Table 39

Costs (£) Incorporated in the Sensitivity Analysis - when multiple episodes of care represent one single admission - Based on 45 Days Observations

	N	Base Cost Drug Rx	Additional NSAID RX	Additional Ulcer Rx	Additional Other Rx	Event Cost All Rx	GP Visit (Rx) Costs	Cost of Endoscopies	Cost of GI admissions	Cost of CV admissions	Cost of RH admissions	Cost of OS admissions	Cost of all admissions	Hidden Costs	Shadow Costs
COMPARATOR															
Female															
50 to 59yrs	8640			1.39	1.50	2.89	1.28	0.51	0.70	0.64	0.00	0.00	1.34	6.02	6.02
60 to 74yrs	11380			1.88	1.26	3.14	1.51	0.44	1.19	1.97	0.22	0.96	4.34	9.42	9.42
75+yrs	5410			2.17	2.02	4.19	1.86	0.27	2.03	23.25	0.00	7.91	33.20	39.51	39.51
sub-total of all female	25432			1.77	1.50	3.28	1.50	0.43	1.20	6.05	0.10	2.11	9.46	14.67	14.67
Male															
50 to 59yrs	9617			1.48	0.85	2.33	0.86	0.37	0.78	3.86	0.00	0.46	5.09	8.65	8.65
60 to 74yrs	9579			2.36	1.30	3.67	1.42	0.48	2.18	3.85	0.28	1.81	8.13	13.69	13.69
75+yrs	2722			2.20	1.39	3.59	1.56	0.08	1.13	7.54	0.00	1.72	10.39	15.63	15.63
sub-total of all male	21918			1.96	1.12	3.07	1.19	0.38	1.44	4.31	0.12	1.21	7.08	11.72	11.72
Total Comparator Cohort	47350			1.86	1.32	3.18	1.36	0.40	1.31	5.24	0.11	1.69	8.36	13.30	13.30
NSAID ONLY															
Female															
50 to 59yrs	9324	8.05	2.47	1.49	2.83	6.79	4.46	0.49	0.92	4.02	0.30	1.81	7.04	18.79	26.84
60 to 74yrs	13319	7.71	2.92	1.85	3.16	7.93	6.01	0.33	4.86	13.45	1.89	4.57	24.76	39.03	46.74
75+yrs	6768	7.55	3.30	1.75	3.67	8.72	7.44	0.22	9.06	30.19	0.96	16.36	56.57	72.94	80.50
sub-total of all female	29411	7.78	2.87	1.71	3.17	7.75	5.85	0.35	4.58	14.31	1.17	6.41	26.46	40.42	48.20
Male															
50 to 59yrs	7185	7.46	2.04	1.42	1.97	5.43	3.76	0.35	2.58	23.78	0.98	1.64	28.98	38.52	45.98
60 to 74yrs	9594	6.98	2.49	1.75	3.21	7.45	5.51	0.33	3.56	31.68	0.00	10.66	45.90	59.20	66.17
75+yrs	3022	6.69	2.80	1.42	3.29	7.51	6.31	0.28	8.92	16.93	0.00	3.46	29.31	43.41	50.10
sub-total of all male	19801	7.11	2.37	1.58	2.77	6.73	5.00	0.33	4.03	26.56	0.35	6.29	37.23	49.29	56.39
Total NSAID Only Sub-Cohort	49212	7.51	2.67	1.66	3.01	7.34	5.51	0.34	4.35	19.24	0.84	6.36	30.80	43.99	51.50
NSAID & MISOPROSTOL															
Female															
50 to 59yrs	33	23.37	5.01	9.66	3.31	17.98	10.05	0.00	0.00	0.00	0.00	0.00	0.00	28.03	51.40
60 to 74yrs	75	25.14	3.07	8.79	4.82	16.68	10.92	0.00	0.00	18.34	0.00	0.00	18.34	45.94	71.08
75+yrs	42	22.17	8.58	11.07	5.05	24.70	15.47	0.00	97.71	97.71	0.00	0.00	195.41	235.58	257.75
sub-total of all female	150	23.92	5.04	9.62	4.55	19.21	12.01	0.00	27.36	36.53	0.00	0.00	63.89	95.10	119.02
Male															
50 to 59yrs	24	26.17	4.05	8.30	2.13	14.48	8.18	0.00	0.00	0.00	0.00	0.00	0.00	22.66	48.83
60 to 74yrs	28	25.04	2.33	11.95	5.85	20.14	12.09	0.00	0.00	0.00	0.00	0.00	0.00	32.22	57.26
75+yrs	10	24.20	3.09	9.83	5.05	17.96	12.86	0.00	0.00	0.00	0.00	0.00	0.00	30.82	55.03
sub-total of all male	62	25.34	3.12	10.20	4.28	17.60	10.70	0.00	0.00	0.00	0.00	0.00	0.00	28.30	53.64
Total NSAID & Misoprostol Sub-Cohort	212	24.34	4.48	9.79	4.47	18.74	11.62	0.00	19.36	25.84	0.00	0.00	45.20	75.56	99.90
NSAID & H2/OMEPRAZOLE															
Female															
50 to 59yrs	339	42.32	3.87	14.88	5.16	23.90	11.02	3.07	5.68	12.01	4.61	27.76	50.06	88.06	130.38
60 to 74yrs	623	40.89	3.64	16.30	6.76	26.70	12.71	2.34	0.00	24.65	0.00	17.26	41.91	83.67	124.56
75+yrs	284	41.08	5.40	18.15	6.34	29.89	17.38	1.47	4.44	23.72	0.00	45.41	73.57	122.30	163.38
sub-total of all female	1246	41.32	4.10	16.33	6.23	26.67	13.32	2.34	2.56	21.00	1.26	26.53	51.34	93.67	134.99
Male															
50 to 59yrs	255	40.28	2.66	13.22	4.17	20.05	9.32	1.63	4.65	59.35	0.00	0.00	64.00	95.00	135.28
60 to 74yrs	492	40.37	3.14	13.48	6.56	23.17	11.01	0.85	22.16	61.24	0.88	21.19	105.48	140.51	180.88
75+yrs	120	37.00	2.98	14.44	6.89	24.31	12.81	0.00	0.00	33.30	0.00	0.00	33.30	70.42	107.42
sub-total of all male	867	39.88	2.98	13.54	5.90	22.41	10.76	0.96	13.95	56.82	0.50	12.03	83.29	117.42	157.30
Total NSAID & H2/Omeprazole Sub-Cohort	2113	40.73	3.64	15.18	6.10	24.92	12.27	1.77	7.23	35.70	0.95	20.58	64.45	103.41	144.14

Table 40

Costs (£) Incorporated in the Sensitivity Analysis - when multiple episodes of care represents one single admission - Based on Six Months Observations

	N	Base Cost Drug Rx	Event Costs NSAID Rx	Event Costs H2/Losec Rx	Event Costs Other Rx	Event Costs All Rx	Costs of GP Visits (Rx)	Cost of Endoscopies	Cost of all GI admissions	Cost of all CV admissions	Cost of all RH admissions	Cost of all OS admissions	Cost of all admissions	Shadow Costs	Total Costs
COMPARATOR															
Female															
50 to 59yrs	8640			6.49	7.90	14.39	4.40	1.30	1.77	3.24	0.00	1.85	6.86	26.94	26.94
60 to 74yrs	11380			8.18	6.69	14.87	4.59	1.52	8.35	16.72	0.45	3.00	28.52	49.50	49.50
75+yrs	5410			9.27	8.77	18.04	5.49	1.16	7.03	91.92	7.51	24.92	131.37	156.06	156.06
sub-total of all female	25432			7.83	7.55	15.38	4.72	1.37	5.83	28.14	1.80	7.27	43.04	64.50	64.50
Male															
50 to 59yrs	9617			6.72	4.12	10.84	2.85	1.45	2.99	16.06	0.00	2.28	21.33	36.47	36.47
60 to 74yrs	9579			9.54	6.67	16.21	4.37	1.81	6.41	17.77	0.28	5.67	30.13	52.51	52.51
75+yrs	2722			8.14	6.65	14.79	4.42	1.15	9.25	78.40	0.00	9.03	96.69	117.04	117.04
sub-total of all male	21918			8.13	5.55	13.68	3.71	1.57	5.26	24.55	0.12	4.60	34.53	53.49	53.49
Total Comparator Cohort	47350			7.97	6.62	14.59	4.25	1.46	5.57	26.48	1.02	6.03	39.10	59.40	59.40
NSAID ONLY															
Female															
50 to 59yrs	9324	8.05	11.16	6.18	16.22	33.56	15.52	2.08	2.68	15.25	2.77	11.27	31.97	83.12	91.17
60 to 74yrs	13319	7.71	13.92	8.44	17.73	40.08	20.38	1.91	11.86	48.61	9.06	25.87	95.40	157.77	165.49
75+yrs	6768	7.55	16.32	8.47	20.59	45.37	24.88	1.79	29.81	141.00	5.35	90.40	266.56	338.59	346.14
sub-total of all female	29411	7.78	13.59	7.73	17.91	39.23	19.87	1.93	13.08	59.30	6.21	36.09	114.68	175.72	183.50
Male															
50 to 59yrs	7185	7.46	8.57	6.31	12.50	27.37	12.76	1.51	6.42	59.36	1.65	13.82	81.25	122.89	130.35
60 to 74yrs	9594	6.98	11.88	8.20	18.28	38.35	19.36	1.74	9.53	113.26	0.54	30.70	154.03	213.48	220.45
75+yrs	3022	6.69	14.27	7.32	20.77	42.36	22.81	1.65	19.73	88.37	0.61	45.63	154.34	221.17	227.86
sub-total of all male	19801	7.11	11.04	7.38	16.56	34.98	17.49	1.64	9.96	89.90	0.95	26.85	127.67	181.78	188.89
Total NSAID Only Sub-Cohort	49212	7.51	12.57	7.59	17.36	37.52	18.91	1.82	11.82	71.61	4.10	32.38	119.91	178.16	185.67
NSAID & MISOPROSTOL															
Female															
50 to 59yrs	33	23.37	12.64	27.76	43.48	83.88	28.72	0.00	0.00	0.00	0.00	0.00	0.00	112.61	135.97
60 to 74yrs	75	25.14	14.82	41.06	23.56	79.44	30.96	5.56	0.00	18.34	0.00	0.00	18.34	134.30	159.44
75+yrs	42	22.17	21.17	36.73	24.30	82.20	34.49	0.00	138.62	944.14	0.00	0.00	1082.76	1199.45	1221.62
sub-total of all female	150	23.92	16.12	36.92	28.15	81.19	31.46	2.78	38.81	273.53	0.00	0.00	312.34	427.77	451.69
Male															
50 to 59yrs	24	26.17	15.34	28.05	12.66	56.04	22.00	0.00	0.00	0.00	0.00	0.00	0.00	78.05	104.22
60 to 74yrs	28	25.04	12.14	47.78	31.44	91.36	32.16	0.00	0.00	0.00	0.00	0.00	0.00	123.52	148.56
75+yrs	10	24.20	16.62	34.93	13.83	65.38	23.70	0.00	0.00	0.00	0.00	0.00	0.00	89.08	113.28
sub-total of all male	62	25.34	14.10	38.07	21.33	73.50	26.86	0.00	0.00	0.00	0.00	0.00	0.00	100.36	125.70
Total NSAID & Misoprostol Sub-Cohort	212	24.34	15.53	37.26	26.15	78.94	30.11	1.97	27.46	193.53	0.00	0.00	221.00	332.02	356.35
NSAID & H2/OMEPRAZOLE															
Female															
50 to 59yrs	339	42.32	20.09	90.27	28.25	138.61	38.90	7.37	18.62	27.83	4.61	52.94	104.01	288.89	331.21
60 to 74yrs	623	40.89	18.96	94.00	36.05	149.01	42.63	7.02	10.77	96.64	12.56	53.88	173.84	372.50	413.39
75+yrs	284	41.08	25.49	104.11	38.46	168.06	52.01	6.60	32.51	130.86	14.80	169.68	347.85	574.53	615.60
sub-total of all female	1246	41.32	20.75	95.29	34.48	150.52	43.76	7.02	17.86	85.72	10.91	80.02	194.50	395.80	437.12
Male															
50 to 59yrs	255	40.28	13.25	75.54	25.34	114.13	33.05	7.35	13.36	147.99	0.00	33.60	194.96	349.50	389.78
60 to 74yrs	492	40.37	15.25	90.20	40.65	146.10	40.43	5.93	81.40	201.00	10.96	49.25	342.61	535.07	575.44
75+yrs	120	37.00	16.11	87.48	39.73	143.33	44.68	5.21	6.75	76.95	0.00	0.00	83.70	276.92	313.92
sub-total of all male	867	39.88	14.78	85.51	36.02	136.31	38.85	6.25	51.06	168.24	6.22	41.29	266.81	448.22	488.10
Total NSAID & H2/Omeprazole Sub-Cohort	2113	40.73	18.30	91.28	35.11	144.69	41.74	6.70	31.48	119.58	8.98	62.71	222.75	415.89	456.62

Table 41 Costs (£) Incorporated in the Sensitivity Analysis - when multiple episodes of care represent one single admission - Based on 12 Months

	N	Base Cost Drug Rx	Event Costs NSAID Rx	Event Costs H2/Losec Rx	Event Costs Other Rx	Event Costs All Rx	Costs of GP Visits (Rx)	Costs of all Endoscpies	Costs of all GI admissions	Costs of all CV admissions	Costs of all RH admissions	Costs of all OS admissions	Costs of all admissions	Shadow Costs	Total Costs
COMPARATOR															
Female															
50 to 59yrs	8640		0.00	13.23	19.74	32.97	8.58	2.75	5.95	8.67	0.57	1.95	17.15	61.44	61.44
60 to 74yrs	11380		0.00	17.48	17.36	34.83	8.81	3.33	17.20	46.18	1.11	8.28	72.77	119.74	119.74
75+yrs	5410		0.00	18.99	22.75	41.74	9.95	2.12	25.06	211.47	7.62	49.70	293.85	347.66	347.66
sub-total of all female	25432		0.00	16.35	19.31	35.67	8.97	2.88	15.05	68.59	2.32	14.94	100.90	148.41	148.41
Male															
50 to 59yrs	9617		0.00	13.89	10.39	24.29	5.52	2.82	19.49	30.90	0.00	7.03	57.41	90.04	90.04
60 to 74yrs	9579		0.00	19.89	17.72	37.61	8.29	3.57	16.12	45.57	0.52	8.21	70.42	119.88	119.88
75+yrs	2722		0.00	16.91	21.11	38.01	8.34	2.76	31.90	225.40	0.00	18.14	275.45	324.56	324.56
sub-total of all male	21918		0.00	16.89	14.93	31.81	7.08	3.14	19.56	61.47	0.23	8.92	90.18	132.21	132.21
Total Comparator Cohort	47350		0.00	16.60	17.28	33.88	8.10	3.00	17.14	65.29	1.35	12.15	95.93	140.91	140.91
NSAID ONLY															
Female															
50 to 59yrs	9324	8.05	21.72	14.02	39.35	75.10	28.30	3.66	6.94	40.69	10.69	26.30	84.63	191.69	199.74
60 to 74yrs	13319	7.71	27.18	18.90	42.14	88.22	36.46	4.19	21.40	105.23	14.67	67.92	209.23	338.10	345.81
75+yrs	6768	7.55	31.91	18.76	45.63	96.29	43.33	3.76	81.68	311.23	17.12	187.97	597.99	741.38	748.93
sub-total of all female	29411	7.78	26.54	17.32	42.06	85.92	35.46	3.92	30.69	132.17	13.97	82.35	259.19	384.49	392.27
Male															
50 to 59yrs	7185	7.46	16.50	14.16	31.87	62.53	23.21	3.65	14.15	118.72	2.71	24.72	160.30	249.70	257.16
60 to 74yrs	9594	6.98	23.45	18.23	46.53	88.20	34.91	3.84	16.54	221.41	1.44	59.95	299.33	426.29	433.27
75+yrs	3022	6.69	28.02	15.78	50.53	94.33	40.77	3.24	45.78	244.10	61.25	90.59	441.70	580.05	586.74
sub-total of all male	19801	7.11	21.63	16.38	41.82	79.82	31.56	3.68	20.13	187.61	11.03	51.84	270.61	385.68	392.79
Total NSAID Only Sub-Cohort	49212	7.51	24.56	16.94	41.96	83.47	33.89	3.83	26.44	154.48	12.79	70.08	263.79	384.96	392.47
NSAID & MISOPROSTOL															
Female															
50 to 59yrs	33	23.37	24.75	52.68	143.66	221.10	44.52	0.00	0.00	0.00	0.00	0.00	0.00	265.62	288.99
60 to 74yrs	75	25.14	30.80	91.23	68.93	190.96	52.54	16.67	0.00	55.57	13.31	116.33	185.22	445.38	470.52
75+yrs	42	22.17	31.20	64.28	49.58	145.07	52.06	0.00	224.68	1601.73	0.00	346.98	2173.40	2370.53	2392.70
sub-total of all female	150	23.92	29.58	75.21	79.95	184.74	50.64	8.33	62.91	476.27	6.66	155.32	701.16	944.88	968.80
Male															
50 to 59yrs	24	26.17	28.29	57.45	42.38	128.11	39.49	8.68	0.00	24.94	0.00	252.42	277.36	453.65	479.82
60 to 74yrs	28	25.04	23.34	96.12	107.54	227.00	52.95	0.00	0.00	149.82	0.00	0.00	149.82	429.76	454.80
75+yrs	10	24.20	31.27	75.05	33.55	139.87	38.59	0.00	0.00	0.00	0.00	0.00	0.00	178.46	202.66
sub-total of all male	62	25.34	26.53	77.75	70.38	174.67	45.42	3.36	0.00	77.31	0.00	97.71	175.03	398.48	423.82
Total NSAID & Misoprostol Sub-Cohort	212	24.34	28.69	75.95	77.15	181.79	49.11	6.88	44.51	359.60	4.71	138.47	547.29	785.08	809.42
NSAID & H2/OMEPRAZOLE															
Female															
50 to 59yrs	339	42.32	39.29	184.48	74.80	298.57	67.80	15.36	35.87	51.75	13.90	103.98	205.51	587.24	629.56
60 to 74yrs	623	40.89	37.32	194.05	89.85	321.22	73.38	17.05	20.63	192.46	23.68	103.75	340.51	752.17	793.06
75+yrs	284	41.08	46.42	211.11	84.65	342.18	86.60	9.54	43.91	761.78	31.75	275.94	1113.38	1551.70	1592.78
sub-total of all female	1246	41.32	39.93	195.33	84.57	319.83	74.88	14.88	30.08	283.94	22.86	143.06	479.94	889.53	930.85
Male															
50 to 59yrs	255	40.28	29.30	165.42	67.39	262.11	59.36	15.52	31.21	275.11	0.00	65.00	371.32	708.32	748.60
60 to 74yrs	492	40.37	30.00	192.37	100.22	322.60	70.93	16.09	115.46	416.52	19.09	117.93	669.01	1078.63	1119.00
75+yrs	120	37.00	31.33	188.51	84.10	303.94	77.80	10.42	16.47	142.90	0.00	0.00	159.37	551.52	588.52
sub-total of all male	867	39.88	29.98	183.91	88.33	302.22	68.48	15.14	76.98	337.06	10.83	86.04	510.91	896.76	936.64
NSAID & H2/Omeprazole Sub-Cohort	2113	40.73	35.85	190.65	86.11	312.61	72.25	14.99	49.33	305.74	17.92	119.66	492.65	892.50	933.23

Table 42 Sensitivity Analysis of Risk Factors - 45 Days Follow-up Period

	N	base drugs	co-Rx nsaid	co-Rx ulcer	co-Rx other	gp visit cost	endoscopy	hospital gi	hospital cv	hospital ra	hospital oa	shadow cost	total cost
non-aspirin takers													
comparator	47350	0.00	0.00	3.70	2.16	1.36	0.40	1.32	5.28	0.11	1.70	16.03	16.03
NSAID	41554	8.48	5.86	3.27	4.57	5.07	0.31	4.27	13.05	0.87	7.19	44.47	52.95
misoprostol	206	24.50	9.07	18.86	7.24	11.44	0.00	19.92	26.60	0.00	0.00	93.12	117.62
h2	1683	41.82	8.38	29.23	9.33	11.63	1.49	7.81	22.09	0.93	19.64	110.54	152.35
aspirin takers													
comparator	0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
NSAID	7658	2.25	2.21	3.42	8.53	7.87	0.52	5.09	53.85	0.70	1.88	84.07	86.32
misoprostol	6	18.73	3.15	35.53	12.45	18.05	0.00	0.00	0.00	0.00	0.00	69.18	87.91
h2	430	36.47	2.68	34.40	15.33	14.75	2.91	5.09	92.02	1.01	24.25	192.44	228.90
no prior gi													
comparator	45338	0.00	0.00	2.68	1.95	1.14	0.28	0.89	4.86	0.06	1.60	13.46	13.46
NSAID	47630	7.51	5.27	2.75	5.06	5.36	0.31	4.06	18.95	0.75	6.48	48.99	56.50
misoprostol	185	24.06	7.91	18.04	6.88	10.76	0.00	22.18	29.62	0.00	0.00	95.39	119.45
h2	1740	40.18	7.11	29.74	10.04	11.96	1.80	2.40	34.48	1.15	13.94	112.61	152.80
had prior gi													
comparator	2012	0.00	0.00	26.69	6.87	6.21	3.11	11.09	14.77	1.25	3.96	73.94	73.94
NSAID	1582	7.47	5.90	19.77	9.09	9.84	1.19	14.61	33.02	3.77	2.96	100.15	107.63
misoprostol	27	26.23	15.68	28.20	10.84	17.55	0.00	0.00	0.00	0.00	0.00	72.27	98.50
h2	373	43.27	7.76	32.81	12.94	13.72	1.68	29.91	44.91	0.00	51.55	195.27	238.54
no prior cv													
comparator	44515	0.00	0.00	3.32	1.91	1.23	0.39	1.32	3.21	0.06	1.56	12.99	12.99
NSAID	43143	7.81	5.42	2.95	4.49	5.05	0.26	3.70	12.48	0.93	6.49	41.78	49.59
misoprostol	183	23.76	8.44	17.23	5.71	10.14	0.00	0.00	7.52	0.00	0.00	49.04	72.80
h2	1665	41.10	7.77	28.74	9.03	11.25	1.50	7.89	15.11	0.94	20.01	102.24	143.34
had prior cv													
comparator	2835	0.00	0.00	9.74	6.06	3.34	0.66	1.34	37.89	0.88	3.87	63.79	63.79
NSAID	6069	5.36	4.37	5.74	10.16	8.77	0.93	9.32	68.62	0.20	5.47	113.56	118.92
misoprostol	29	27.95	11.78	32.61	17.94	21.01	0.00	141.51	141.51	0.00	0.00	366.35	394.30
h2	448	39.34	5.19	36.03	16.23	16.03	2.79	4.89	115.16	0.97	22.69	219.98	259.32
no prior endoscopy													
comparator	43892	0.00	0.00	2.08	1.74	1.00	0.20	0.98	4.62	0.12	1.65	12.38	12.38
NSAID	45340	7.50	5.33	2.15	4.81	5.21	0.25	3.76	19.03	0.63	6.40	47.58	55.08
misoprostol	170	24.25	8.81	17.71	7.20	11.59	0.00	24.14	32.23	0.00	0.00	101.68	125.92
h2	1433	38.52	7.29	28.01	8.98	11.71	0.73	7.84	41.63	0.00	18.26	124.44	162.95
had prior endoscopy													
comparator	3458	0.00	0.00	24.34	7.58	5.96	2.95	5.63	13.66	0.00	2.30	62.42	62.42
NSAID	3872	7.59	4.88	16.76	9.64	8.94	1.40	11.80	23.69	3.28	5.98	86.38	93.97
misoprostol	42	24.70	9.25	25.91	8.16	11.77	0.00	0.00	0.00	0.00	0.00	55.09	79.78
h2	680	45.39	7.09	35.07	13.87	13.44	3.98	6.04	25.14	2.94	25.47	133.03	178.42
no prior nsaid													
comparator	47350	0.00	0.00	3.70	2.16	1.36	0.40	1.32	5.28	0.11	1.70	16.03	16.03
NSAID	37871	7.00	4.19	3.52	4.91	4.74	0.34	5.14	20.58	0.45	4.27	48.15	55.14
misoprostol	193	24.23	8.35	18.95	7.40	11.12	0.00	21.26	28.39	0.00	0.00	95.47	119.70
h2	1452	40.11	4.85	28.90	10.53	10.69	1.87	3.22	37.22	0.30	17.03	114.60	154.70
had prior nsaid													
comparator	0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
NSAID	11341	9.23	8.99	2.55	6.13	8.06	0.35	1.90	15.45	2.14	13.35	58.92	68.15
misoprostol	19	25.40	14.48	23.26	7.24	16.75	0.00	0.00	0.00	0.00	0.00	61.72	87.12
h2	661	42.10	12.44	33.32	10.62	15.74	1.58	16.11	34.35	2.37	28.38	154.90	196.99
no risk factors													
comparator	40612	0.00	0.00	0.76	0.88	0.84	0.19	0.83	2.77	0.07	1.51	7.84	7.84
NSAID	27635	7.77	2.29	0.91	2.02	3.80	0.17	4.29	10.22	0.24	5.11	29.05	36.82
misoprostol	116	23.08	3.28	6.40	3.12	8.29	0.00	0.00	11.86	0.00	0.00	32.94	56.02
h2	610	38.15	3.03	11.68	3.71	8.45	0.68	0.00	17.62	0.00	0.00	45.17	83.32
no mortality (survivors)													
comparator	42081	0.00	0.00	3.50	2.11	1.31	0.38	1.11	2.31	0.06	1.63	12.41	12.41
NSAID	42445	7.55	5.08	3.23	4.84	5.15	0.35	3.35	14.00	0.66	5.56	42.23	49.78
misoprostol	184	24.47	8.61	18.05	7.51	10.67	0.00	22.30	29.78	0.00	0.00	96.91	121.38
h2	1767	40.81	6.99	29.68	10.12	11.77	2.12	2.78	32.14	0.89	24.61	121.11	161.91
mortality													
comparator	5269	0.00	0.00	5.32	2.58	1.77	0.59	2.98	28.98	0.51	2.26	45.00	45.00
NSAID	6767	7.24	6.65	3.70	7.35	7.74	0.31	10.92	53.26	1.99	11.42	103.33	110.57
misoprostol	24	23.43	10.84	27.77	6.60	17.89	0.00	0.00	0.00	0.00	0.00	63.10	86.53
h2	346	40.33	8.41	33.38	12.74	14.81	0.00	30.09	57.66	1.25	0.00	158.35	198.68
survivors with no risk factors													
comparator	36721	0.00	0.00	0.73	0.84	0.82	0.19	0.66	1.57	0.00	1.53	6.33	6.33
NSAID	25332	7.74	2.22	0.87	1.95	3.65	0.16	3.11	8.76	0.26	4.62	25.61	33.35
misoprostol	105	23.36	3.15	5.72	3.09	7.35	0.00	0.00	13.10	0.00	0.00	32.41	55.77
h2	548	37.91	3.12	11.41	3.72	8.28	0.76	0.00	16.67	0.00	0.00	43.95	81.86

Table 43 Sensitivity Analysisof Risk Factors - Six Months Follow-up Period

	N	base drugs	co-Rx nsaid	co-Rx ulcer	co-Rx other	gp visit cost	endoscopy	hospital gi	hospital cv	hospital ra	hospital oa	shadow cost	total cost
non-aspirin takers													
comparator	47350	0.00	0.00	7.97	6.62	4.25	1.46	5.63	26.63	1.03	6.04	59.63	59.63
NSAID	41554	8.48	13.50	7.40	14.43	16.85	1.64	10.71	50.64	4.28	35.94	155.40	163.88
misoprostol	206	24.50	15.24	36.23	26.13	29.45	2.02	28.34	199.24	0.00	0.00	336.65	361.15
h2	1683	41.82	21.02	86.65	29.77	39.57	5.94	23.87	76.43	10.26	62.86	356.38	398.20
aspirin takers													
comparator	0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
NSAID	7658	2.25	7.51	8.59	33.29	30.10	2.75	18.45	189.91	3.20	13.31	307.11	309.37
misoprostol	6	18.73	25.51	72.45	26.84	53.03	0.00	0.00	0.00	0.00	0.00	177.84	196.57
h2	430	36.47	7.69	109.40	56.03	50.22	9.69	62.34	297.68	4.34	62.79	660.17	696.63
no prior gi													
comparator	45338	0.00	0.00	5.89	6.09	3.65	1.12	3.59	25.32	0.96	5.88	52.49	52.49
NSAID	47630	7.51	12.55	6.40	16.97	18.54	1.64	9.55	68.62	3.65	32.23	170.15	177.66
misoprostol	185	24.06	14.68	34.68	23.43	28.03	0.00	31.55	50.28	0.00	0.00	182.65	206.71
h2	1740	40.18	18.18	87.67	33.48	40.74	6.23	12.53	114.24	5.57	50.66	369.29	409.48
had prior gi													
comparator	2012	0.00	0.00	54.84	18.52	17.83	9.22	51.73	56.33	2.58	9.68	220.72	220.72
NSAID	1582	7.47	13.00	43.42	29.34	30.13	7.24	83.22	183.64	17.87	37.94	445.80	453.27
misoprostol	27	26.23	21.33	54.95	44.81	44.38	15.43	0.00	1175.64	0.00	0.00	1356.55	1382.78
h2	373	43.27	18.89	108.11	42.70	46.43	8.94	122.90	155.11	25.30	119.70	648.09	691.35
no prior cv													
comparator	44515	0.00	0.00	7.18	5.77	3.93	1.36	5.18	18.11	1.03	5.26	47.81	47.81
NSAID	43143	7.81	12.74	6.80	14.61	17.40	1.68	9.96	45.78	3.66	32.58	145.20	153.02
misoprostol	183	23.76	14.69	30.68	21.61	26.75	2.28	0.00	180.97	0.00	0.00	276.97	300.73
h2	1665	41.10	19.48	86.21	27.86	39.06	6.01	24.55	46.55	6.86	69.07	325.64	366.74
had prior cv													
comparator	2835	0.00	0.00	20.37	19.96	9.33	3.09	12.72	160.53	0.88	18.36	245.24	245.24
NSAID	6069	5.36	11.30	13.22	36.95	29.69	2.82	25.83	260.94	7.32	31.26	419.32	424.68
misoprostol	29	27.95	20.84	78.76	54.86	51.36	0.00	201.29	273.33	0.00	0.00	680.43	708.38
h2	448	39.34	13.94	110.11	62.06	51.70	9.30	58.30	399.86	17.19	39.73	762.19	801.54
no prior endoscopy													
comparator	43892	0.00	0.00	4.53	5.46	3.24	0.72	3.63	25.34	0.88	5.27	49.07	49.07
NSAID	45340	7.50	12.64	5.10	16.26	18.17	1.27	9.98	69.97	3.19	33.00	169.58	177.08
misoprostol	170	24.25	16.25	35.16	22.88	30.03	2.45	34.34	241.44	0.00	0.00	382.55	406.79
h2	1433	38.52	18.24	80.02	30.38	39.69	2.62	29.73	121.09	10.29	65.17	397.23	435.75
had prior endoscopy													
comparator	3458	0.00	0.00	51.64	21.31	17.05	10.84	31.07	43.09	2.91	15.82	193.74	193.74
NSAID	3872	7.59	11.69	36.69	30.34	27.64	8.18	34.62	99.73	14.94	25.56	289.39	296.97
misoprostol	42	24.70	12.61	43.92	39.40	30.47	0.00	0.00	0.00	0.00	0.00	126.39	151.09
h2	680	45.39	18.44	115.00	45.09	46.06	15.32	35.86	122.24	6.44	57.95	462.39	507.78
no prior nsaid													
comparator	47350	0.00	0.00	7.97	6.62	4.25	1.46	5.63	26.63	1.03	6.04	59.63	59.63
NSAID	37871	7.00	7.83	7.78	15.81	15.20	1.77	12.27	68.18	1.80	19.28	149.93	156.92
misoprostol	193	24.23	13.52	36.63	26.54	28.38	2.16	30.25	212.66	0.00	0.00	350.13	374.36
h2	1452	40.11	9.43	83.28	33.57	35.97	6.31	27.64	135.77	5.30	52.41	389.70	429.81
had prior nsaid													
comparator	0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
NSAID	11341	9.23	28.37	6.94	22.56	31.31	1.97	10.73	86.12	11.84	76.27	276.11	285.34
misoprostol	19	25.40	35.94	43.66	22.27	47.75	0.00	0.00	0.00	0.00	0.00	149.62	175.01
h2	661	42.09	37.79	108.84	38.46	54.53	7.56	40.62	90.02	17.29	85.77	480.88	522.97
no risk factors													
comparator	40612	0.00	0.00	3.38	4.67	2.82	0.65	2.79	16.30	0.89	4.52	36.01	36.01
NSAID	27635	7.77	8.15	4.11	10.83	11.87	1.03	8.41	32.62	0.93	21.76	99.72	107.50
misoprostol	116	23.08	12.91	22.54	18.79	21.77	0.00	0.00	11.86	0.00	0.00	87.87	110.95
h2	610	38.15	10.28	56.80	18.59	27.41	2.39	2.42	37.76	0.00	38.83	194.49	232.64
no mortality (survivors)													
comparator	42081	0.00	0.00	7.59	6.41	4.15	1.36	4.38	10.60	0.22	4.14	38.85	38.85
NSAID	42445	7.55	11.88	7.33	15.95	17.74	1.76	9.40	49.45	2.72	24.48	140.70	148.25
misoprostol	184	24.47	13.92	34.95	23.84	27.93	2.26	31.72	223.07	0.00	0.00	357.70	382.18
h2	1767	40.81	17.56	89.35	31.12	40.36	7.43	11.45	95.94	7.73	59.20	360.15	400.95
mortality													
comparator	5269	0.00	0.00	11.02	8.30	5.02	2.29	15.64	154.69	7.47	21.19	225.61	225.61
NSAID	6767	7.24	16.86	9.23	26.23	26.31	2.19	27.74	215.73	12.85	82.17	419.31	426.55
misoprostol	24	23.43	26.07	52.40	41.34	44.49	0.00	0.00	0.00	0.00	0.00	164.30	187.73
h2	346	40.33	22.10	101.14	55.47	48.78	3.01	135.12	251.79	15.80	81.47	714.68	755.00
survivors with no risk factors													
comparator	36721	0.00	0.00	3.25	4.44	2.78	0.62	2.52	7.88	0.18	3.89	25.57	25.57
NSAID	25332	7.74	7.85	3.90	10.48	11.48	0.99	6.61	25.01	0.99	18.79	86.09	93.83
misoprostol	105	23.36	11.96	19.72	12.11	19.47	0.00	0.00	13.10	0.00	0.00	76.36	99.72
h2	548	37.91	10.50	55.87	18.88	26.94	2.28	1.12	17.80	0.00	26.69	160.09	197.99

Table 44 Sensitivity Analysis of Risk Factors - One Year Follow-up Period

	N	base drugs	co-Rx nsaid	co-Rx ulcer	co-Rx other	gp visit cost	endoscopy	hospital gi	hospital cv	hospital ra	hospital oa	shadow cost	hidden cost
non-aspirin takers													
comparator	47350	0.00	0.00	16.60	17.28	8.10	3.00	17.33	65.68	1.35	12.16	141.51	141.51
NSAID	41554	8.48	26.07	16.38	35.25	30.13	3.54	25.43	113.59	12.48	76.74	339.62	348.10
misoprostol	206	24.50	28.45	73.84	73.40	48.05	7.08	46.32	371.58	4.85	142.76	796.31	820.81
h2	1683	41.82	40.82	181.22	73.74	68.61	14.48	39.72	220.49	19.18	131.62	789.87	831.69
aspirin takers													
comparator	0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
NSAID	7658	2.25	16.39	19.96	78.40	54.28	5.36	33.48	386.65	14.59	34.54	643.66	645.91
misoprostol	6	18.73	37.11	148.42	206.12	85.75	0.00	0.00	0.00	0.00	0.00	477.41	496.13
h2	430	36.47	16.40	227.54	134.53	86.53	16.76	88.76	657.83	14.59	73.70	1316.65	1353.11
no prior gi													
comparator	45338	0.00	0.00	12.46	16.00	7.09	2.34	13.40	63.31	1.23	11.57	127.40	127.40
NSAID	47630	7.51	24.54	14.45	40.97	33.27	3.49	22.77	149.63	12.34	69.33	370.79	378.30
misoprostol	185	24.06	27.68	69.36	72.37	45.52	4.50	51.58	225.78	5.40	101.19	603.38	627.44
h2	1740	40.18	35.72	181.23	80.27	70.52	13.05	20.69	303.52	13.86	109.97	828.83	869.02
had prior gi													
comparator	2012	0.00	0.00	109.82	46.31	30.91	17.81	105.79	118.99	4.25	25.49	459.38	459.38
NSAID	1582	7.47	25.09	91.96	71.82	52.35	14.09	144.61	350.39	26.91	95.65	872.87	880.35
misoprostol	27	26.23	35.60	121.14	109.93	73.72	23.15	0.00	1287.97	0.00	395.87	2047.37	2073.61
h2	373	43.27	36.45	234.56	113.39	80.31	24.02	185.03	337.36	38.21	165.84	1215.17	1258.44
no prior cv													
comparator	44515	0.00	0.00	15.02	15.35	7.56	2.86	13.24	46.33	1.32	9.47	111.14	111.14
NSAID	43143	7.81	24.81	15.18	35.56	31.28	3.56	23.99	97.59	13.13	70.45	315.56	323.38
misoprostol	183	23.76	27.93	66.46	59.32	44.21	7.97	0.00	287.47	5.46	83.19	582.01	605.78
h2	1665	41.10	37.82	179.94	65.75	67.83	14.51	42.93	185.71	9.83	113.58	717.92	759.02
had prior cv													
comparator	2835	0.00	0.00	41.36	47.69	16.58	5.14	81.57	369.53	1.92	54.50	618.31	618.31
NSAID	6069	5.36	22.77	29.43	87.48	52.39	5.73	45.83	571.89	10.53	68.18	894.23	899.59
misoprostol	29	27.95	33.49	135.82	189.68	80.07	0.00	329.02	825.44	0.00	489.12	2082.63	2110.58
h2	448	39.34	28.51	230.44	161.78	88.67	16.74	74.85	769.52	49.11	143.08	1562.72	1602.06
no prior endoscopy													
comparator	43892	0.00	0.00	9.69	14.76	6.39	1.66	14.25	61.57	1.04	10.62	119.97	119.97
NSAID	45340	7.50	24.73	11.82	39.34	32.66	2.82	22.65	147.68	12.30	72.35	366.35	373.85
misoprostol	170	24.25	30.17	71.21	69.80	48.27	8.58	56.13	441.02	5.87	172.99	904.04	928.29
h2	1433	38.52	35.44	163.63	76.42	68.23	6.69	33.10	327.71	14.55	117.32	843.10	881.61
had prior endoscopy													
comparator	3458	0.00	0.00	104.38	49.34	29.78	20.00	56.44	117.90	5.32	31.78	414.93	414.93
NSAID	3872	7.59	22.65	76.92	72.74	48.26	15.60	73.91	254.42	18.78	44.67	627.93	635.52
misoprostol	42	24.70	22.69	95.14	106.92	52.55	0.00	0.00	37.41	0.00	0.00	314.71	339.41
h2	680	45.39	36.70	247.58	106.52	80.73	32.48	84.76	271.09	25.78	125.13	1010.77	1056.16
no prior nsaid													
comparator	47350	0.00	0.00	16.60	17.28	8.10	3.00	17.33	65.68	1.35	12.16	141.51	141.51
NSAID	37871	7.00	14.49	17.09	40.03	27.37	3.70	27.78	143.26	7.17	40.95	321.82	328.82
misoprostol	193	24.23	25.41	75.81	78.96	46.37	7.56	49.44	396.60	0.00	130.89	811.03	835.27
h2	1452	40.11	17.77	173.62	86.71	62.53	14.20	41.39	271.37	13.28	93.28	774.15	814.26
had prior nsaid													
comparator	0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
NSAID	11341	9.23	58.18	16.44	48.43	55.67	4.26	23.01	198.91	31.66	167.77	604.33	613.56
misoprostol	19	25.40	62.03	77.43	58.79	76.96	0.00	0.00	0.00	52.55	218.28	546.05	571.45
h2	661	42.09	75.55	228.05	84.81	93.60	16.70	67.95	393.24	28.89	178.17	1166.97	1209.07
no risk factors													
comparator	40612	0.00	0.00	7.37	12.84	5.66	1.52	8.79	42.07	0.99	8.04	87.30	87.30
NSAID	27635	7.77	14.74	9.49	28.23	21.46	2.39	21.45	66.64	4.65	44.61	213.67	221.44
misoprostol	116	23.08	24.75	49.92	55.70	35.83	7.18	0.00	174.71	0.00	42.81	390.92	414.00
h2	610	38.15	18.25	114.10	41.75	47.18	6.83	4.95	79.16	3.42	80.45	396.09	434.24
no mortality (survivors)													
comparator	42081	0.00	0.00	15.74	16.72	7.97	2.65	9.32	27.68	0.22	7.27	87.57	87.57
NSAID	42445	7.55	23.19	16.31	38.33	31.93	3.61	17.78	92.77	6.38	56.62	286.92	294.47
misoprostol	184	24.47	26.22	72.38	63.49	46.21	7.93	51.86	304.73	0.00	107.62	680.43	704.90
h2	1767	40.81	34.81	186.98	76.07	70.19	15.33	23.52	176.25	11.23	118.77	713.14	753.94
mortality													
comparator	5269	0.00	0.00	23.45	21.81	9.11	5.77	81.31	369.21	10.42	51.23	572.31	572.31
NSAID	6767	7.24	33.15	20.89	64.76	46.16	5.20	82.52	553.19	53.17	155.20	1014.24	1021.48
misoprostol	24	23.43	44.93	99.43	166.97	68.18	0.00	0.00	731.24	35.66	343.10	1489.51	1512.95
h2	346	40.33	41.17	209.36	137.43	82.81	13.25	183.40	989.96	53.54	125.29	1836.18	1876.51
survivors with no risk factors													
comparator	36721	0.00	0.00	7.02	12.24	5.62	1.36	5.80	21.00	0.18	5.93	59.14	59.14
NSAID	25332	7.74	14.20	9.02	26.15	20.84	2.15	12.38	44.93	4.60	38.37	172.65	180.39
misoprostol	105	23.36	22.97	45.45	28.88	32.95	7.94	0.00	34.45	0.00	47.30	219.93	243.28
h2	548	37.91	18.49	112.62	38.85	46.66	6.84	3.94	54.01	3.81	65.53	350.75	388.66

REFERENCES

1. Yuen P. OHE Compendium of health statistics: Office of Health Economics, 2002.

2. Audit Scotland. Overview of the National Health Service in Scotland 2000/2001. Edinburgh: Audit Scotland, 2001.

3. Sani M. Put drug costs in perspective. *Pharmacy in Practice* 1998;**July/August:**273.

4. Scotland NHSi. Scottish Health Statistics 2000. Edinburgh: ISD, 2001.

5. Rimmer B, Ross SK. Perspectives on primary care prescribing. *Health Bull* 1997;**55:**243-262.

6. McGavock H. Strategies to improve the cost effectiveness of general practitioner prescribing. An international perspective. *Pharmacoeconomics* 1997;**12**(3)**:**307-11.

7. National Health Service in Scotland. National Health Service in Scotland: annual report 1998-9. Edinburgh: ISD, 1999.

8. Select Committee on Health. The cost and availability of generic drugs to the NHS. London: Stationary Office, 1999.

9. British National Formulary (No 44). London: BMA, RPS, 2002.

10. Scottish Intercollegiate Guidelines Network (SIGN). Community management of lower respiratory tract infection in adults (SIGN publication No 59). Edinburgh: SIGN, 2002.

11. Ryan M, Yule B, Bond C, Taylor RJ. Scottish general practitioners' attitudes and knowledge in respect of prescribing costs. *BMJ* 1990;**300**(6735)**:**1316-8.

12. The future of NHS: a framework for debate. London: King's Fund, 2002.

13. Hart J, Salman H, Bergman M, Neuman V, Rudniki C, al. e. Do drug costs affect physicians' prescription decisions? *J Int Med* 1997;**241:**415-20.

14. Drummond M, Jonsson B, Rutten F. The role of economic evaluation in the pricing and reimbursement of medicines. *Health Policy* 1997;**40**(3)**:**199-215.

15. Kernick D, Cox A, Powell R, Reinhold D, Sawkins J, Warin A. A cost consequence study of the impact of a dermatology-trained practice nurse on the quality of life of primary care patients with eczema and psoriasis. *Br J Gen Pract* 2000;**50**(456)**:**555-8.

16. O'Brien B, Levine M, Willan A, et al. Economic evaluation of outpatient treatment with low-molecular-weight heparin for proximal vein thrombosis. *Arch Intern Med* 1999;**159**(19)**:**2298-304.

17. Mugford M, Kingston J, Chalmers I. Reducing the incidence of infection after caesarean section: implications of prophylaxis with antibiotics for hospital resources. *BMJ* 1989;**299**(6709)**:**1003-6.

18. Jonsson B, Christiansen C, Johnell O, Hedbrandt J. Cost-effectiveness of fracture prevention in established osteoporosis. *Osteoporos Int* 1995;**5**(2)**:**136-42.

19. Ryan M, Miedzybrodzka Z, Fraser L, Hall M. Genetic information but not termination: pregnant women's attitudes and willingness to pay for carrier screening for deafness genes. *J Med Genet* 2003;**40**(6)**:**e80.

20. de Pouvourville G. The economic consequences of NSAID-induced gastropathy: the French context. *Scand J Rheumatol Suppl* 1992;**96:**49-53.

21. Knill-Jones R. An economic evaluation of arthrotec in the treatment of arthritis. *Br J Med Econ* 1992;**5:**51-58.

22. Australia Co. Guidelines for the pharmaceutical industry on preparation of submissions to the Pharmaceutical Benefits Advisory Committee: including submissions involving economic analyses. Canberra: Australian Government Printing Office, 1995.

23. Assessment CCOfHT. Guidelines for economic evaluation of pharmaceuticals: Canada. Ottawa: Canadian Coordinating Office for Health Technology Assessment, 1997.

24. HEALTH 21: an introduction to the health for all policy framework for the WHO European region, 1998.

25. Excellence NIfC. Old guidance - Zanamivir (Relenza): http://www.nice.org.uk/page.aspx?o=7486, 1999 (last accessed June 2004).

26. Dent TH, Sadler M. From guidance to practice: Why NICE is not enough. *BMJ* 2002;**324**(7341):842-5.

27. Burke K. No cash to implement NICE, health authorities tell MPs. *BMJ* 2002;**324:**258.

28. World Health Organization (WHO). International drug monitoring: the role of national centres. *Tech Rep Ser WHO* 1972;**498**.

29. Committee of Safety of Medicine (CSM). Suspected adverse drug reaction (ADR) reporting and the Yellow Card Scheme: guidance notes. London: CSM, 2002.

30. Drug Safety Research Unit (DSRU) Southampton, UK: www.dsru.org, last accessed June 2004.

31. Medicines & Healthcare products Regulatory Agency (MHRA) London. General practice research database (GPRD): www.gprd.com, last accessed June 2004.

32. IMS Health: http://www.ims-global.com/disease_analyzer/patient_and_features.htm, last accessed June 2004.

33. NATIOnal Health Service in Scotland. General Practice Administration System for Scotland (GPASS): www.gpass.co.uk, last accessed June 2004.

34. National Health Service Scotland: Information and Statistics Division. Continuous Morbidity Recording: www.show.scot.nhs.uk/isdonline/CMR, last accessed June 2004.

35. Primary Care Clinical Informatics Unit (PCCIU). PCCIU Services for practice: http://www.abdn.ac.uk/~gpr180/practice_services.htm, last accessed June 2004.

36. Primary Care Clinical Informatics Unit (PCCIU). Practice report utility for old GPASS: http://www.abdn.ac.uk/~gpr180/oldpru.htm, last accessed June 2004.

37. Committee of Safety of Medicine (CSM). Adverse drug reactions (ADRs) and reporting to the Yellow Card Scheme. Liverpool: CSM, 2002.

38. Smith CC, Bennett PM, Pearce HM, et al. Adverse drug reactions in a hospital general medical unit meriting notification to the Committee on Safety of Medicines. *Br J Clin Pharmacol* 1996;**42**(4):423-9.

39. Rawlins MD. Pharmacovigilance: paradise lost, regained or postponed? The William Withering Lecture 1994. *J R Coll Physicians Lond* 1995;**29**(1):41-9.

40. Committee of Safety of Medicine (CSM) Scotland. Annual CSM Scotland report: CSM Scotland, 2002.

41. Information and Statistics Division. Summary statistics for Scotland 2003: http://www.isdscotland.org/isd/info3.jsp?pContentID=2226&p_applic=CCC&p_service=Content.show&, last accessed June 2004.

42. Einarson TR. Drug-related hospital admissions. *Ann Pharmacother* 1993;**27:**832.

43. Lazarou J, Pomeranz BH, Corey PN. Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. *JAMA* 1998;**279**(15)**:**1200-5.

44. Wiffen P, Gill M, Edwards J, Moore A. Adverse drug reactions in hospital patients: a systematic review of the prospective and retrospective studies. *Bandolier Extra* 2002;**June**.

45. Beijer HJ, de Blaey CJ. Hospitalisations caused by adverse drug reactions (ADR): a meta-analysis of observational studies. *Pharm World Sci* 2002;**24**(2)**:**46-54.

46. Lumley CE, Walker SR, Hall GC, Staunton N, Grob PR. The under-reporting of adverse drug reactions seen in general practice. *Pharm Med* 1986;**1**(205-212).

47. Lacoste-Roussillon C, Pouyanne P, Haramburu F, Miremont G, Begaud B. Incidence of serious adverse drug reactions in general practice: a prospective study. *Clin Pharmacol Ther* 2001;**69**(6)**:**458-62.

48. CSM update. *BMJ* 1986;**292:**614.

49. CSM update. *BMJ* 1986;**292:**1190-1191.

50. Alhava E. Reported adverse drug reactions and consumption of non-steroidal anti-inflammatory drugs. *Pharmacol Toxicol* 1994;**75 Suppl 2:**37-43.

51. Brooks PM, Day RO. Nonsteroidal antiinflammatory drugs--differences and similarities. *N Engl J Med* 1991;**324**(24)**:**1716-25.

52. Furst DE. Are there differences among nonsteroidal antiinflammatory drugs? Comparing acetylated salicylates, nonacetylated salicylates, and nonacetylated nonsteroidal antiinflammatory drugs. *Arthritis Rheum* 1994;**37**(1):1-9.

53. Keys J, Beardon PH, Lau C, Lang CC, McDevitt DG. General practitioners' use of non-steroidal anti-inflammatory drugs in Tayside and Fife regions. *J R Soc Med* 1992;**85**(8):442-5.

54. Henry D, Lim LL, Garcia Rodriguez LA, et al. Variability in risk of gastrointestinal complications with individual non-steroidal anti-inflammatory drugs: results of a collaborative meta-analysis. *BMJ* 1996;**312**(7046):1563-6.

55. Henry DA. Side-effects of non-steroidal anti-inflammatory drugs: anti-rheumatic drugs. *Baillieres Clin Rheumatol* 1998;**2**(2):425-454.

56. Rostom A, Wells G, Tugwell P, Welch V, Dube C, McGowan J. The prevention of chronic NSAID induced upper gastrointestinal toxicity: a Cochrane collaboration metaanalysis of randomized controlled trials. *J Rheumatol* 2000;**27**(9):2203-14.

57. Coles LS, Fries JF, Kraines RG, Roth SH. From experiment to experience: side effects of nonsteroidal anti-inflammatory drugs. *Am J Med* 1983;**74**(5):820-8.

58. Husby G, Holme I, Rugstad HE, Herland OB, Giercksky KE. A double-blind multicentre trial of piroxicam and naproxen in osteoarthritis. *Clin Rheumatol* 1986;**5**(1):84-91.

59. Kaufman DW, Kelly JP, Sheehan JE, et al. Nonsteroidal anti-inflammatory drug use in relation to major upper gastrointestinal bleeding. *Clin Pharmacol Ther* 1993;**53**(4):485-94.

60. Singh G, Ramey DR, Morfeld D, Fries JF. Comparative toxicity of non-steroidal anti-inflammatory agents. *Pharmacol Ther* 1994;**62**(1-2):175-91.

61. Allison MC, Howatson AG, Torrance CJ, Lee FD, Russell RI. Gastrointestinal damage associated with the use of nonsteroidal antiinflammatory drugs. *N Engl J Med* 1992;**327**(11):749-54.

62. Levi S, Goodlad RA, Lee CY, et al. Inhibitory effect of non-steroidal anti-inflammatory drugs on mucosal cell proliferation associated with gastric ulcer healing. *Lancet* 1990;**336**(8719):840-3.

63. Venning GR. Identification of adverse reactions to new drugs. II--How were 18 important adverse reactions discovered and with what delays? *BMJ* 1983;**286**(6361):289-92.

64. Langman MJ, Weil J, Wainwright P, et al. Risks of bleeding peptic ulcer associated with individual non-steroidal anti-inflammatory drugs. *Lancet* 1994;**343**(8905):1075-8.

65. NSAID: time to re-evaluate gut toxicity. *Lancet* 1994;**343:**1051.

66. Jacyna M. Serious gastrointestinal adverse events to NSAID: complicatioons in the treatment of arthritis. *Br J Med Econ* 1992;**5:**15-22.

67. Clive DM, Stoff JS. Renal syndromes associated with nonsteroidal antiinflammatory drugs. *N Engl J Med* 1984;**310**(9):563-72.

68. Nephrotoxicity of non-steroidal anti-inflammatory drugs. *Lancet* 1994;**344:**515-518.

69. Bunning RD, Barth WF. Sulindac. A potentially renal-sparing nonsteroidal anti-inflammatory drug. *JAMA* 1982;**248**(21):2864-7.

70. Garcia Rodriguez LA, Williams R, Derby LE, Dean AD, Jick H. Acute liver injury associated with nonsteroidal anti-inflammatory drugs and the role of risk factors. *Arch Intern Med* 1994;**154**(3):311-6.

71. Carson JL, Willett LR. Toxicity of nonsteroidal anti-inflammatory drugs. An overview of the epidemiological evidence. *Drugs* 1993;**46 Suppl 1:**243-8.

72. Stern RS, Bigby M. An expanded profile of cutaneous reactions to nonsteroidal anti-inflammatory drugs. Reports to a specialty-based system for spontaneous reporting of adverse reactions to drugs. *JAMA* 1984;**252**(11)**:**1433-7.

73. Day RO, Graham GG, Williams KM, al. e. Clinical pharmacology for non-steroidal anti-inflammatory drugs. New York: Perganon Press Inc.

74. Hoppmann RA, Peden JG, Ober SK. Central nervous system side effects of nonsteroidal anti-inflammatory drugs. Aseptic meningitis, psychosis, and cognitive dysfunction. *Arch Intern Med* 1991;**151**(7)**:**1309-13.

75. Carson JL, Strom BL, Duff A, Gupta A, Das K. Safety of nonsteroidal anti-inflammatory drugs with respect to acute liver disease. *Arch Intern Med* 1993;**153**(11)**:**1331-6.

76. Pope JE, Anderson JJ, Felson DT. A meta-analysis of the effects of nonsteroidal anti-inflammatory drugs on blood pressure. *Arch Intern Med* 1993;**153**(4)**:**477-84.

77. MacGillivray S, Arroll B, Hatcher S, et al. Efficacy and tolerability of selective serotonin reuptake inhibitors compared with tricyclic antidepressants in depression treated in primary care: systematic review and meta-analysis. *BMJ* 2003;**326**(7397)**:**1014.

78. Price JS, Waller PC, Wood SM, MacKay AV. A comparison of the post-marketing safety of four selective serotonin re-uptake inhibitors including the investigation of symptoms occurring on withdrawal. *Br J Clin Pharmacol* 1996;**42**(6)**:**757-63.

79. Trindade E, Menon D. Selective serotonin reuptake inhibitors (SSRIs) for major depression part 1: evaluation of the clinical literature. *Canadian Coordiating Office for Health Technology Assessment* 1997.

80. Song F, Freemantle N, Sheldon TA, et al. Selective serotonin reuptake inhibitors: meta-analysis of efficacy and acceptability. *BMJ* 1993;**306**(6879):683-7.

81. Goldstein BJ, Goodnick PJ. Selective serotonin reuptake inhibitors in the treatment of affective disorders--III. Tolerability, safety and pharmacoeconomics. *J Psychopharmacol* 1998;**12**(3 Suppl B):S55-87.

82. Rosen RC, Lane RM, Menza M. Effects of SSRIs on sexual function: a critical review. *J Clin Psychopharmacol* 1999;**19**(1):67-85.

83. Ferguson JM, Feighner JP. Fluoxetine-induced weight loss in overweight non-depressed humans. *Int J Obes* 1987;**11 Suppl 3:**163-70.

84. Sussman N, Ginsberg D. Rethinking side effects of the selective serotonin reuptake inhibitors: sexual dysfunction and weight gain. *Psychiatr Ann* 1998;**28:**89-97.

85. De Wilde J, Spiers R, Mertens C, Bartholome F, Schotte G, Leyman S. A double-blind, comparative, multicentre study comparing paroxetine with fluoxetine in depressed patients. *Acta Psychiatr Scand* 1993;**87**(2):141-5.

86. Ambrosioni E, Leonetti G, Pessina AC, Rappelli A, Trimarco B, Zanchetti A. Patterns of hypertension management in Italy: results of a pharmacoepidemiological survey on antihypertensive therapy. Scientific Committee of the Italian Pharmacoepidemiological Survey on Antihypertensive Therapy. *J Hypertens* 2000;**18**(11):1691-9.

87. Materson BJ, Preston RA. Angiotensin-converting enzyme inhibitors in hypertension. A dozen years of experience. *Arch Intern Med* 1994;**154**(5):513-23.

88. Kalra PA, Kumwenda M, MacDowall P, Roland MO. Questionnaire study and audit of use of angiotensin converting enzyme inhibitor and monitoring in general practice: the need for guidelines to prevent renal failure. *BMJ* 1999;**318**(7178):234-7.

89. Kvasz M, Allen IE, Gordon MJ, et al. Adverse drug reactions in hospitalized patients: A critique of a meta-analysis. *MedGenMed* 2000;**2**(2):E3.

90. Bates DW, Spell N, Cullen DJ, et al. The costs of adverse drug events in hospitalized patients. *JAMA* 1997;**277**(4):307-311.

91. Classen DC, Pestotnik SL, Evans RS, Lloyd JF, Burke JP. Adverse drug events in hospitalized patients: excess length of stay, extra costs, and attributable mortality. *JAMA* 1997;**277**(4):301-6.

92. Blower AL, Brooks A, Fenn GC, et al. Emergency admissions for upper gastrointestinal disease and their relation to NSAID use. *Aliment Pharmacol Ther* 1997;**11**(2):283-91.

93. Hawkey CJ, Cullen DJ, Greenwood DC, Wilson JV, Logan RF. Prescribing of nonsteroidal anti-inflammatory drugs in general practice: determinants and consequences. *Aliment Pharmacol Ther* 1997;**11**(2):293-8.

94. MacDonald TM, Morant SV, Robinson GC, et al. Association of upper gastrointestinal toxicity of non-steroidal anti-inflammatory drugs with continued exposure: cohort study. *BMJ* 1997;**315**(7119):1333-7.

95. National Health Service in Scotland. Scottish Health Statistics 2000. Edinburgh: ISD, 2001.

96. Moore RA, Philllips CJ. Cost of NSAID adverse effects to the NHS. *J Med Econ* 1999;**2:**45-55.

97. Simon GE, VonKorff M, Heiligenstein JH, et al. Initial antidepressant choice in primary care. Effectiveness and cost of fluoxetine vs tricyclic antidepressants. *JAMA* 1996;**275**(24)**:**1897-902.

98. Jönsson B, Bebbington P. Economic studies of the treatment of depressive illness. Chichester: John Wiley & Sons, 1993.

99. Revicki DA, Brown RE, Keller MB, Gonzales J, Culpepper L, Hales RE. Cost-effectiveness of newer antidepressants compared with tricyclic antidepressants in managed care settings. *J Clin Psychiatry* 1997;**58**(2)**:**47-58.

100. Doyle JJ, Casciano J, Arikian S, Tarride JE, Gonzalez MA, Casciano R. A multinational pharmacoeconomic evaluation of acute major depressive disorder (MDD): a comparison of cost-effectiveness between venlafaxine, SSRIs and TCAs. *Value Health* 2001;**4:**16-31.

101. Hotopf M, Lewis G, Normand C. Are SSRIs a cost-effective alternative to tricyclics? *Br J Psychiatry* 1996;**168**(4)**:**404-9.

102. Heart and stroke statistical update. Dallas: American Heart Association, 1998.

103. Care. SCoTAiH. Moderately elevated blood pressure. *J Int Med* 1996;**238**(1-225).

104. Ramsey SD, Neil N, Sullivan SD, Perfetto E. An economic evaluation of the JNC hypertension guidelines using data from a randomized controlled trial. Joint National Committee. *J Am Board Fam Pract* 1999;**12**(2)**:**105-14.

105. Hilleman DE, Mohiuddin SM, Lucas BD, Jr., Stading JA, Stoysich AM, Ryschon K. Cost-minimization analysis of initial antihypertensive therapy in patients with mild-to-moderate essential diastolic hypertension. *Clin Ther* 1994;**16**(1):88-102; discussion 87.

106. Pearce KA, Furberg CD, Psaty BM, Kirk J. Cost-minimization and the number needed to treat in uncomplicated hypertension. *Am J Hypertens* 1998;**11**(5):618-29.

107. Roth MS, Davenport RC, Simpson WJ. Assessing the econoic value of antihypertensive medications. *Am J Manag Care* 1998;**4:**1267-75.

108. Gray A, Clarke P, Raikou M, et al. An economic evaluation of atenolol vs. captopril in patients with Type 2 diabetes (UKPDS 54). *Diabet Med* 2001;**18**(6):438-44.

109. Briscoe TA, Dearing CJ. Clinical and economic effects of replacing enalapril with benazepril in hypertensive patients. *Am J Health Syst Pharm* 1996;**53**(18):2191-3.

110. Gill TH, Hauter F, Pelter MA. Conversions from captopril to lisinopril at a dosage ratio of 5:1 result in comparable control of hypertension. *Ann Pharmacother* 1996;**30**(1):7-11.

111. McDonough KP, Weaver RH, Viall GD. Enalapril to lisinopril: economic impact of a voluntary angiotensin-converting enzyme-inhibitor substitution program in a staff-model health maintenance organization. *Ann Pharmacother* 1992;**26**(3):399-404.

112. Drummond M, Cooke J, Walley T. Economic evaluation under managed competition: evidence from the U.K. *Soc Sci Med* 1997;**45**(4):583-95.

113. Hoffmann C, Graf von der Schulenburg JM. The influence of economic evaluation studies on decision making. A European survey. The EUROMET group. *Health Policy* 2000;**52**(3):179-92.

114. Duthie T, Trueman P, Chancellor J, Diez L. Research into the use of health economics in decision making in the United Kingdom--Phase II. Is health economics 'for good or evil'? *Health Policy* 1999;**46**(2):143-57.

115. Hoffmann C, Stoykova BA, Nixon J, Glanville JM, Misso K, Drummond MF. Do health-care decision makers find economic evaluations useful? The findings of focus group research in UK health authorities. *Value Health* 2002;**5**(2):71-8.

116. Walley T, Barton S, Cooke J, Drummond M. Economic evaluations of drug therapy: attitudes of primary care prescribing advisers in Great Britain. *Health Policy* 1997;**41**(1):61-72.

117. Ross J. The use of economic evaluation in health care: Australian decision makers' perceptions. *Health Policy* 1995;**31**:103-110.

118. Bandolier: "evidence based thinking about health care": http://www.jr2.ox.ac.uk/bandolier/, last accessed June 2004.

119. NHS Centre for Review and Dissemination. Effective health care. London: Royal Society of Medicine Press, 1999.

120. Durgs and Therapeutics Bulletin: http://www.dtb.org.uk/dtb/, last accessed June 2004.

121. Drummond MF, Stoddart GL, Torrance GW. Critical assessment of economic evaluation. Economic Evaluation of Health Care Programmes. 2nd edition ed. Oxford: Oxford Medical Publications, 1997.

122. National Health Service in Scotland. Scottish health service costs 1994/5. Edinburgh: Information and Statistics Division (ISD), 1995.

123. McMahon AD. Observation and experiment with the efficacy of drugs: a warning example from a cohort of nonsteroidal anti-inflammatory and ulcer-healing drug users. *Am J Epidemiol* 2001;**154**(6):557-62.

124. Bentkover JD, Baker AM, Kaplan H. Nabumetone in elderly patients with osteoarthritis. *Pharmacoeconomics* 1994;**5**(4):335-342.

125. Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials* 1996;**17**(1):1-12.

126. Jones MI, Greenfield SM, Jowett S, Nayak A, Stevenson FA, Bradley C. Monitoring prescribign: GP's use of prescribing analysis and cost (PACT) data. *Primary Health Care Reserach and Development* 2002;**3:**105-114.

127. Manson J. Qualitative researching. London: SAGE Publications, 2002.

128. ATLAS.ti: http://www.dtb.org.uk/dtb/, last accessed June 2004.

129. Abe T. Piroxicam as a new adjunct for the treatment of rheumatoid arthritis. *Am J Med* 1982;**72:**39-44.

130. Abruzzo JL, Gordon GV, Meyers AR. Double-blind study comparing piroxicam and aspirin in the treatment of osteoarthritis. *Am J Med* 1982;**Feb 16:**45-49.

131. Aylward M, Holly F, Maddock J, Wheeldon R. Treatment of rheumatoid arthritis with tolmetin: a comparison with alclofenac. *Curr Med Res Opin* 1977;**4**(10):695-702.

132. Bellamy N, Buchanan WW, Grace E. Double-blind randomized controlled rial of isoxicam vs piroxicam in elderly patients with osteoarthritis of the hip and knee. *Br J Clin Pharmac* 1986;**22:**149S-155S.

133. Berry H, Coquelin J-P, Gordon A, Seymour D. Antrafenine, naproxen and placebo in osteoarthritis: a comparative study. *Br J Rheumatol* 1983;**22:**89-94.

134. Bijlsma A. The long-term efficacy and tolerability of voltaren (diclofenac sodium) and indomethacin in rheumatoid arthritis. *Scand J Rheumatol* 1978;**Suppl 22:**74-80.

135. Blechman WJ, Schmid FR, April PA, Wilson CH, Brooks CD. Ibuprofen or aspirin in rheumatoid arthritis therapy. *JAMA* 1975;**233:**336-339.

136. Bowers DE, Dyer HR, Fosdick WM, et al. Naproxen in rheumatoid arthritis. *Ann Intern Med* 1975;**83:**470-475.

137. Brewis IDL. A comparative study of flurbiprofen and indomethacin in rheumatoid arthritis. *Curr Med Res Opin* 1977;**5**(1)**:**48-52.

138. Brooke JW. Fenoprofen therapy in large-joint osteoarthritis: double-blind comparison with aspirin and longterm experience. *J Rheumatol* 1976;**2:**71-5.

139. Brown BL, Johnson JH, Hearron MS. Double-blind comparison of flurbiprofen and sulindac for the treatment of osteoarthritis. *Am J Med* 1986;**80**(suppl 3A)**:**112-117.

140. Cardoe M, Steele CE. A double-blind crossover comparison of tolmetin sodium and phenylbutazone in the treatment of rheumatoid arthritis. *Curr Med Res Opin* 1977;**4**(10)**:**688-694.

141. Castles JJ, Moore TL, Vaughan JH, et al. Multicentre comparison of naproxen and indomethacin in rheumatoid arthritis. *Arch Intern Med* 1978;**138:**362-366.

142. Daymond TJ, Thompson M, Akbar FA, Chestney V. A controlled trial of tiaprofenic acid versus ibuprofen in rheumatoid arthritis. *Rheumatol Rehabil* 1979;**18**(4)**:**257-60.

143. Fries JF, Britton MC. Fenoprofen calcium in rheumatoid arthritis. A controlled double-blind crossover evaluation. *Arthritis Rheum* 1973;**16**(5):629-34.

144. Gyory AN, Bloch M, Burry HC, Grahame R. Orudis in management of rheumatoid arthritis and osteoarthrosis of the hip: comparison with indomethacin. *BMJ* 1972;**4**(837):398-400.

145. Kirchheiner B, Fossgreen J, Tophoj E, Zachariae E. Clinical evaluation of ketoprofen (Orudis) in rheumatoid arthritis: a double-blind cross-over comparison with indomethacin. *Rheumatol Rehabil* 1976;**Suppl:**50-1.

146. Kruger HH. Flurbiprofen and indomethacin in the treatment of rheumatoid arthritis: a double-blind crossover study. *Curr Med Res Opin* 1977;**5**(1):77-84.

147. Liyanage SP, Macauley DI, English JR. Naproxen and sulindac in the treatment of osteoarthritis of the hip and knee. *Rheumatol Rehabil* 1981;**20**(3):184-7.

148. McMillen JI. Tolmetin sodium vs ibuprofen in rheumatoid arthritic patients previously untreated with either drug: a double-blind crossover study. *Curr Ther Res Clin Exp* 1977;**22**(2):266-275.

149. Mills SB, Bloch M, Bruckner FE. Double-blind cross-over study of ketoprofen and ibuprofen in management of rheumatoid arthritis. *BMJ* 1973;**4**(5884):82-4.

150. Vasey FB, Germain BF, Espinoza LR, et al. Controlled evaluation of nabumetone in the treatment of active adult rheumatoid arthritis. Nabumetone versus naproxen double-blind parallel study. *Am J Med* 1987;**83**(4B):55-9.

151. Vetter G. Double-blind comparative clinical trial with S-adenosylmethionine and indomethacin in the treatment of osteoarthritis. *Am J Med* 1987;**83**(5A):78-80.

152. Wollheim FA, Lindroth Y, Sjoblom KG. A comparison of ketoprofen and naproxen in rheumatoid arthritis. *Rheumatol Rehabil* 1978;**Suppl:**78-83.

153. Ansseau M, Papart P, Troisfontaines B, et al. Controlled comparison of milnacipran and fluoxetine in major depression. *Psychopharmacology* 1994;**114:**131-137.

154. Bennie EH, Mullin JM, martindale JJ. A double-blind multicenter trial comparing sertraline and fluoxetine in outpatients with major depression. *J Clin Psychiatry* 1995;**56**(6)**:**229-237.

155. Bersani G, Rapisarda V, Ciani N, Bertolino A, Sorge G. A double-blind comparative study of sertraline and amitripytling in outpatients with major depressive episodes. *Hum Psychopharmacol* 1994;**9:**63-68.

156. Byerley WF, Reimherr FW, Wood DR, Grosser BI. Fluoxetine, a selective serotonin uptake inhibitor, for the treatment of outpatients with major depression. *J Clin Psychopharmacol* 1988;**8**(2)**:**112-115.

157. Claghorn JL, Earl CQ, Walczak DD, et al. Fluvoxamine maleate in the treatment of depression: a single-centre, double-blind, placebo-controlled comparison with imipramine in outpatients. *J Clin Psychopharmacol* 1996;**16:**113-120.

158. Dunbar GC, Cohn JB, Fabre LF, et al. A comparison of paroxetine, imipramine and placebo in depressed out-patients. *Br J Psychiatry* 1991;**159:**394-8.

159. Fabre LF, Scharf MB, Itil TM. Comparative efficacy and safety of nortriptyline and fluoxetine in the treatment of major depression: a clinical study. *J Clin Psychiatry* 1991;**52 Suppl:**62-7.

160. Feighner JP. A comparative trial of fluoxetine and amitriptyline in patients with major depressive disorder. *J Clin Psychiatry* 1985;**46**(9):369-72.

161. Geretsegger C, Stuppaeck CH, Mair M, Platz T, Fartacek R, Heim M. Multicenter double blind study of paroxetine and amitriptyline in elderly depressed inpatients. *Psychopharmacology* 1995;**119**(3):277-81.

162. Guelfi JD, Dreyfus JF, Pichot P. A double-blind controlled clinical trial comparing fluvoxamine with imipramine. *Br J Clin Pharmacol* 1983;**15 Suppl 3:**411S-417S.

163. Itil TM, Shrivastava RK, Mukherjee S, Coleman BS, Michael ST. A double-blind placebo-controlled study of fluvoxamine and imipramine in out-patients with primary depression. *Br J Clin Pharmacol* 1983;**15 Suppl 3:**433S-438S.

164. Keller MB, Kocsis JH, Thase ME, et al. Maintenance phase efficacy of sertraline for chronic depression: a randomized controlled trial. *JAMA* 1998;**280**(19):1665-72.

165. Kiev A, Feiger A. A double-blind comparison of fluvoxamine and paroxetine in the treatment of depressed outpatients. *J Clin Psychiatry* 1997;**58**(4):146-52.

166. Lapierre YD, Browne M, Horn E, et al. Treatment of major affective disorder with fluvoxamine. *J Clin Psychiatry* 1987;**48**(2):65-8.

167. Muijen M, Roy D, Silverstone T, Mehmet A, Christie M. A comparative clinical trial of fluoxetine, mianserin and placebo in depressed outpatients. *Acta Psychiatr Scand* 1988;**78**(3):384-90.

168. Noguera R, Altuna R, Alvarez E, Ayuso JL, Casais L, Udina C. Fluoxetine vs. clomipramine in depressed patients: a controlled multicentre trial. *J Affect Disord* 1991;**22**(3):119-24.

169. Norton KR, Sireling LI, Bhat AV, Rao B, Paykel ES. A double-blind comparison of fluvoxamine, imipramine and placebo in depressed patients. *J Affect Disord* 1984;**7**(3-4)**:**297-308.

170. Perry PJ, Garvey MJ, Kelly MW, Cook BL, Dunner FJ, Winokur G. A comparative trial of fluoxetine versus trazodone in outpatients with major depression. *J Clin Psychiatry* 1989;**50**(8)**:**290-4.

171. Rickels K, Amsterdam J, Clary C, Fox I, Schweizer E, Weise C. A placebo-controlled, double-blind, clinical trial of paroxetine in depressed outpatients. *Acta Psychiatr Scand* 1989;**350:**117-23.

172. Reimherr FW, Chouinard G, Cohn CK, et al. Antidepressant efficacy of sertraline: a double-blind, placebo- and amitriptyline-controlled, multicenter comparison study in outpatients with major depression. *J Clin Psychiatry* 1990;**51 Suppl B:**18-27.

173. Young JP, Coleman A, Lader MH. A controlled comparison of fluoxetine and amitriptyline in depressed out-patients. *Br J Psychiatry* 1987;**151:**337-40.

174. Beevers DG, Blackwood RA, Garnham S, et al. Comparison of lisinopril versus atenolol for mild to moderate essential hypertension. *Am J Cardiol* 1991;**67:**59-62.

175. Bolzanok K, Arriaga J, Bernal R, et al. The anithypertensive effect of lisinopril compared to atenolol in patients with mild to moderate hypertension. *J Cardiovascular Pharmacol* 1987;**9**(suppl 3)**:**S43-S47.

176. Chrysant SG. Antihypertensive effectiveness of low-dose lisinopril-hydrochlorothiazide combination. *Arch Intern Med* 1994;**154:**737-743.

177. Cushman WC, Cohen JD, Jones RP, Marbury TC, Rhoades RB, Smith LK. Comparison of the fixed combination of enalapril/diltiazem ER and their monotherapies in stage 1 to 3 essential hypertension. *Am J Hypertens* 1998;**11:**23-30.

178. Ferme I, Djian J, Tcherdakoff P. Comparative study on monotherapy with sustained-release diltiazem 300 mg and enalapril 20 mg in mild to moderate arterial hypertenison. *J Cardiovascular Pharmacol* 1990;**16**(suppl 1):S46-S50.

179. Fernandez M, Madero R, Gonzalex D, Camacho P, Villalpando J, Arriaga J. Combined versus single effect of fosinopril and hydrochlorothiazide in hypertensive patients. *Hypertension* 1994;**23**(suppl 1):I207-I210.

180. Gradman AH, Arcuri KE, Goldberg AI, et al. A randomized, placeb-controlled, double-blind, parallel study of various doses of losartan potassium compared with enalapril maleate in patients with essential hypertension. *Hypertension* 1995;**25:**1345-1350.

181. Gradman AH, Cutler NR, Davis PJ, Robbins JA, Weiss RJ, Wood BC. Combined enalapril and felodipine extended release (ER) for systemic hypertension. *Am J Cardiol* 1997;**79**(4):431-435.

182. Grunfeld J-P, Wehrlen M, Pelletier B, Capron M-H. Spironolactone and altizide versus converting enzyme inhibitor (enalapril). *Am J Cardiol* 1990;**65:**28k-32k.

183. Lacourciere Y, Poirier L, Porovencher P. Comparison of amlodipine and captopril in hypertension based on 24-hour ambulatory monitoring. *Am J Cardiovasc Pharmacol* 1993;**22**(suppl A):S20-S23.

184. Mehta J, Lopez LM, Thorman AD. Lisinopril versus linsinopril plus hydrochlorothiazide in essential hypertension. *Am J Cardiol* 1988;**61:**803-806.

185. Messerli F, Frishman WH, Elliott WJ, Group ftTS. Efffects of verapamil and trandolapril in the treatment of hypertension. *Am J Hypertens* 1998;**11:**322-327.

186. Morgan TO, Louis WJ, MacDonald GJ, et al. Antihypertensive efficacy and safety of perindopril in mild-to-moderate essential hypertension: results of a double-blind multicenter study versus atenolol. *Am J Med* 1992;**92**(suppl 4B)**:**73S-78S.

187. Morlin C, Baglivo H, Boeijinga JK, et al. Comparative trial of lisinopril and nifedipine in mild to servere essential hypertenison. *J Cardiovascular Pharmacol* 1987;**9**(suppl 3)**:**S48-S52.

188. Mroczek WJ. Efficacy and safety of a new angiotensin-converting enzyme inhibitor, rampipril vs enalapril in essential hypertension: a multicenter trial. *J Cardiovascular Pharmacol* 1991;**18**(suppl 2)**:**S147-S149.

189. Nicaise J, Neveux E, Blondin P, Group tDS. Antihypertensive efficacy and safe use of once-daily sustained-release diltiazem in the elderly: a comparison with captopril. *J Int Med Res* 1995;**23:**244-253.

190. Prisant LM, Weir MR, papademetriou V, et al. Low-dose drug combination therapy: an alternative first-line approach to hypertension treatment. *Am Heart J* 1995;**130**(2)**:**359-366.

191. Stimpel M, Koch B, Jansen T, Fox A, Loh I. Moexipril versus captopril in patients with mild to moderate hypertension. *J Cardiovascular Pharmacol* 1996;**28**(6)**:**769-773.

192. Thijs l, Celis H, Kiowski W, et al. Double-blind comparison of antihypertensive treatment with ramipril and piretanide, given alone or in combination. *J Cardiovascular Pharmacol* 1995;**26**(1)**:**33-38.

193. Vasmant D, Lendresse O, Lemarie J-C, Gallet M. Comparison of response rates to the angiotensine-converting enzyme inhibitor ramipirl in mild-to-moderate hypertension in a double-blind, parallel-group study and an open single-blind study. *J Cardiovascular Pharmacol* 1991;**18**(suppl 2):S144.

194. Verkaaik R, Hogewind BL, Woittiez AJJ. A comparative study of the effects of nitredipine and enalapril in essential hypertension. *J Cardiovascular Pharmacol* 1991;**18**(suppl 1):S63-S66.

195. Zachariah PK, Bonnet G, Chrysant SG, et al. Evaluation of antihypertensive efficacy of lisinopril compard to metoprolol in moderate to severe hypertension. *J Cardiovascular Pharmacol* 1987;**9**(suppl 3):S53-S58.

196. Enalapril in Hypertension Study Group. Enalapril in essential hypertension: a comparative study with propranolol. *Br J Clin Pharmac* 1984;**18:**51-56.

197. The Treatment of Mild Hypertension Research Group. The treatment of mild hypertension study: a randomized, placebo-controlled trial of a nutritional-hygienic regimen aong with various drug monotherapies. *Arch Intern Med* 1991;**151:**1413-1423.

198. Rosenbaum PR, Rubin DB. The central role of the propensity score in observational studies for causal effect. *Biometrika* 1983;**70**(1):41-55.

199. Silverstein FE, Graham DY, Senior JR, et al. Misoprostol reduces serious gastrointestinal complications in patients with rheumatoid arthritis receiving nonsteroidal anti-inflammatory drugs. A randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 1995;**123**(4):241-9.

200. Johnson AG, Nguyen TV, Day RO. Do nonsteroidal anti-inflammatory drugs affect blood pressure? A meta-analysis. *Ann Intern Med* 1994;**121**(4):289-300.

201. Johnson AG. NSAIDs and increased blood pressure. What is the clinical significance? *Drug Saf* 1997;**17**(5):277-89.

202. Fierro-Carrion GA, Ram CV. Nonsteroidal anti-inflammatory drugs (NSAIDs) and blood pressure. *Am J Cardiol* 1997;**80**(6):775-6.

203. Brook RD, Kramer MB, Blaxall BC, Bisognano JD. Nonsteroidal Anti-Inflammatory Drugs and Hypertension. *J Clin Hypertens* 2000;**2**(5):319-323.

204. Ridker PM, Hennekens CH, Buring JE, Rifai N. C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. *N Engl J Med* 2000;**342**(12):836-43.

205. Drummond M. Economic analysis alongside clinical trials: problems and potential. *J Rheumatol* 1995;**22**(7):1403-7.

206. Undertaking systematic reviews of research on effectiveness. CRD Report Number 4. 2nd Edition ed: Centre for Review and Dissemination, 2001.

207. Verhagen AP, de Vet HC, de Bie RA, et al. The Delphi list: a criteria list for quality assessment of randomized clinical trials for conducting systematic reviews developed by Delphi consensus. *J Clin Epidemiol* 1998;**51**(12):1235-41.

208. Scottish Executive Health Department. A Focus on Quality: http://www.show.scot.nhs.uk/sehd/publications/afoq/afoq-09.htm, last accessed June 2004.

209. Somberg JC. Class effects of pharmaceuticals and therapeutic interchangeability. *Am J Ther* 2001;**8**(4):221-2.

210. Johannesson M, O'Conor RM, Kobelt-Nguyen G, Mattiasson A. Willingness to pay for reduced incontinence symptoms. *Br J Urol* 1997;**80**(4):557-62.

211. Ryan M, Ratcliffe J, Tucker J. Using willingness to pay to value alternative models of antenatal care. *Soc Sci Med* 1997;**44**(3):371-80.

212. Wensing M, van der Weijden T, Grol R. Implementing guidelines and innovations in general practice: which interventions are effective? *Br J Gen Pract* 1998;**48**(427):991-7.

213. Salisbury C, Bosanquet N, Wilkinson E, Bosanquet A, Hasler J. The implementation of evidence-based medicine in general practice prescribing. *Br J Gen Pract* 1998;**48**(437):1849-52.

214. Elting LS, Martin CG, Cantor SB, Rubenstein EB. Influence of data display formats on physician investigators' decisions to stop clinical trials: prospective trial with repeated measures. *BMJ* 1999;**318**(7197):1527-31.

215. Prescribing Pricing Authority. Introduction to prescribing toolkit and ePACT.NET: http://www.ppa.org.uk/education/toolkit_and_epactnet.htm, last accessed June 2004.

216. PRODIGY: http://www.prodigy.nhs.uk/, last accessed June 2004.

217. Avery AJ, Heron T, Lloyd D, Harris CM, Roberts D. Investigating relationships between a range of potential indicators of general practice prescribing: an observational study. *J Clin Pharm Ther* 1998;**23**(6):441-50.

218. Campbell SM, Cantrill JA, Roberts D. Prescribing indicators for UK general practice: Delphi consultation study. *BMJ* 2000;**321**(7258):425-8.

219. Willmot M, Sullivan F. NHSnet in Scottish primary care: lessons for the future. *BMJ* 2000;**321**(7265):878-81.

220. Moffat MO, Moffat KJ, Cano V. General practitioners and the Internet--a questionnaire survey of Internet connectivity and use in Lothian. *Health Bull* 2001;**59**(2):120-6.

221. Mason J, Eccles M, Freemantle N, Drummond M. A framework for incorporating cost-effectiveness in evidence-based clinical practice guidelines. *Health Policy* 1999;**47**(1):37-52.

222. Avery T. Report on UK-DURG conference held in Nottingham 8 May 1998. *Pharmacoepidemiol Drug Saf* 1998;**7**:419-422.

223. Hughes D, McGuire A. Patient charges and the utilisation of NHS prescription medicine: some estimates using a cointegration procedure. *Health Econ* 1995;**4**:213-20.

224. Suh DC, Okpara IR, Agnese WB, Toscani M. Application of pharmacoeconomics to formulary decision making in managed care organizations. *Am J Manag Care* 2002;**8**(2):161-9.

225. Do formularies work? *Bandolier* 2002;**9**:7.

226. Ain KB, Pucino F, Csako G, et al. Effects of restricting levothyroxine dosage strength availability. *Pharmacotherapy* 1996;**16**(6):1103-10.

227. Avery AJ, Walker B, Heron T, Teasdale SJ. Do prescribing formularies help GPs prescribe from a narrower range of drugs? A controlled trial of the introduction of prescribing formularies for NSAIDs. *Br J Gen Pract* 1997;**47**(425):810-4.

228. Hill-Smith I. Sharing resources to create a district drug formulary: a countywide controlled trial. *Br J Gen Pract* 1996;**46**(406):271-75.

229. Sloan FA, Gordon GS, Cocks DL. Hospital drug formularies and use of hospital services. *Med Care* 1993;**31**(10):851-67.

230. Scottish Intercollegiate Guidelines Network (SIGN). Prophylaxis of venous thromboembolism. Edinburgh: SIGN, 2002. (SIGN publication no. 62).

231. Ryan M, Yule B. Switching drugs from prescription-only to over-the-counter availability: economic benefits in the United Kingdom. *Health Policy* 1990;**16**(3):233-9.

232. Allery LA, Owen PA, Robling MR. Why general practitioners and consultants change their clinical practice: a critical incident study. *BMJ* 1997;**314:**870-4.

233. Baines DL, Tolley KH, Whynes DK. Prescribing, budgets and fundholding in general practice. London: Office of Health Economics, 1997.

234. Bradlow J, Coulter A. Effect of fundholding and indicative prescribing schemes on general practitioners' prescribing costs. *BMJ* 1993;**307**(6913):1186-9.

235. Wilson RP, Hatcher J, Barton S, Walley T. General practice fundholders' prescribing savings in one region in the United Kingdom, 1991-1994. *Health Policy* 1997;**42:**29-37.

236. Smith PC. Setting budgets for general practice in the new NHS. *BMJ* 1999;**318:**776-779.

237. Audit Scotland. Paying dividends: local healthcare co-operatives bulletin. Edinburgh, 2001.