Implementing Formulary Recommendations

in Primary Care:

Effect on Patient Outcomes

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A thesis submitted in partial fulfilment of the requirements of The Robert Gordon University for the degree of Doctor of Philosophy

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Aberdeen

Scotland

February 1998

To my wife Michelle and children,

Cameron and Caitlin,

for their continued support and encouragement

Abstract

This research aimed to measure the effect on health outcomes of implementing selected recommendations of the Grampian Joint Drug Formulary in primary care. Antibiotics used in the treatment of uncomplicated lower urinary tract infections (UTIs), ulcer healing agents and peripheral vasodilators were selected for study, thereby reflecting both acute and chronic prescribing.

For the UTI study, 12 randomly selected high and low prescribers of trimethoprim, the recommended agent, each agreed to distribute 20 patient questionnaires. Following a period of 18 months and despite repeated contact with the GPs, only 89/480 (19%) questionnaires had been distributed. Patient response was, however, very high with 80 (90%) questionnaires returned. Health outcome measures identified that trimethoprim resulted in no or mild symptoms in 40/45 (91%) of patients. These findings must be interpreted with caution due to the low level of questionnaire distribution and thus cannot be extrapolated to the total population of patients. In addition, the poor questionnaire distribution did not permit comparison between trimethoprim and non-recommended therapy.

One hundred and eighty four patients receiving repeat prescriptions for ulcer healing agents were identified from one general practice. Therapy in 95 patients did not adhere to formulary recommendations. Changes to therapy were considered inappropriate in 11 patients due to factors such as severe depression

and a further 8 were deemed unsuitable for participation for non-clinical reasons. The remaining 76 patients were contacted with 19 (25%) refusing to participate. Fifty seven patients were interviewed using the Glasgow Dyspepsia Severity Score and Short Form 36 (SF-36). Changes in health outcomes were measured for 21 patients where a change in therapy had taken place. These results were difficult to interpret due to the diversity of changes recommended and the lack of data relating to those patients not participating.

Work involving peripheral vasodilators aimed to determine the effect on health outcomes of cessation of therapy. Forty five patients receiving these agents in 2 practices were identified, although 8 had not requested a prescription in the previous year. Two further patients were excluded from the study due to cancer and old age. The remaining 35 agreed to be interviewed using the Walking Impairment Questionnaire and SF-36. All patients were subsequently instructed to stop therapy for 2 months, although 6 (17%) refused to follow this instruction, one patient was seriously ill thus was excluded and 3 refused to be re-interviewed. Of the remaining 25 patients, no significant differences were observed in the domains studied. Seventeen patients (68%) expressed no desire to restart therapy, generating considerable savings. These results must be interpreted with caution since those not stopping therapy or refusing re-interview are likely to have responded differently to those completing the study.

The measurement of health outcomes following formulary implementation deserves further work.

Acknowledgements

I would like to thank the following for their valuable contributions to this research:

- Dr Janet Krska, director of studies, who provided motivation, encouragement and constructive criticism throughout; Professor Keith Kendle, supervisor, for providing statistical advice and general support.

- Dr David Bell, the General Medical Practice Facilitator and Dr John Reid the Medical Prescribing Advisor, both of Grampian Health Board for general advice and the provision of prescribing data.

- The 92 general practices in Grampian which allowed access to prescribing data.

- For the UTI study: Dr Ian Gould, consultant microbiologist; the 24 GPs who agreed to distribute questionnaires; Dr John Curnow and staff of the Grampian Communicable Diseases Team for providing a medium for distribution of results.

- For the ulcer healing agents study: Dr Douglas Harris, all further GPs and reception staff at Peterculter Health Centre for all support and assistance provided; Professor K McColl, Western Infirmary, Glasgow, for permitting the use of the Glasgow Dyspepsia Severity Score and providing assistance with interpretation of results; Nuffield Institute for Health, University of Leeds for providing information relating to the use of SF-36.

- For the peripheral vasodilator study: Dr David Wintour, all further GPs and reception staff at East Wing Practice, Denburn Health Centre for all support and assistance provided; similarly Dr Campbell MacGregor, all further GPs and reception staff at Viaduct Practice, Denburn Health Centre; Dr Judith Regensteiner, University of Colorado Health Sciences Centre for permitting use of the Walking Impairment Questionnaire.

- Probably the biggest thanks should go to all patients involved in each of the 3 studies for giving up their time to either complete a questionnaire, be contacted by telephone or interviewed in their own home.

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Chapter 1

Prescribing in Primary Care

1.1 Expenditure on prescribing in primary care

Prescribing is a fundamental activity in primary care, with data showing that in the UK a prescription will be issued in 7 out of every 10 consultations with a general practitioner (GP) (Audit Commission 1994). Such acute and repeat prescribing is responsible for consuming vast NHS resources. In 1992/1993 10% of all NHS expenditure in England and Wales, £3.6 billion, was due solely to primary care prescribing (Audit Commission 1994). UK figures for 1992/1993 showed a 14% increase over the previous year, with a further 11% increase occurring in 1993/1994, both increases against a low rate of inflation (Department of Health 1994). An Audit Commission report of prescribing in primary care identified main areas to target in an attempt to optimise use of these resources, including: less overprescribing of certain drugs; reduced prescribing of drugs of limited clinical value; substitution of cheaper but comparable drugs; generic prescribing; and appropriate use of expensive preparations. Implementation of these recommendations would have reduced primary care drug expenditure by 11.8% in 1992/93 (Audit Commission 1994).

1.2 Reviews of influences on prescribing

Prescribing is, however, a complex process, influenced by the interaction of very many variables. Three reviews of the influences on prescribing have been published, identifying these variables.

Hemminiki (1975) reviewed the literature on factors influencing prescribing in Western countries. Although detailing areas of advertising, prescriber education, influences of colleagues, control and regulatory measures, demands of patients, society, and prescriber characteristics, no large scale, controlled studies were cited, focusing solely on observational studies. The author concluded that the available literature was extremely scanty.

A later review by Bradley (1991) cited studies of the variation in the quantity and quality of prescribing. Prescribing and the decision making process were dealt with in more detail, identifying the 3 main decisions to be made as: whether or not to prescribe at all; which medicine to prescribe; when to start using or stop using certain products. This review highlighted the lack of work in the UK.

Denig and Haaijer-Ruskamp (1995), while reviewing the influence of cost on prescribing decisions, summarised studies involving groups of prescribers rating criteria for drug selection. To facilitate comparison, all studies were converted to the same 10 point rating scale. Results showed cost to be an important criterion, but less so than considerations of efficacy, adverse drug reactions, patient

acceptability and prescribers' experience of particular drugs. However, only a limited number of studies were reviewed, none of which were carried out in the UK.

1.3 Factors influencing whether or not to prescribe

As identified by Bradley (1991), initially the prescriber must decide whether or not to issue a prescription. Although information relating to the UK is sparse, it has been shown that factors other than clinical need will influence this decision.

Virji and Britten (1991) measured patients' attitudes towards the issue of a prescription and recorded whether or not a prescription was issued. Results indicated that the attitude of the patient influenced the outcome, with patient preference for treatment being associated with prescribing behaviour.

Bradley (1992a) explored discomfort experienced by general practitioners surrounding decisions they had taken about whether or not to prescribe. Interviews were carried out with 69 general practice principals (51%) in one English region. Drug groups for prescriptions which most often led to such feelings included antibiotics, tranquillisers and hypnotics, with reasons for discomfort including concerns about drug toxicity and appropriateness of treatment. Patient expectation was voiced as being the most common reason for such a decision. Further analysis of this work (Bradley 1992b) examined patient factors associated with this discomfort. These were found to include: knowledge

of the patient; the need to preserve the doctor-patient relationship; patient communication problems; social class and occupation.

1.4 Factors influencing drug choice

Having decided to issue a prescription, the prescriber must next choose from the available range of drugs. None of the early work researching this decision making process was carried out in the UK, and generally involved small groups of prescribers ranking criteria for drug selection based on hypothetical case descriptions.

Harrell and Bennett (1974), proposed a model based on marketing theory which stated that prescribing of a specific drug was related to belief about the outcomes of that behaviour, the relative desirability of each outcome, the belief about what colleagues would advise in a similar situation and motivation to comply with that advice. They attempted to test this model using oral hypoglycaemics. A list of possible outcomes arising from such treatment was identified from group interviews with 31 prescribers. A questionnaire was subsequently developed and used during interview with 93 prescribers and mailed to 52 others. The questionnaire measured the following: beliefs about possible outcomes identified in relation to each oral hypoglycaemic, rated from extremely probable to extremely improbable; the relative desirability of each, either desirable or undesirable; beliefs about colleagues advice, rated from extremely improbable to extremely probable; motivation to comply, rated from don't care at all to care a

great deal. Actual prescribing data was collected from those who completed the questionnaire. Results identified that there were 6 main drug attributes for oral hypoglycaemics: efficacy; short duration of action; absence of serious adverse drug reactions; minimal hypoglycaemic effects; minimal cardiovascular effects; weight reducing effects. Overall a relatively weak link was demonstrated between prescribing behaviour and beliefs.

Segal and Hepler (1982) similarly proposed that, according to cognitive theories of behaviour, a prescriber's drug choice resulted from the interaction of beliefs about the recognised outcome of drug choice and the values attached to those outcomes. Twelve physicians were interviewed to identify commonly occurring outcomes. Values were measured using one hypothetical clinical case, with prescribers rating each outcome from -10 (avoid at all costs) through 0 (no value) to +10 (most valued). Seventeen different outcomes were identified, the 6 most highly valued being: control of the disease state; patient compliance; minimal side effects; cost; patient demand; minimal colleague criticism.

The same authors tested this relationship between prescriber's beliefs of possible outcomes and prescribing decisions under actual clinical conditions using case descriptions of 3 recent diabetic and 3 recent hypertensive presentations (Segal, Hepler 1985). A sample of 40 prescribers rated disease severity and resulting outcome values, using the same outcomes and rating scale as before (Segal, Hepler 1982). Each was also asked to outline the treatment plan for the patient. Results indicated that prescribers rated control of disease state highest, followed

by ease of compliance and lack of side effects for both clinical situations. Actual prescribing was found to relate highly to that predicted by the values attached to the treatment outcomes.

Zelnio (1982) surveyed 250 randomly selected prescribers in Iowa, each rating 8 prescribing criteria identified by previous work. Using a paired comparisons method, where all possible pairs of the criteria were presented in randomised order, with the prescriber selecting the most important from each pair, an order of importance was established. From a response rate of 69%, the most highly rated criteria were absence of potential side effects, probable efficacy and minimal contraindications. Less highly rated were dosage form, cost, source of drug information, frequency of administration and manufacturer's reputation.

Lilja (1976) carried out similar work with Swedish prescribers. Using a mailed questionnaire detailing case histories of a non insulin diabetic and adult presentation of acute pneumonia, the following were determined: spontaneous drug choice; prescribers' attitudes towards 10 mentioned antidiabetics and antibiotics; judgements of the side effects for the 10 drugs; judgement as to the curing effects; judgements of costs. A response rate of 81% was obtained, with results showing that the curing effect was rated most important for both clinical situations. Absence of side effects was rated more important than cost when considering antidiabetics, but not antibiotics. The results for diabetes were similar to those of Harrell and Bennett (1985), but respondents could only rate the 3 criteria listed.

The studies described above have several limitations: most involved small numbers of selected prescribers; few therapeutic areas were studied, mainly involving hypothetical cases where treatment decisions may vary greatly from real clinical situations.

1.5 Factors influencing drug choice - the UK perspective

As outlined earlier, there is a lack of research into factors influencing drug choice in the UK. In a study involving 75% of all general practitioners in one Scottish region, Taylor and Bond (1991) used duplicate prescription pads to collect data relating to 100 initial prescription situations. Each prescription was classified by the prescriber as being an established drug habitually selected, one newly adopted in the previous 12 months or superseded in the last 12 months but still being prescribed for an individual patient. Each prescriber was asked to indicate the major influence on the change leading to adoption or deletion. Individual GPs were found to prescribe from a relatively limited list of 100-200 different preparations, with the proportion of new drugs being low at 4.5% of all prescriptions and those deleted only 0.9%. Although only 2 influences could be cited for each change of prescription, major influences identified were government regulations, pharmaceutical representatives and hospital doctors.

Several authors have studied GPs' attitudes towards the influence of cost on drug selection. The majority of GPs surveyed were found to agree that prescribing costs should be taken into account when prescribing and that costs could be

reduced without affecting patient care (Ryan *et al* 1990 Ryan *et al* 1992. Silcock *et al* 1997).

Ryan *et al* (1996) investigated the actual relationship between cost and prescribing. Postal questionnaires measuring attitudes towards considering costs when prescribing were sent to all GP principals in one Scottish region. To ensure representativeness, the questionnaire was also sent to 94 GPs outwith the study region. To identify whether attitudes influenced prescribing, all prescriptions issued at consultations during 7 sample periods over a period of one year were recorded using duplicate prescription pads. A total response rate of 64% was achieved, with 76% agreeing that costs should be taken into account, a similar finding for GPs outwith the study region. For certain therapeutic groups (H_2 receptor antagonists and analgesics), prescribing was shown to be influenced by attitudes.

Several workers have investigated the effects of the introduction of Government regulations on prescribing. The "limited list", which restricts prescribing of drugs in certain categories under the NHS, was introduced into the UK in April 1985. Following its introduction, questionnaires were sent to 1500 randomly selected GPs in the UK to determine the effect on prescribing (Anon 1987). A response rate of 48% was achieved, with only 8% stating that prescribing had changed considerably.

Other government initiatives have resulted in more marked changes in prescribing.

The Indicative Prescribing Scheme (IPS) and general practice fundholding were both introduced into the UK in 1991 (Walley *et al* 1995). Under the IPS, an indicative prescribing amount is set to cover the costs of prescribing for the following year. Now termed "target budgets", these are set according to practice size, patient age and gender distribution. Originally these budgets were not linked to any penalty nor incentive to meet the defined target, however, certain regions have now introduced incentives schemes, allowing GPs to retain a proportion of the savings. Fundholding allows practices with list sizes over 5000 to hold a budget to pay for specific hospital care, drugs, staffing, community services, differing from the IPS in that any savings accrued in the drugs budget can be retained by the practice.

Harris and Scrivener (1996) reviewed studies of the effect of fundholding on prescribing. By measuring costs and number of items, with non-fundholding practices as controls, they concluded that fundholding appeared to be having some success in reducing prescribing costs. The authors, however, commented that the control and active groups were not matched and that many of the control practices were also involved with regional incentive schemes.

Bateman *et al* (1996) examined the effect of implementing an incentive scheme related to target budgets for prescribing in non-fundholding practices in one

region of England. Twenty three per cent of practices achieved the incentive target, saving between 1 and 3% on the target budget. Although no control group was involved in this study, the authors claimed that use of such an incentive could have a considerable effect on prescribing costs.

Armstrong *et al* (1996) performed qualitative interviews with a selected sample of 18 general practitioners to identify reasons for recent changes in their prescribing behaviour. All identified two to five specific changes in the previous six months, mainly being antidepressants, angiotensin converting enzyme inhibitors and *Helicobacter pylori* eradication regimes. Several factors were identified for most changes including: an accumulation model of change, where new treatments were reinforced repeatedly from various sources including journal articles, talks, consultant letters; a challenge model of change, where the change was more immediate, for example, as a result of a specific clinical disaster; and a continuity model of change, based on a pre-existing willingness to change, for example, as a result of cost pressures.

Weiss *et al* (1996) also reported on qualitative interviews with 23 general practitioners to explore whether a variety of pressures in primary care, including fundholding and the development of the Patient's Charter were actually felt as concerns and whether the perceptions of these pressures influenced prescribing decisions. These interviews resulted in the development of a questionnaire to address main themes of: GPs sense of burden; financial constraints and incentives; prescribing as a coping strategy; and patient demand. Questionnaires

were distributed to 386 GPs in Southern England, with a response rate of 59%. Permission was also obtained to access prescribing data. Financial constraints and incentives were found to be related to the prescribing variables studied. Those most concerned about the adverse effects of financial pressure were found to prescribe less generically, had higher practice costs, issued more prescriptions and issued more antibiotics compared to the average FHSA practice. Many GPs also reported a sense of burden in meeting society and patient demands and using a prescription as a way of coping with increasingly demanding patients.

1.6 Rational prescribing

Decisions regarding drug choice may thus be influenced by the interaction of many, and often competing variables. To ensure optimal use of scarce NHS resources, prescribing should be responsible and rational. Parish (1973) originally defined responsible prescribing as being based on a clear clinical need and that the actions of the prescriber could be defended to both peers and patients. He defined rational prescribing as being appropriate for the patient, effective, safe and economical. This definition of rational prescribing was later refined by Barber (1995) who proposed that there were 4 aims a prescriber was trying to achieve: maximise effectiveness; minimise risk; minimise cost, taking account not solely of drug costs but also associated costs such as any necessary laboratory monitoring; respect the patient's choices. He acknowledged that trade offs may often need to be made between conflicting aims and that, depending on the situation, patient choice may be the most important consideration.

The Audit Commission report of prescribing in primary care (Audit Commission 1994) compared national prescribing and expenditure with that of 50 selected practices, chosen on the basis of quality prescribing. It was estimated that poor prescribing in primary care in the UK had cost the NHS £425m in 1992/93. Although such an extrapolation may not be entirely valid, it does provide evidence for some degree of irrational prescribing.

Hogerzeil (1995) described such irrational prescribing as a global problem. He identified many studies from both developed and developing countries showing evidence of polypharmacy, use of therapies not clinically indicated, use of unnecessarily expensive drugs, inappropriate use of antimicrobials.

1.7 Drug formularies in primary care

Rational prescribing can be promoted by the use of a drug formulary, defined as "a selection of medicines, a preferred list voluntarily arrived at by prescribers" (Waine 1989). Medicines within such a formulary are selected on the criteria outlined by Parish (1973) and Barber (1995): efficacy; safety, cost-effectiveness; patient acceptability. Formularies have been widely recommended in primary care (Jolles 1981, Anon 1986a, Essex 1989, Drury 1990). The Greenfield Report of The Informal Working Group on Effective Prescribing (1982) strongly recommended the development of local formularies as a mechanism for improving prescribing. To facilitate this, the Royal College of General Practitioners produced practical advice for GPs, detailing tasks involved in

production, with sources of information and advice (Waine 1989). The recommendations were later reinforced by the Audit Commission report of prescribing in primary care (1994).

There is, however, little published work detailing the development or use of practice formularies in the UK. Telling *et al* (1984) described how one practice used a computerised repeat prescribing system to produce reports of drugs prescribed as a starting point for the compilation of the practice formulary. The authors maintained that this process would allow production of a formulary not restricting drug choice. No data, however, was given on which to base this conclusion and, in particular, no patient experiences before and after implementation of the formulary recommendations were described.

Grant *et al* (1985) provided a model for the development of a local formulary, describing the experience as being an enjoyable and dynamic educational exercise, leading to more rational and safer prescribing. They aimed to compile a formulary for use in primary care covering 90% of conditions, providing treatment for 90% of patients, compiled by and acceptable to GPs, taking cost into account. A select group of 19 GPs, responsible for undergraduate teaching at Newcastle University, agreed upon a list of drugs for inclusion in a practice formulary. Prescriptions were recorded by the participants for 2 short periods of 2 weeks, with 10 further GPs acting as controls. Results indicated that involvement in formulary development was associated with higher levels of prescribing recommended agents. Formulary adherence was significantly higher for acute

rather than repeat prescribing, highlighting the additional difficulties associated with changing established therapies. This study did not, however, analyse prescribing trends over a longer period of time.

Green (1985) described the creation, implementation and monitoring of such a formulary in one general practice. Using the prescribing data of each GP, the formulary was built up over a period of one year, covering 35 BNF categories, aiming to cover 80-90% of common conditions, providing treatment for 70-80% of cases. Drugs were selected on the basis of available evidence of efficacy, safety, cost and current prescribing levels, indicated by detailed analysis of prescribing data. Prescribing was monitored prior to and following the implementation of the formulary, focusing on antacids, laxatives, hypnotics and sedatives, cough preparations and analgesics. Results indicated that changes in line with the recommendations occurred in all therapeutic areas, with changes persisting for one year after formulary introduction, generating considerable savings. No data relating to patient experiences following formulary introduction were presented.

Beardon *et al* (1987) reported on similar work. Prescribing data was again used to assess formulary success, with data indicating that use of formulary agents increased on introduction and was maintained in the following year. This study also involved regular feedback of performance to prescribers which may well have influenced prescribing behaviour.

Van Zwanenberg *et al* (1987) assessed the prescribing of a small group of 12 young prescribers before and after educational intervention focusing on rational prescribing. Prescribing of 150 consecutive consultations was recorded by each before and after these sessions. None of the participants had been involved in the formulary described by Grant *et al* (1985). Data, however, indicated a significant increase in formulary prescribing following such intervention. Although no control group was included, these results indicated that the actual educational aspects of formulary development may themselves lead to improved prescribing.

More recently, Eccles *et al* (1996), as part of a larger study of all non-fundholding practices in the Northern region of England, identified that of the 78% of respondents, 98% had a written or computerised formulary but that only 85% reported that the practice always or usually used it.

Voss *et al* (1997), interviewed either the practice manager or a GP of 75% of practices in Southampton and south west Hampshire to identify their use of practice formularies. Only 48% of practices had a formulary, the majority of which (63%) only covered drug choice in certain therapeutic areas. Main criteria for drugs included were: efficacy; patient compliance; lack of side effects; prescriber familiarity; generic availability; cost. Neither of these studies provided any data relating to effectiveness of the formularies in achieving rational prescribing, nor patient acceptability.

It has been recognised that adherence to practice formularies may be reduced when patients are discharged from hospital on a non-formulary agent.(Turner 1984, Anon 1986, Anon 1989). Indeed, Bond and Taylor (1991) identified that hospital prescribers were a major influence on primary care prescribing. As a result, the development and use of joint formularies between primary and secondary care has been widely advocated (Greenfield 1982, Anon 1989, Essex 1989, Anon 1991). Work by Joshi *et al* (1994) showed that of all the hospital formularies in the UK in 1993, only 2 recommended agents for use in both primary and secondary care. NHS Circular MEL (The Scottish Office 1993) 12 indicated that all health boards and NHS trusts in Scotland should have produced such a formulary by March 1994.

Garvey *et al* (1990) described the development of a model for creating such a joint formulary. Stewart (1989) had previously shown considerable overlap between the hospital formulary in Grampian and repeat prescribing of selected therapeutic areas in primary care. A formulary development group consisting of 4 GPs, 3 pharmacists and 2 clinical pharmacologists co-ordinated the development of the Grampian Joint Drug Formulary. Of fifty randomly selected GPs invited to receive a copy of the existing hospital formulary 49 responded positively. Based on this high level of interest, GPs were invited to comment on draft guidelines for each group of drugs to be included. Sixty GPs expressed an interest, resulting in the completion and distribution of the formulary in 1992. A further revision took place in 1995 (Grampian Medicines Committee 1995, Ferrow *et al* 1996). Drugs in the formulary are listed in therapeutic category, following BNF classification.

Within each section, first choice drugs are highlighted, along with brief information about the recommended drugs. A special indications category is used for those drugs not recommended as first line, fulfilling the following criteria: used in special situations; specialist supervision required; less favourable side effect profile; more expensive than first choice agents. Revision of the formulary is co-ordinated by the Grampian Medicines Committee Formulary Sub-Committee, a multi-disciplinary group comprising hospital consultants, GPs, hospital and community pharmacists. Wide consultation takes place between this group and practitioners with declared interests in particular therapeutic areas.

Stewart *et al* (1996) measured adherence to Grampian Joint Formulary recommendations as patients were admitted to hospital, showing a high level of adherence (84%) to the recommended drugs. This study did, however, have several limitations in that the patients were elderly, being admitted to hospital and mainly receiving repeat prescriptions, hence represented neither patients nor prescribing in general.

1.8 Clinical guidelines in primary care

In addition to recommending particular drugs, the Grampian Joint Drug Formulary contains detailed prescribing policies for the use of antibiotics and hypnotics. Such guidelines have been defined as "systematically developed statements to assist practitioner and patient decisions about appropriate healthcare for specific clinical circumstances" (Field, Lohr 1990). Clinical guidelines aim to

"improve the effectiveness and efficiency of clinical care through the identification of clinical practice and desired clinical outcomes" (Scottish Intercollegiate Guidelines Network 1995).

The development, dissemination and implementation of guidelines have been well described elsewhere (Grimshaw, Russell 1993a, Woolf 1993, Onion, Walley 1995, Thomson *et al* 1995), identifying the need to: carefully choose the subject area; select the members of the development group; present, disseminate and implement the guideline; measure the impact of the guideline in terms of adherence and changes in health outcomes.

Many terms have been used in the context of clinical guidelines, including policies, protocols, algorithms. There is currently much emphasis being placed on these developments in the NHS. A report by the Clinical Resource and Audit Group (Scotland) (1993) commended the development of national guidelines. Simultaneously, the Scottish Intercollegiate Guidelines Network (SIGN) was established by the Confederation of Royal Colleges in Scotland to sponsor and support the development of national guidelines on a multi-professional basis (Scottish Intercollegiate Guidelines Network 1995). It is anticipated that these guidelines will be reviewed and modified to produce local protocols, defined as "detailed developments of nationally derived guidelines for local application" (Clinical Resource and Audit Group 1993).

Siriwardena (1995) surveyed all GPs in Lincolnshire to determine attitudes to and behaviour surrounding clinical guidelines. Using a postal questionnaire with a response rate of 65%, he identified that 78% of GPs reported involvement in developing local guidelines. In general, response to the attitude statements indicated general support for such guidelines. The majority (69%) felt that guidelines were effective in improving patient care, although no data was presented to support this belief.

Newton *et al* (1996), carried out similar work with a random selection of 1 in 7 GPs in North Yorkshire. In addition, they measured knowledge and use of 3 national guidelines: the British Thoracic Society guidelines for managing acute asthma; the Royal College of Radiologists guidelines for making the best use of radiology departments; the Royal College of General Practitioners guidelines for the care of patients with diabetes. From a response of 54%, they identified that GPs were most familiar with the BTS guidelines for acute asthma, although less had actually used or changed their practice as a result. As found previously (Siriwardena 1995), analysis of attitude statements indicated general support for clinical guidelines, with most agreeing that guidelines helped to improve the quality of care. Again, no data was given to support this belief.

1.9 The effect of formularies and guidelines on health outcomes

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

Field (1989) determined whether the introduction of a formulary was acceptable to doctors and whether any changes implemented as a result would be acceptable to patients. A formulary was developed in one practice, aiming to cover 50% of prescribing, with 3 neighbouring practices acting as controls. Doctors attitudes towards formularies were measured prior to and following formulary introduction. Results indicated that those in the active practice were more in favour of the use of a formulary. Groups of 90-100 consecutive patients per year for 3 years receiving repeat prescriptions, without consultation, in all 4 practices were selected and interviewed to measure satisfaction with therapy. Those patients in whom therapy had changed (17.7%) were less satisfied than those where no change had occurred, however, the data presented did not demonstrate that those less satisfied belonged to the active practice, nor that the change was actually as a result of implementing formulary recommendations.

More recently, Dowell *et al* (1995) measured patient satisfaction upon the introduction of a generic formulary in one practice. Questionnaires were sent to a random sample of 280 patients where therapy had been changed to the formulary recommendation, including substitution of a generic equivalent. A response rate

of 60% was obtained, with 46% being either slightly or very unhappy with the change, although this was thought to be associated with inadequate communication relating to the change. Semi-structured interviews conducted with 16 patients 1 week and 6 months following the change showed that almost all patients were aware that reducing expenditure was at least part of the reason for the change, but that none felt that trial of a cheaper medicine to be unreasonable.

Pearce and Begg (1992), while reviewing the literature relating to drug formularies in primary and secondary care, identified that no research focused on the area of change in health outcomes arising as a result of such developments.

In a review on the effect of guidelines on medical practice, Grimshaw and Russell (1993b), identified 59 published evaluations of clinical guidelines that met defined criteria for scientific rigour. All but 4 detected significant changes relating to guideline adherence. Only 11 studies, however, measured changes in health outcomes as a result of such guidelines, the vast majority of which were in secondary care. Of those in primary care, the only area studied was smoking cessation.

More recently, Conroy and Shannon (1995) reviewed the literature with regard to clinical guideline implementation in primary care, with particular emphasis on: potential conflict with clinical freedom; need for local ownership of guidelines; adherence to guidelines. No reference was made as to the effect of such guidelines on health outcomes.

Despite increasing emphasis being place on the development and use of formularies and clinical guidelines, there is a lack of research investigating the effect of such developments on health outcomes. The need for and importance of such research has been voiced by many workers (Pearce, Begg 1992, Woolf 1993, Onion, Walley 1995, Voss 1997).

Chapter 2

Patient Outcome Measures

2.1 Health outcomes

A health outcome was defined by Donabedian (1985) as being a "change in patients' current and future health status that can be attributed to antecedent health care." McCallum (1993) more recently defined a health outcome as "a natural or artificially designated point in the care of an individual or population suitable for assessing the effect of an intervention, or the natural history of a condition". Shanks and Frater (1993) proposed a classification scheme for outcomes, acknowledging the problem of attributing change in health status to intervention. Four levels of outcome were identified: outcome; health outcome; health care outcome; and health outcome of health care. The latter was defined as being "a result evident in terms of health status which is attributable and responsive to health care", differing from health care outcome where the area of change could as equally be economic or social. A health outcome was defined as "an effect manifest as change in health status" but the cause of such a change could be unknown, whereas an outcome was simply a change in any sphere of life. This terminology does not appear to have been adopted enthusiastically and the most widely used term remains health outcome.

Increasing emphasis has been placed on the need to measure health outcomes, thereby providing an objective means of monitoring patients' progress. Shanks and Frater (1993) suggested that health service users, managers and clinicians would benefit from increased measurement of and importance being placed on health outcomes.

Indicators of health outcome most frequently reported in the medical literature include: morbidity, mortality rates and changes in physical or physiological measurements. Further indicators reported include service use indicators, such as hospital admission and re-admission rates, adverse reactions and economic effects (Bowling 1995, Bowling 1997, McCallum 1993).

Lohr (1988) classified health outcomes into the "five Ds": death; disease; disability; discomfort and dissatisfaction, with those of death, disease, disability, discomfort grouped into mortality indicators and disease, disability, discomfort into morbidity indicators. The author, however, provided little justification for classifying disease, disability and discomfort as mortality indicators.

The most appropriate health outcome measure may be influenced by many variables including: the patient's environment; nature of disease state; type of health intervention. For patients in primary care, with an acute self-limiting disease state, the outcome indicator must be patient centred, primarily relief of symptoms. For many chronic disease states cure may not always be a realistic goal, and many have recommended that additional outcome measures should be

included and that the most important outcome measure may be health related quality of life, measured from the patient's perspective (Guyatt *et al* 1993, Tsevat *et al* 1994, Ebbs *et al* 1989).

2.2 Health related quality of life

Quality of life has been defined as "an individual's perception of their position in life in the context of the culture and value systems in which they live in relation to their goals, expectations, standards and concerns" (WHOQOL Group 1993). It has been stated to be a broad ranging concept, affected in a complex way by not only physical health, but also psychological state, level of independence, social relationships, housing and occupation which are not directly linked with health. This has led to the adoption of the term health related quality of life, defined by Bowling (1995) as "the optimum level of mental, physical, role and social functioning, including relationships, perceptions of health, fitness, life satisfaction and well being." This is in accordance with the World Health Organisation definition of health (1948) as a "state of complete physical, mental and social well-being, and not merely the absence of disease or infirmity".

Several comprehensive reviews on the subject of health related quality of life have been published (McDowell and Newell 1996, Bowling 1995, Bowling 1997, Fitzpatrick *et al* 1992, Guyatt *et al* 1993, Tsevat *et al* 1994).

Although the term health related quality of life is considered synonymous with health status and functional status (McDowell and Newell 1996), MacKeigan and

Pathak (1992) described a hierarchy of terminology, differentiating between these three concepts. Health related quality of life was described as representing functional status, physiological status, well being and life satisfaction; health status representing functional status and well being; and functional status representing physical, mental and social aspects.

Many benefits derived from the measurement of health related quality of life have been described (McDowell and Newell 1996, Bowling 1995, Bowling 1997, Fitzpatrick *et al* 1993, MacKeigan, Pathak 1992, Guyatt *et al* 1993). These include broadening the scope of outcome measurements, obtaining the patients' view of aspects of their lives considered most important and providing a formal means whereby patients can judge the effectiveness of treatment. The impact of intervention on patients' emotions, physical functioning and lifestyle can be measured, focusing on any patient concerns. Research has shown that clinical indicators are not always good measures of outcome and that patients with identical clinical criteria may have widely differing views on the success of treatment (McDowell and Newell 1997, Bowling 1995, Bowling 1997, Fitzpatrick *et al* 1992, Guyatt *et al* 1993). Measures of health related quality of life are being increasingly included in population surveys of perceived health problems, medical audit, outcome measures in health services, evaluation research and clinical trials (Fitzpatrick *et al* 1992).

2.3 Health related quality of life instruments

Health related quality of life instruments may be described as questionnaires comprising a number of questions or items, grouped together in a number of domains or dimensions. Each domain represents a distinct area of health status such as social functioning, emotional functioning or specific symptoms.

Such instruments may be categorised as health profiles or health indices. Health profiles provide separate scores for each different domain being measured, thereby providing a degree of detail for both individual and investigator. Health indices, however, describe health related quality of life as a single score ranging from 0 (death) to 1 (perfect health), and are most often used in economic analyses.

A further classification describes these instruments as either disease specific, domain specific or generic. A disease specific instrument includes questions and domains most appropriate for that particular disease state. Domain specific measures simply contain items referring to one particular domain, for example, physical functioning or symptom severity. Generic scales are much broader measures of health status, commonly measuring physical, mental and social health. Whereas disease and domain specific measures are often criticised for their narrow focus, generic measures may fail to identify small but important changes in health status. Many researchers in this field have recommended using an appropriate disease or domain specific instrument alongside a generic

measure, thereby ensuring both the ability to detect small alterations in health status while retaining the broader measures (McDowell and Newell 1996, Bowling 1995, Bowling 1997, Fitzpatrick *et al* 1992, MacKeigan, Pathak 1992, Malek 1997).

2.4 Scientific review criteria for health related quality of life instruments

Many instruments claiming to measure health related quality of life have been developed but prior to use, it is essential to ensure their appropriateness. To aid this task, defined scientific review criteria have been established.

The Scientific Advisory Committee of the United States Medical Outcomes Trust, a world-wide distributor of health outcome measurement instruments (Perrin 1995), reviews instruments against a rigorous set of 8 attributes, with only those fulfilling these requirements being included in the Trust library. The necessary attributes are: conceptual and measurement model; reliability; validity; responsiveness; interpretability; respondent and administrative burden; alternative forms; cultural and language adaptations (Lohr 1996). Several others have recommended similar criteria (McDowell and Newell 1996, MacKeigan, Pathak 1992, Fletcher *et al* 1992, Fitzpatrick *et al* 1992).

The conceptual model describes the different domains which an instrument is claimed to measure and the relationship between these domains, with the measurement model being defined by the method of instrument scoring. Suitable

instruments should provide the rationale for combining items into domains. documented procedures for determining scores and evidence of distribution of scores.

Measures of reliability and validity have been extensively described by others (McDowell and Newell 1996, Bowling 1995, Deyo *et al* 1991, Hays *et al* 1993).

Reliability is the degree to which an instrument is free from random error, that is will produce consistent results on different occasions when there is no evidence of change. This is generally assessed in 2 ways: the test-retest; and internal consistency. Test-retest is the relationship between the scores obtained by the same person on two or more occasions. For continuous data, this may be established by determining the Pearson product-moment correlation coefficient or intraclass correlation coefficient (Deyo 1991). Internal consistency tests how well individual items on a scale are inter-correlated and the extent with which they correlate with overall scores, determined by calculation of Cronbach's alpha. For all tests of reliability, a minimum score of 0.7 is recommended for group comparisons (Nunally 1978). Intra and inter-rater reliability estimates are appropriate for instruments administered by interview and test the reliability when administered by the same interviewer on different occasions or different interviewers and are determined by calculation of kappa for categorical data.

Validity, the extent to which an instrument measures what it is intended to measure, may be assessed in several ways: face validity, content validity.

criterion validity and construct validity. Face validity is a subjective measure of whether the instrument appears appropriate and unambiguous. Content validity is similarly subjective and refers to how well the questions reflect the aims of the instrument, generally determined by lay and expert panel judgements. Criterion validity tests how well the instrument correlates with the "gold standard" measure in a particular field. This is rarely carried out in health related quality of life research, due to the lack of a suitable "gold standard". In such circumstances, it then becomes necessary to establish construct validity. This is determined by assembling multiple indicators of validity. As many of the instrument domains as possible are correlated with other instruments or health outcome indicators. Convergent validity should be established, testing for high levels of correlation between related health outcome indicators and discriminant validity, testing for lack of correlation between unrelated indicators.

Responsiveness is the least studied criterion, particularly when compared to the mass of literature relating to reliability and validity. Guyatt *et al* (1987) defined responsiveness as "the ability of an instrument to detect minimal clinically important differences." One problem frequently encountered in this field of health outcomes is that the minimal clinically important difference may not be well defined. Additionally, many health related quality of life instruments do not yield a summary score, but provide scores for separate domains, with the minimal clinically important difference very possibly differing among these domains. Jaeschke *et al* (1989) defined the minimal clinically important difference as "the smallest difference in score in the domain of interest which patients perceive as

beneficial". Determination of such a difference has important implications for sample size calculations in clinical studies. Deyo *et al* (1991) recommended comparing scores before and after an intervention of known efficacy, with any improvement in score representing the minimal clinically important difference. Jaeschke *et al* (1989) used this approach with a small number of patients suffering from chronic heart or chronic lung disease. They identified that the minimal clinically important difference was represented by a change of 0.5 on a 7 point Likert scale. This approach has not been shown to be appropriate with larger patient numbers, nor a range of disease states. Drummond and O'Brien (1993) acknowledged problems in determining such a difference and concluded that often value judgements were necessary. Fletcher (1995) also stated that instruments which yielded high levels of floor or ceiling effects (very high or very low scores) were less likely to be responsive.

Other less well documented criteria of the Scientific Review Committee include: interpretability, the degree to which clinical meaning can be assigned to instrument scores; instruments should require minimal respondent and administrative time and cost; instruments should ideally be available for different modes of administration and should be translated widely.

The Scientific Advisory Committee also stressed that such properties are context specific in terms of setting, population and disease states and that it cannot be assumed that an instrument which works well in one situation will necessarily be appropriate for another.

2.5 Generic measures

Several instruments have been developed specifically as generic measures of health related quality of life. Of these, the more commonly used include: the COOP charts for primary care, which provide a rapid assessment of health for patients in primary care (Nelson *et al* 1987); DUKE health profile, similarly developed to measure outcomes in a primary care setting (Parkerson *et al* 1990); McMaster health index questionnaire, developed primarily as a research tool (Chambers 1984); Sickness impact profile, recommended for use in a variety of settings (Gilson *et al* 1975); Nottingham health profile, originally developed for use in primary care, but subsequently included in clinical trial evaluations (Hunt *et al* 1985). These measures have been superseded by the recently introduced Short Form 36 (SF-36) which has been claimed to be the generic measure of choice, measuring health status from the patient's point of view (Ware 1993).

2.6 Short Form 36 Health Survey (SF-36)

SF-36 was developed from the Rand Corporation Health Insurance Experiment (Lohr *et al* 1986) in the United States, which used a 245 item questionnaire to compare the impact of alternative health insurance systems on health status. While this outcome measure fulfilled its original purpose, its length prohibited its subsequent use in both practice and research. The original 245 questions were refined to 20 producing SF-20 (Ware *et al* 1992), but this was criticised for failing to retain the broad measures of health outcomes compared to the original

(McDowell and Newell 1996), resulting in the development of SF-36 (Ware *et al* 1993). This instrument measures each of 8 health domains: physical functioning (10 items); role limitation because of physical health problems (4 items); bodily pain (2 items); social functioning (2 items); general mental health (5 items); role limitation because of emotional problems (3 items); vitality (4 items); general health perceptions (5 items); and one item relating to transition in health status over the last year. SF-36 can be administered as a self completion questionnaire, telephone interview or face to face interview. It is presented as a health profile, with each domain scored from 0 to 100, a higher score indicating a better health status (Ware, Sherbourne 1992).

SF-36 has been tested for validity and reliability and indeed these studies have been described as "exemplary" (Newell and McDowell 1996). SF-36 was constructed to measure those domains most frequently included in health surveys (physical, role and social functioning, mental health and general health perceptions) as well as 2 additional measures (bodily pain, vitality), providing evidence of both face and content validity. More objective data relating to construct validity was provided by McHorney *et al* (1993) in a study conducted in the United States. Patients aged over 18 years presenting to a clinician were asked to complete questionnaires centring around chronic disease, depressive symptoms, sociodemographic characteristics and general health status, with clinicians providing information relating to diagnosis and disease severity for all 21564 patients. Those with hypertension, diabetes, congestive cardiac failure, recent myocardial infarction and depression were identified and completed a

further questionnaire containing SF-36. Patients with serious medical conditions were found to score significantly lower on all 8 scales, compared to those with minor conditions, indicating poorer health related quality of life. The physical functioning, role limitation due to physical functioning and vitality scales were most valid in detecting differences between patients with minor and serious medical conditions whereas the mental health, role limitation due to emotional problem and social functioning scales were most valid in distinguishing between severity of psychiatric conditions. The authors claimed that the observed differences in scores could be of value in predicting sample sizes for comparative studies. Additionally, these differences in scores obtained with differing severity of clinical conditions could be useful for interpreting scores. Further evidence of validity was provided by Ware *et al* (1993), with data showing high levels of correlation between SF-36 and 15 other health outcome measures.

Reliability was also tested by McHorney *et al* (1994), using data from the same population as previously described (McHorney *et al* 1993). Internal consistency reliability coefficients (Cronbach's alpha) were calculated for each of the 8 domains, yielding values ranging from 0.78 to 0.93, in excess of the recommended values of 0.5-0.7 (Nunally 1978). Ware *et al* (1993) combined results of 14 studies, giving a median alpha score exceeding 0.8 for all scales, except social functioning, which scored 0.76.

The responsiveness of SF-36 is the least studied of the criteria applied by the United States Medical Outcomes Trust. However, it has been stated that measures

which discriminate between groups of patients at one time are likely to be responsive (Ware 1993). Indeed, SF-36 has been included in the Trust library.

2.7 SF-36 - the UK perspective

Several workers have confirmed the usefulness of SF-36 in primary care settings in the UK. Brazier *et al* (1992) tested the validity, reliability and acceptability of SF-36 and compared it to the Nottingham Health Profile. Face to face interviews using the original US version of SF-36, were conducted with healthcare professionals in one general practice, resulting in slight alterations to the wording of 6 questions. This anglicised version of SF-36 and the Nottingham Health profile were sent to a large sample of 1980 randomly selected patients aged 16 to 74 years from 2 general practices in Sheffield, with a high response rate of 83%. This new version of SF-36 was found to be internally consistent, with Cronbach's alpha exceeding 0.85 for all domains. Although none of the US studies had evaluated test-retest reliability of SF-36, this was assessed by mailing a further copy to 250 randomly selected respondents after 2 weeks. The test-retest scores were found to be highly correlated with those from the main survey. Further results demonstrated evidence of construct validity in that health related quality of life scores decreased with social class for all dimensions; those consulting a GP in the previous 2 weeks had poorer health status, as did those for whom the GP had diagnosed one or more chronic problems. Each item on the Nottingham Health Profile is simply answered yes or no, compared to SF-36 where responses are rated yes or no for only 2 domains, the remaining 6 being rated on 3 to 6 point

scales. On comparing the results obtained with these 2 instruments, SF-36 was shown to have greater discriminatory powers, producing less skewed frequency distributions than the Nottingham Health Profile. Using the latter, many respondents scored the best possible health, the questionnaire failing to discriminate between groups of patients.

In a further large study based in primary care, Jenkinson *et al* (1993) provided population norms for SF-36 and provided further evidence of reliability and validity in such a setting. SF-36 was mailed to 13042 randomly selected adults from 4 English health authorities, with a response rate of 73%. This instrument was again shown to be internally consistent, with Cronbach's alpha greater than 0.8 for all dimensions except social functioning (0.76). Evidence of construct validity was provided in that patients with long standing illnesses were found to score significantly lower on all domains, as did those consulting a GP in the previous 2 weeks. The authors concluded that SF-36 was a particularly suitable measure for clinical research in primary care, but would require supplementation with a disease or domain specific measure.

Further analysis of this work (Jenkinson *et al* 1994) showed that scores for the 7 domains measuring functioning and well-being were strongly associated with patient responses to the single item asking patients to rate overall health on a scale of poor to excellent.

Garratt *et al* (1993) similarly tested the validity, reliability and acceptability of SF-36 in primary care using 4 clinical conditions: low back pain; menorrhagia; suspected peptic ulcer; varicose veins. A total of 1700 patients in Grampian were recruited, identified in 1 of 2 ways: those referred to outpatient departments and those identified by their GPs. A random sample of 900 members of the general public acted as controls. All those included were mailed a copy of SF-36. Response rates of 76% of patients and 60% of controls were achieved. Again, internal consistency was high, with Cronbach's alpha exceeding 0.8 for all domains. Construct validity was shown in several ways: scores for the patient population were significantly lower than those of the control group, thus indicating lower health related quality of life; referred patients had lower scores than non-referred; high levels of agreement were obtained for SF-36 scores and GP's perceptions of disease severity. Not only did this study confirm the usefulness of SF-36 in primary care, its design included common clinical conditions, several of which were minor.

While most studies of SF-36 have included patients aged 18-64 years, Lyons *et al* (1994) administered SF-36 by interview to 1201 randomly selected individuals in West Glamorgan aged 20-89 years of age. Of the 827 patients (69%) agreeing to participate, 216 (26%) were aged between 65 and 89 years. Analysis of data from this elderly subgroup again identified SF-36 as being internally consistent with Cronbach's alpha values greater than 0.8 for all domains. Again, patients with long standing disability, those admitted to hospital or attending outpatients departments in the previous year scored significantly lower on almost all

domains. Despite the smaller sample size, this study provided further information on the usefulness of SF-36.

A manual containing this anglicised version of SF-36 is now available (Ware *et al* 1993), which recommends its use either by self completion, telephone or face to face interview, in subjects aged 14 years and over.

Chapter 3

Therapeutic Areas, Including Health Outcome Measures

3.1 Urinary Tract Infections

3.1.1 Clinical presentation

Urinary tract infections (UTIs) are associated with multiplication of micro-organisms in any part of the urinary tract. These infections may be classified anatomically as either upper, occurring in the kidneys and/or ureters, or lower, the site of infection being the bladder and/or urethra. A further classification indicates likely response to therapy, describing UTIs as either uncomplicated or complicated. With complicated UTIs, the presence of certain risk factors may result in less favourable response to therapy. These risk factors have been defined as: anatomical abnormalities of the urinary tract, presence of an indwelling catheter, recent urinary tract instrumentation, diabetes mellitus, other immunosuppressed conditions, immunosuppressant drugs, recent antibiotic use, hospital acquired infections, symptoms lasting more than 7 days at presentation, male sex, age (children, elderly), pregnancy (Johnson, Stamm 1989, Hooton, Stamm 1991, Ronald *et al* 1992, Wilkie *et al* 1992). Lower uncomplicated UTIs are the most prevalent, with data showing that the annual GP consultation rate for females is 6.25/100 (Royal College of General Practitioners 1986). These patients

present with symptoms of urinary frequency and dysuria which will often remit spontaneously. Indeed, the goal of antibiotic therapy is simply to provide resolution of symptoms in the shortest possible time with the minimum of adverse effects as economically as possible (Nicolle 1990, Ronald *et al* 1992).

3.1.2 Ideal antibiotic therapy

Neu (1992) outlined the optimal characteristics of antibiotic therapy for uncomplicated lower UTI as being: active against the major pathogens, shown to be primarily *Escherichia coli* (Wilkie *et al* 1992); adequate urinary concentrations for sufficiently long periods to eliminate these pathogens; low potential for the development of resistance; lack of major alteration of intestinal flora; does not lead to perianal fungal colonisation; minimal adverse effects. Rubin *et al* (1992) stated that almost every antibiotic with high levels of activity against Gram negative organisms such as *E. coli* would fulfil these criteria, providing success rates in excess of 80%.

3.1.3 Comparative clinical trials

Many poorly designed clinical trials of uncomplicated lower UTI have been conducted, each claiming evidence of the superiority of one form of therapy over another. Fihn and Stamm (1985) critically reviewed all published studies from 1981-1983 against a set of 12 criteria, derived from published methodological standards for conducting clinical trials, adapted for studies of lower UTI. Those

studies reviewed fulfilled an average of only 56% of criteria. Particular areas of concern were: the lack of adequate power to detect clinically important differences; no clear definitions for diagnosing either cure or failure; no stratification of patients with previously defined risk factors. As a result, the authors defined standards to be incorporated into the design of future studies. The main recommendation was that studies should have adequate power to detect clinically important differences. Other recommendations were: excluding patients with risk factors for complicated infections or at least stratifying these patients within the study design; criteria for diagnosing UTI should be clearly defined; study duration should be at least 4 to 6 weeks following completion of therapy, to allow for any relapses; adverse drug reactions should be monitored. Similar standards have been described by others (Working Party of the British Society of Antimicrobial Chemotherapy 1989, Rubin *et al* 1992). Norrby ((1992) and (1994)) further recommended that these studies should have at least an 80% power to detect a clinically important difference of not greater than 10% at a significance level of 5% (2 tailed test). The results of well designed, prospective, randomised, controlled clinical trials form the basis of evidence for inclusion of drugs into local antibiotic policies.

3.1.4 Antibiotic policies in primary care

Antibiotic policies have been widely adopted in secondary care, aiming to provide a unified approach to the treatment of infections, taking into account local resistance patterns (Gould 1988). Remington and Hepburn (1990) described

a similar approach to policy development in primary care. Despite the mass of literature relating to the development and implementation of antibiotic policies in secondary care, little has been published relating to primary care.

Wyatt *et al* (1990) aimed to determine the need for a primary care based antibiotic policy in Northern Ireland. Prescribing data was surveyed over a 5 year period to determine those antibiotics most frequently prescribed, changes in prescribing patterns and resulting cost implications. While results indicated no great changes in terms of numbers of prescriptions, the use of certain newer entities (minocycline, co-amoxiclav, ciprofloxacin) and resultant costs had increased substantially. The authors concluded that an antibiotic policy would help rationalise prescribing of these newer agents.

Further work by the same authors (Wyatt *et al* 1992) attempted to monitor the effect of introducing an antibiotic policy into primary care in Northern Ireland. Prescribing data from one small general practice was collected over two 6 month periods, before and 1 year following policy introduction. Consistent antibiotic prescribing within the practice during the first period reduced the likelihood of demonstrating any positive impact of the policy. Accordingly, an increase in non-policy prescribing was achieved during the second period of data collection.

Swann and Clark (1994) similarly described policy development in two areas of England. Data from questionnaires completed by GPs in Leicester relating to choice of antibiotic therapy identified the lack of a consistent approach. This was

communicated to those involved as part of a newsletter containing additional educational material. The eventual result was the production of a local antibiotic policy. The stimulus for policy development in Derbyshire came from analysis of prescribing data which identified the diversity of antibiotics being prescribed. No attempt was made to measure the impact of either of these policies on prescribing patterns or health outcomes.

Needham *et al* (1988) reported on an audit of antibiotic prescribing in one general practice prior to and following the introduction of an antibiotic policy devised by the GPs, local pharmacists and a consultant microbiologist. Details of antibiotics prescribed over a 1 month period prior to and 12 months following completion of the policy were analysed. Results indicated that prescribing of several non-recommended agents reduced and that prescribing costs overall fell by 25%. The authors made some attempt to measure outcomes, with no increase in hospital admissions, patient consultations or home visits occurring during the study period. No measures of patients' perceptions of symptom resolution were included.

3.1.5 Antibiotic policy recommendations

The Grampian Joint Drug Formulary (Grampian Medicines Committee 1995) contains antibiotic policies specifically developed for both primary and secondary care. The primary care section recommends trimethoprim as first line therapy in patients presenting with an uncomplicated lower UTI. Cephalexin should be used

in patients having experienced treatment failure with trimethoprim or with a history of allergy to this agent.

3.2 Ulcer Healing Agents

3.2.1 Dyspepsia, clinical presentation

Dyspepsia has been defined as any "upper abdominal or retrosternal pain, discomfort, heartburn, nausea, vomiting or other symptoms considered to be referable to the proximal alimentary tract" (Colin-Jones *et al* 1988). Community based research identified that approximately 40% of the adult population experienced dyspepsia during a 6 month period, with 25% consulting their GP due to such symptoms (Jones, Lydeard 1989). Common causes include gastro-oesophageal reflux and oesophagitis, duodenal and gastric ulceration, non-ulcer dyspepsia, non-steroidal anti-inflammatory drugs (NSAID), over-indulgence in alcohol (Crean 1992).

It has been estimated that approximately 10% of the adult population of Western countries will suffer from either duodenal or gastric ulceration at some point in their lives, with 80% of ulcers recurring in 1 year (Kurata, Haile 1984). Reflux of acidic stomach contents may lead to oesophagitis, which is classified according to endoscopic findings of mucosal damage (Skoutakis *et al* 1995). Up to 25% of patients consulting their GP due to dyspepsia have non-ulcer dyspepsia, defined by an international working party as "upper abdominal or epigastric pain,

discomfort, heartburn, nausea, vomiting or other symptoms considered to be referable to the upper gastrointestinal tract, and lasting for more than 4 weeks. unrelated to exercise and for which no focal lesion or systemic disease can be found responsible" (Patchett *et al* 1991).

3.2.2 Role of *Helicobacter pylori*

The isolation of *Helicobacter pylori* (*H. pylori*), a small curved or spiral Gram negative, flagellated bacterium, from gastric samples (Warren, Marshall 1983) and demonstration of an association with gastritis was the stimulus for much further research. The microbiology, epidemiology, clinical manifestations and particularly therapeutics relating to *H. pylori* have been extensively reviewed (Axon 1991, Anon 1993, Marshall 1994, Tytgat 1994, Lee 1994, Owen 1995, Rauws and Tytgat 1995). *H. pylori* is found principally in the gastric antrum, surviving the acid environment by the action of the enzyme urease, converting urea to ammonia, thereby increasing the intragastric pH. In Western countries, approximately 20% of adults under 40 years and 50% over 60 years are thought to be infected with *H. pylori*. Colonisation of the stomach leads to gastritis in nearly all those infected, but is without symptoms in the vast majority. It has been shown to be associated with 60-70% of gastric ulcers and 95% of duodenal ulcers, due to gastric metaplasia of the duodenal mucosa. Accumulated evidence now indicates that *H. pylori* infection is the main causative factor associated with ulcer development, since eradication of infection results in very low levels of ulcer recurrence. The role of *H. pylori* in oesophagitis is less well established,

with the frequency of occurrence being similar in both infected and non-infected individuals. There is also a lack of data relating to the role in non-ulcer dyspepsia and NSAID induced ulceration.

3.2.3 Therapeutic Strategies

Histamine$_2$ receptor antagonists (H_2RAs) are well established drugs for the treatment of both duodenal and gastric ulcers, with healing of the vast majority of duodenal ulcers being obtained in 4 weeks, although gastric ulcers may take longer to heal. There appears to be little difference in efficacy between H_2RAs, the main differences being in terms of drug costs and potential for interaction with other drugs. Cimetidine, although cheaper than ranitidine, inhibits microsomal cytochrome P450, leading to elevation of plasma levels of drugs metabolised by this system. Proton pump inhibitors (PPIs) have been shown to provide slightly faster healing rates, but whichever agent is used for initial therapy, 70-80% of ulcers relapse within 1 year. This may be reduced by continuous low dose maintenance therapy but his does not alter the tendency for ulcer recurrence on withdrawal of therapy (Feldman, Burton 1990a, Feldman, Burton 1990b, Brooks 1992, Pentson, Wormsley 1992).

More recently, the role of *H. pylori* has led to the development of regimes to eradicate this organism, with studies identifying that successful eradication results in very low recurrence rates. The choice of eradication therapy has been the subject of much debate. A meta-analysis (Chiba *et al* 1992) identified much

poor quality research in this area. Of 150 studies, only 20 met standard criteria for the conduct of clinical trials and warranted inclusion in the systematic overview. Triple therapy with an ulcer healing agent and 2 antibiotics was shown to be the most effective but interpretation of results was complicated by the use of different doses and durations of therapy in those studies reviewed. Similar conclusions were reached by Tytgat (1994) and Pentson (1994). Harris and Misiewicz (1995), however, stated that it was not possible to recommend the most appropriate therapy until well designed, randomised, controlled trials had been reported.

Less research has been published in relation to the treatment of oesophagitis and the choice of agent for NSAID prophylaxis. For oesophagitis, a step-wise approach to treatment is most commonly recommended, initially with an anti-motility agent initially before progressing to H_2RAs and finally PPIs. H_2RAs typically relieve symptoms in 50% of patients after 4 weeks and heal oesophagitis after 8 weeks therapy. PPIs have been shown to be superior in terms of both symptom relief and healing but at higher drug cost. Accordingly, these agents are recommended for use in cases of therapeutic failure or in patients with severe erosive oesophagitis (Medicines Resource Centre 1993, Wilde, McTavish 1994, Skoutakis 1995, Anon 1996b). Few large clinical studies comparing agents for NSAID prophylaxis have been reported. In particular, no study compares different H_2RAs. Misoprostol, a prostaglandin analogue, has been shown to be more effective than H_2RAs in preventing gastric ulceration, and as effective for duodenal ulceration, but at an increased risk of adverse effects (Nash *et al* 1994).

3.2.4 Ulcer healing agents, drug utilization in primary care

Ulcer healing agents are commonly prescribed drugs. UK prescribing data for 1992 identified that H_2RAs and PPIs accounted for 10% of the drugs bill, over £250 million, and 2% of all dispensed prescriptions (Medicines Resource Centre 1993). Scottish data for 1994/95 showed that expenditure on these agents had increased 12% on the previous year, being responsible for 19% of the drugs bill and 10% of dispensed prescriptions in primary care (Anon 1995). There are also substantial differences in costs between these agents, with one months treatment with ranitidine 150mg twice daily being £27.89, compared to cimetidine 400mg twice daily £6.94 and omeprazole 20mg once daily £35.45. It is of extreme importance to ensure that drug utilization studies are carried out to establish that these agents are being used appropriately.

Ryder *et al* (1994) reported on such a study involving seven general practices (60148 patients), which identified the need for further guidelines to ensure appropriate use. Patients prescribed ulcer healing agents for longer than 6 months were identified from computerised repeat prescribing systems. Results showed that 493 patients (0.82%) were receiving long term therapy, with 75% of patients exceeding 5 years treatment. The most common indication was duodenal ulcer (37%), followed by oesophageal disease (24%), with gastric ulcer relatively uncommon at 5%. No diagnosis was documented in the medical notes of 15% of patients. The most commonly prescribed agent was ranitidine (80%), with many

patients still receiving treatment doses of 150mg twice daily, as opposed to maintenance doses of 150mg at night.

3.2.5 Treatment guidelines

Several guidelines relating to the appropriate use of eradication therapy have now been published. The first of these recommended reserving therapy for *H. pylori* positive patients with a diagnosed duodenal ulcer associated with management problems resulting in frequent recurrences requiring either maintenance therapy or possible surgery (Anon 1993). A similar approach was recommended by Neeman and Kadish (1994). Several have, however, recommended treating all *H. pylori* positive patients with a history of duodenal ulceration (Anon 1994, Rauws, van der Hulst 1995). Delaney (1995) reviewed the evidence relating to primary care and recommended treating all *H. pylori* positive patients with either duodenal or gastric ulceration. National guidelines have now been developed and distributed throughout Scotland for implementation (Scottish Intercollegiate Guidelines Network 1996), recommending eradication therapy in all patients with either duodenal or gastric ulceration. Unlike previous publications, this guideline recommends specific therapy using one weeks treatment with a PPI plus 2 antibiotics and provides advice on the need to determine the presence of *H. pylori*.

Such guidelines do not, however, exist for the treatment of oesophagitis, nor the choice of agent for NSAID prophylaxis. National publications have, however,

recommended increased use of cimetidine relative to other H_2RAs, notably ranitidine. The Audit Commission report of prescribing in primary care identified that due to the low incidence of interactions of cimetidine with other drugs and the lower cost of cimetidine, that such substitution would produce annual savings of £45 million for the UK (Audit Commission 1994).

3.2.6 Grampian Joint Drug Formulary Recommendations

The Grampian Joint Drug Formulary generally follows this recommendation, listing cimetidine as the first choice H_2RA for use in gastric and duodenal ulceration as well as oesophagitis. Ranitidine is recommended in situations where cimetidine would be unsuitable, namely in combination with warfarin, phenytoin, theophylline and aminophylline. Omeprazole is recommended for use in patients who are unresponsive to H_2RAs or in severe oesophagitis. For use in NSAID prophylaxis, concurrent administration of either an H_2RA or misoprostol is recommended. Little reference is made to eradication therapy, other than stating that several regimes have been proposed and that there may be a role for patients with duodenal ulceration (Grampian Medicines Committee 1995).

3.2.7 Implementing recommendations

Relatively little UK work in primary care has examined the effect of implementing recommendations regarding *H. pylori* eradication therapy.

Cotrill (1994) used computerised repeat prescribing systems to identify 206 patients (2.4% of the practice population) receiving repeat prescriptions for either ranitidine or cimetidine. Those patients with either a duodenal or gastric ulcer were identified from their medical notes and those patients consenting tested for the presence of *H. pylori*. Positive patients were randomised to receive either triple or dual therapy. Use of H_2RAs in these patients reduced substantially in the year following eradication, generating considerable economic savings. A similar study was reported more recently. Rosengren and Polson (1996) identified 277 patients (3.9%) receiving long term ulcer healing therapy, 45 of whom had duodenal ulceration. Only 29 patients were willing to undergo testing, 20 of whom were found to be positive and 18 expressed an interest in eradication therapy. *H. pylori* was successfully eradicated in all patients. Although these 2 studies followed patients for periods of 4 months (Rosengren and Polson) and 12 months (Cotrill), little measures of health outcomes were included in the study designs, with only confirmation of eradication and use of H_2RAs being reported. No attempt was made to quantify patients' experiences of symptoms nor health related quality of life.

Much of the work relating to cimetidine substitution was performed in the United States, with several researchers focusing solely on intravenous therapy (Foulke and Sieper 1990, Fudge *et al* 1993). Of those relating to oral therapy, the only outcome reported following the change was the use of antacids.

Falbe *et al* (1992) only reported pharmacy issues of H_2RAs following a hospital based initiative to increase cimetidine use.

DeZearn *et al* (1996) promoted cimetidine in a study centred around managed care organisations. Individual patient summaries were sent to prescribers, detailing current therapy, indication, dose, requesting a switch to generic cimetidine, with results compared to those of a control group. Although an increase in cimetidine was observed, no attempt was made to ensure that the control group was appropriate, nor that the changes were as a direct result of the information supplied.

Keith *et al* (1994) aimed to limit excessive use of treatment doses of H_2RAs in a state correctional system. Continued use of treatment doses beyond the recommended 8 weeks required the completion of an authorisation form by the prescriber. Results indicated a reduction in mean daily dose and total duration of therapy, generating considerable cost savings. Similar results in both long term and ambulatory care were obtained by Zimmerman *et al* (1994). Neither of these studies incorporated any health outcome measures.

In the UK, McKenzie *et al* (1996) aimed to evaluate the effect on primary care prescribing of a series of interventions. Guidelines were launched at educational sessions with prescribers throughout Glasgow, aiming to increase cimetidine use relative to other H_2RAs, limit omeprazole to use in moderate to severe oesophagitis and to increase the use of eradication therapy in duodenal ulceration.

These points were later reinforced in a series of bulletins. Prescribing data was used to monitor guideline impact, with Lothian acting as a control. A non-significant rise in the ratio of cimetidine to ranitidine was observed in the target area compared to control. No real effect was observed in relation to omeprazole use nor the use of eradication therapy.

Similarly disappointing results were described by Roberts *et al* (1997), who issued reports on methods of altering prescribing with no detriment to patient care to all practices in the Northern Regional Health Authority. One such recommendation involved increasing the use of cimetidine relative to related agents. Results failed to demonstrate any subsequent increase in cimetidine use.

3.2.8 Health outcome measures

If studies aim to investigate the effect of implementing guidelines or changing established therapy, consideration must be given to the effect on health outcomes, using measures meeting approved scientific criteria previously described. In disease states such as duodenal and gastric ulceration and oesophagitis, this should ideally consist of both disease specific and generic measures of health related quality of life.

Hallerback (1993), Korman (1993) and Wilhelmsen and Berstad (1994) constructed or used existing measures in patients with various upper

gastointestinal diseases but failed to provide any data relating to validity, reliability or responsiveness.

Glise (1993) used the Psychological General Well Being Index (PGWB), a measure of feelings of well being and distress, as a generic measure in duodenal ulcer patients pre-endoscopy and at a further 4 stages during a 1 year follow up period. Of those questionnaires distributed, 392 (95%) were returned, with results showing pre-endoscopy scores lower than population values, indicating discriminatory validity. The measure was shown to possibly be responsive, with scores increasing during treatment with ulcer healing agents, although no tests of statistical significance were included. No data was provided relating to scale reliability and no disease specific measure was included.

Svedlund *et al* (1988) described the construction of a disease specific measure, Gastrointestinal Symptom Rating Scale (GSRS), for use in patients with irritable bowel syndrome and peptic ulcer disease. Items were selected from the literature and on the basis of clinical experience. Inter-rater reliability was evaluated with a small sample of 20 patients, interviewed by 2 psychiatrists on different occasions, with high levels of agreement. No attempt was, however, made to measure construct validity, internal consistency nor responsiveness.

Further data relating to GSRS and PGWB was provided by Dimenas *et al* (1993) in a study of 146 patients before and 4 weeks following endoscopy. Patients completed 3 questionnaires, PGWB, GSRS and Ulcus Esophageal Subjective

Symptom Scale (UESS), a new scale developed to quantify symptoms frequently experienced and to extend the range of GSRS to areas other than peptic ulcer disease and irritable bowel syndrome. Sixty eight patients provided initial data leading to slight modification of UESS, following which a further 78 completed questionnaires pre-endoscopy, 57 of whom completed a follow up questionnaire 4 weeks later. Internal consistency for 3 dimensions of UESS was acceptable but was poor for the fourth dimension. Similarly, only 3 dimensions were responsive to treatment. Construct validity was established by comparing GSRS and UESS with PGWB and each other showing high degrees of correlation. This work was limited by the small sample size and the failure to include data relating to test-retest reliability. Further evaluation would be required prior to use in a clinical setting.

Martin *et al* (1994) developed a further measure for use in peptic ulcer disease, the Quality of Life in Duodenal Ulcer Patients (QLDUP). This was derived from the full version of SF-36, with a further anxiety dimension added and 5 dimensions specifically relating to gastrointestinal symptoms. Data was collected from 3 groups of patients: 80 with acute duodenal ulcer; 69 with history of duodenal ulcer but in remission; 82 non-ulcer controls. Results of the SF-36 components revealed acceptable internal consistency, test-retest reliability and discriminatory validity. Further work in the UK also tested SF-36 in patients with peptic ulcer disease, as described in chapter 2. PGWB described by Glise (1992) and Dimenas *et al* (1993) was included in the Rand Corporation Health Insurance Experiment from which SF-36 was developed. Stacey *et al* (1996)

extended the use of SF-36 in patients with gastro-oesophageal reflux disease. Results were provided for 354 patients suffering from reflux for 1 month and receiving no medication. Initial SF-36 scores were lower than population values, providing evidence of discriminatory validity. Significant increases in scores in all 8 dimensions were obtained following 2 weeks treatment with ranitidine. SF-36 would appear to be an appropriate generic measure of health related quality of life in patients with symptoms of dyspepsia.

Two further UK studies focused on the development of disease specific measures. Garratt *et al* (1996) developed a measure for patients with dyspepsia and ulcer related symptoms, which was tested in 135 patients referred to an outpatient gastroenterology department and 152 further patients not referred but identified by their GPs. Internal consistency proved acceptable and dyspepsia scores were found to correlate well with the GP's perception of symptom severity. Further evidence of validity was provided by comparing dyspepsia scores with those obtained from completion of SF-36, with high correlations being observed in 5 domains, pain, social functioning, energy and fatigue, mental health and role limitation attributable to physical problems. Test-retest in a sample of 114 patients was shown to be acceptable. Limitations of this measure include the lack of data relating to responsiveness and the fact that all questions relate to experiences in just the previous 2 weeks.

El-Omar *et al* (1996), developed the Glasgow Dyspepsia Severity Score for any symptom or combination of symptoms related to the upper gastro-intestinal tract.

Acceptable levels of inter and intra-reliability were obtained with samples of 50 and 30 patients respectively. Discriminant validity was shown in 3 groups of patients: 80 healthy controls; 80 with non-ulcer dyspepsia; 70 with duodenal ulcer. No difference was identified between the duodenal ulcer and non-ulcer dyspepsia groups, but scores for the control group were significantly lower. Responsiveness was tested for by comparing scores before and 1 year following eradication therapy in 48 patients, with a significant reduction in scores. No data was, however, provided to allow evaluation of responsiveness in other disease states and data relating to internal consistency was lacking. This measure does, however, measure dyspepsia scores over a longer period and, in combination with SF-36, may be the best available measure of health related quality of life in patients with dyspepsia.

3.3 Peripheral Vasodilators

3.3.1 Peripheral vascular disease, clinical presentation

Peripheral vascular disease occurs as a result of slowly progressing arteriosclerosis of the major arteries of the lower limbs, rarely affecting those of the upper limbs (Balkau *et al* 1994). Intermittent claudication, defined as "cramping discomfort in the calf clearly provoked by exercise and relieved by some minutes rest" is the commonest presenting symptom (Kannel, McGee 1985). Peripheral vascular disease is more common in males and usually presents after the age of 50 years, with peak presentation rates occurring between the ages

of 65 and 74 years. Predisposing risk factors include cigarette smoking, diabetes mellitus, elevated blood pressure and obesity (Kannel, McGee 1985). Approximately 20% of patients with intermittent claudication require surgical treatment with the remainder either improving or remaining unchanged over time. Hiatt *et al* (1995) defined the major goals of therapy in intermittent claudication as relief of symptoms and improvement of health related quality of life. The mortality rate of patients with intermittent claudication, however, approaches that of a population aged 10 years older with the majority of patients dying from arteriosclerotic cardiac complications (Balkau *et al* 1994).

3.3.2 Standards for clinical trials of peripheral vasodilators

Several agents, including naftidrofuryl, oxerutins and oxpentifylline, are marketed for the treatment of intermittent claudication. Heidrich *et al* (1992) proposed standards for the conduct of clinical trials of such agents. Optimal study design should be double-blind with random allocation of treatments. A placebo control must be included with a run in period of at least 2 weeks. A parallel group study is recommended with a treatment period of at least 2 to 6 months. The main method of assessment of response centres around the measurement of both pain free walking distance and absolute walking distance. These measures should be performed using standardised treadmill gradients and speeds and should be carried out at least twice during the run in phase and at monthly intervals during the trial. Additional forms of assessment include the use of self-assessment questionnaires to provide an estimate of the patients' evaluation of any effects of

treatment. Other workers have proposed guidelines for interpreting results of such trials. Due to the large placebo response often obtained, a difference of less than 40% improvement between drug and placebo may be unimportant (Cameron *et al* 1988). Rudofsky and van Laak (1994) further recommended that successful treatment must increase pain free walking distance by 50-60%.

3.3.3 Reviews of clinical trials involving peripheral vasodilators

Verstraete (1982) reviewed the evidence for the use of peripheral vasodilators, identifying that, while these agents may increase resting blood flow in normal subjects, clinical experience had proved disappointing. A more critical review was undertaken by Cameron *et al* (1988). All trials in patients with intermittent claudication published between 1965 and 1985 were reviewed. Many of the 75 trials identified were of very poor quality with very few meeting standards previously described. In particular, 33% included no control group and those with a placebo control often had no run-in period. No trial documented the method of estimating sample size with some trials reporting data from only 7 patients (median 35). The method of assessing the effects of treatment was also poorly reported. Of those describing treadmill testing, no consistent gradients nor speeds were used. Although 39 trials had claimed a positive benefit from the use of peripheral vasodilators, the outcome was shown to be related to design, with uncontrolled trials being three times more likely to show benefit. The authors concluded that no trial with adequate methods had produced positive results which others had been able to confirm.

Lehert *et al* (1990) reported on a meta-analysis of 4 clinical trials of naftidrofuryl versus placebo involving a total of 776 patients. Data was provided for 449 patients, the remainder being excluded for reasons not fully documented in the meta-analysis. These trials adhered to several of the standards previously described, being double blind, randomised, parallel group comparisons but the method of treadmill testing varied between the trials. At 3 months naftidrofuryl increased pain free walking distance by 55% compared to 25% for placebo. Of the 3 trials continuing for 6 months, painfree walking distance on naftidrofuryl increased by 76% and 41% for placebo. Although statistically significant, these differences are unlikely to be clinically important, according to criteria proposed by Cameron *et al* (1988).

Data from these 4 studies were included with one later trial in a further meta-analysis by Lehert *et al* (1994). Comparison of results obtained for naftidrofuryl and placebo showed that although naftidrofuryl increased pain free walking distance, this increase was only 22m greater than that obtained by placebo, a difference of doubtful clinical importance (Cameron *et al* 1988). Lehert *et al* (1994), however, claimed that treatment with naftidrofuryl consistently increased walking distance. More recent meta-analyses of the same trials have reached similar conclusions (Barradell, Brogden 1996, Anon 1996a).

3.3.4 Use of peripheral vasodilators in primary care

Given the lack of evidence to support widespread prescribing of these agents, many have recommended restricting their use to those patients with severe disabling symptoms. Treatment should initially be for a limited trial of 2 to 3 months followed by withdrawal to ascertain any need for continued use (Ruckley 1986, Lowe 1990, Waller, Chant 1995). Excessive use of these agents has been identified as a marker of poor prescribing (Avorn, Soumerai 1983). The Audit Commission report of prescribing in primary care recommended a general reduction in the use of agents of limited clinical efficacy and estimated that restricted use of peripheral vasodilators would generate savings amounting to £8.8 million per annum in England and Wales (Audit Commission 1994). Accordingly, peripheral vasodilators are not recommended in the Grampian Joint Drug Formulary.

3.3.5 Health outcome measures

Outcome measures used in studies of patients with intermittent claudication have traditionally centred around treadmill testing. This measure may be limited by the lack of practicality in the primary care setting and failure to evaluate the patients' perceived ability to walk. As previously stated, the aims in the treatment of intermittent claudication are to relieve symptoms and improve health related quality of life, increasing the need to incorporate such measures in the evaluation

of any treatment effects. Joyce (1994) described the lack of and need for suitable measures.

Several health outcome measures have been described in patients with severe disease undergoing vascular surgery. Hunt *et al* (1982) used the Nottingham Health Profile as a generic measure, showing reduced health status compared to a control group. Humphreys *et al* (1994) used the Rosser system, a limited generic measure of health related quality of life focusing only on mobility and pain, and Euroqol, a more recently introduced generic measure. Euroqol was developed to provide a generic measure in areas of mobility, self-care, role activity, family and leisure activities, pain and mood in a single index score (Euroqol Group 1990). Results using these 2 measures showed a high level of correlation, with the authors concluding that Euroqol may be the more superior measure but that further evaluation would be required prior to more widespread use.

SF-36 was used as a generic measure to assess the effects of exercise in 202 patients referred for vascular out-patient investigation (Currie *et al* 1995). Patients were treated either surgically or commenced on an exercise programme. Results showed that exercise produced statistically significant changes in the domain of bodily pain, whereas surgery affected areas of physical functioning, role limitation due to physical functioning, bodily pain and vitality. No disease specific measure was included in this evaluation.

The Walking Impairment Questionnaire was developed by Regensteiner *et al* (1990), to characterise speed and distance of walking reflecting treadmill testing. This questionnaire quantifies self-reported severity of claudication pain and ability to walk defined distances and speeds. Results are scored on a scale of 0% (unable to perform due to severe claudication) to 100% (no impairment). This was administered to a small sample of 19 patients (10 active, 9 control) as part of a study to evaluate the effects of a structured exercise programme. Seven further patients completed questionnaires before and after vascular surgery. Results showed the questionnaire to be internally valid in that walking ability decreased with increasing distances and speeds. Further evidence of validity was provided from high levels of correlation between questionnaire scores and treadmill test results. Control patients completed questionnaires on 2 separate occasions, with results providing evidence of the measure's reliability. The questionnaire was also shown to be responsive to the effects of surgery and exercise.

The Walking Impairment Questionnaire and SF-20, an earlier version of SF-36, were used in a further study to evaluate the effects of a structured exercise programme in patients with intermittent claudication (Regensteiner *et al* 1996). Twenty nine patients completed questionnaires prior to and following periods of either supervised treadmill training, strength training or no intervention. Results showed significant increases in SF-20 scores in the domain of physical functioning following 12 weeks of treadmill training and significant increases in walking impairment scores at 24 weeks. Strength training increased walking impairment scores at 12 weeks.

Hiatt *et al* (1995) concluded that the use of a disease specific and generic measure should be included in the assessment of interventions in patients with intermittent claudication and recommended combining the Walking Impairment Questionnaire with SF-36.

Chapter 4

Methodology

4.1 Introduction

4.1.1 Aim

The aim of this research was to evaluate the effect on health outcomes of implementing selected recommendations of the Grampian Joint Drug Formulary in primary care.

4.1.2 Areas of study

Drug groups were selected to reflect both acute and chronic prescribing as follows:

1. antibiotics used in the treatment of uncomplicated lower urinary tract infections, representing acute prescribing.

2. ulcer healing agents, which may be prescribed in acute courses but, in selected patients, may be continued over longer periods of time.

3. peripheral vasodilators, representing chronic prescribing.

4.1.3 General methodology

Prescribing Information System for Scotland (PRISMS), a software system capable of performing rapid analysis of prescribing data, was developed by a team of computer programmers and medical prescribing advisers in 1991. This system allows analysis of all prescribing data collected by the Pharmacy Practice Division of the Common Services Agency, down to the level of root drug and individual prescriber. Data is now sent to all health boards in Scotland within 8 weeks of prescriptions being dispensed (Donald 1995). PRISMS data was used as a means of identifying both general practices and individual GPs within Grampian for possible inclusion in the study. Prior to accessing this data, it was necessary to obtain permission from all general practices in Grampian. This was requested in writing from all 93 practices, with only one practice (1.1%) unwilling to participate.

4.1.4 Study approval

The study was approved by the Joint Ethical Committee of Grampian Health Board and The University of Aberdeen. Approval was also obtained from the Area General Practice Sub-committee.

4.1.5 Statistical analysis

Statistical analysis was performed and graphics produced using SPSS for Windows Release 6.0. Sample size calculations were performed using nQuery Advisor Release 2.0.

4.1.6 Systematic Review of Literature

Medline and International Pharmaceutical Abstracts were used as databases employing the following search terms: prescribing, prescribe, drug formulary, policy, protocol, guideline, outcome, health outcome, quality of life, health related quality of life, antibiotic policy, urinary tract infection, dyspepsia, *Helicobacter pylori*, ulcer healing agent, arterial occlusive disease, peripheral vascular disease, peripheral vasodilator, research methods and primary care, research methods and general practice. The UK Clearing House for Information on the Assessment of Health Outcomes at the Nuffield Institute for Health provided database searches for outcome measures used in dyspepsia and peripheral vascular disease.

4.2 Urinary Tract Infections

4.2.1 Objectives

The objectives of this part of the research were to:

1. identify the antibiotic therapy prescribed to females aged 18-60 years presenting in primary care with symptoms of lower uncomplicated urinary tract infections.

2. identify any patient factors influencing drug selection.

3. measure health outcomes resulting from such treatment.

4. compare the outcomes of those patients receiving therapy in line with the recommendations of the Grampian Joint Drug Formulary to those receiving non-recommended therapy.

4.2.2 Method

4.2.2.1 Questionnaire validation

This study was carried out over an 18 month period from March 1995 until September 1996. Information relating to antibiotic prescribing and health

outcomes were obtained from 2 sources. The GP provided drug utilization information, detailing drug prescribed, dose, duration of therapy, any patient factors which influenced drug choice and the use of microbiological sensitivity testing. Measures of health outcome centred around the patient's perception of symptoms experienced, severity, symptoms on completion of treatment and adverse drug reactions. Further information was obtained from the patient relating to compliance with therapy and the need for further GP consultation. Draft questions were prepared and tested for face and content validity by a panel consisting of a consultant microbiologist, general practitioner, medical prescribing advisor, community pharmacist, hospital pharmacist and several lay persons, resulting in slight alteration to the wording of some of the questions.

4.2.2.2 Selection of patients

The study was designed to include only female patients, aged 18 to 60 years presenting to their GP with symptoms of uncomplicated lower UTI. Those with risk factors predisposing to complicated infections and therefore likely to adversely affect outcomes were excluded from the study as follows: anatomical abnormalities of the urinary tract; presence of an indwelling catheter; recent urinary tract instrumentation; diabetes mellitus; other immunosuppressed conditions; immunosuppressant drugs; antibiotic use in the previous 2 weeks; symptoms of acute pyelonephritis; pregnancy, breast feeding. Patients with a UTI in the previous 3 months were also excluded as response to therapy and results of any microbiological sensitivity test may have altered drug selection.

4.2.2.3 Calculation of Sample Size

To enable comparison of health outcomes between patients receiving formulary and non-formulary therapy, adequate sample sizes were necessary. This calculation required an estimate of the likelihood of treatment success with the formulary recommendation and the clinically important difference to be detected at a particular level of significance. Due to the lack of data relating to the efficacy of trimethoprim in Grampian, other indicators of the likelihood of success were used. Local sensitivity data identified that approximately 80% of all urinary isolates in Grampian were sensitive to trimethoprim (Gould 1993). Furthermore, Rubin *et al* (1992) had stated that all marketed antibiotics should provide cure in at least 80% of patients. It was therefore estimated that trimethoprim, the first line formulary recommendation, would provide favourable outcome in 80% of patients. In trials of lower uncomplicated UTIs, the clinically important difference should not be greater than 10%, with a power of 80% at a significance level of 5% (2-tailed test) (Norrby 1992, Norrby 1994). This resulted in 199 patients being required for both the formulary and non-formulary groups. The study therefore initially aimed to recruit 240 patients to each of these groups, assuming that 80% of patients would return the questionnaire.

4.2.2.4 Selection of prescribers

This study required 2 populations of prescribers: those adhering to the formulary recommendations prescribing trimethoprim first line; and those prescribing

alternative agents. The main indication for trimethoprim is in the treatment of uncomplicated lower UTI (Joint Formulary Committee 1997). To enable identification of these 2 populations, it was assumed that those GPs with higher prescribing frequencies of trimethoprim were adhering to the recommendations, those with lower prescribing frequencies were not. Analysis of PRISMS data for Grampian was used to determine the median prescribing frequency of trimethoprim over a 3 month period. Using this data, prescribers were stratified into those prescribing more or less than the median amount. Given the common presentation of females with lower uncomplicated UTI in primary care (6.25/100 consultations), it was estimated that 12 prescribers in both groups, each distributing 20 questionnaires, would result in a study duration of approximately 10 to 20 weeks, with minimal demands being made of any of the participating GPs. This short duration also allowed for the recruitment of further GPs, if necessary, to provide the required patient numbers in both groups.

4.2.2.5 Data collection

To enable identification and correction of any potential problems with study design, the method was piloted with one randomly selected GP. Further randomly selected GPs were contacted and permission sought for a meeting during which the study aims were explained. During these meetings, care was taken not to inform the GPs that prescribing of different individuals would be compared as such information itself may have altered prescribing habits. Particular emphasis was, however, placed on the anticipated extent of GP and patient involvement.

Access to patients' medical notes was also requested during this meeting. Sufficient GPs were contacted until agreement to distribute 20 questionnaires was obtained from 12 high and low prescribers of trimethoprim. Each participant was provided with a desk top organiser, clearly displaying the inclusion and exclusion criteria. This system served 2 purposes: acting as a constant reminder of the study; and providing easy storage for the patient questionnaires and reply paid envelopes. In addition, the questionnaires were coloured yellow to facilitate easy recall by both GP and patient. The top sheet of the questionnaire (Appendix 1) was completed by the GP at the time of the consultation, during which informed consent for participation was also obtained from the patient. These top sheets were detached from the remainder of the questionnaire and stored at the practice reception for collection each week by the researcher. The patient completed the remainder of the questionnaire outwith the surgery. This was organised in 2 parts: section 1 was completed prior to the commencement of the prescribed antibiotic; section 2 following completion of the course of medication (Appendix 2). The patients were instructed to return the questionnaires in the reply paid envelopes. Those patients not returning the questionnaire within 2 weeks of collecting the top sheets from the practice received reminder letters and a maximum of 3 further questionnaires at weekly intervals (Appendix 3). All patients in agreement were contacted either by letter or telephone 4-6 weeks following completion of antibiotic to identify any return of symptoms and subsequent action (Appendices 4,5). Further data was collected from the medical notes of all patients who either consulted their GP at a later stage or had urine samples cultured using a standard data collection form (Appendices 6,7).

4.2.2.6 GP follow up

All participating GPs were contacted a few weeks into the study to determine any difficulties being experienced with carrying out the study. Further contact was made in writing at a later stage to determine any problems and to provide information relating to their own rate of questionnaire distribution and those of all other participating GPs (Appendix 8). Following a period of 18 months of data collection, all GPs were informed in writing that no further questionnaires should be distributed (Appendix 9).

4.2.2.7 GP Feedback

Results of questionnaire distribution, drugs prescribed, use of microbiological sensitivity testing and resultant health outcomes were communicated to all GPs in Grampian via a newsletter distributed by the Communicable Disease Team of Grampian Health Board (Appendix 10).

4.3 Ulcer Healing Agents

4.3.1 Objectives

The objectives of this part of the research were to:

1. identify patients in primary care receiving repeat prescriptions for ulcer healing agents.

2. identify for each patient the ulcer healing agent prescribed, dose, duration of therapy, indication and results of any investigations.

3. identify patients receiving therapy not in accordance with the recommendations of the Grampian Joint Drug Formulary.

4. measure the effect on health outcomes of changing therapy in line with the recommendations of the Grampian Joint Drug Formulary.

4.3.2 Method

4.3.2.1 Selection of practice

Potential practices for inclusion in the study had to fulfil 2 criteria: relatively low use of cimetidine, identified as a low ratio of cimetidine to ranitidine from

PRISMS data; no current initiative to identify suitable patients for *H. pylori* eradication therapy, identified from discussions with the medical prescribing adviser and the general medical practice facilitator of Grampian Health Board. A meeting was arranged with one such practice, during which the study aim and objectives were discussed, with particular emphasis being placed on the anticipated demands on both prescribers and patients. The practice, which was fund-holding, with 3.5 whole time equivalent GPs and a practice list size of 6551 patients, was both supportive of the study aims and objectives and fully agreed to participate. Selection of a practice in this way allowed a cluster sample of patients to be obtained for the study. Data was collected over a 20 month period, from December 1995 to August 1997.

4.3.2.2 Selection of patients

The practice computer system (EMIS, Egton Medical Information Systems) was used to identify those patients receiving ulcer healing agents on repeat prescription. A data collection form (Appendix 11) was devised and piloted to record the following information from these patients' medical notes: age, current ulcer healing agent prescribed, dose, duration of therapy, indication, investigations, previous ulcer healing agent use, other current therapy and medical problems. This form was subsequently used to collect this information for all patients. An interim drug utilization report was prepared and distributed to the GPs involved.

4.3.2.3 Guidelines

A guideline for appropriate ulcer healing agent use in these patients was devised, based on the recommendations of the Grampian Joint Drug Formulary, and agreed by all GPs within the practice. In general, this recommended eradication therapy in patients with a history of duodenal or gastric ulcer unless shown previously to be *H. pylori* negative, or where there were valid reasons for continuous prescription of an ulcer healing agent, for example, NSAID prophylaxis, severe oesophagitis. Cimetidine was recommended for all indications, except in those patients receiving concurrent warfarin, phenytoin, theophylline or aminophylline. Omeprazole was to be restricted for use in severe oesophagitis or where poor response had been demonstrated with H_2RAs. Maintenance doses of cimetidine 400mg at night, ranitidine 150mg at night and omeprazole 10mg daily were recommended. Cimetidine was to be used for NSAID prophylaxis as the GPs were reluctant to use misoprostol due to past experience indicating a high frequency of adverse effects. Patients suitable for having their therapy changed were identified and possible savings arising from guideline implementation estimated.

4.3.2.4 Health outcome measurements

A list of potential patients for interview was prepared and circulated to all GPs for comment as regards suitability for domiciliary interview. Those suitable were

contacted in writing, explaining the method of patient selection for inclusion in the study, nature and likely duration of interview (Appendix 12). These patients were further contacted by telephone a few days later to seek permission for this interview and to arrange a convenient time. Informed patient consent (Appendix 13) was obtained prior to commencement of each interview, which was undertaken in 3 stages. During stage 1, information relating to the ulcer healing agent prescribed, dose, duration of therapy and indication were obtained, along with data relating to smoking, analgesic use and the effect of the medical condition on diet. The Glasgow Dyspepsia Severity Score (El-Omar *et al* 1996) was used as a specific disease state measure in stage 2 and SF-36 (Ware *et al* 1993) as a generic measure in stage 3 (Appendix 14). Permission to use these 2 measures had previously been obtained. Each interview was carried out in the patient's home and lasted approximately 45 minutes. In those patients previously identified as being suitable candidates for *H. pylori* eradication therapy, further discussion took place regarding the nature and possible benefits, following which these patients were asked to indicate their willingness to receive such therapy.

Results of each interview were fed back to the GP responsible for each patient using a form devised for this purpose (Appendix 15), outlining possible options for therapy based on the guideline. Space was included for the GP to indicate agreement with the recommendation and to specify the actions taken. For each candidate likely to receive *H. pylori* eradication therapy, a patient information leaflet (Appendix 16) was included in the information given to the GP, to be

given to the patient along with any prescription for eradication therapy. The GPs retained the responsibility for explaining any changes to the patients.

The practice was visited regularly to collect completed feedback forms. In those patients where a change in therapy had been indicated by the GP, further information was obtained from the medical notes and practice computer to identify if the agreed change had been implemented, and to record any further GP or hospital visits, new diagnoses or changes in therapy likely to influence measurement of health outcomes (Appendix 17) Each patient was contacted six months following a change in treatment and permission requested to repeat the interview, using a slightly modified interview schedule (Appendix 18).

Glasgow Dyspepsia Severity Scores were calculated by summing the responses for each item, giving a maximum score of 20, a higher score indicating poorer control of symptoms (El-Omar *et al* 1996). SF-36 scores were calculated as recommended (Ware *et al* 1993) with a score being obtained for each domain on a scale of 0-100%, a higher score indicating a better health status.

4.4 Peripheral Vasodilators

4.4.1 Objectives

The objectives of this part of the research were to:

1. identify patients in primary care receiving repeat prescriptions for peripheral vasodilators.

2. identify for each patient the peripheral vasodilator prescribed, dose, duration of therapy, indication and original prescriber.

3. measure the effect on health outcomes of withdrawing therapy in line with the recommendations of the Grampian Joint Drug Formulary.

4.4.2 Method

4.4.2.1 Selection of practices

Potential practices for inclusion in the study had to fulfil 2 criteria: relatively high use of peripheral vasodilators, identified from PRISMS data; no current initiative to reduce prescribing of these agents, identified from information supplied by the Grampian General Practice Audit Committee. Meetings were arranged with 2 practices, during which study aim and objectives were discussed, with particular

emphasis being placed on the anticipated demands on both prescribers and patients. Selection of these practices allowed cluster samples of patients to be obtained for the study. The practices, both fund-holding with practice list sizes of 5579 and 5343 patients respectively, were both supportive of the study aim and objectives and fully agreed to participate. Data was collected over a 14 month period, from July 1996 to September 1997.

4.4.2.2 Selection of patients

The practice computer systems (EMIS, Egton Medical Information Systems and G-PASS, General Practice Administration System for Scotland) were used to identify those patients receiving repeat prescriptions for peripheral vasodilators. A data collection form (Appendix 19) was devised and piloted to record the following information from these patients' medical notes: age, peripheral vasodilator prescribed, dose, duration of therapy, indication, original prescriber, vascular investigations, concurrent therapy and medical problems. This form was subsequently used to collect this information for all patients. An interim drug utilization report was prepared and distributed to the GPs involved.

4.4.2.3 Health outcome measurements

A list of those patients receiving continuous therapy was prepared and circulated to all GPs for comment as regards suitability for domiciliary interview. Suitable patients were contacted in writing by the GPs, explaining the method of patient

selection for inclusion in the study, nature and likely duration of interview (Appendix 20). These patients were further contacted by telephone a few days later to seek permission for this interview and to arrange a convenient time. Informed patient consent (Appendix 21) was obtained prior to commencement of each interview, with each patient receiving a patient information leaflet (Appendix 22). During stage 1 of the interview information relating to the peripheral vasodilator prescribed, dose, duration of therapy and indication were obtained, along with any history of smoking. The Walking Impairment Questionnaire (Regensteiner *et al* 1990) was used as a disease specific measure in stage 2 and SF-36 (Ware *et al* 1993) as a generic measure in stage 3 (Appendix 23). Permission to use these 2 measures had previously been obtained. Each interview was carried out in the patients' homes and lasted approximately 45 minutes.

Results of each interview were fed back to the GP responsible for each patient using a form devised for this purpose (Appendix 24). Letters signed by the GPs were sent to these patients instructing them to stop taking their peripheral vasodilator (Appendix 25). Patients were informed that they would be reviewed after a period of 2 months and to contact the surgery with any queries.

Following this 2 month period, the practices were visited and further information obtained from the patients' medical notes regarding any further GP or hospital visits, new diagnoses or changes in therapy likely to influence measurement of

health outcomes (Appendix 26). Each patient was subsequently contacted by telephone and permission requested to repeat the interview.

Walking Impairment Questionnaire scores were calculated as recommended (Regensteiner *et al* 1990), providing separate scores for walking distance, walking speed and claudication pain on a scale of 0 (unable to perform due to severe claudication) to 100% (no impairment). SF-36 scores were calculated as before.

Chapter 5

Urinary Tract Infections: Results and Discussion

5.1 Results

5.1.1 GP response

Telephone contact with 27 randomly selected GPs resulted in meetings being arranged with 24, during which all agreed to participate in the study. Initial rates of questionnaire distribution were much lower than had been anticipated. On contacting all GPs, several admitted having forgotten about the study, but no particular problems were voiced by the remainder and all wished to continue their involvement. This contact resulted in only a modest increase in questionnaire distribution, thus it became necessary to contact all GPs in writing to inform them of rates of distribution and further identify any contributing factors. Again, no such problems were identified by the GPs and this contact had very little effect on the rate of questionnaire distribution. Due to this poor response, the study was brought to a close after 18 months of data collection, with only 89 of the planned 480 questionnaires (19%) having been given out during this period. Figure 5.1 illustrates the distribution rates of all the GPs involved.

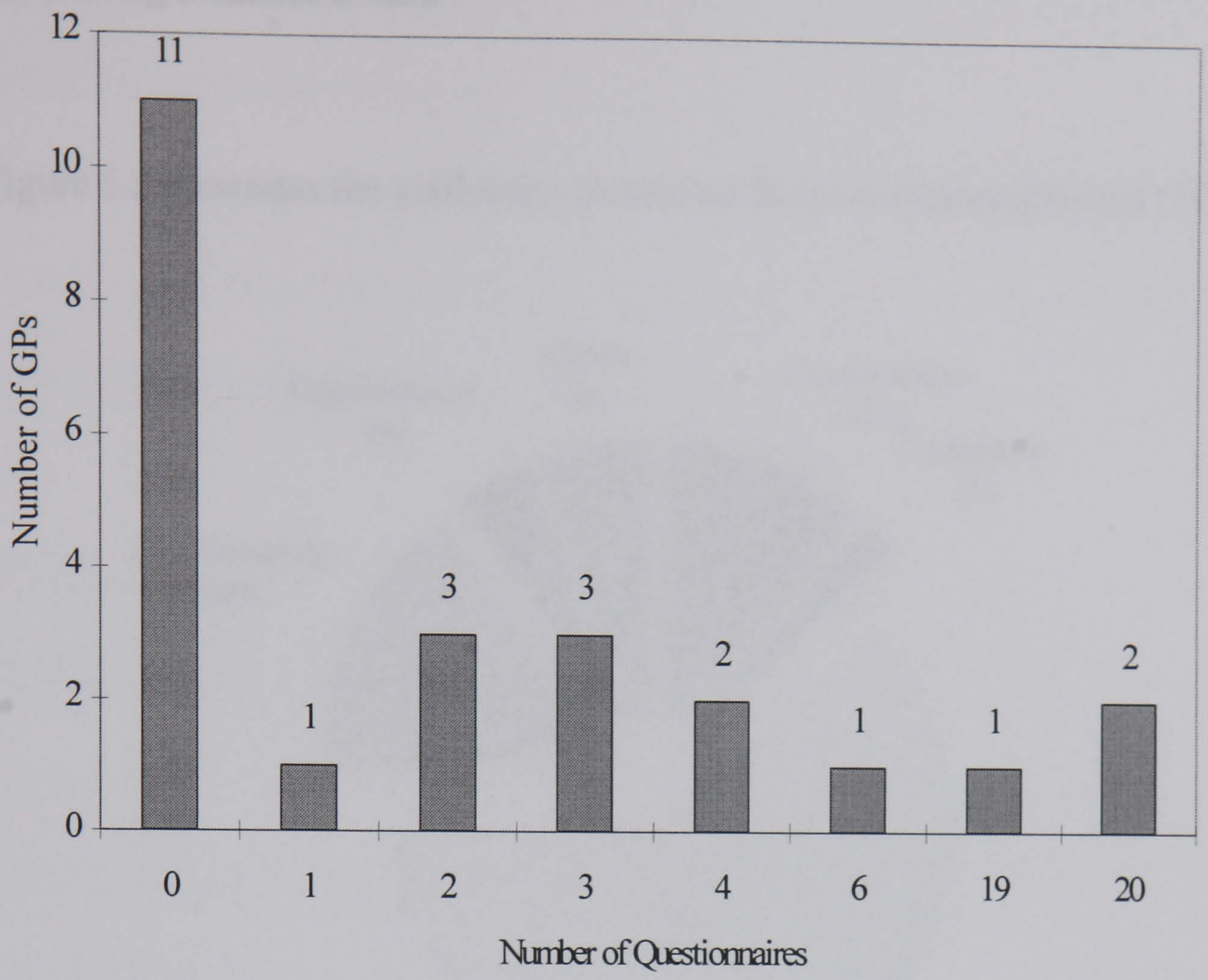

Figure 5.1: Questionnaire distribution rates over an 18 month period.

The majority of questionnaires 59 (66%) were distributed by 3 GPs, all of whom had been previously identified as prescribing below the median frequency of trimethoprim. Of the 89 questionnaires distributed, 17 (19%) were from those GPs identified as prescribing higher than the median and 72 (81%) lower than the median frequency. There was no association between previously identified prescribing frequency for trimethoprim and whether or not any questionnaires had been distributed ($\chi^2 = 0.17$, $p = 0.68$, 1 df).

5.1.2 Drug utilization data

Figure 5.2 illustrates the antibiotics prescribed for lower uncomplicated UTIs.

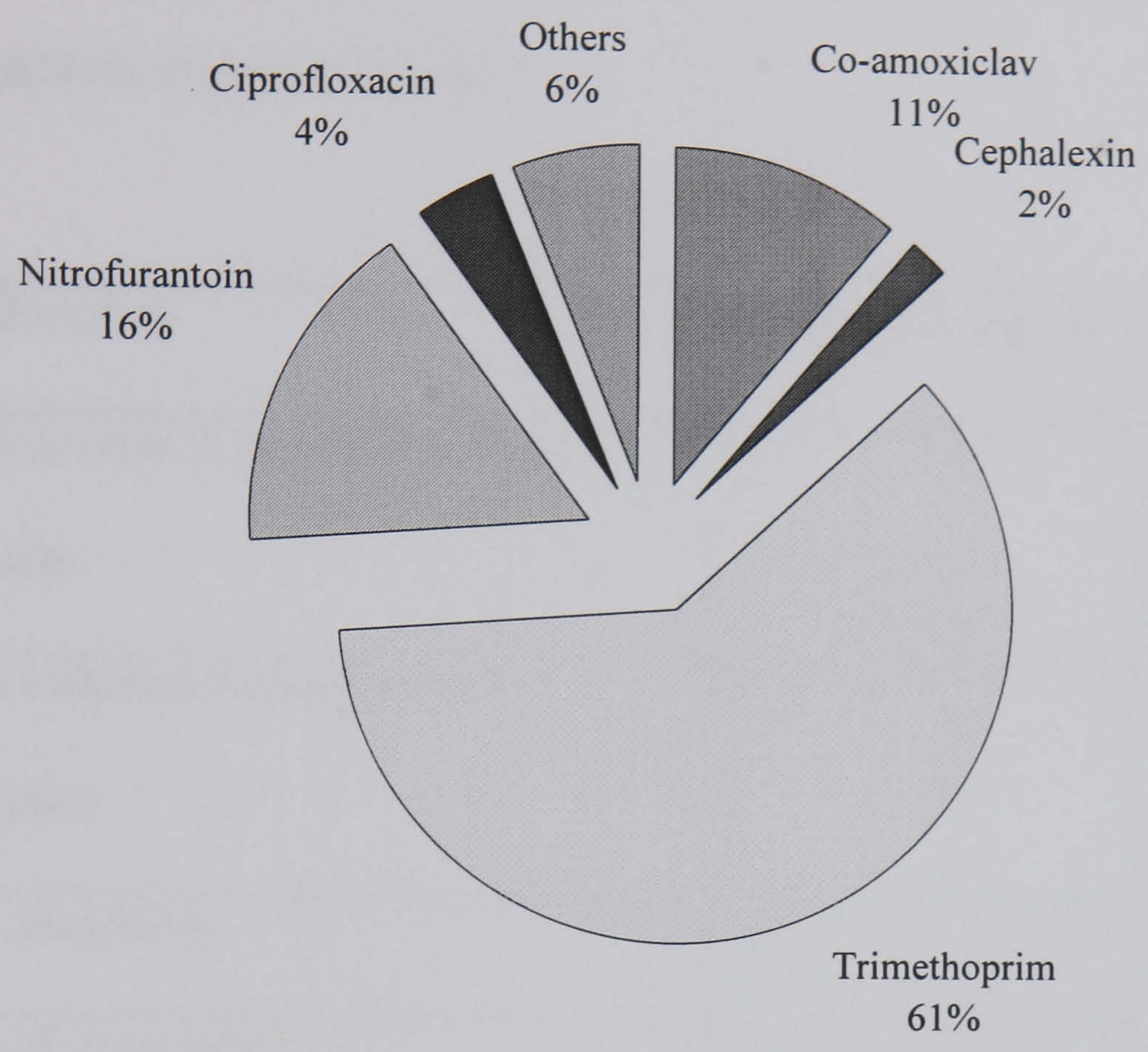

Figure 5.2: Antibiotics prescribed to patients presenting with symptoms of a lower uncomplicated UTI.

The "other" category comprised 1 prescription for each of the following: amoxycillin, cephradine, cefaclor, fosfomycin, nalidixic acid.

Trimethoprim was the most commonly prescribed agent (54 patients), representing a level of adherence to the antibiotic policy of 61% (95% confidence intervals 51 - 71). There was no association between those prescribing above and

below the median frequency of trimethoprim and the observed prescribing rate of policy and non-policy therapy ($\chi^2 = 0.87$, p = 0.35 1 df).

A variety of patient factors influencing selection of therapy were identified in 22 further patients as shown in table 5.1.

Factor Identified	Number of patients
Previous adverse drug reaction to co-trimoxazole	5
Previous infection unresponsive to trimethoprim	4
Possible pregnancy	3
Severity of symptoms	2
Penicillin allergy	2
Recurrent infection	1
Receiving carbamazepine	1
Concurrent chest infection	1
Concurrent skin infection	1
Prescribed therapy effective in past	1
Patient prone to thrush	1

Table 5.1: Patient factors influencing selection of therapy identified by GPs.

Only 1 patient with a history of previous adverse drug reaction on exposure to co-trimoxazole was prescribed cephalexin as recommended in the policy, the remaining patients receiving a variety of agents. Several of the above identified factors such as possible pregnancy and concurrent infections would render trimethoprim less appropriate, hence adherence to the policy may be potentially higher.

All patients prescribed trimethoprim received a dose of 200mg twice daily, with the median duration being 5 days (range 3-7 days) as shown in table 5.2.

Duration (days)	Number of patients (%)
3	21 (39)
5	24 (44)
7	9 (17)

Table 5.2: Duration of trimethoprim therapy.

5.1.3 Measures of health outcome

The fate of patients in terms of this study is summarised in figure 5.3.

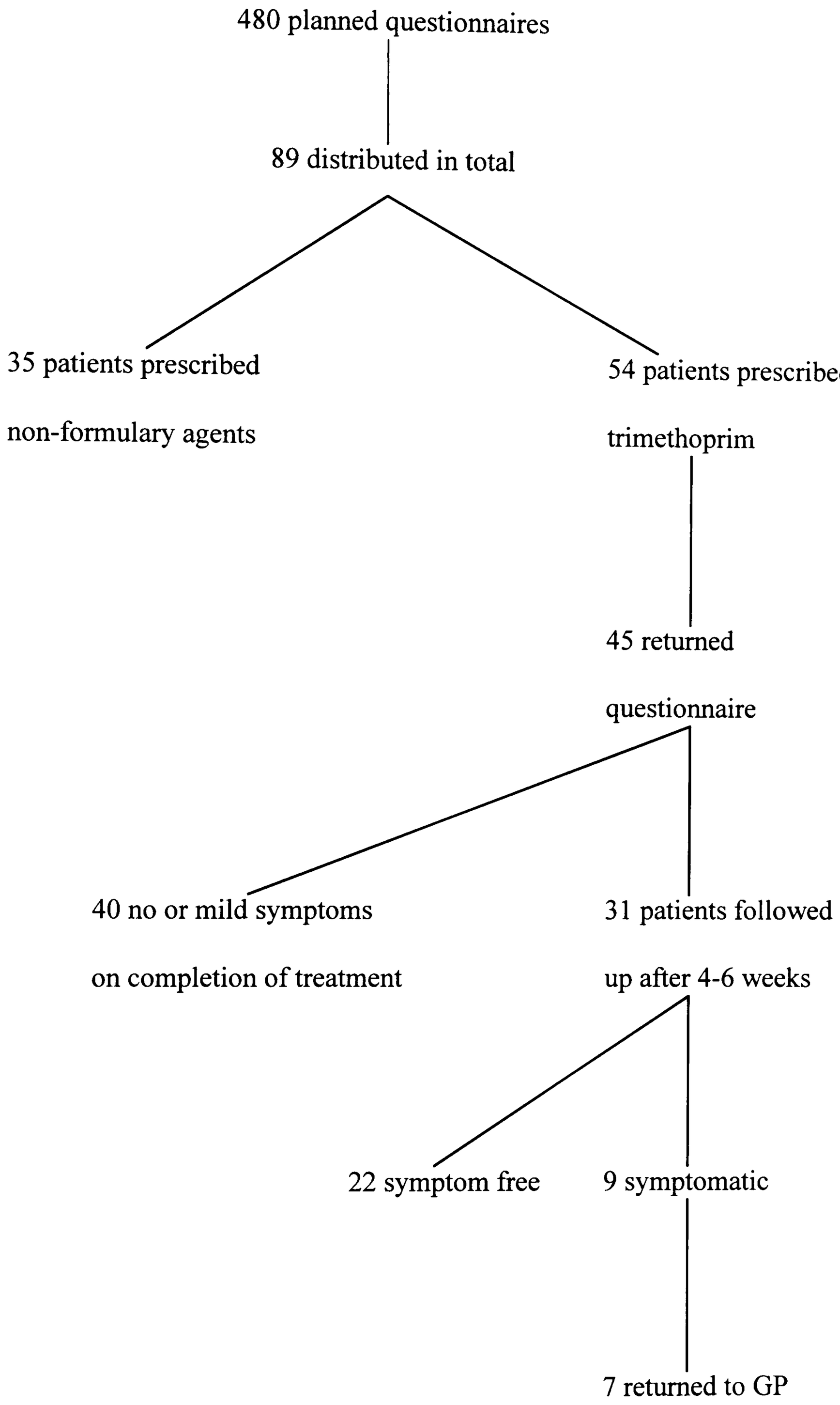

Figure 5.3: Flow chart indicating fate of patients during study.

Questionnaires were returned by 80/89 patients (90%), with the majority being returned without need of further reminders as shown in table 5.3.

Number of Reminders	Number of Patients (%)
0	60 (75)
1	11 (14)
2	7 (9)
3	2 (2)

Table 5.3: Questionnaire return rates.

Samples sizes of 199 patients receiving both formulary and non-formulary agents had been calculated to allow detection of a clinical difference of 10% with a power of 80%. Given the small sample sizes obtained, comparisons of health outcomes between these groups were not made and only health outcomes resulting from trimethoprim, the recommended agent, are reported.

Of the 54 patients prescribed trimethoprim, 45 (83%) returned the questionnaire, of which forty patients (91%) reported no or only mild symptoms on completion of treatment as shown in table 5.4.

Symptom Description	Number of Patients (%)
Gone away	33 (73)
Mild	7 (16)
Moderate	4 (9)
Severe	1 (2)

Table 5.4: Symptoms reported on completion of trimethoprim therapy.

The median time for symptoms to resolve completely was 3-4 days. Two of the patients reporting mild and all with moderate or severe symptoms on treatment completion returned to their GP.

Of the 80 patients returning the questionnaire, 60 (75%) agreed to be contacted by letter or telephone 4-6 weeks later. Of those prescribed trimethoprim initially, 31 (69%) agreed to be contacted. Of these, 22 (71%) were symptom free, while 9 (29%) had experienced either symptoms on completion of treatment or within this follow up period, 7 of whom returned to their GP. One patient was referred for gynaecological opinion, the remainder being treated with further courses of antibiotics.

Two patients prescribed trimethoprim (4%) reported possible side effects sufficiently serious to warrant discontinuing treatment and consulting their GP (itch 1 patient, nausea 1 patient). Four further patients reported less troublesome

adverse events (tiredness 2 patients, nausea 1 patient, thrush 1 patient). All others completed the prescribed courses.

5.1.4 Microbiological testing

Microbiological sensitivity testing was performed at the time of initial presentation for 37 of the 89 patients (42%). The results of these were obtained from the patients' medical notes, but were unavailable for 9 patients, 8 of whom had moved outwith the practice boundary and had been misplaced for 1 patient. Data obtained for 28 patients indicated that no growth was present in the urine samples of 11 (39%). *E. coli* was found to be the most common infecting organism, being the sole pathogen in 9 patients and along with *E. faecalis* in 1 patient. Other infecting organisms were *Coliform* (5 patients) and *S. saprophyticus* (2 patients). Resistance to trimethoprim was observed in 6/18 (33%) instances. Sensitivity reports indicated that 10 of these 17 patients were receiving an antibiotic with the appropriate spectrum of activity. Two further patients were sent prescriptions for agents with appropriate spectra, but in both cases cheaper agents would have been more appropriate. Of the 6 patients who were initially prescribed trimethoprim and received further courses of antibiotic for symptom recurrence, 4 had not had a urine sample cultured on initial presentation. Three of these received further courses of empirical therapy. The urine samples of the remainder, who had also received further treatment, demonstrated no microbial growth on either initial or follow up culture.

5.2 Discussion

No previous research in primary care has measured patient centred health outcomes resulting from implementing antibiotic policy recommendations. The outcome measure in this study was primarily the patient's perspective of the speed and extent of symptom resolution experienced. In acute self limiting infections such as uncomplicated lower UTIs, this is of much more relevance to the patient than measures such as microbiological cure (Nicolle 1990, Ronald *et al* 1992). This general approach to health outcome measurement for acute and self limiting disease states has been recommended by several authors (Guyatt *et al* 1993, Tsevat *et al* 1994, Ebbs *et al* 1989).

5.2.1 Interpretation of Findings

Health outcomes results obtained in this study are limited and should be interpreted with caution, principally due to the small sample sizes of both prescribers and patients. Of particular note, it was not possible to compare health outcomes resulting from formulary and non-formulary treatment, one of the main objectives at the outset of the study. Instead, the majority of health outcomes are simply presented in terms of trimethoprim, the first line recommendation, and indeed the majority of these prescriptions came from 3 GPs. Treatment with this agent was found to provide favourable results in 91% of patients at the point of treatment completion, with few patients discontinuing treatment because of possible adverse events and similarly low numbers returning to the prescriber at

this point. Previous standards for the design and conduct of studies in this area (Working party of the British Society of Antimicrobial Chemotherapy 1989, Rubin *et al* 1992) recommended following patients for a period of no less than 4 weeks as shorter periods had been shown to miss the return of symptoms in many patients. Data from the present study supports this recommendation, with 29% of patients experiencing symptoms on follow up. Although this represents a marked deterioration of health outcomes when compared to the initial resolution of symptoms, not all patients felt that these symptoms warranted a further visit to their GP. As stated above, the majority of these patients were recruited by 3 GPs and thus are unlikely to be representative of the majority of patients in primary care. Accordingly, these results must be interpreted with great caution.

The drug utilization data yielded 61% adherence to the recommendation of the policy, in terms of selecting trimethoprim as a first line agent. This result cannot be compared to earlier studies since previous work simply determined whether antibiotics prescribed were included in a list of recommended drugs, with no information provided relating to indication of therapy. Kelsey *et al* (1996) recommended that 85% of all prescribed antibiotics should be included in such a list. Such an approach is, however, limited since information relating to the indication for therapy is essential in order to determine the appropriateness of prescribing. Although the level of adherence obtained in this study was considerably lower than 85%, clinical factors affecting drug selection were identified in many instances, and although several of these, such as penicillin allergy, concurrent carbamazepine therapy would not alter the appropriateness of

trimethoprim, others such as the presence of simultaneous chest and skin infections render trimethoprim less suitable. The most common factor identified was past adverse drug reactions experienced with co-trimoxazole. Although these are most likely to be associated with the sulphamethoxazole component (Anon 1986b), it may also be appropriate to avoid trimethoprim, particularly in primary care, where the patient will be monitored less closely than in secondary care.

5.2.2 Limitations of antibiotic policy

The antibiotic policy recommendations for primary care simply list the selected drugs to be used for each indication, with no guidance provided on the need for microbiological sensitivity testing, nor the appropriate duration of therapy. The results of this study would appear to identify that such guidance is necessary, with considerable variation being observed in both of these areas. The median duration of trimethoprim was found to be 5 days, with a range of 3 to 7 days. The optimal duration of therapy in uncomplicated lower UTIs has been greatly debated in the medical literature. Bailey (1990), while reviewing studies of single dose therapy, cited studies demonstrating that for several agents, including co-trimoxazole, trimethoprim, nitrofurantoin, 4-quinolones, single dose was as effective as longer courses, but with lower incidence of adverse effects and reduced drug costs. Failure of single dose therapy was identified as being an indication for further urinary investigations. On the basis of this evidence an algorithm for the management of uncomplicated lower UTIs was produced, recommending single dose therapy first line (Bailey 1993). The author, however,

failed to critically review those studies cited. Leibovici and Wysenbeek (1991) and Stamm (1992) demonstrated that most of the studies cited were not of sufficient size to allow detection of a clinical difference with a power of 80%. Meta-analysis of studies fulfilling minimal inclusion criteria (Norrby 1990, Leibovici, Wysenbeek 1991) identified that 3 days therapy with many agents was the optimal duration, being more effective than single dose and as effective as longer courses. No major differences in the frequencies of adverse effects were identified between single dose and 3 days treatment. Studies of β-lactams produced lower cure rates than observed with other agents, regardless of treatment duration. Many have now recommended that such uncomplicated lower UTIs are treated initially with a 3 day course of antibiotics other than β-lactams (Johnson, Stamm 1989, Norrby 1990, Leibovici, Wysenbeek 1991, Wilkie *et al* 1992).

E. coli was found to be the most common infecting organism, a finding consistent common with that of previous work (Wilkie *et al* 1992). Of greater interest was the high frequency with which no growth was identified in urine samples. An inconsistent approach was demonstrated in the use of microbiological sensitivity testing with such tests being performed in less than half of patients and, in many cases, no action was taken on receipt of these results even on recurrence of symptoms. These findings highlight the need for guidance to be provided within the antibiotic policy. Many have recommended that such testing is unnecessary in females presenting with symptoms of uncomplicated lower UTI, with initial treatment simply directed towards *E. coli* (Johnson, Stamm 1989, Brooks 1990,

Hooton, Stamm 1991, Stamm, Hooton 1993). Olesen and Oestergaard (1995), however, identified differences in treatment strategies between Danish GPs, urologists and microbiologists, with GPs being more likely to include sensitivity testing as part of the overall management in younger patients.

The need to include guidance on the role of microbiological sensitivity testing is of particular importance since, for all antibiotics used in the treatment of uncomplicated lower UTIs, the cost of such testing greatly outweighs drug costs. Previous work has shown that drug costs comprise only 13% of the overall cost of treatment if microbiological sensitivity testing is performed both initially and on completion of treatment (Schultz *et al* 1984). This highlights the need for well designed pharmacoeconomic evaluation of different strategies for treating these infections. Such an evaluation was described by Carlson and Mulley (1985) who developed a decision analysis model to compare effects and costs of single and multiple doses of amoxycillin and co-trimoxazole in the management of uncomplicated lower UTIs. Using cure rates identified from previous studies, single dose therapy was shown to be most effective at reducing symptoms, at a lower cost, with initial microbiological sensitivity testing increasing speed of symptom resolution by 10%, but at an increase in cost of 40%. These findings must, however, be interpreted cautiously since much of the data was derived from poorly designed studies with limited patient numbers. In addition, only direct costs of drugs and microbiological sensitivity testing were considered. More recently, several authors have described additional costs which should be incorporated into such analyses, including further direct costs of GPs' time,

treatment of adverse effects and symptom recurrence, and indirect costs associated with loss of work, pain and suffering by the patient. (Patton *et al* 1991. MacDonald 1994, MacDonald *et al* 1995, Plumridge, Colledge 1996) These studies may indeed identify that initial therapy with a more expensive agent may provide improved patient outcomes at lower overall costs, but at a higher drug cost. Despite these recommendations, pharmacoeconomic studies relating to the treatment of uncomplicated lower UTI in primary care have not been described.

5.2.3 Critical Appraisal of Method

As stated earlier, results of health outcomes reported in this study are limited, primarily due to the poor response from those GPs involved and thus the lack of representativeness of the patients involved. Jones (1993) described the problems for researchers trying to become integrated into a non-research culture in primary care medicine, where little enthusiasm from GPs is not uncommon. In this present study, considerable time and effort were expended to ensure that the GPs were fully informed of the study aims and requirements and indeed 89% of GPs contacted were keen to be involved. The study was deliberately designed to place minimal burdens on the GPs and many steps were taken to ensure continued awareness of the study by the GPs. For example, desk top organisers were provided for displaying the questionnaires, which were brightly coloured. Each practice was visited weekly to collect the informed consent sheets, simultaneously acting as further prompts to all reception staff and GPs. Contact with the GPs was made on several occasions to determine any problems being

experienced. Informing GPs of their individual distribution rates and those of others, some of whom had distributed all questionnaires in a short period of time similarly had little effect on questionnaire distribution, resulting in the study being halted with only 19% of questionnaires given out. A duration of 10-20 weeks had originally been estimated for this data collection period. Following analysis of results, it had been planned that the results would be communicated to the GPs, with a later period of data collection to measure any resulting changes in prescribing and health outcomes. Those GPs adhering to the policy, prescribing trimethoprim, may have been keener to record their prescribing and distribute questionnaires, but no association was identified between distributing any questionnaires and whether the GP had been identified previously as prescribing above or below the median frequency for trimethoprim.

There is a need to study drug utilization evaluation of acutely prescribed medicines in primary care, particularly comparing recommended and non-recommended therapies. Although the GP is in the prime position to identify suitable patients for these studies, perhaps alternative methods of patient recruitment or encouraging GP participation are necessary. It has been suggested that financial incentives could alter GP response rates for mailed questionnaires (Deehan *et al* 1997) and perhaps such an approach could have been used in this study in order to aid patient recruitment.

Despite the disappointing performance of the GPs, patient response rate was extremely high, with 89% of questionnaires being returned. This may have been

due to the questionnaire being short, brightly coloured and including a reply paid envelope, methods shown previously to increase response (Childers, Ferrell 1979, Nedrhof 1978). A further contributing factor may have been due to the patients being recruited by their GP, a further reason for identifying methods of increasing GPs involvement in research.

This study was designed with dual purposes of collecting drug utilization data and comparing health outcomes derived from recommended and non-recommended therapies. Although it was not designed to be a clinical trial, all recommended standards for conducting such a trial were incorporated into the design. Sample sizes were calculated to provide a power of 80% to identify a clinical difference of 10% at a significance level of 5%. Only patients with symptoms of uncomplicated lower UTIs were included, excluding those with risk factors known to predispose to complicated infections, therefore potentially altering health outcomes. Patients were followed for the recommended period of 4-6 weeks after completion of antibiotic therapy to identify symptom persistence or recurrence.

Despite these measures, the method was limited in several respects. The estimation of trimethoprim success rate at 80% was based on sensitivity data and a recommendation by Rubin *et al* (1992). The link between sensitivity data of all urinary isolates and cure rate for uncomplicated lower UTI has not been established and Rubin *et al* provided no objective data relating to their claims. Despite these deficiencies, sample size was calculated based on estimated success

rate with a plan to repeat this calculation using actual data from those patients receiving trimethoprim. The planned comparison of policy and non-policy as described may not have been appropriate, since the non-policy agents may not have been a homogenous group, particularly in terms of efficacy. Research has shown that β-lactam antibiotics have been associated with poorer health outcomes in comparison to other agents. The method of stratifying GPs into 2 groups of higher and lower prescribers of trimethoprim may not have produced the diverse groups anticipated. Strickland-Hodge and Jepson (1981) recommended a method of stratifying into 3 groups of high, medium and low prescribers, with high prescribers being more than 1 standard deviation above and low 1 standard deviation below the median. Analysis of prescribing data for Grampian identified less than 20% of GPs being outwith 1 standard deviation unit on either side of the median frequency of trimethoprim, with many of these located in very rural areas. Using the method of Strickland-Hodge and Jepson (1981) would have produced a study with great practical limitations. As a result, prescribers were simply stratified into those above and below the median, with a plan to recruit further GPs at a later stage until the necessary 199 patients in each group were obtained. Most of the prescribers in both groups were probably better described as medium prescribers and indeed no difference was observed in trimethoprim prescribing during the study between those classed initially as high and low prescribers. Alternatively, there may have been a Hawthorne type effect (Roethlisberger, Dickson 1939) on those previously prescribing lower amounts of trimethoprim.

5.2.4 Conclusion

Little conclusion can be drawn from these results relating to the efficacy of trimethoprim as recommended in the Grampian Joint Drug Formulary. This research provides more data relating to the difficulties of collecting data relating to acute prescribing in primary care, an area which deserves more attention.

Chapter 6

Ulcer Healing Agents: Results and Discussion

6.1 Results

6.1.1 Drug utilization

A total of 184 patients (3% of the practice list) were identified from the practice computer system as receiving repeat prescriptions for ulcer healing agents. Ninety seven patients (53%) were female and 87 (47%) male with a median age of 63 years (range 13 - 87). Fourteen patients (8%) had not received a prescription during the previous 6 months, 51 (28%) had received prescriptions on an intermittent basis. The remaining 119 patients (65%, 2% of the practice list) had received continuous prescriptions for at least the previous 6 months.

The fate of these patients in this study is summarised in figure 6.1

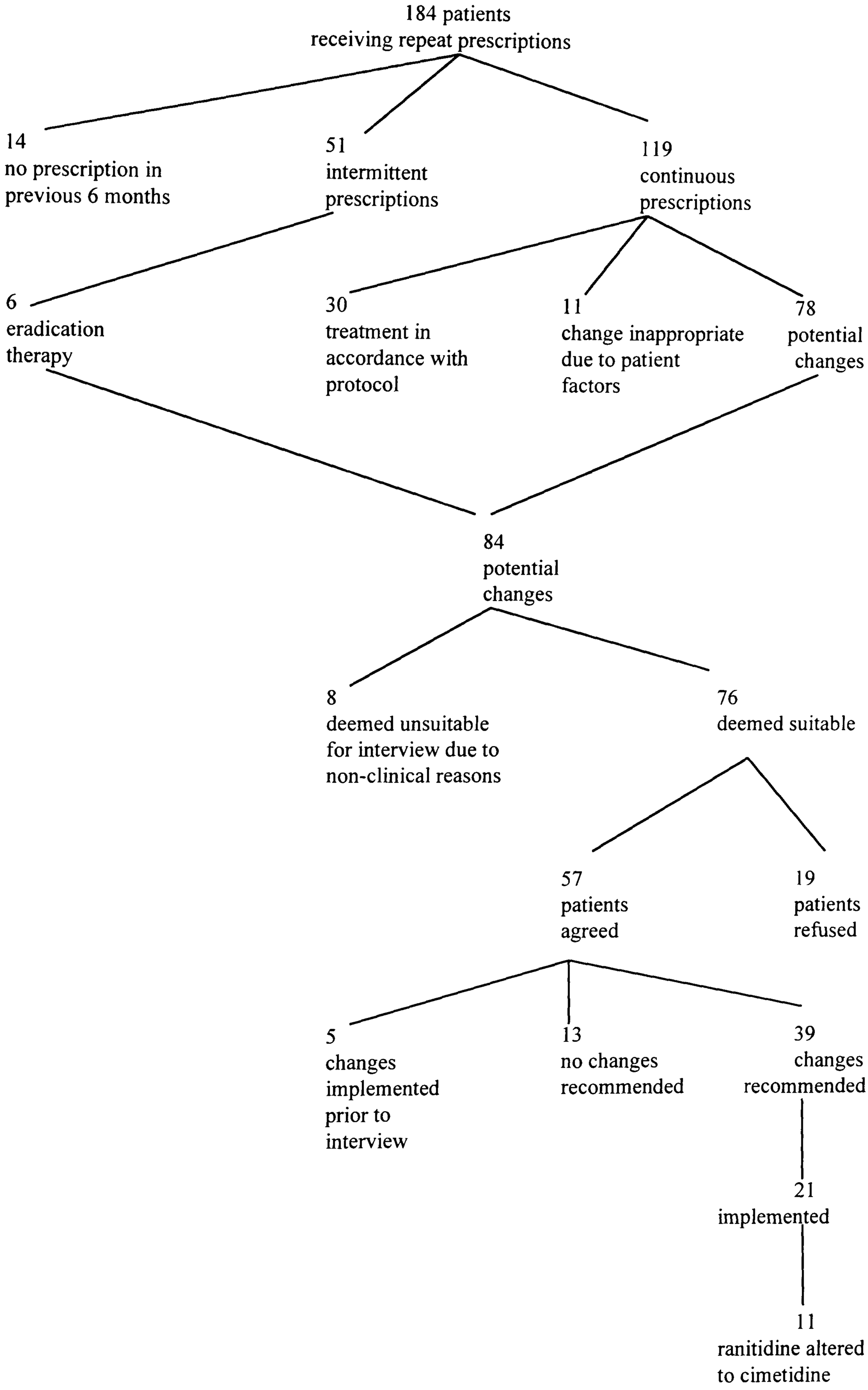

Figure 6.1: Flow chart indicating fate of patients during study.

Duration of continuous therapy is shown in figure 6.2.

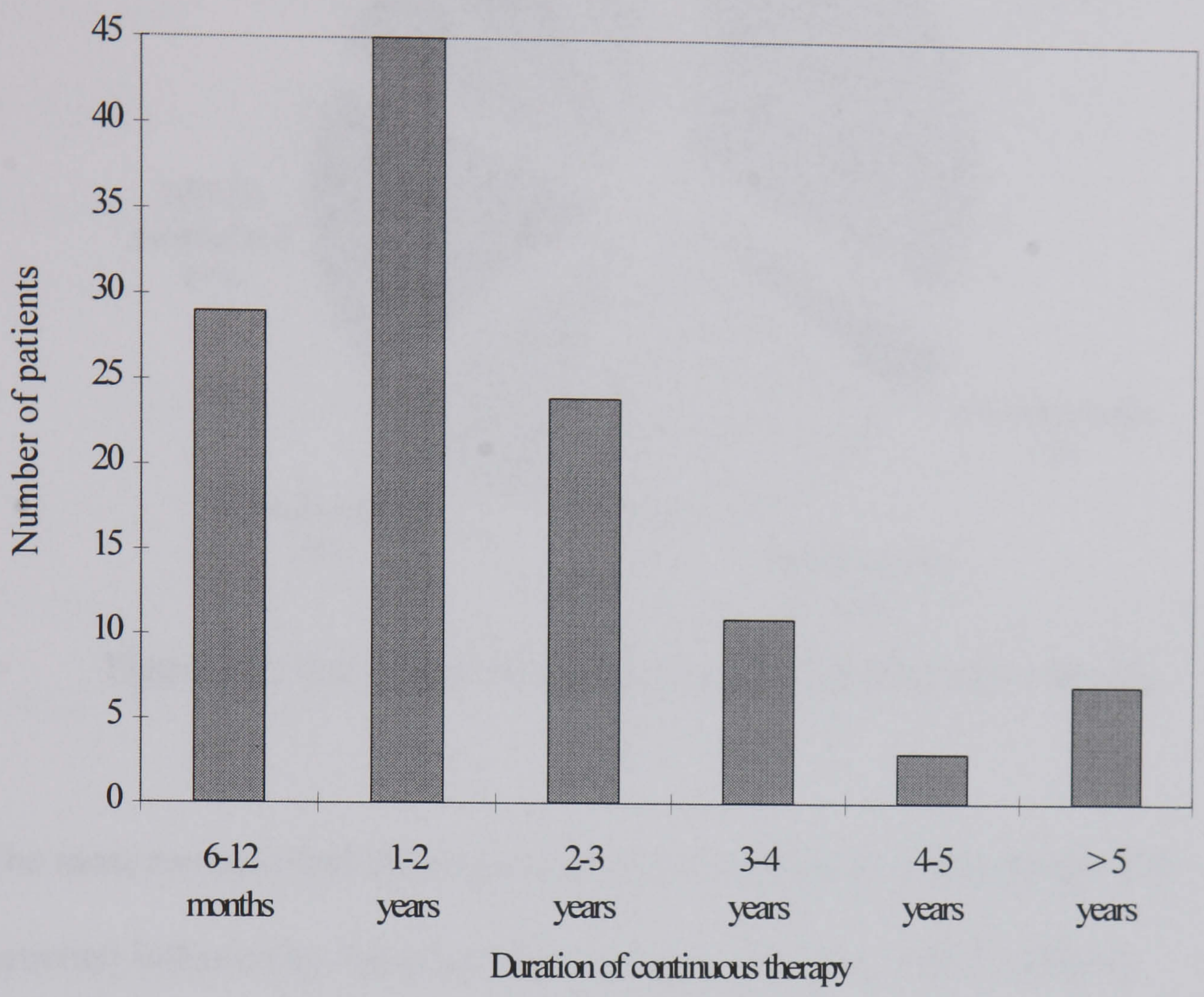

Figure 6.2: Duration of continuous ulcer healing agent use.

The median duration was found to be 1-2 years, with only 7 patients (6%) having received therapy for greater than 5 years.

Diagnosed indications for therapy in these 119 patients are illustrated in figure 6.3.

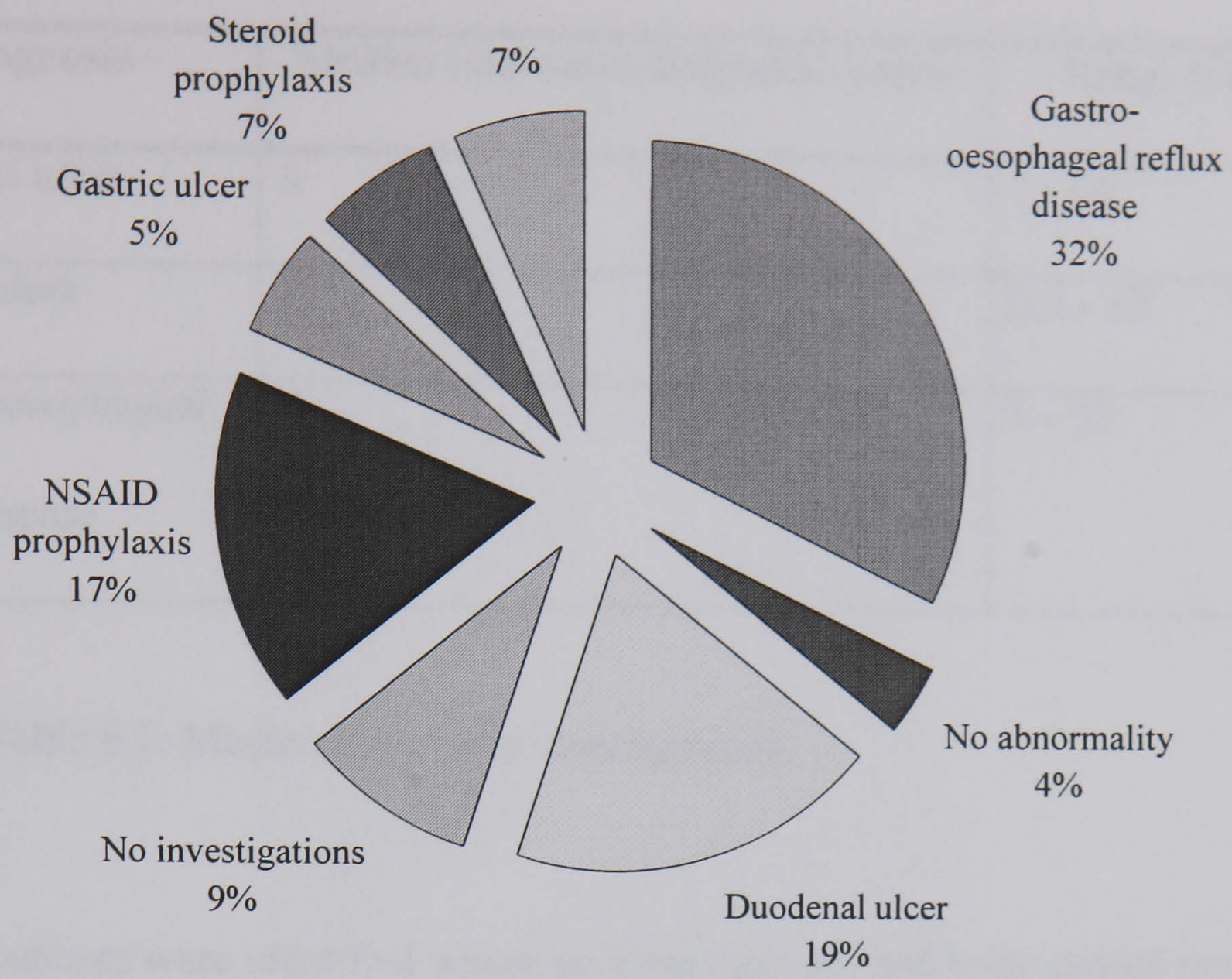

Figure 6.3: Indications for continuous ulcer healing agent therapy.

The most common indications were gastro-oesophageal reflux disease (38 patients) followed by duodenal ulcer (23 patients). The "other" category comprised 6 cases of gastritis, 4 with duodenitis and 1 case of gastric carcinoma. Multiple indications were identified in several patients. For example, 14 patients had a history of duodenal ulceration and gastro-oesophageal reflux disease; twelve patients with a history of duodenal ulceration were receiving concomitant NSAID therapy.

In some patients, the investigation on which the diagnosis was based had been carried out many years earlier, as shown in table 6.1.

Diagnosis	Median time since diagnosis (years)	Range (years)
Duodenal ulcer	9	1 - 40
Gastric ulcer	2	0.5 - 17
Gastro-oesophageal reflux disease	2	1 - 23

Table 6.1: Median time since investigations.

Fifteen patients were identified where no investigations had been carried out, as described in table 6.2.

Reason for therapy	Number of patients
Dyspepsia	7
Chemotherapy induced dyspepsia	1
Dyspepsia associated with severe depression	2
Dyspepsia associated with pancreatitis	1
Dyspepsia associated with personality disorder	1
Dyspepsia associated with surgery	1
No indication, commenced by secondary care	1
No indication, commenced by GP	1

Table 6.2: Indications for therapy in patients not investigated.

The following ulcer healing agents were prescribed to the 119 patients receiving continuous therapy.

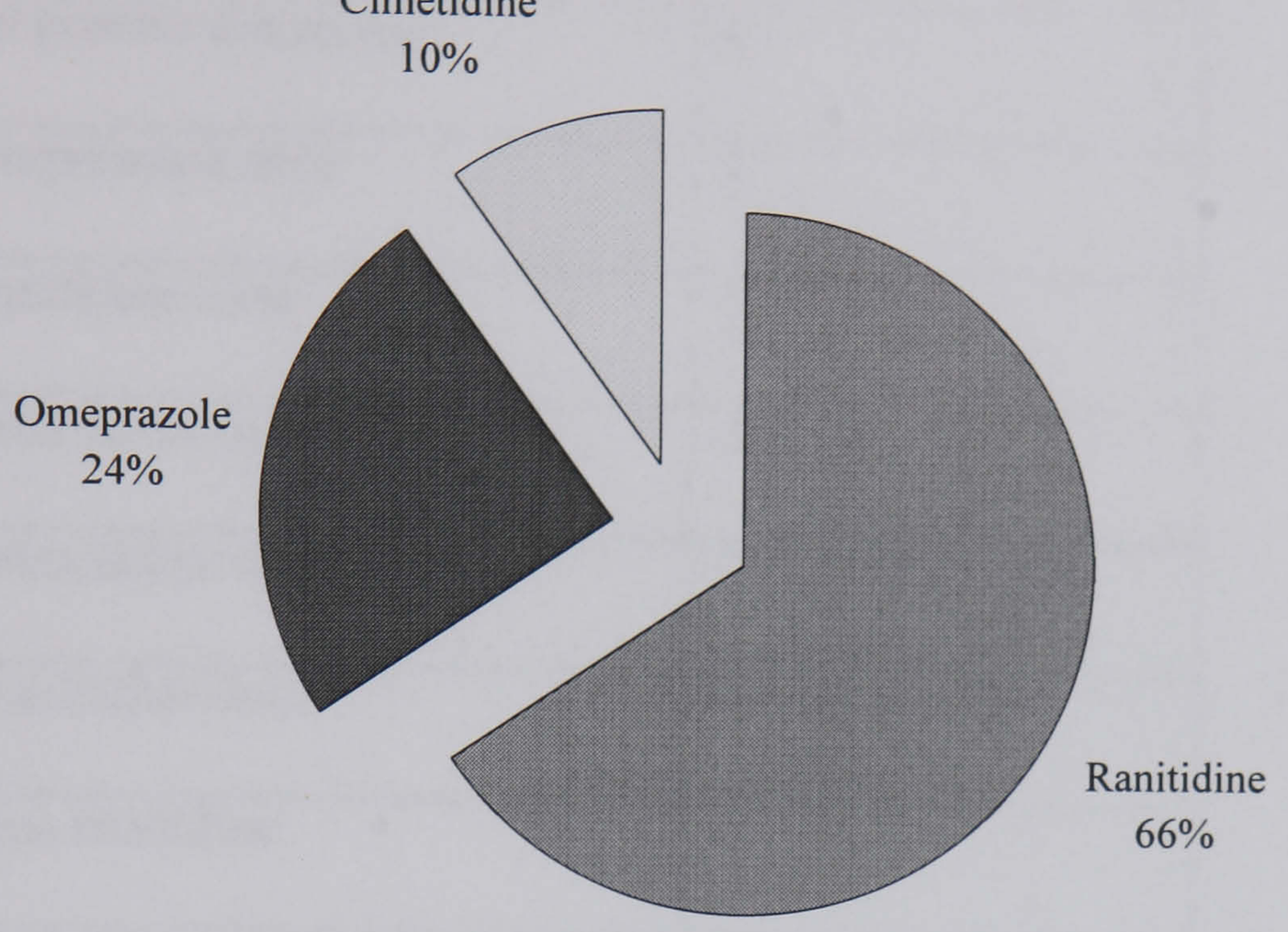

Figure 6.4: Ulcer healing agents prescribed, continuous therapy.

This represents 100% adherence to the Grampian Joint Drug Formulary in terms of drug choice. Thirty patients were receiving therapy in accordance with the guideline previously described. In a further 11 patients, changing therapy would have been unsuitable for a variety of reasons including poor prognosis, severe depression. In the remaining 78 patients, potential changes were identified as shown in table 6.3.

Potential Change	Number of patients
Eradication therapy	13
Change to cimetidine	47
Change to generic cimetidine	4
Reduce omperazole dose	9
Reduce ranitidine dose	1
Reduce cimetidine dose	1
Increase cimetidine dose	1
Increase ranitidine dose	1
Discontinue ranitidine	1
Total	78

Table 6.3: Potential changes to therapy.

The most common change was to alter ulcer healing agent to cimetidine. Only 13 potential candidates for *H. pylori* eradication therapy were identified. Of the 9 patients with a history of gastric ulceration, only 1 patient was deemed a suitable candidate, with 2 patients previously testing negative for *H. pylori*, 3 were receiving continuous NSAID therapy requiring continued prophylaxis, the causative agent had previously been identified as an NSAID in 2 patients, and 1 patient suffered from severe oesophagitis, requiring continuous treatment. Of the 32 patients with duodenal ulceration, only 12 (38%) were potential candidates for *H. pylori* eradication therapy. In the remaining patients, either continuous therapy

with an ulcer healing agent was required (10 were taking NSAIDs, 2 had Barrett's oesophagus and 1 an oesophageal stricture) or *H. pylori* was not the causative agent (3 patients had previous negative *H. pylori* tests and NSAID use was responsible for the ulcer in a further 3 patients), hence eradication therapy would not have been appropriate. A possible increase to a treatment dose of H_2RA was identified in 2 patients, both with a history of duodenal ulceration, receiving concurrent NSAIDs. One further patient was identified as receiving both ranitidine and misoprostol as prophylaxis. Only 2/119 patients (2%) were receiving other therapy with which cimetidine would interact in a clinically important manner (1 theophylline, 1 warfarin).

Of the 51 patients receiving intermittent ulcer healing agents during the previous 6 months, 36 (71%) had received greater than 2 months therapy. Eleven patients were identified with a history of either gastric or duodenal ulceration. In these patients, 3 had recently received eradication therapy, 1 was receiving NSAID therapy intermittently and 1 patient had been shown to be *H. pylori* negative. The remaining 6 patients were identified as further suitable candidates for *H. pylori* eradication therapy.

Estimated cost savings arising from implementation of these changes exceeded £14,000 in the first year, including the cost of eradication therapy.

6.1.2 Patient interviews

The GPs indicated that 8 of the 84 patients identified as potential candidates for altering therapy would be unsuitable for interview for non-clinical reasons, primarily patients known to be aggressive or demanding. Letters were sent to the remaining 76 patients, of whom 57 (75%) agreed to participate.

On interview, only one of these patients was completely unaware of the indication for therapy, the remainder describing either the correct term such as "duodenal ulcer" or symptoms such as "indigestion". Five patients with no indication for therapy documented in their medical notes listed indications of indigestion (3 patients), hiatus hernia (1 patient), nausea (1 patient). Sixteen patients (28%) continued to smoke, despite repeated advice to stop and few patients described any major alterations to diet other than general healthy eating. Five patients reported experience of possible adverse effects with ulcer healing agents. Four of these were as a result of ranitidine therapy, mild diarrhoea in all cases. One patient receiving Tagamet described breast swelling.

On interview, it was identified that changes in line with the recommendations of the interim report had already been implemented in 5 patients, with 1 receiving eradication therapy, 3 being changed to cimetidine and ranitidine discontinued in the remaining patient. None of these 5 patients expressed concern regarding this change and all were satisfied with their current therapy. Cost savings due to these changes were calculated at £930 in the first year following the change.

In 13 patients, no changes were recommended, due to a variety of reasons. Four patients previously identified as suitable candidates for *H. pylori* eradication therapy were reluctant to alter existing treatment, which they viewed as very effective. Treatment in a further 4 patients had recently been altered by secondary care making it inappropriate to further alter treatment. Ulcer healing agent therapy had been discontinued completely in 3 patients and altered recently by the GP in 1 patient. One further patient expressed concerns regarding the efficacy and toxicity of Tagamet.

As a result of the information obtained from interview and the medical notes, changes were recommended as shown in table 6.4.

Change Recommended	Number of Patients
Eradication therapy	6
Change to cimetidine	23
Reduce omeprazole dose	2
Change ranitidine to omeprazole	2
Change omeprazole to ranitidine	1
Change omeprazole to Tagamet	1
Reduce ranitidine dose	1
Increase ranitidine dose	1
Increase cimetidine dose	1
Change Tagamet to ranitidine	1
Total	39

Table 6.4: Recommended changes to therapy.

Several recommendations were different from those previously identified. Changing Tagamet to ranitidine rather than cimetidine was recommended for a patient with possible cimetidine induced gynaecomastia. A patient previously receiving Tagamet had been recently altered to omeprazole by secondary care, for no apparent reason. Information from the patient indicated a past problem of itch with generic cimetidine, thus the most appropriate recommendation appeared to be to revert to the prescription for Tagamet. In 2 instances a change from ranitidine to omeprazole rather than cimetidine was recommended due to poor

symptom control. In particular, one of these patients was taking ranitidine 150mg five times daily.

Information documented on the feedback forms indicated that the GPs were in agreement with all recommendations. However, after a period of 12 months, only 21 changes (54%) had actually been implemented, despite repeated reminders. In many cases, the GP had made an entry in the patient's medical notes indicating such change to be made at the next patient appointment, but had failed to do so. In those patients where a change in therapy had been implemented, no further GP or hospital visits, new diagnoses nor further changes in therapy had occurred which were likely to influence health outcomes.

6.1.3 Health outcomes

Differences in scores for the Glasgow Dyspepsia Severity Score and the 8 domains of SF-36 were tested for Normality as shown in table 6.5.

Domain	Shapiro-Wilk W statistic	Level of Significance
Dyspepsia Score	0.94	0.43
General health	0.97	0.76
Mental health	0.92	0.078
Bodily pain	0.93	0.18
Physical functioning	0.96	0.52
Social functioning	0.96	0.46
Vitality	0.96	0.46
Role limitation due to physical functioning	0.86	< 0.01*
Role limitation due to emotional functioning	0.86	< 0.01*

Table 6.5: Tests for normal distribution of data (n = 21, df = 21).

Two of the above domains gave significance levels less than 0.05 (*) therefore indicating deviation from a normal distribution, and were thus analysed using non-parametric methods.

For those domains following a normal distribution, the following differences in scores were observed following implementation of recommendations:

Domain	Mean difference in score	95% confidence intervals	Paired t-test statistic	Level of significance
Dyspepsia Score	0.5	-0.8 to 1.8	0.84	0.41
General health	1.7	-5.0 to 8.5	0.53	0.60
Mental health	0.6	-6.2 to 7.4	0.17	0.86
Bodily pain	8.9	-4.0 to 21.8	1.43	0.17
Physical functioning	5.2	-0.4 to 10.9	1.94	0.67
Social functioning	11.4	-1.5 to 24.2	1.85	0.079
Vitality	0	-9.2 to -9.2	0.00	1.00

Table 6.6: Changes in health outcomes following implementation of recommendations (n = 21, df = 20).

As can be seen from the above table, implementation had no significant effect on the health outcomes studied.

For the 2 domains not following a normal distribution, no significant difference in the domain of role limitation due to emotional functioning was observed. (Wilcoxon matched pairs signed-ranks test, $z = -0.59$, $p = 0.55$, $n = 21$, $df = 20$). A difference was, however, observed in the data for role limitation due to physical functioning ($z = -2.12$, $p = 0.034$, $n = 21$, $df = 20$) with higher scores. and thus improved health outcome, being obtained following the change.

The sample size of 21 patients was calculated to be sufficient to detect a difference of 2 points on the Glasgow Dyspepsia Severity Score (range 0-20) from a mean score of 7.4 prior to change in therapy (standard deviation = 2.9), with a power of 80% at a significance level of 5% (2-tailed test).

Changes in these 21 patients consisted of changing ranitidine to cimetidine (11 patients), eradication therapy (4), reducing omeprazole dose (2), changing omeprazole to Tagamet (1), changing omeprazole to ranitidine (1), reducing ranitidine dose (1), changing omeprazole to ranitidine (1). Analysis of data solely relating to change of ranitidine to cimetidine is given in table 6.7.

Domain	Mean difference in scores	95% confidence intervals	Paired t-test statistic	Level of significance
Dyspepsia Score	1.1	-0.0 to 2.2	2.21	0.052
General health	-1.1	-10.0 to 7.8	-0.27	0.79
Mental health	2.5	-6.5 to 11.6	0.62	0.55
Bodily pain	18.4	-2.1 to 38.8	2.00	0.073
Physical functioning	7.3	0.5 to 14.1	2.39	0.038*
Social functioning	14.7	-3.5 to 33.0	1.80	0.10
Vitality	4.1	-9.7 to 17.9	0.66	0.53

Table 6.7: Changes in health outcomes following substitution of ranitidine with cimetidine (n = 11, df = 10).

A significant increase in the score for physical functioning was observed, indicating an improvement in health status.

On analysing the data resulting from replacing ranitidine with cimetidine, no differences were observed in role limitation due to emotional functioning

$z = -1.28$, $p = 0.20$, $n = 11$, $df = 10$; or role limitation due to physical functioning

$z = -1.94$, $p = 0.052$, $n = 11$, $df = 10$.

The above sample size was calculated to be sufficient to detect a difference of 1.5 points on the Glasgow Dyspepsia Severity Score (range 0-20) from a mean score of 8.0 prior to change in therapy (standard deviation = 1.6), with a power of 80% at a significance level of 5% (2-tailed test).

No correlations were identified between the changes in the Glasgow Dyspepsia Severity Score and the changes observed in any of the 8 domains of SF-36 as illustrated in table 6.8.

Domain	Correlation coefficient	Level of significance
General health	0.018	0.94
Mental health	-0.13	0.58
Bodily pain	-0.006	0.98
Physical functioning	0.046	0.84
Social functioning	0.13	0.58
Vitality	-0.10	0.66
Role limitation due to emotional functioning	0.032	0.89
Role limitation due to physical functioning	-0.22	0.34

Table 6.8: correlation between differences in dyspepsia score and SF-36 domains (n = 21).

Pearsons correlation coefficient was used for normally distributed data, Spearmans correlation coefficient used for data not shown to be normally distributed (role limitation due to emotional and physical functioning).

During the course of the study, six of the 21 patients had their treatment altered back to the original prescription. In 4 of the patients, the original change had been from ranitidine to cimetidine, 1 further patient had received eradication therapy

and subsequently restarted cimetidine 400mg bd, the remaining patient had tried a reduced dose of omeprazole. One diabetic patient was changed back to ranitidine from cimetidine due to worsening of blood glucose control, which continued to be elevated on reinstating ranitidine. Results for these patients are presented relating to the time prior to reverting to the original therapy. The small patient numbers involved, however, do not permit comparison of health outcomes between patients remaining on therapy and those reverting back.

Overall cost savings arising from the changes in therapy in these 21 patients were estimated at £3717 in the first year, including the cost of eradication therapy.

6.2 Discussion

The main aim of this research was to implement selected formulary recommendations and measure the subsequent effect on health outcomes. All patients studied had previously been receiving repeat prescriptions for ulcer healing agents. Two measures of outcome were used, the Glasgow Dyspepsia Severity Score, a disease specific measure and SF-36, a generic measure of health related quality of life. Despite repeated general guidance to prescribe eradication therapy for appropriate patients and to increase the ratio of cimetidine relative to other H_2RAs, no previous work has focused on the resultant effect on health outcomes such as these.

An initial drug utilization review of ulcer healing agent use in one general practice in Aberdeen indicated that 2% of the practice were receiving continuous therapy. Similar work by others had produced figures of 0.8% (Ryder *et al* 1994), 2.2% (Cotrill 1994), 3.9% (Rosengren, Polson 1996). These figures would confirm that these agents are widely prescribed and thus should be high priority agents for regular review. Unlike the study of Ryder *et al* (1994), where the majority of patients (75%) had been prescribed these agents for more than 5 years, only 6% of patients in this study had been receiving these agents for such a period. The 2 most common indications for therapy were identified as gastro-oesophageal reflux and duodenal ulcer, a similar finding to that of Ryder *et al* (1994). Although 9% of patients receiving continuous therapy had not undergone any diagnostic investigations, in many cases patient factors such as severe

depression or undergoing chemotherapy rendered such investigations inappropriate. In those patients previously having undergone investigation, many were identified as still receiving therapy years later without further investigation. For example, the median time since diagnosis of duodenal ulcer was found to be 9 years. Several sources have recommended eradication therapy in patients with a diagnosis of duodenal or gastric ulceration (Delaney 1995, Scottish Intercollegiate Guidelines Network 1996), however, this may not alleviate symptoms if patients have developed further causes of dyspepsia, such as gastro-oesophageal reflux, in the interim period. Indeed, Rosengren and Polson (1996) proposed that patients receiving long term therapy may no longer have active duodenal ulcer disease but they provided little evidence to substantiate this statement.

Ranitidine was found to be the most commonly prescribed agent, with only 10% receiving cimetidine. A commonly cited reason for avoiding the use of cimetidine is the potential for drug interactions due to inhibition of microsomal cytochrome P450 (Sabesin 1993). Relatively few patients (1.68%) were, however, identified where the use of cimetidine would have been problematic as a result of interacting therapy. Nevertheless, it is important that prescribers are aware of those agents whose serum levels are altered to a clinically important degree by cimetidine.

This study illustrated the difference between formulary adherence and adherence to a prescribing guideline. Only ranitidine, omeprazole and cimetidine were

issued on repeat prescriptions, all of which are recommended in the Grampian Joint Drug Formulary. In many patients, however, prescribing was not in line with the guideline produced based on the recommendations of the formulary.

The initial patient interview was conducted for 2 reasons: to confirm the ulcer healing agent therapy actually being taken; and to provide baseline data on health outcomes prior to any change in therapy. The importance of obtaining this information prior to any such change was demonstrated in several patients. Instances of previous adverse drug reactions and changes in ulcer healing agents were identified which had not been documented in the patients' medical notes.

6.2.1 Interpretation of Findings

Results of changes in health outcomes following the implementation of a recommendation were obtained for 21 patients. The distributions of changes were found to approximate to a normal distribution for all domains studied except those of role limitation due to emotional and social functioning. This is in contrast to advice provided by the developers of SF-36 who recommend using parametric statistics in any analysis (Ware *et al* 1993). The absence of a normal distribution in these 2 domains is most likely due to the relatively small sample size of 21 patients.

Results obtained for differences in health outcome measures before and following a change in therapy indicated no significant difference in any of the areas studied

except for role limitation due to physical functioning, which appeared to improve following the change. In particular no change was observed in the Glasgow Dyspepsia Severity Score. In measuring health outcomes, a disease specific measure is included to ensure responsiveness to small changes in outcome unlikely to be detected by a more generic measure (Bowling 1995, McDowell and Newell 1996, Bowling 1997). Prospective calculation of sample size necessary to detect a clinically important difference was not possible since this required an estimate of the mean baseline score and variance of the differences. Research centring around the use of the Glasgow Dyspepsia Severity Score is limited. In particular, no work has estimated clinically important differences. Determination of a clinically important difference in the field of health outcomes may be problematic. Deyo *et al* (1991) recommended measuring the difference obtained by administering an intervention of known efficacy. The present study did not aim to identify this difference, since all patients were receiving therapy with efficacious agents prior to any change. The sample size of 21 was, however, calculated to be sufficient to detect a difference of 2 points, on a scale ranging from 0-20, with a power of 80%. Drummond and O'Brien (1993) stated that value judgements may be required to determine the minimal clinically important difference. Contact with one of the developers of the Glasgow Dyspepsia Severity Score provided information that clinical experience indicated that a difference in 2 units would be clinically important. Calculation of sample size required to demonstrate a difference in the domains represented by SF-36 is similarly complicated since results are presented as 8 separate domains, rather than being summed to produce one summary statistic. Calculation of sample size for each of

these domains requires knowledge of a clinically important difference for each and is likely to produce different results for each domain. It has therefore been recommended that focus is placed on the domain of greatest interest (Jaeschke *et al* 1989). This approach was employed in this study and the difference which could be identified calculated for the disease specific measure.

Further analysis of data obtained from these 21 patients, however, identified that this was not a homogenous group, containing patients where different types of changes had been implemented including those: attempting to improve symptoms; reducing dose of ulcer healing agent; increasing dose; prescribing eradication therapy; altering ulcer healing agent prescribed. Health outcomes arising from such a diversity of changes are likely to be different and, in some cases, actually oppose each other. For example, changing from ranitidine to omeprazole may reduce dyspepsia score whereas reduction in omeprazole dose will not reduce score and may indeed actually increase score. Including such data in an overall analysis is less likely to identify any real changes.

Changing therapy from ranitidine to cimetidine formed the largest group. Further analysis of the data relating solely to these patients identified that the only difference observed was in the domain of physical functioning with scores actually increasing following this change, indicating an improvement in health outcomes in this domain. Caution must, however, be exercised in interpretation of the data since the probability value for the Glasgow Dyspepsia Severity Scale was very close to 0.05 and thus there is a high likelihood that changing from

ranitidine to cimetidine may worsen dyspepsia. However, it is also possible that non-identified factors occurring in the interim period other than the change in drug choice may have influenced this outcome. Although no such information relating to hospital or general practice attendances, new diagnoses were identified from the patients' medical notes, changes important to the patients may not have been recorded in this way. Indeed, as stated earlier, the drug utilization data ontained from the patients' medical notes often contrasted with that obtained from the patient.

The data relating to changes in health outcomes obtained in this study must be interpreted with caution primarily due to the lack of information available to establish representativeness of the final group of 21 patients relative to the overall population of patients. There were several points at which patients were "lost". For example, change to therapy was considered inappropriate in 11 patients due to clinical factors such as severe depression. A further 8 patients were deemed unsuitable for interview by the GPs and 19 patients refused to be interviewed. The results of any changes in health outcomes in these patients may have been different from those of the 21 patients completing the study.

6.2.3 Critical Appraisal of Method

Patients in this study were not randomly selected from practices throughout Grampian. Instead, cluster sampling was used as a method of obtaining a sample of patients in a geographical area. The assumption was made that these patients

would only differ from the population of patients in terms of their GP, which would be unlikely to have an effect of changes in health outcomes.

Following the initial drug utilization study, patients were identified in whom there was the potential for a change in therapy due to non-adherence to the agreed guideline. The GPs agreed with all recommendations for changing therapy. In several patients, the recommendations had been implemented prior to interview, resulting in health outcome scores not being included in any further analysis. None of these patients expressed any dissatisfaction with the change in therapy, which generated considerable savings. Only 54% of recommendations were actually implemented, despite several meetings at which GPs were reminded of those patients where no change had occurred. Perhaps the study protocol should have identified the pharmacist as being responsible for implementing recommendations once agreement from the GPs had been obtained. A pharmacist run clinic aiming to identify appropriate patients for eradication therapy has been described (Moorhouse *et al* 1996). Results indicated improved symptoms, measured subjectively by patients, and reduced use of ulcer healing agents. In the present study, several further patients were reluctant to receive *H. pylori* eradication therapy, despite explanation of possible benefits. Similar reluctance was observed by Rosengren and Polson (1996) in a study involving 40 duodenal ulcer patients receiving continuous ulcer healing agent therapy.

An appropriate health outcome measure must be valid, reliable and responsive. Previous validity data for the Glasgow Dyspepsia Severity Score showed its

ability to discriminate between both duodenal ulcer, non-ulcer dyspepsia and control patients with no complaints of dyspepsia. Responsiveness was shown in a sample of patients receiving eradication therapy (El-Omar *et al* 1996). The present study involved many types of recommendations other than eradicating *H. pylori* in patients with duodenal or gastric ulcer. There is a lack of data relating to the ability of the Glasgow Dyspepsia Severity Score to be responsive in these areas, despite the claim by the authors that it is suitable for any symptoms related to the upper gastro-intestinal tract. For example, when altering from one H_2RA to another, the likely change in dyspepsia score would be expected to be minimal and this measure may fail to detect such a change. Similarly, this measure has not been used in patients receiving an ulcer healing agent for NSAID prophylaxis, where many of the patients may not actually experience any symptoms of dyspepsia and indeed dyspepsia itself is a poor indicator of outcome.

SF-36 has been evaluated in patients with duodenal ulcer (Garratt *et al* 1993) and gastro-oesophageal reflux disease (Stacey *et al* 1996). These studies identified that SF-36 scores were lower in patients with these disease states than control groups and indicated that scores increased following treatment, particularly the domain of bodily pain in patients with gastro-oesophageal reflux disease. However, these patients had not previously received any treatment which increased the likelihood of responsiveness following treatment with an ulcer healing agent. The possibility of being responsive to the types of changes involved in this study may be much lower. Similarly, SF-36 has not been evaluated in areas of NSAID prophylaxis.

Previous work with SF-36 has shown that the domains of physical functioning, role limitation due to physical functioning and vitality are those most likely to identify differences between minor and serious medical conditions (McHorney *et al* 1993). Garratt *et al* (1993) proposed a relationship between the crude measure of GP's perception of symptom severity and SF-36 scores. Results of correlation tests between the more objective Glasgow Dyspepsia Severity Scores and the domains of SF-36, however, failed to identify any correlation. However, correlation may be difficult to demonstrate between measures scored in such different ways, the Glasgow Dyspepsia Severity Score ranging from 0 to 20 in increments of 1 unit, SF-36 from 0 to 100, and for some domains the incremental unit being 33.

6.2.3 Conclusions

Despite the above limitations, this study measured health outcomes following changes in ulcer healing agent in line with the recommendations of the Grampian Joint Drug Formulary. While considerable cost savings were generated, results of health outcomes are more difficult to interpret due to the lack of data relating to representativeness of the patient group, the diversity of the changes made and the possible lack of suitable outcome measures. The measurement of health outcomes is extremely important but may require the development or testing of more appropriate measures.

Chapter 7

Peripheral Vasodilators: Results and Discussion

7.1 Results

7.1.1 Drug utilization

A total of 45 patients from both practices (0.4% of the combined practice lists) were identified from the computer systems as receiving repeat prescriptions for peripheral vasodilators. Thirty three patients (73%) were female and 12 (27%) male with a median age of 74 years (range 36-88). Eight patients (18%) had not received a prescription in the previous year.

The fate of these patients in this study is summarised in figure 7.1

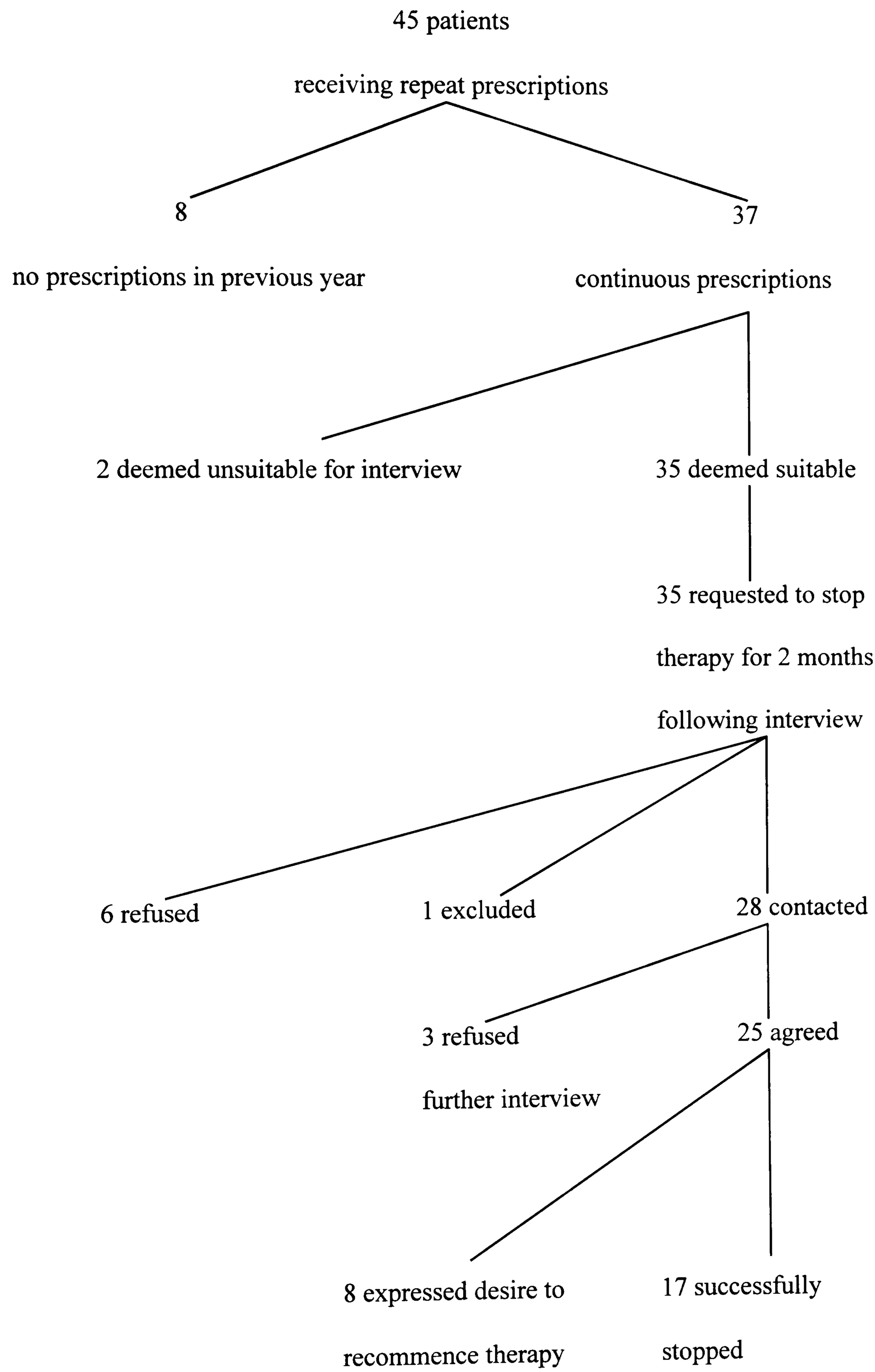

Figure 7.1: Flow chart indicating fate of patients during study.

The range of peripheral vasodilators prescribed continuously to the remaining 37 patients (82%) is shown in figure 7.2.

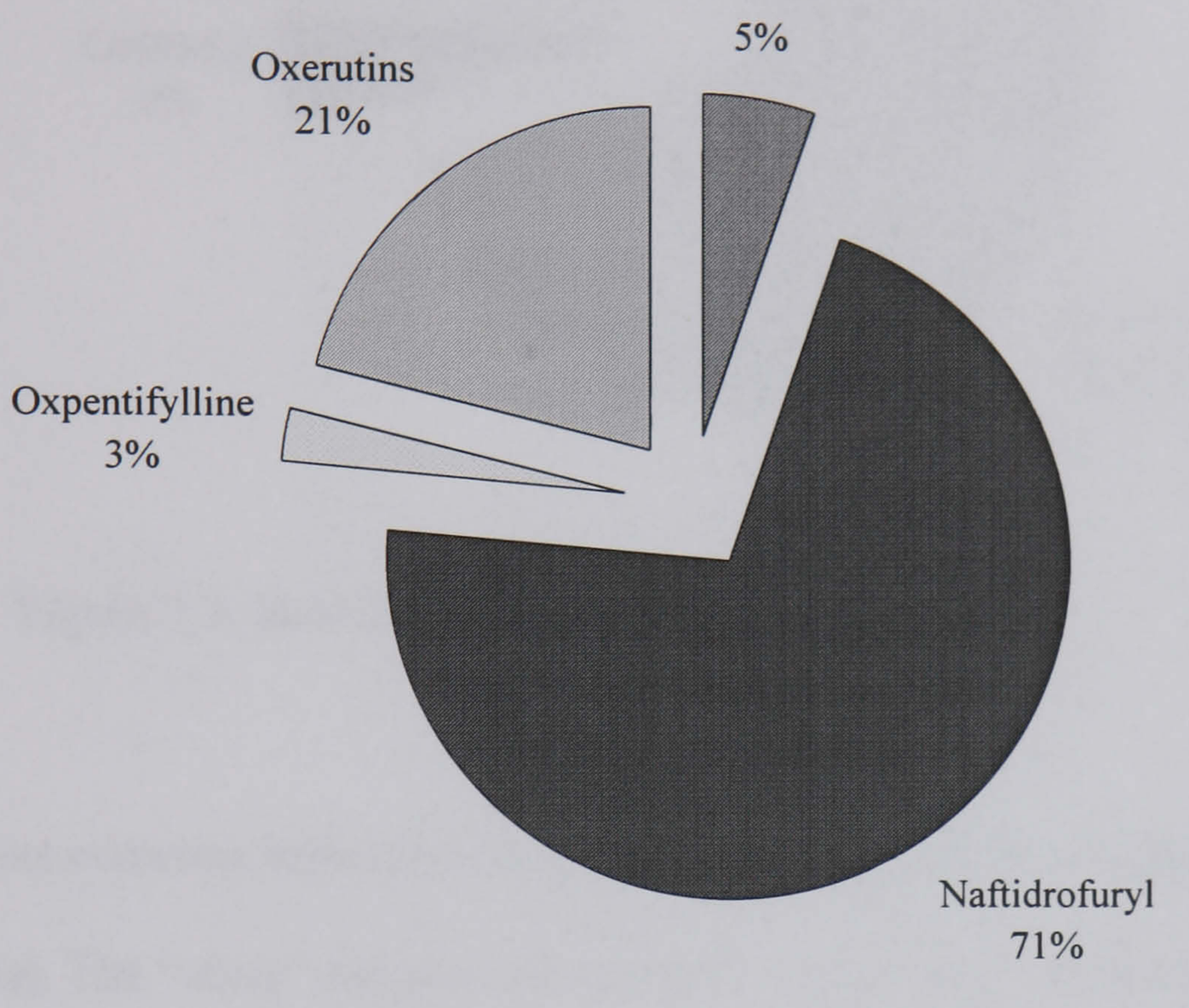

Figure 7.2: Peripheral vasodilators prescribed on repeat prescriptions.

The most commonly prescribed agent was naftidrofuryl (27 patients) followed by oxerutins (8 patients). One patient was receiving both of these drugs simultaneously.

Indications for therapy documented in these patients' medical notes are illustrated in figure 7.3.

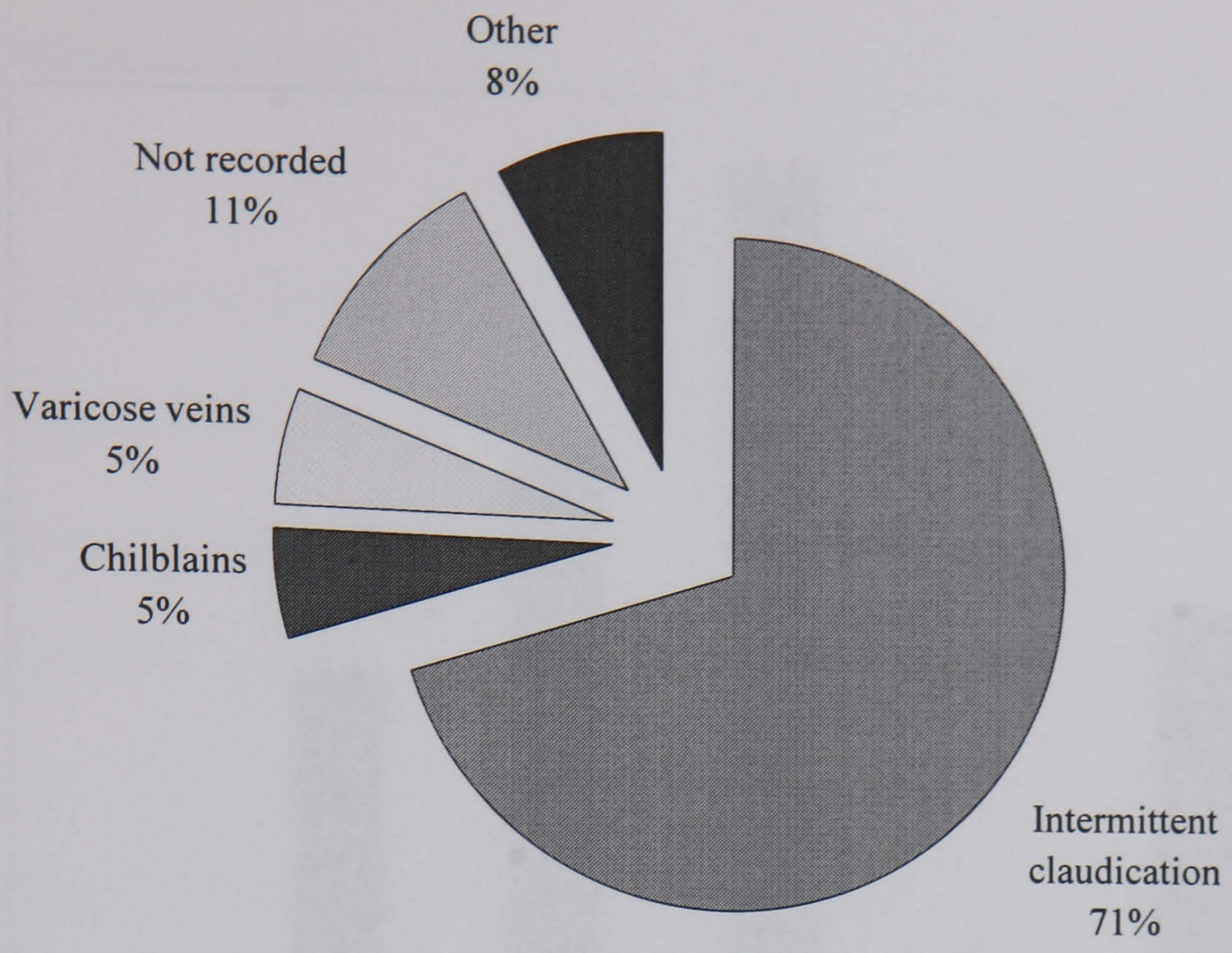

Figure 7.3: Indications for peripheral vasodilators.

The most common indication for therapy was intermittent claudication (26 patients). The "other" category comprised 1 case of each of the following: gangrenous toes; cold hands and feet; and leg cramps. Four patients were identified with no documented indication. One of these patients had herself requested a trial of naftidrofuryl which had then continued, without review, for 13 years.

Therapy had been initiated in primary care in 32 patients (87%), compared to 5 patients (13%) in secondary care.

Duration of continuous therapy is shown in figure 7.4.

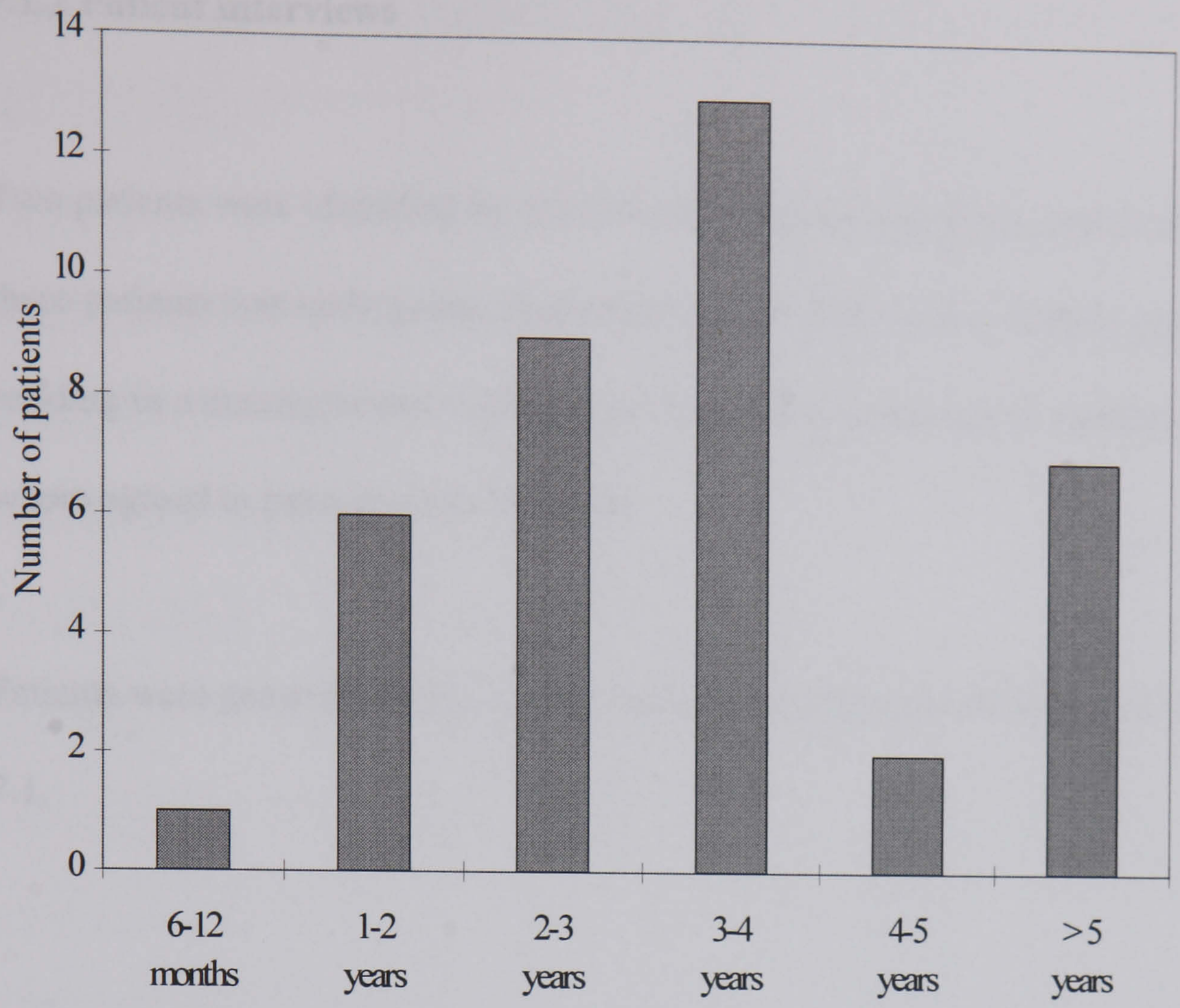

Figure 7.4: Duration of continuous peripheral vasodilator use.

The median duration was 3.5 years (range 0.5-17), with seven patients continuing therapy for greater than 5 years. Review of the continued need for therapy was documented in the medical notes of only 1 patient (2%) where discontinuation had resulted in symptom recurrence. No details of such reviews were documented in the medical notes of the remaining 36 patients.

The total annual cost of peripheral vasodilators in both practices amounted to £6105.

7.1.2 Patient interviews

Two patients were identified by the GPs as being unsuitable for interview. One of these patients was undergoing chemotherapy, the other was an elderly gentleman residing in a nursing home. Letters were sent to the remaining 35 patients, all of whom agreed to participate in the study.

Patients were generally aware of the indication for therapy as illustrated in table 7.1.

Cited Indication	Number of patients
Poor circulation	15
Leg pains	8
Blood disorders	2
Blood clots	1
Hardening of arteries	1
Blocked arteries	1
Cold feet	1
Worn muscles	1
Varicose veins	1
Chilblains	1
Intermittent claudication	1
Not aware of indication	2

Table 7.1: Indications cited by patients.

Three of the 4 patients where no indication had been recorded in their medical notes described circulation problems (2 patients), leg pains (1 patient). The remaining patient with no documented indication was unaware of the reason for therapy.

Eleven patients (31%) continued to smoke despite repeated advice to stop.

Following interview and feedback of results to the GPs, all patients were sent letters instructing them to stop therapy for a period of 2 months. Information from the medical notes identified that 6 patients (17%) had not stopped their peripheral vasodilator with no reason documented in 4 of these 6 patients. Of the remaining 2 patients, 1 had recently undergone surgery for gastric cancer and the other had previously suffered return of symptoms on discontinuation of therapy. One patient who had stopped therapy had been severely ill in hospital suffering from peritonitis, duodenal ulceration and stroke and therefore took no further part in the study. The remaining 28 patients were contacted by telephone. Three patients were not keen to be re-interviewed as they had suffered return of symptoms on cessation of therapy. Twenty five patients agreed to be re-interviewed to determine the effect of stopping therapy.

7.1.3 Health outcome measures

Differences in scores between the 2 interviews for the Walking Impairment Questionnaire and the 8 domains of SF-36 were tested for Normality as shown in table 7.2.

Domain	Shapiro-Wilk W statistic	Level of Significance
Walking impairment	0.82	<0.01*
Walking distance	0.86	<0.01*
Walking speed	0.95	0.37
General health	0.96	0.44
Mental health	0.94	0.16
Bodily pain	0.96	0.50
Physical functioning	0.97	0.74
Social functioning	0.88	<0.01*
Vitality	0.97	0.70
Role limitation due to physical functioning	0.93	0.14
Role limitation due to emotional functioning	0.67	<0.01*

Table 7.2: Tests for normal distribution of data (n = 25, df = 25)

Four domains gave significance levels less than 0.05 (*) therefore indicating deviation from a normal distribution and were thus analysed using non-parametric methods.

For those domains following a normal distribution, the following differences in scores were observed following cessation of therapy:

Domain	Mean difference in score	95% confidence intervals	Paired t-test statistic	Level of significance
Walking speed	1.2	-3.4 to 5.7	0.52	0.61
General health	-2.0	-7.5 to 3.4	-0.78	0.45
Mental health	-0.7	-7.1 to 5.6	-0.23	0.82
Bodily pain	-0.7	-10.5 to 1.9	0.13	0.90
Physical functioning	-4.0	-9.8 to 1.8	-1.43	0.17
Vitality	-3.2	-10.7 to 4.3	-0.88	0.39
Role limitation due to physical functioning	-1.0	-17.2 to 15.2	-0.13	0.90

Table 7.3: Changes in health outcomes following cessation of peripheral vasodilators (n = 25, df = 24).

As can be seen from the above results, stopping peripheral vasodilators had no significant effect on health outcomes.

This sample size was adequate to detect a difference in walking speed of 6.5% from a mean walking speed of 28.5% (standard deviation = 11.1), with a power of 80% at a significance level of 5% (2-tailed test).

For those domains deviating from a normal distribution, no significant differences in outcomes were observed.

Domain	Wilcoxon Matched Pairs Signed-Ranks test (z value)	Level of significance
Walking impairment	-1.60	0.11
Walking distance	-0.28	0.78
Social functioning	-1.45	0.15
Role limitation due to emotional functioning	-0.94	0.35

Table 7.4: Changes in health outcomes following cessation of peripheral vasodilators (n = 25, df = 24).

The sample size was adequate to detect a difference in walking distance of 16.6 from a mean walking distance of 60.5% (standard deviation = 28.5), with a power of 80% at a significance level of 5% (2-tailed test).

Twenty patients (80%) were identified where factors such as shortness of breath, backache, caused the same or greater impairment to walking as pain or aching in calves.

Of those 25 patients re-interviewed, 8 had either recommenced therapy or expressed a desire to do so. The remaining 17 patients (68%) had successfully stopped therapy resulting in annual cost savings amounting to £2768.

There was no association between successfully stopping therapy and whether or not the patient smoked ($\chi^2 = 1.21$, $p = 0.27$). Similarly there was no association between successfully stopping therapy and whether or not the patient had previously been referred for vascular opinion ($\chi^2 = 0.00$, $p = 1.00$).

On comparing those patients who had successfully stopped with those either restarting or expressing an interest to do so, a significant difference was observed in changes in walking distance with those in the latter group requesting therapy having a reduced walking distance (Mann-Whitney U test , $z = -2.42$, $p = 0.016$). The mean walking distance decreased by a mean of 30% in those restarting therapy compared to a mean increase of 5.6% in those successfully stopping.

Data were tested for correlation between the differences in scores from the Walking Impairment Questionnaire and the 8 domains of SF-36. Pearsons correlation coefficient was used for normally distributed data, Spearmans correlation coefficient for data not shown to be normally distributed.

Changes in walking distance were found to correlate with changes in walking speed (correlation coefficient 0.46, p = 0.022).

On comparing changes in walking distance with changes in SF-36 domains, the following results were obtained.

Domain	Correlation coefficient	Level of significance
General health	0.40	0.05*
Mental health	0.061	0.77
Bodily pain	0.11	0.61
Physical functioning	-0.11	0.63
Social functioning	0.57	0.003*
Vitality	-0.15	0.47
Role limitation due to emotional functioning	0.22	0.30
Role limitation due to physical functioning	0.046	0.83

Table 7.5: Correlation between differences in walking distance and SF-36 domains (n = 25, * indicates significant correlation).

Similarly, comparison was made between changes in walking speed and SF-36 domains.

Domain	Correlation coefficient	Level of significance
General health	0.42	0.037*
Mental health	0.047	0.82
Bodily pain	0.30	0.14
Physical functioning	0.16	0.44
Social functioning	0.49	0.013*
Vitality	-0.13	0.56
Role limitation due to emotional functioning	0.070	0.74
Role limitation due to physical functioning	0.093	0.66

Table 7.6: Correlation between differences in walking speed and SF-36 domains (n = 25, * indicates significant correlation).

Changes in both walking distance and walking speed correlated with changes in general health and social functioning.

7.2 Discussion

7.2.1 Interpretation of Findings

No previous work in the UK provided data relating to the use of peripheral vasodilators in primary care. This study identified that 0.4% of listed patients were receiving these agents on repeat prescriptions and, in the majority of cases, treatment had been initiated in primary care. Previous work showed intermittent claudication to be most prevalent in elderly males (Kannel, McGee 1985). Although the present study identified that patients were generally elderly (median 74 years), many more females were prescribed these agents than males. This comparison to previous work should be interpreted with caution since the present study did not aim to identify all patients with intermittent claudication, rather focusing on those prescribed peripheral vasodilators, who may not have been representative of the population of patients with intermittent claudication.

Naftidrofuryl was the most commonly prescribed peripheral vasodilator, being used to treat the symptoms of intermittent claudication in the majority of patients. Further indications identified such as varicose veins, chilblains and leg cramps are outwith data sheet recommendations. The use of peripheral vasodilators for these indications is not based on the results of any published work. Although peripheral vasodilators are not recommended in the Grampian Joint Drug Formulary, several sources (Ruckley 1986, Lowe 1990, Waller, Chant 1995) have acknowledged a limited role in those with severe, disabling symptoms. It is,

however, recommended that in these patients, treatment should be for an initial period of 2 to 3 months followed by cessation of therapy in order to ascertain continued need for treatment. This study identified that these agents had been prescribed for considerable periods of time (median 3.5 years) without further review. Indeed cessation of therapy had only been documented in the medical notes of 1 patient.

The main aims in treating intermittent claudication have been defined as being relief of symptoms and improvement of health related quality of life (Hiatt *et al* 1995). Health outcomes measures used in this study were chosen in an attempt to reflect these aims with the Walking Impairment Questionnaire representing a disease specific measure and SF-36 a generic measure of health status.

Patients were interviewed on 2 occasions with the first interview providing drug utilization information and baseline measurements of health status. The second interview which took place 2 months later determined the effect of cessation of therapy. A period of 2 months was considered sufficient to determine such effects since this represents an appropriate period during which a beneficial response to treatment would be evident (Ruckley 1986, Lowe 1990, Waller, Chant 1995).

Withdrawal of peripheral vasodilators, as recommended in the Grampian Joint Drug Formulary, appeared to have no significant effect on any of the domains measured. Of particular importance was the lack of effect on walking distance and speed as measured by the Walking Impairment Questionnaire. Prospective

calculation of sample size was not possible since no data was available to allow determination of mean values prior to intervention, nor standard deviation of any differences. Similarly the clinically important difference had not been defined. Analysis of results identified that the sample studied was sufficient to detect differences of 6.5 and 16.6% in walking speed and walking distances respectively. These differences are less than those obtained by Regensteiner *et al* (1996) in a study of treadmill testing and strength testing, who identified that a difference of 31% in walking distance was of importance. This would appear to confirm that the sample size used in the present study was sufficient. Although the Shapiro-Wilk W statistic for walking distance identified a significant deviation from a normal distribution, further exploration of the data showed values grouped around a mean and thus sample size calculations were performed based on parametric principles.

Eight patients had either restarted therapy during the course of the study or had expressed an interest to do so. On comparing differences in scores for walking distances between this group and those who had successfully stopped therapy, a statistically significant and apparently clinical difference was observed. This may indeed indicate that some patients obtain some benefit from the continued use of these agents. The present study did not intend to be a clinical trial and included no placebo control group. These agents have been shown to produce a high placebo response (Anon 1996), which may be the basis for worsening walking distance on cessation of therapy. The differences in scores between those patients

successfully stopping therapy and those not may provide evidence for the responsiveness of the Walking Impairment Questionnaire.

Results of changes in health outcomes must be interpreted with caution since those patients completing the study may not be representative of the total population of patients. In particular, 6 patients (17%) had not stopped therapy as instructed and a further 3 patients (9%) refused to take part in the second interview. Results of these patients could not be included in any final analysis but are likely to have differed from those patients completing the study.

Patient reluctance to alter long term therapy was previously identified as a major reason for the continued prescribing of inappropriate drugs in primary care. Britten *et al* (1995) reported a study of 7 GPs who used various methods to identify patients in their practices whose drug therapy was regarded as being inappropriate. Peripheral vasodilators were amongst those drugs identified that patients were reluctant to stop.

Many patients continued to smoke despite repeated advice to stop. Although more patients successfully stopping were non-smokers, this association did not reach statistical significance. In patients with intermittent claudication, the most appropriate treatment has been defined as cessation of smoking accompanied by an increase in daily walking (Housley 1988). Indeed, it has been recommended that if peripheral vasodilators are to be prescribed, this should only be after the effects of stopping smoking have been determined (Ruckley 1986). Given the

increased risk of cardiac arteriosclerotic complications in these patients, this area requires further attention as part of overall patient management.

Patients referred for vascular investigations may be those with more severe symptoms but again no association was observed between successfully stopping therapy and previous vascular referral.

Changes in walking speed were found to correlate with changes in walking distance, providing further evidence of the usefulness of the instrument. Several correlations were observed between both of these domains and SF-36. Changes in both walking distance and speed were found to correlate most highly with both general health and social functioning. These results are unexpected since the domains of physical functioning, role limitation due to physical functioning and vitality had previously been shown to be most affected by medical conditions (Ware *et al* 1993). In addition, bodily pain was significantly affected by an exercise programme; surgery produced changes in the domains of physical functioning, role limitation due to physical functioning, bodily pain and vitality (Currie *et al* 1995); treadmill training produced most effect on physical functioning (Regensteiner *et al* 1996). Data from this study showed changes in walking distance to be poorly correlated with bodily pain and physical functioning. These findings may question the validity of the SF-36 results. Although no information was identified from the patients' medical notes to indicate other changes likely to influence health outcomes, such unidentified factors may have been present.

7.2.2 Critical Appraisal of Method

As outlined in chapter 6, cluster sampling was used as a method of obtaining a group of patients assumed to be representative of all patients in Grampian. No data was provided to establish the validity of this assumption.

For health outcome measures to be appropriate, they must be shown to be valid, reliable and responsive in the population of patients under study. The Walking Impairment Questionnaire has previously been used in studies measuring the effects of surgery and structured exercise programmes, with results providing evidence of validity, reliability and responsiveness (Regensteiner *et al* 1996). However, no work using this measure has been published relating to studies of peripheral vasodilators. Similarly, there is a lack of data relating to SF-36 in this area.

The walking impairment domain of this questionnaire rates the extent to which calf pain limits the ability to walk over the previous month. Data from this study identified that in 80% of patients, further problems such as shortness of breath, leg weakness caused greater impairment to walking than claudication pain. This may have complicated the measurement of health outcomes on cessation of therapy and may have masked differences in walking distance or walking speed attributable solely to changes in claudication. Several patients were identified where peripheral vasodilators were prescribed for indications other than

intermittent claudication. In such situations, perhaps alternative disease specific measures should have been sought.

7.2.3 Conclusion

Despite the limitations described above, this study attempted to measure health outcomes resulting from the implementation of formulary recommendations. Data obtained identified that, in this group of patients, peripheral vasodilators were successfully withdrawn in the majority of patients with no effects on health outcomes such as walking distance and speed and appeared to have no effect on health related quality of life while generating considerable cost savings. These findings require to be replicated in larger numbers of patients.

Chapter 8

General Discussion

8.1 Drug Formularies

Previous work in the field of drug formularies in primary care focused on the effect on of implementing recommendations on prescribing patterns and drug costs (Grant *et al* 1985, Green 1985, Beardon *et al* 1987, Van Zwanenberg *et al* 1987), with little reference made to the effect on health outcomes. The present study aimed to address this deficiency by measuring changes in health outcomes arising from implementation of selected recommendations of the Grampian Joint Drug Formulary in areas of both acute and repeat prescribing.

Drugs for inclusion in a formulary are selected on the basis of efficacy, safety, cost-effectiveness and patient acceptability, in accordance with previous definitions of rational prescribing (Parish 1973, Barber 1995). More recently, Janknegt and Steenhoek (1997) described further factors of dosage frequency, likelihood of drug interactions, documentation of clinical experience, pharmacokinetic profile and pharmaceutical aspects. They acknowledged that trade-offs may require to be made between these criteria and proposed a more objective method to enable drug selection. This method, termed the System of Objectified Judgement Analysis (SOJA), involves prospectively defining

selection criteria, with each criterion being weighted for importance by an expert panel. The extent to which individual drugs fulfil each criterion is studied and a rating determined by the same expert panel. The final scores for each drug within a class are compared and that with the highest score selected for inclusion in the formulary.

One of the most important steps in this selection process is critical appraisal of the available evidence. The emphasis placed on this evidence may, however, be influenced by emotional criteria arising from either positive or negative past experiences with either certain drugs or drug companies (Janknegt and Steenhoek 1997). In the present study, the GPs were reluctant to prescribe misoprostol for NSAID prophylaxis due to their experience of adverse effects from this agent. This was despite the evidence that misoprostol will afford superior protection against NSAID induced duodenal and particularly gastric ulceration compared to H_2RAs (Raskin *et al* 1996). Use of a more objective system for drug selection may reduce the influence of these highly emotional past experiences.

Limitations of the SOJA method include the lack of data for many individual drugs and drug classes and that a subjective assessment of relative weightings and ratings for each drug are still required. In addition, the only health outcomes considered appear to be clinical efficacy and occurrence of adverse drug reactions.

Implementation of recommendations in this study generated considerable savings in relatively small numbers of patients. It must, however, be appreciated that the aim of developing and implementing a drug formulary is to rationalise prescribing, not solely to reduce costs and indeed, in certain therapeutic areas drug costs may actually increase. In addition, drug costs may differ substantially from overall treatment costs which will include costs associated with consultation, investigation, subsequent treatment and monitoring. There is a general lack of comparative pharmacoeconomic data which can be used to aid this drug selection process.

This study involved both acute (antibiotics for the treatment of uncomplicated lower UTIs) and established long term prescribing (ulcer healing agents, peripheral vasodilators). Changing established therapy has been associated with many difficulties. Several workers have identified patient reluctance as being one of the main reasons for continuing to prescribe drugs with either little evidence of efficacy or which have been surpassed by superior therapies (Schwartz *et al* 1989, Britten *et al* 1995). In the present work, several of the patients prescribed peripheral vasodilators were reluctant to stop therapy for even a short period. Of those patients prescribed ulcer healing agents, several patients previously identified as candidates for *H. pylori* eradication did not wish this treatment despite explanation of the possible benefits. Excluding those receiving *H. pylori* eradication therapy, most other changes to repeat prescriptions were either associated with cessation of therapy, dose reduction or therapeutic substitution. These changes may not provide any additional benefit to the patient in terms of

health outcomes, other than possibly reducing the number of medicines to take each day and reduced likelihood of adverse drug reactions. As a consequence, patients may be less willing to have their treatment altered.

This research did not aim to evaluate the role of the pharmacist in implementing and monitoring a drug formulary in primary care. Little research relating to pharmacist involvement with drug formularies in primary care has been described. Green (1985) and Beardon *et al* (1987) provided details of involvement mainly relating to the process of formulary development. Wider roles in this area have been recommended (Greenfield 1982, Audit Commission 1994). Hughes and McFerran (1996) provided data describing views of community pharmacists towards formulary involvement. A structured questionnaire was sent to 100 randomly selected pharmacists in Northern Ireland. From a response rate of 66%, they identified that 52 (79%) agreed or strongly agreed that pharmacist involvement in formulary development was important, with two thirds stating that they would be prepared to approach GPs in relation to work in this area, but only 27% had previously collaborated. No data was, however, collected relating to further roles of monitoring formulary use, nor measuring the impact on health outcomes. This current research provides some information relating to pharmacist involvement in this area. Those GPs involved were extremely willing to have pharmacist input in this area, although improved mechanisms for implementing change in established therapy require to be evaluated. Kozma *et al* (1993) proposed a model for measuring the outcomes of pharmaceutical care incorporating economical, clinical (morbidity and mortality)

and humanistic outcomes (health related quality of life, satisfaction which could be used to measure pharmacist activities.

8.2 Measurement of Health Outcomes

The measurement of health outcomes provides an objective means of monitoring the patient's progress over time. Different outcome measures were used in the present research. For acute prescribing, the extent and speed of symptom relief was the main measure whereas in areas of repeat prescribing, measures of disease specific and generic health related quality of life were included. Disease specific measures were included to detect small changes in health status whereas generic measures provided much broader measures of health related quality of life. In relation to the effect of formulary implementation, the disease specific measure should provide the most valuable information.

Several difficulties were associated with the interpretation of the scores of SF-36, the generic measure for both the ulcer healing agent and peripheral vasodilator studies. Estimating adequate sample size based on these scores was not performed due primarily to separate scores being determined for each of the 8 domains, thus requiring separate sample size calculations. Brazier (1995) outlined methods for deriving a single index score for SF-36, aiming to reflect the strength of patient preference for the different aspects of health. Methods included combining domain scores into a single index using an assumed set of weights or alternatively valuing all possible health states defined by SF-36. Brazier

identified many limitations and concluded that further work in this area was required.

Despite the absence of a valid method for calculating a single index of SF-36, sample sizes could be calculated for each domain using parametric principles as recommended (Ware *et al* 1993). The present work, however, identified that not all domains of SF-36 followed a normal distribution. Julious *et al* (1995) similarly described the inappropriateness of parametric evaluation of SF-36 data since the scores obtained represent categorical rather than continuous data.

In the areas of repeat prescribing, health outcome measures were administered before and at a period following the change in treatment. Attempts were made to collect information relating to factors which may have influenced any health outcomes during this period but little information was documented in the patients' medical notes. Many patients were, however, elderly with multiple medical problems receiving multiple drugs, thus increasing the likelihood of further changes occurring which may have influenced health outcome measurement. This would be particularly important for the generic measure which is by definition a broad measure of health. A similar problem with SF-36 was described by Hill and Harries (1993) who used this measure before and 3 months after referral for visual difficulties, continence services or mental health services. They acknowledged that patients had multiple health problems and that effective intervention for one problem may not improve health status scores if other problems worsened or were considered more important. They identified

further problems associated with SF-36 including the difficulty that many patients experienced in comprehending many of the questions and the failure of SF-36 to identify improvements in health related quality of life experienced by the patients. Although several workers have identified SF-36 to be responsive to ulcer healing agents in gastro-oesophageal reflux disease (Stacey *et al* 1996) and surgery or exercise in peripheral vascular disease (Currie *et al* 1995, Regensteiner *et al* 1996), responsiveness may be highly dependent on the nature of the intervention.

SF-36 may not be a practical measure in the clinical setting with most interviews in the present research lasting approximately 45 minutes.

As explained above, this research identified several problems associated with the use of this generic measure, as summarised below:

- inability to easily estimate sample sizes.
- data strictly categorical thus limiting statistical manipulations.
- lack of responsiveness to small but important changes.
- some questions difficult for patients to comprehend.
- lack of practicality in the clinical setting.

A further criticism previously levelled at all generic measures is that they impose the choice of domains and attached values on the patient and that these may not be the domains which the patient considers most important (Ruta *et al* 1994).

They described a truly valid measure of health outcome as being one which fulfils the following: describes the effect of conditions on those aspects of lives that the patients consider most important; allows patients to rate the extent to which those aspects of life are affected; responds to change over time; reliable; suitable for a variety of patients in different settings; brief and simple. They produced the patient generated index (PGI) which involves the patients listing the 5 most important areas of their lives affected and a sixth for rating all other areas of their lives. Patients are then asked to rate how badly affected they are in each area on a scale of 0 (worse than they can imagine) to 100 (exactly as they would like to be). Patients then choose to spend a total of 60 points on those areas which they could improve. An index is generated by multiplying the 6 ratings by the proportion of the 60 points allocated to each and summing the results to produce a patient generated index. This measure was tested in 359 patients with low back pain. Scores were compared with SF-36 and a back pain questionnaire showing correlation with SF-36 domains of bodily pain, social functioning, role limitation due to physical functioning and with the back pain questionnaire. PGI scores were significantly lower in those patients referred to secondary care and reflected the GPs perception of pain severity. The authors concluded that the PGI had considerable potential for routine use in clinical settings.

A similar measure, the "measure yourself medical outcome profile" (MYMOP) was described by Paterson (1996) who identified little work focusing on responsiveness of most health outcome measures and the lack of practicality of measures such as SF-36 in clinical settings. MYMOP consists of 4 items scored

on a 7 point scale (1, as good as it could be to 7, as bad as it could be). The first 2 scales represent symptoms the patient considers most important. The third scale represents an activity of daily living disrupted and the fourth asks patients to rate general well-being in the previous week. The profile score is calculated as a mean of the 4 scores. MYMOP was compared to SF-36 in a sample of 265 patients presenting in primary care. Patients completed MYMOP initially and then 2 and 4 weeks later with SF-36 completed initially and 4 weeks later. Patients also rated overall change in symptoms on a 5 point scale from much better to much worse. Of the 265 patients, 193 completed all questionnaires. Changes in MYMOP scores at 2 and 4 weeks were consistent with ratings on the 5 point scale. The instrument was also able to detect more change in acute rather than chronic conditions. MYMOP was more responsive than SF-36 when comparing changes in scores in those rating overall symptoms "a little better" to those "about the same". Although MYMOP relates to symptoms over the preceding 7 days, measures such as this and PGI may be more appropriate than earlier measures of health outcome and require further evaluation.

8.3 Primary Care Research Methods

The present research involved the use of different methods of patient recruitment, data collection and measurement of health outcomes in the 3 therapeutic areas, each of which was associated with practical difficulties and limitations. The main problem associated with the urinary tract infection study was the lack of response from GPs who initially agreed to fully participate. Different methods of collecting

data relating to acutely prescribed drugs require to be developed. With repeat prescribing in the areas of ulcer healing agents and peripheral vasodilators, several deficiencies of the computer prescribing systems were highlighted. Many patients were identified who had not requested prescriptions for considerable periods of time but these items had not been deleted from the patients' prescription files. Several further patients were taking regimes different from those recorded. These findings reduce the value of such systems which would otherwise be useful tools for both drug utilization research and audit. A higher proportion of patients agreed to be involved in the study of peripheral vasodilators than ulcer healing agents. Although the methods of patient recruitment used in these 2 areas were similar, letters informing patients of the study were signed by the GPs for peripheral vasodilators but by the researcher who was not known to the patients for ulcer healing agents. This simple change may have encouraged more patients to participate and should be borne in mind for further research in primary care.

8.4 Conclusions

Overall, this research highlighted the lack of work surrounding drug formularies in primary care. Further methods require to be developed for researching the use of acutely prescribed drugs based on formulary recommendations, measuring appropriate health outcomes. Such outcomes may need to be further refined but are generally less complex than those for repeat prescribing. In this latter area, further work is needed to determine the most appropriate method of

implementing change in patients established on long term therapy, including measures of patient satisfaction with any change. Appropriate health outcome measures require to be developed. Very few disease specific measures are available and patient generated measures require more attention.

Health outcomes data provided by this research are limited and must therefore be interpreted with great caution. In each of the 3 areas less patients completed the studies than had been anticipated. This was a particular problem with data collection relating to uncomplicated lower UTIs and ulcer healing agents. As a result the data obtained cannot be extrapolated to the general population of patients in Grampian. This work should be replicated in greater numbers of representative patients.

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Appendix 1

confidential

Urinary Tract Infection Study

To be completed by the doctor

Was a urine specimen sent for culture ?

☐ yes

☐ no

please tick the appropriate box

Did any factor affect drug choice ?

e.g. drug interaction, contra-indication

☐ yes

☐ no

If yes, please state factor

.....

.....

Please state

drug prescribed .....

dose .....

duration .....

To be completed by the patient

I have had the above study explained to me by my doctor and have had the opportunity to ask any questions. I understand that this is a study to look at cure rates and re-infection rates of urine infections and has been approved by the Joint Ethical Committee. I also understand that my doctor has agreed that I can take part and that I am completely free to withdraw from the study at any time I wish. I hereby fully and freely consent to take part.

Name ..... Date.....

Address .....

Telephone number .....

Once this has been signed, please tear this page off and hand to the receptionist.

Patient number.....

Appendix 2

confidential

Dear patient,

I would like to thank you for agreeing to take part in this survey.

Your doctor has diagnosed that you have a urine infection. This is a common condition in females.

This survey is going to look at both cure rates and re-infection rates of urine infections. To do this, I would like you to fill in this questionnaire.

The questionnaire comes in 2 parts.

Part 1 should be filled in before you start taking the medicine your doctor has prescribed for your urine infection.

Part 2 should be filled in after you stop taking this medicine.

Once you have completed the questionnaire, please send it back to me ***in the self addressed envelope.***

Please don't worry

All information collected will be treated in the strictest confidence. There is no need to take part in the study and you can pull out at any time. But it would be great if you could help me.

I would like to thank you for taking the time to fill in the questionnaire.

Yours faithfully,

Lecturer, School of Pharmacy

confidential

Part 1 : complete before you start taking the medicine prescribed by your doctor for your urine infection

1. Which of the following symptoms were you suffering from when you visited your doctor ?

- ☐ passing urine more often
- ☐ pain when passing urine
- ☐ urine had a different smell
- ☐ other - please describe .....

.....

tick more than one box if appropriate

2. How would you describe these symptoms ?

- ☐ mild
- ☐ moderate
- ☐ severe

3. How long after first noticing these symptoms did you go to your doctor ?

- ☐ 1 to 2 days
- ☐ 3 to 4 days
- ☐ more than 4 days

4. Did you give a urine sample to your doctor ?

- ☐ yes
- ☐ no

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Part 2 : complete after you stop taking the medicine prescribed by your doctor for your urine infection

5. Did you take all of the medicine prescribed by your doctor for your urine infection ?

☐ yes

☐ no

If no, please explain why not .....

.....

6. Once you stopped taking this medicine, how would you describe your symptoms ?

☐ gone away

☐ mild

☐ moderate

☐ severe

7. If your symptoms went away, how long after you started taking this medicine did they go away ?

☐ 1 to 2 days

☐ 3 to 4 days

☐ more than 4 days

8. Did you get any side effects which you think may have been caused by this medicine ?

☐ yes

☐ no

If yes, please describe these side effects .....

.....

.....

Please describe what you did when you got these side effects .....

.....

.....

confidential

9. Apart from the medicine prescribed by your doctor did you take any other medicine for your urine infection ?

☐ yes

☐ no

If yes, what did you take ? .....

.....

10. Have you had to go back to your doctor because of your urine infection ?

☐ yes

☐ no

If yes, why ? .....

.....

11. Did you take time off work because of your urine infection ?

☐ yes

☐ no

Sometimes urine infections can come back. To check that this has not happened, I would like to contact you in about 4 weeks time. This will only involve asking one or two questions. I could either write or phone you.

☐ contact me by letter

☐ contact me by phone phone no.....best time to phone.....

☐ please do not contact me

Thank you very much for helping me with this study.

Please put the questionnaire in the self addressed envelope and return it to me.

Patient number .....

Appendix 3

Dear Patient

I am a lecturer at the School of Pharmacy, The Robert Gordon University, Aberdeen. I am carrying out a study looking at cure rates and re-infection rates for urine infections.

A few weeks ago your doctor gave you a questionnaire to fill in and send back to myself. As yet I have not received this. I wonder if I could ask you to fill this in and return to me. I have included another questionnaire and envelope just in case you have misplaced it. Thank you very much for helping me.

Yours sincerely

Derek C Stewart

Appendix 4

confidential

Urine Infection Study

Dear patient,
A few weeks ago your doctor asked you to complete a questionnaire about a urine infection. Thank you very much for completing that questionnaire and returning it. I would be very grateful if you could now complete this small questionnaire and return it to me ***in the self addressed envelope***.

Since completing the last questionnaire about your urine infection

1. Have the symptoms of your urine infection come back ?

   ☐ yes

   ☐ no **tick the appropriate box**

2. If yes, how would you describe these symptoms ?

   ☐ mild

   ☐ moderate

   ☐ severe

3. If yes, what action did you take ?

   ☐ nothing

   ☐ returned to doctor

   ☐ other

If other, please describe what you did .....

.....

4. If you returned to your doctor, were you given more medicine ?

   ☐ yes

   ☐ no

Thank you very much for helping me with this study.
Please put the questionnaire in the self addressed envelope and return it to me.

Appendix 5

Patient number

URINARY TRACT INFECTION STUDY

FOLLOW UP TELEPHONE QUESTIONNAIRE

Since completing the last questionnaire about your urine infection

1. Have your symptoms come back ?

☐ yes

☐ no

2. If yes, how would you describe these symptoms ?

☐ mild

☐ moderate

☐ severe

3. If yes, what action did you take ?

☐ nothing

☐ returned to doctor

☐ other - please describe

.....

.....

4. If you returned to your doctor, were you given more medicine ?

☐ yes

☐ no

Appendix 6

UTI Data Collection Form: Patients Returned

Name _____

Address _____

Practice _____

Date of UTI Prescription _____

Date returned to GP _____

Reason returned _____

_____

_____

_____

_____

Consequences

Prescription given ☐ y ☐ n

Drug _____

Dose _____

Duration _____

Sample sent ☐ y ☐ n

Other _____

_____

Comments

Appendix 7

UTI Data Collection Form: Sensitivity Reports

Name _____

Address _____

Practice _____

Date of UTI prescription _____

Drug Prescribed _____

Sample Results

Isolate 1		Isolate 2	
Resistant	Sensitive	Resistant	Sensitive

Was drug appropriate ? ☐ y ☐ n

Was new prescription sent ? ☐ y ☐ n

Drug _____

Dose _____

Duration _____

Was new drug most appropriate ? ☐ y ☐ n

Other Comments

Appendix 8

Dr D. C. Gould
Keith Medical Group
Turner Street
Keith
AB55 3DJ

Urinary Tract Infection Study

Dear Dr Gould

I am writing to give you a progress report on the above study which forms part of my PhD, the development of drug utilisation evaluation studies in primary care.

Twenty four general practitioners in Grampian agreed to help with the study which involves giving out 20 questionnaires to females presenting with an uncomplicated urinary tract infection. This study has now been running for approximately 12 months. The tables below show the number of questionnaires given out by each participant, with your particular rate of distribution highlighted.

GP	1	2	3	4	5	6	7	8	9	10	11	12
Number of questionnaires distributed	1	0	2	20	2	1	1	0	0	0	3	20

GP	13	14	15	16	17	18	19	20	21	22	23	24
Number of questionnaires distributed	18	3	3	0	0	0	0	0	4	0	0	6

Of those questionnaires distributed, a high return rate of 76/84 (90%) has been achieved. It was initially estimated that 250 patients were required to provide meaningful results, but it now seem unlikely that this figure will be reached. I would, however, like to continue to collect data until September 1996, after which I will bring the study to a close.

I would be extremely grateful if you could continue to give out as many questionnaires as possible (the inclusion, exclusion criteria are shown on the front of the desk top organiser). The top sheet of the questionnaire should be completed during the consultation, removed and passed to reception, to be sent on to myself.

If this study is causing any problems or if I can help in any way, please do not hesitate to contact me.

Kind regards.

Yours sincerely

Derek C Stewart

Appendix 9

28 August 1996

Dr DC Gould
Keith Medical Group
Turner Street
Keith
AB55 3DJ

Dear Dr Gould

Previously you indicated your willingness to assist with part of my PhD, regarding drug utilisation studies, by distributing questionnaires to females presenting with symptoms of lower urinary tract infection. I am now writing to inform you that this study is being brought to a close. I would be very grateful if you could pass any remaining questionnaires and envelopes to the practice manager for collection. Please keep the desk top organiser - I am sure that you will be able to find a use for it.

Overall a disappointing number of questionnaires were distributed, which may reduce the value of any findings.

I would, however, like to thank you for your support in this project.

Yours sincerely

Derek C Stewart

Appendix 10

May 1997

No.15

GHB

Grampian Health Board

Communicable Disease & Environmental Medicine Information Sheet for General Practitioners

Urinary Tract Infections in Primary Care

We have been asked by our colleagues at RGU to convey to you the results of a recent project, co-ordinated by the School of Pharmacy, The Robert Gordon University, which looked at the treatment of uncomplicated urinary tract infections in primary care.

The objectives of the project were to:

- identify the treatment of young females presenting with uncomplicated urinary tract infections, in terms of drug, dose, duration of treatment.
- identify any factors affecting drug selection.
- compare treatment with that recommended in the Grampian Joint Drug Formulary antibiotic policy.
- investigate the use of microbiological testing.
- measure patient outcomes.

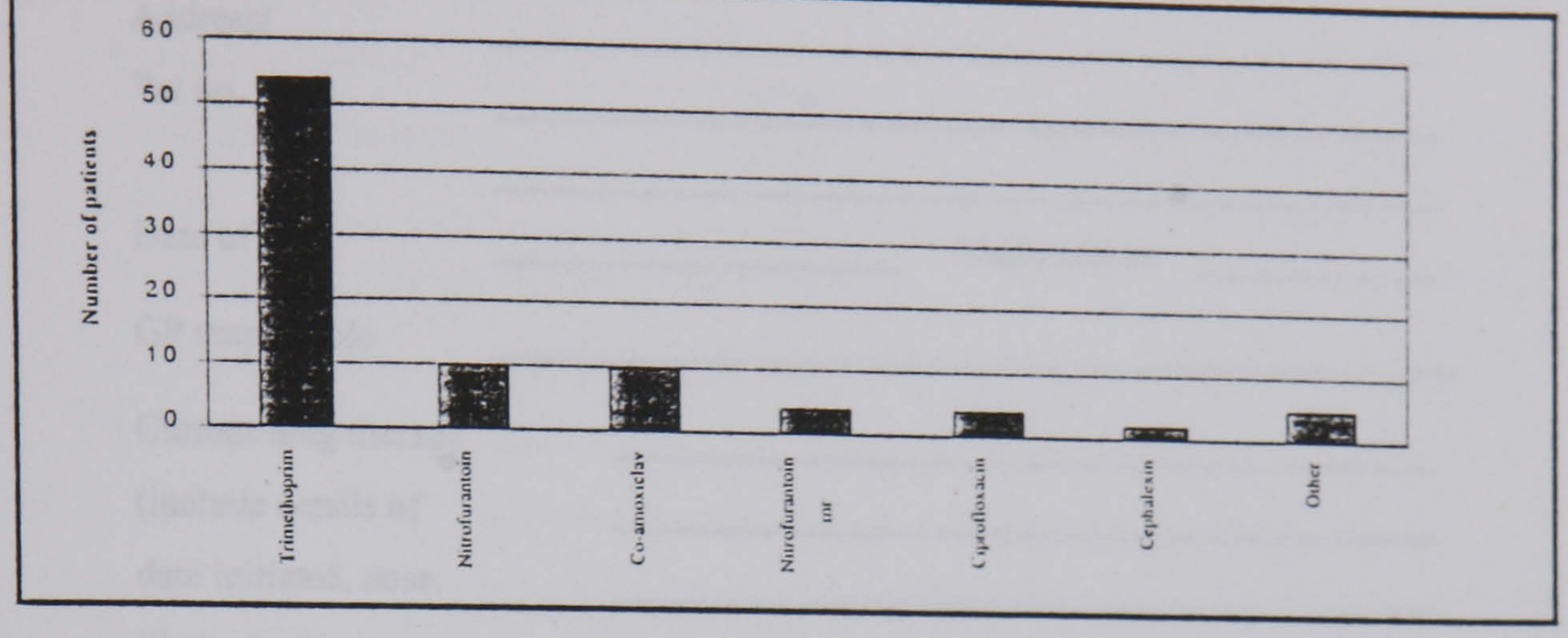
Twenty four randomly selected general practitioners throughout Grampian each agreed to distribute 20 questionnaires to young females presenting with symptoms of an uncomplicated UTI. Patients excluded from the study included those pregnant; breast feeding; recently prescribed antibiotics; recurrent UTIs.

Results

Of the planned 480 questionnaires, only 89 (18.5%) were given out, which limits the value of any findings. Patient response was, however, very high with 80 (90%) questionnaires returned.

The antibiotic policy recommends **trimethoprim** as first line treatment. Antibiotics used in this study are shown in the following graph:

Published by the Communicable Disease Team
Grampian Health Board
Foresterhill, Westburn Road,
Aberdeen AB25 2XH - Tel 01224 404008



This represents **61% adherence** to the recommendations of the policy.

Factors affecting selection of antibiotic were identified in 22 patients. Several of these would contraindicate trimethoprim including past adverse drug reaction to co-trimoxazole, trying to conceive and hence the level of adherence is potentially much higher.

The most common duration of therapy was 5 days (44%), with a range of 3 to 7 days. More than 90% of patient prescribed trimethoprim reported no or mild symptoms following treatment and only 2 patients returned to the GP.

At a cost of 20p for 3 days and 34p for 5 days of trimethoprim, **this appears to be very cost-effective.**

Microbiological Sampling

Urine samples were cultured for 37 (42%) patients. Of these 37, 8 patients had moved practices and the report had not been filed in the notes of one further patient. Of the remaining patients, sensitivity reports indicated the following:

* no growth for 11 patients.
* *E. Coli* was the most common infecting organism, being the sole infecting organism in 9 patients and along with *E. faecalis* in 1 patient.
* other infecting organism were *S. Saprophyticus* (2 patients) and *Coliform* (5 patients).
* 5 instances of trimethoprim resistance were identified yet only 1 patient returned with symptoms. Sensitivity reports rarely resulted in a change in therapy.

Derek C Stewart
Lecturer in Clinical Pharmacy
The Robert Gordon University
School of Pharmacy -Faculty of Health and Food
Schoolhill, Aberdeen Tel: 01224 262000

Appendix 11

Data collection form - Ulcer healing agents
Peterculter Health Centre

Patient's name _____

Address/ _____

Tel no. _____

_____

Date of birth _____ Unit number _____

GP responsible _____

Current drug therapy _____
(include details of _____
date initiated, dose, _____
likely duration) _____
_____
_____
_____
_____
_____
_____
_____

Disease states _____
_____
_____
_____
_____
_____
_____
_____
_____
_____

Allergies/ADR _____

Relevant biochemistry/haematology _____
_____
_____

History of ulcer healing agent

Current ulcer healing agent prescribed _____

Commenced by _____

Date commended _____

Reason commenced _____

Investigations performed _____

Results _____

Complications of peptic disease eg bleed, stricture _____

_____

Comments on review _____

_____

_____

_____

_____

_____

_____

_____

_____

_____

Previous ulcer healing agents prescribed (include details of why commenced, investigations and results, when and why therapy stopped or altered.)

_____

_____

_____

_____

_____

_____

_____

_____

_____

Other relevant data

_____

_____

Appendix 12

Dear _____

I am a lecturer at the School of Pharmacy, The Robert Gordon University, Aberdeen. I am carrying out a study with the doctors at the Peterculter practice. Many patients are prescribed medicines such as _____ and we are interested to find out how well these medicines work.

From the computer at the practice, we have found that you get prescriptions for _____. As part of the study, I would like to come and interview you at home. This interview will last for about 45 minutes and will ask about how well this medicine works, any side effects that you think you might get from it, and whether you think that you still need to take it.

Please do not worry
All information collected will be treated in the strictest confidence. There is no need for you to take part in the study if you do not want to and you can pull out at any time but I will very grateful if you agree to take part. I will telephone you in the next few days to find out if you agree to be interviewed and if you do, we will arrange a suitable time for the interview.

Thank you very much for your help. I look forward to meeting you, if you decide to take part.

Yours sincerely

Derek C Stewart

Appendix 13

CONSENT FORM

Consent by patients to participate in the study on the effect of various types of stomach medicines.

Name of patient .....

Principal Investigator: Derek Stewart

I have read the information leaflet, which was previously sent to me, and have had the opportunity to discuss the details with Derek Stewart and to ask questions.

I understand that this is part of a research project to study the use of various types of stomach medicines and has been approved by the Joint Ethical Committee of the University of Aberdeen and Grampian Health Board.

I also understand that the doctors at Peterculter Health Centre have agreed that I can participate in the study.

I have agreed to take part in the study as it has been described to me, but I understand that I am completely free to withdraw from the study at any time I wish.

I hereby fully and freely consent to participate in the study which has been fully explained to me.

Signature of patient..... Date.....

I confirm that I have explained to the patient named above the nature and purpose of the study.

Signature of investigator..... Date.....

Appendix 14

Interview Schedule for review of ulcer healing agents

Patient name..... Date of birth.....

Ulcer healing agent being taken .....

How much of the above medicine do you take? .....

How long have you taken this for? .....

Why are you taking this? .....

Do you think you get any side effects from it? .....

Do you take any indigestion remedies? .....

Do tou take any pain killers? .....

Do you smoke? .....

How much alcohol do you drink per week? .....

Have you changed your diet? .....

Symptom Severity

a. Frequency of dyspeptic symptoms

Over the past 6 months, have you experienced dyspeptic symptoms ?

never	0
on only 1 or 2 days	1
on approximately 1 day per month	2
on approximately 1 day per week	3
on approximately 50% of days	4
on most days	5

b. Effect on normal activities

Does the dyspepsia interfere with normal activities such as eating, sleeping or socialising?

never	0
sometimes	1
regularly	2

c. Time off work

How many days have you lost off work due to your dyspepsia in the past six months ?

none	0
1-7 days	1
more than 7 days	2

d. Consultation with medical profession

How often have you attended a doctor due to dyspepsia in the past six months ?

none	0
once	1
twice or more	2

e. GP visits to patient's home

How often have you called your GP to visit you at home because of your dyspepsia in the last six months ?

none	0
once	1
twice or more	2

f. Tests for dyspepsia

How many tests have you had for your dyspepsia in the past six months ?

none	0
one	1
two or more	2

g. Treatment for dyspepsia

1. Over the last six months, how frequently have you used medicines for your dyspepsia which you have obtained by yourself ?

never	0
less than once per week	1
more than once per week	2

2. Over the last six months, for how long have you used medicines for your dyspepsia which were prescribed by a doctor ?

never	0
for 1 month or less	1
for 1-3 months	2
for more than 3 months	3

SF-36

1. In general, would you say your health is :

excellent	1
very good	2
good	3
fair	4
poor	5

2. Compared to one year ago, how would you rate your health in general now ?

much better now than one year ago	1
somewhat better now than one year ago	2
about the same as one year ago	3
somewhat worse than one year ago	4
much worse now than one year ago	5

3. The following items are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much ?

ACTIVITIES	Yes, limited a lot	Yes, limited a little	No, not limited at all
a. Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports	1	2	3
b. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	1	2	3
c. Lifting or carrying groceries	1	2	3
d. Climbing several flights of stairs	1	2	3
e. Climbing one flight of stairs	1	2	3
f. Bending, kneeling or stooping	1	2	3
g. Walking more than a mile	1	2	3
h. Walking half a mile	1	2	3
i. Walking one hundred yards	1	2	3
j. Bathing or dressing yourself	1	2	3

4. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health ?

	YES	NO
a. Cut down on the amount of time you spent on work or other activities	1	2
b. Accomplished less than you would like	1	2
c. Were limited in the kind of work or other activities	1	2
d. Had difficulty performing the work or other activities (for example, it took extra effort)	1	2

5. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious) ?

	YES	NO
a. Cut down on the amount of time you spent on work or other activities	1	2
b. Accomplished less than you would like	1	2
c. Didn't do work or other activities as carefully as usual	1	2

6. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours, or groups ?

Not at all	1
Slightly	2
Moderately	3
Quite a bit	4
Extremely	5

7. How much bodily pain have you had during the past 4 weeks ?

None	1
Very mild	2
Mild	3
Moderate	4
Severe	5
Very severe	6

8. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework) ?

Not at all	1
A little bit	2
Moderately	3
Quite a bit	4
Extremely	5

9. These questions are about how you feel and how things have been during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling.
How much of the time during the past 4 weeks

	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
a. Did you feel full of life	1	2	3	4	5	6
b. Have you been a very nervous person	1	2	3	4	5	6
c. Have you felt so down in the dumps that nothing could cheer you up	1	2	3	4	5	6
d. Have you felt calm and peaceful	1	2	3	4	5	6
e. Did you have a lot of energy	1	2	3	4	5	6
f. Have you felt downhearted and low	1	2	3	4	5	6
g. Did you feel worn out	1	2	3	4	5	6
h. Have you been a happy person	1	2	3	4	5	6
I. Did you feel tired	1	2	3	4	5	6

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives etc.) ?

All of the time	1
Most of the time	2
Some of the time	3
A little of the time	4
None of the time	5

11. How TRUE or FALSE is each of the following statements for you ?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a. I seem to get ill more easily than other people	1	2	3	4	5
b. I am as healthy as anybody I know	1	2	3	4	5
c. I expect my health to get worse	1	2	3	4	5
d. My health is excellent	1	2	3	4	5

Appendix 15

PETERCULTER HEALTH CENTRE

EVALUATION OF ULCER HEALING AGENTS

Name

Usual GP

Address

Date of Birth

Date of Interview

Findings on Interview

Symptom score (range 0 to 20. 0 indicates best control of symptoms)

Options for therapy

1.

2.

Signature

Date

Action taken

Signature

Date

Appendix 16

Helicobacter pylori Eradication Information

Your doctor has prescribed medication which may reduce your need to take medicines such as Zantac, ranitidine or cimetidine.

Please read the following before you start to take this medication.

What is Helicobacter pylori ? This is a bacterium that is found in the stomach and has been shown to cause ulcers to form.

How can I get rid of it ?

A combination of antibiotics and a medicine to heal ulcers taken for a short period of time can kill these bacteria in most people.

You **must** make sure that you take the medicine as prescribed for the full course or it may not be effective.

If you miss even a few doses or stop the medicine too soon the bacteria may not be completely killed and your ulcer may come back.

Once you have killed the Helicobacter pylori, you will no longer need to take your ulcer healing medicine and your ulcer is less likely to come back.

Will I have any side effects ?

A few people will suffer from headache, nausea, sickness or diarrhoea. You may also notice a metallic taste. These are usually mild and last only a few days.

Try very hard to put up with these side effects for the full course.

If you are worried about any of these side effects, speak to your doctor or pharmacist.

Appendix 17

INTERIM FOLLOW UP FOR ULCER HEALING AGENTS

Name

Address

Date of Birth

Changes to drug therapy since 1.96

GP/Hospital Consultations since 1.96

Appendix 18

Interview Schedule for review of ulcer healing agents

Patient name..... Date of birth.....
Previous ulcer healing therapy.....
Change in therapy.....
Date of change.....
How much of the above medicine do you take ?.....
Have you noticed any side-effects?.....
Do you take any indigestion remedies ?.....

Symptom Severity

a. Frequency of dyspeptic symptoms

Over the past 6 months, have you experienced dyspeptic symptoms ?

never	0
on only 1 or 2 days	1
on approximately 1 day per month	2
on approximately 1 day per week	3
on approximately 50% of days	4
on most days	5

b. Effect on normal activities

Does the dyspepsia interfere with normal activities such as eating, sleeping or socialising ?

never	0
sometimes	1
regularly	2

c. Time off work

How many days have you lost off work due to your dyspepsia in the past six months ?

none	0
1-7 days	1
more than 7 days	2

d. Consultation with medical profession

How often have you attended a doctor due to dyspepsia in the past six months ?

none	0
once	1
twice or more	2

e. GP visits to patient's home

How often have you called your GP to visit you at home because of your dyspepsia in the last six months ?

none	0
once	1
twice or more	2

f. Tests for dyspepsia

How many tests have you had for your dyspepsia in the past six months ?

none	0
one	1
two or more	2

g. Treatment for dyspepsia

1. Over the last six months, how frequently have you used medicines for your dyspepsia which you have obtained by yourself ?

never	0
less than once per week	1
more than once per week	2

2. Over the last six months, for how long have you used medicines for your dyspepsia which were prescribed by a doctor ?

never	0
for 1 month or less	1
for 1-3 months	2
for more than 3 months	3

SF-36

1. In general, would you say your health is :

excellent	1
very good	2
good	3
fair	4
poor	5

2. Compared to one year ago, how would you rate your health in general now ?

much better now than one year ago	1
somewhat better now than one year ago	2
about the same as one year ago	3
somewhat worse than one year ago	4
much worse now than one year ago	5

3. The following items are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much ?

ACTIVITIES	Yes, limited a lot	Yes, limited a little	No, not limited at all
a. Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports	1	2	3
b. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	1	2	3
c. Lifting or carrying groceries	1	2	3
d. Climbing several flights of stairs	1	2	3
e. Climbing one flight of stairs	1	2	3
f. Bending, kneeling or stooping	1	2	3
g. Walking more than a mile	1	2	3
h. Walking half a mile	1	2	3
i. Walking one hundred yards	1	2	3
j. Bathing or dressing yourself	1	2	3

4. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health ?

	YES	NO
a. Cut down on the amount of time you spent on work or other activities	1	2
b. Accomplished less than you would like	1	2
c. Were limited in the kind of work or other activities	1	2
d. Had difficulty performing the work or other activities (for example, it took extra effort)	1	2

5. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious) ?

	YES	NO
a. Cut down on the amount of time you spent on work or other activities	1	2
b. Accomplished less than you would like	1	2
c. Didn't do work or other activities as carefully as usual	1	2

6. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours, or groups ?

Not at all	1
Slightly	2
Moderately	3
Quite a bit	4
Extremely	5

7. How much bodily pain have you had during the past 4 weeks ?

None	1
Very mild	2
Mild	3
Moderate	4
Severe	5
Very severe	6

8. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework) ?

Not at all	1
A little bit	2
Moderately	3
Quite a bit	4
Extremely	5

9. These questions are about how you feel and how things have been during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling.
How much of the time during the past 4 weeks

	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
a. Did you feel full of life	1	2	3	4	5	6
b. Have you been a very nervous person	1	2	3	4	5	6
c. Have you felt so down in the dumps that nothing could cheer you up	1	2	3	4	5	6
d. Have you felt calm and peaceful	1	2	3	4	5	6
e. Did you have a lot of energy	1	2	3	4	5	6
f. Have you felt downhearted and low	1	2	3	4	5	6
g. Did you feel worn out	1	2	3	4	5	6
h. Have you been a happy person	1	2	3	4	5	6
i. Did you feel tired	1	2	3	4	5	6

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives etc.) ?

All of the time	1
Most of the time	2
Some of the time	3
A little of the time	4
None of the time	5

11. How TRUE or FALSE is each of the following statements for you ?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a. I seem to get ill more easily than other people	1	2	3	4	5
b. I am as healthy as anybody I know	1	2	3	4	5
c. I expect my health to get worse	1	2	3	4	5
d. My health is excellent	1	2	3	4	5

Appendix 19

DATA COLLECTION FORM - PERIPHERAL VASODILATORS

Name	Address	D. O. B.	Telephone no.

Past Medical History (indicate if active, inactive, with dates)	Current Drug Therapy

Weight	Smokes	Relevant Biochemistry	Allergies/ ADRs
Height	Y		
BMI	N		

Relevant Past Drug Therapy

Vasodilator Prescribed	Dose	Date Initiated	Initiated By	Comments on Review

Duration of Continuous Vasodilator Therapy

Appendix 20

Dear

We are carrying out a review of all patients prescribed medicines such as .....

Derek Stewart, who is a pharmacist, is helping us with this. He would like to come and speak to you about this medicine and how well it works. This will take place in your own home and will only last for about 30 minutes.

We would be very grateful if you could make time to see him and he will telephone you in the next few days to arrange a suitable time.

Yours sincerely

Dr

Appendix 21

PATIENT CONSENT FORM

Name of patient .....

Principal Investigator: Derek Stewart

I have read the information leaflet on the above study and have had the opportunity to discuss the details with Derek Stewart and to ask questions.

I understand that this is part of a research project to study the use of medicines such as ..... and has been approved by the Joint Ethical Committee of the University of Aberdeen and Grampian Health Board.

I also understand that my doctor has agreed that I can participate in the study.

I have agreed to take part in the study as it has been described to me, but I understand that I am completely free to withdraw from the study at any time I wish.

I hereby fully and freely consent to participate in the study which has been fully explained to me.

Signature of patient .....
Date .....

I confirm that I have explained to the patient named above the nature and purpose of the study.

Signature of investigator .....
Date .....

Appendix 22

PATIENT INFORMATION LEAFLET

Many patients are prescribed medicines such as .....

This review will look at the patients prescribed these medicines. To do this, I need to talk to these patients. This will involve one or perhaps two interviews, lasting about 30 minutes. During this interview, I will ask questions about:

- What you take this medicine for
- If you get any side effects from it
- How well this medicine works
- Your health in general

After the interview, if it seems that you are not getting the best from this medicine or that you no longer need to take it, your doctor may alter things. I would then like to come back to find out how the change has affected you.

Please do not worry. Everything that you tell me will be treated in the strictest confidence.

Appendix 23

Name _____ Date of Birth _____

Address _____

Peripheral Vasodilator Prescribed _____

How many of the above do you take per day ? _____

What are you taking this medicine for ? _____

How long have you been taking this medicine ? _____

Do you think that you get any side-effects ? _____

Do you smoke ? _____ If yes, how much per day _____

WALKING IMPAIRMENT QUESTIONNAIRE

A. WALKING DISTANCE

For each of the following distances, tell me the degree of difficulty that best describes how hard it was for you to walk without stopping to rest.

During the past month, how much physical difficulty did you have

	None	Some	Much	Did not do
1. Walking indoors, such as around your home	3	2	1	0
2. Walking 50 ft	3	2	1	0
3. Walking 150 ft	3	2	1	0
4. Walking 300 ft	3	2	1	0
5. Walking 600 ft	3	2	1	0
6. Walking 900 ft	3	2	1	0
7. Walking 1500 ft	3	2	1	0

B. WALKING SPEED

These questions refer to how fast you were able to walk 300 ft. Please tell me the degree of difficulty required for you to walk at each of these speeds without stopping to rest.

During the past month how much physical difficulty did you have

	None	Some	Much	Did not do
1. Walking 300 ft slowly	3	2	1	0
2. Walking 300 ft at average speed	3	2	1	0
3. Walking 300 ft quickly	3	2	1	0
4. Running or jogging 300 ft	3	2	1	0

C. WALKING IMPAIRMENT

These questions ask about the reasons why you had difficulty walking. I would like to know how much difficulty you had walking because of each of these problems. By difficulty, we mean how hard it was or how much physical effort it took to walk because of each of these problems. For each reason tell me which best describes your degree of difficulty.

During the past month how much difficulty walking did you have because of

	None	Slight	Some	Much	Very
1. Pain or aching in your calves	4	3	2	1	0
2. Pain or aching in your thighs	4	3	2	1	0
3. Pain, stiffness, or aching in you joints (knees or hips)	4	3	2	1	0
4. Pain or discomfort in your chest	4	3	2	1	0
5. Weakness in one or both of your legs	4	3	2	1	0
6. Shortness of breath	4	3	2	1	0
7. Heart palpitations	4	3	2	1	0
8. Other problems	4	3	2	1	0

If there are other problems, please describe these to me.

SF-36

1. In general, would you say your health is :

excellent	1
very good	2
good	3
fair	4
poor	5

2. Compared to one year ago, how would you rate your health in general now ?

much better now than one year ago	1
somewhat better now than one year ago	2
about the same as one year ago	3
somewhat worse than one year ago	4
much worse now than one year ago	5

3. The following items are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much ?

ACTIVITIES	Yes, limited a lot	Yes, limited a little	No, not limited at all
a. Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports	1	2	3
b. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	1	2	3
c. Lifting or carrying groceries	1	2	3
d. Climbing several flights of stairs	1	2	3
e. Climbing one flight of stairs	1	2	3
f. Bending, kneeling or stooping	1	2	3
g. Walking more than a mile	1	2	3
h. Walking half a mile	1	2	3
i. Walking one hundred yards	1	2	3
j. Bathing or dressing yourself	1	2	3

4. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health ?

	YES	NO
a. Cut down on the amount of time you spent on work or other activities	1	2
b. Accomplished less than you would like	1	2
c. Were limited in the kind of work or other activities	1	2
d. Had difficulty performing the work or other activities (for example, it took extra effort)	1	2

5. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious) ?

	YES	NO
a. Cut down on the amount of time you spent on work or other activities	1	2
b. Accomplished less than you would like	1	2
c. Didn't do work or other activities as carefully as usual	1	2

6. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours, or groups ?

Not at all	1
Slightly	2
Moderately	3
Quite a bit	4
Extremely	5

7. How much bodily pain have you had during the past 4 weeks ?

None	1
Very mild	2
Mild	3
Moderate	4
Severe	5
Very severe	6

8. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework) ?

Not at all	1
A little bit	2
Moderately	3
Quite a bit	4
Extremely	5

9. These questions are about how you feel and how things have been during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling.
How much of the time during the past 4 weeks

	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
a. Did you feel full of life	1	2	3	4	5	6
b. Have you been a very nervous person	1	2	3	4	5	6
c. Have you felt so down in the dumps that nothing could cheer you up	1	2	3	4	5	6
d. Have you felt calm and peaceful	1	2	3	4	5	6
e. Did you have a lot of energy	1	2	3	4	5	6
f. Have you felt downhearted and low	1	2	3	4	5	6
g. Did you feel worn out	1	2	3	4	5	6
h. Have you been a happy person	1	2	3	4	5	6
I. Did you feel tired	1	2	3	4	5	6

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives etc.) ?

All of the time	1
Most of the time	2
Some of the time	3
A little of the time	4
None of the time	5

11. How TRUE or FALSE is each of the following statements for you ?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a. I seem to get ill more easily than other people	1	2	3	4	5
b. I am as healthy as anybody I know	1	2	3	4	5
c. I expect my health to get worse	1	2	3	4	5
d. My health is excellent	1	2	3	4	5

Which doctor do you usually see ?

Appendix 24

Name:
Address:

Date of Birth:
Usual GP:

Date of Interview:
Peripheral vasodilator therapy:
Indication, according to patient:

Walking impairment score (due to pain or aching in calves):
(range 0-100%. 0 indicates total impairment)

Walking distance score:
(range 0-100%. 100% indicates no problems in walking distances up to 500 yards)

Walking speed score:
(range 0-100%. 100% indicates no problems in walking 100 yards at any speed, including jogging)

Comments:

Quality of Life

SF-36 measures health from the patient's point of view by scoring standardised responses to standardised questions in 9 separate areas.
In each area, **a higher score indicates a better health state.**

Physical Functioning:
(extent to which health limits physical activities)

Role Functioning - Physical:
(extent to which physical health interferes with work or other daily activities)

Bodily Pain:
(Intensity and effect of pain on normal activities)

General Health:

Vitality:

Social Functioning:
(extent to which physical health or emotional problems interfere with normal social activities)

Role Functioning - Emotional:
(extent to which emotional problems interfere with work or other daily activities)

Mental Health:

Reported Health Transition:
(evaluation of current health compared to one year ago)

Appendix 25

Dear

You will recently remember meeting a pharmacist who had a few questions to ask about your ..... tablets.

To allow us to see how much benefit you are still getting from your ..... tablets, we would now like you to stop these for a couple of months. The pharmacist will then arrange to see you again.

We would therefore be grateful if you could stop taking your ..... tablets and you will be reveiwed in due course.

If you have any queries, contact me at the surgery.

Yours sincerely

Dr

Appendix 26

INTERIM FOLLOW UP FOR PERIPHERAL VASODILATORS

Name

Address

Date of Birth

Changes to drug therapy since commencement of study

GP/Hospital Consultations since commencement of study