Health Technology Assessment 2008; Vol. 12: No. 31

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September 2008

Health Technology Assessment
NIHR HTA Programme
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[1]Health Services Research Unit, Health Sciences Building, University of Aberdeen, Foresterhill, Aberdeen AB25 2ZD, UK
[2]Centre for Health Economics, University of York, Heslington, York YO1 5DD, UK
[3]Aberdeen Royal Infirmary, Foresterhill, Aberdeen AB25 1LD, UK
[4]Department of Gastroenterology, Royal Infirmary, Glasgow G4 0SF, UK
[5]Faculty of Medicine, Imperial College, St Mary's Campus, London W2 1PG, UK
[6]IMSCar, University of Wales, Bangor LL57 2AS, UK

*Corresponding author

Declared competing interests of authors: none known

Published September 2008

This report should be referenced as follows:

Grant A, Wileman S, Ramsay C, Bojke L, Epstein D, Sculpher M, *et al*. The effectiveness and cost-effectiveness of minimal access surgery amongst people with gastro-oesophageal reflux disease – a UK collaborative study. The REFLUX trial. *Health Technol Assess* 2008;**12**(31).

Health Technology Assessment is indexed and abstracted in *Index Medicus*/MEDLINE, *Excerpta Medica*/EMBASE, *Science Citation Index Expanded* (*SciSearch*®) and *Current Contents*®/Clinical Medicine.

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The research findings from the HTA Programme directly influence decision-making bodies such as the National Institute for Health and Clinical Excellence (NICE) and the National Screening Committee (NSC). HTA findings also help to improve the quality of clinical practice in the NHS indirectly in that they form a key component of the 'National Knowledge Service'.

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The research reported in this issue of the journal was commissioned by the HTA Programme as project number 97/10/03. The contractual start date was in June 2000. The draft report began editorial review in November 2006 and was accepted for publication in April 2008. As the funder, by devising a commissioning brief, the HTA Programme specified the research question and study design. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

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ISSN 1366-5278

Published by Prepress Projects Ltd, Perth, Scotland (www.prepress-projects.co.uk), on behalf of NCCHTA.

Printed on acid-free paper in the UK by the Charlesworth Group.

Abstract

The effectiveness and cost-effectiveness of minimal access surgery amongst people with gastro-oesophageal reflux disease – a UK collaborative study. The REFLUX trial

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[1]Health Services Research Unit, Health Sciences Building, University of Aberdeen, Foresterhill, Aberdeen AB25 2ZD, UK
[2]Centre for Health Economics, University of York, Heslington, York YO1 5DD, UK
[3]Aberdeen Royal Infirmary, Foresterhill, Aberdeen AB25 1LD, UK
[4]Department of Gastroenterology, Royal Infirmary, Glasgow G4 0SF, UK
[5]Faculty of Medicine, Imperial College, St Mary's Campus, London W2 1PG, UK
[6]IMSCar, University of Wales, Bangor LL57 2AS, UK

*Corresponding author

Objectives: To evaluate the clinical effectiveness, cost-effectiveness and safety of a policy of relatively early laparoscopic surgery compared with continued medical management amongst people with gastro-oesophageal reflux disease (GORD) judged suitable for both policies.
Design: Relative clinical effectiveness was assessed by a randomised trial (with parallel non-randomised preference groups) comparing a laparoscopic surgery-based policy with a continued medical management policy. The economic evaluation compared the cost-effectiveness of the two management policies in order to identify the most efficient provision of future care and describe the resource impact that various policies for fundoplication would have on the NHS.
Setting: A total of 21 hospitals throughout the UK with a local partnership between surgeon(s) and gastroenterologist(s) who shared the secondary care of patients with GORD.
Participants: The 810 participants, who were identified retrospectively or prospectively via their participating clinicians, had both documented evidence of GORD (endoscopy and/or manometry/24-hour pH monitoring) and symptoms for longer than 12 months. In addition, the recruiting clinician(s) was clinically uncertain about which management policy was best.
Intervention: Of the 810 eligible patients who consented to participate, 357 were recruited to the randomised arm of the trial (178 allocated to surgical management, 179 allocated to continued, but optimised, medical management) and 453 recruited to the parallel non-randomised preference arm (261 chose surgical management, 192 chose to continue with best medical management). The type of fundoplication was left to the discretion of the surgeon.
Main outcome measures: Participants completed a baseline REFLUX questionnaire, developed specifically for this study, containing a disease-specific outcome measure, the Short Form with 36 Items (SF-36), the EuroQol-5 Dimensions (EQ-5D) and the Beliefs about Medicines and Surgery questionnaires (BMQ/BSQ). Postal questionnaires were completed at participant-specific time intervals after joining the trial (equivalent to approximately 3 and 12 months after surgery). Intraoperative data were recorded by the surgeons and all other in-hospital data were collected by the research nurse. At the end of the study period, participants completed a discrete choice experiment questionnaire.
Results: The randomised groups were well balanced at entry. Participants had been taking GORD medication for a median of 32 months; the mean age of participants was 46 years and 66% were men. Of 178 randomised to surgery, 111 (62%) actually had fundoplication. There was a mixture of clinical and personal reasons why some patients did not have surgery, sometimes

related to long waiting times. A total or partial wrap procedure was performed depending on surgeon preference. Complications were uncommon and there were no deaths associated with surgery. By the equivalent of 12 months after surgery, 38% in the randomised surgical group (14% amongst those who had surgery) were taking reflux medication compared with 90% in the randomised medical group. There were substantial differences (one-third to one-half standard deviation) favouring the randomised surgical group across the health status measures, the size depending on assumptions about the proportion that actually had fundoplication. These differences were the same or somewhat smaller than differences observed at 3 months. The lower the REFLUX score, the worse the symptoms at trial entry and the larger the benefit observed after surgery. The preference surgical group had the lowest REFLUX scores at baseline. These scores improved substantially after surgery, and by 12 months they were better than those in the preference medical group. The BMQ/BSQ and discrete choice experiment did distinguish the preference groups from each other and from the randomised groups. The latter indicated that the risk of serious complications was the most important single attribute of a treatment option. A within-trial cost-effectiveness analysis suggested that the surgery policy was more costly (mean £2049) but also more effective [+0.088 quality-adjusted life-years (QALYs)]. The estimated incremental cost per QALY was £19,000–£23,000, with a probability between 46% (when 62% received surgery) and 19% (when all received surgery) of cost-effectiveness at a threshold of £20,000 per QALY. Modelling plausible longer-term scenarios (such as lifetime benefit after surgery) indicated a greater likelihood (74%) of cost-effectiveness at a threshold of £20,000, but applying a range of alternative scenarios indicated wide uncertainty. The expected value of perfect information was greatest for longer-term quality of life and proportions of surgical patients requiring medication.

Conclusions: Amongst patients requiring long-term medication to control symptoms of GORD, surgical management significantly increases general and reflux-specific health-related quality of life measures, at least up to 12 months after surgery. Complications of surgery were rare. A surgical policy is, however, more costly than continued medical management. At a threshold of £20,000 per QALY it may well be cost-effective, especially when putative longer-term benefits are taken into account, but this is uncertain. The more troublesome the symptoms, the greater the potential benefit from surgery. Uncertainty about cost-effectiveness would be greatly reduced by more reliable information about relative longer-term costs and benefits of surgical and medical policies. This could be through extended follow-up of the REFLUX trial cohorts or of other cohorts of fundoplication patients.

Trial registration: Current Controlled Trials ISRCTN15517081.

Contents

List of abbreviations

BMQ	Beliefs about Medicines Questionnaire
BSQ	Beliefs about Surgery Questionnaire
CI	confidence interval
DCE	discrete choice experiment
DMC	Data Monitoring Committee
EQ-5D	EuroQol-5 Dimensions
EVPI	expected value of perfect information
GORD	gastro-oesophageal reflux disease
H_2RA	histamine receptor antagonist
HRQoL	health-related quality of life
HSR	Health Services Research
ICER	incremental cost-effectiveness ratio
ITT	intention to treat
IQR	interquartile range
MCS	mental component score
NICE	National Institute for Health and Clinical Excellence
ONS	Office for National Statistics
PCA	principal components analysis
PCS	physical component score
PP	per protocol
PPI	proton pump inhibitor
QALY	quality-adjusted life-year
QoL	quality of life
RCT	randomised controlled trial
RQLS	Reflux quality of life score
SD	standard deviation
SE	standard error
SF-36	Short Form with 36 Items
VAS	visual analogue scale

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS) or it has been used only once or it is a non-standard abbreviation used only in figures/tables/appendices, in which case the abbreviation is defined in the figure legend or in the notes at the end of the table.

Executive summary

Background

The advent of less invasive fundoplication performed laparoscopically offers new opportunities for the management of people with chronic symptoms of gastro-oesophageal reflux disease (GORD).

Objectives

To evaluate the clinical effectiveness, cost-effectiveness and safety of a policy of relatively early laparoscopic surgery compared with continued medical management amongst people with GORD judged suitable for both policies.

Methods

Design

(a) A randomised trial (with parallel non-randomised preference groups) comparing a laparoscopic surgery-based policy with a continued medical management policy to assess their relative clinical effectiveness.
(b) An economic evaluation of laparoscopic surgery for GORD, comparing the cost-effectiveness of the two management policies, to identify the most efficient provision of future care and describe the resource impact that various policies for fundoplication would have on the NHS.

Setting

A total of 21 hospitals throughout the UK with a local partnership between surgeon(s) and gastroenterologist(s) who shared the secondary care of patients with GORD.

Participants

The 810 participants, who were identified retrospectively or prospectively via their participating clinicians, had both documented evidence of GORD (endoscopy and/or manometry/24-hour pH monitoring) and symptoms for longer than 12 months. In addition, the recruiting clinician(s) was clinically uncertain about which management policy was best.

Intervention

Of the 810 eligible patients who consented to participate, 357 were recruited to the randomised arm of the trial (178 allocated to surgical management, 179 allocated to continued, but optimised, medical management) and 453 were recruited to the parallel non-randomised preference arm (261 chose surgical management, 192 chose to continue with best medical management). The type of fundoplication was left to the discretion of the surgeon.

Main outcome measures

Participants completed a baseline questionnaire containing a disease-specific outcome measure (the REFLUX questionnaire, developed specifically for this study), the Short Form with 36 Items (SF-36), the EuroQol-5 Dimensions (EQ-5D) and the Beliefs about Medicines and Surgery questionnaires (BMQ/BSQ). Postal questionnaires were completed at participant-specific time intervals after joining the trial (these were at times equivalent to approximately 3 and 12 months after surgery). Intraoperative data were recorded by the surgeons and all other in-hospital data were collected by local research nurses. At the end of the study period, participants completed a discrete choice experiment questionnaire.

Results

The randomised groups were well balanced at entry. Participants had been taking GORD medication for a median of 32 months; the mean age of participants was 46 years and 66% were men. Of 178 randomised to surgery, 111 (62%) actually had fundoplication. There was a mixture of clinical and personal reasons why some patients did not have surgery, sometimes related to long waiting times. A total or partial wrap procedure was performed, depending on surgeon preference. Complications were uncommon and there were no deaths associated with surgery.

By the equivalent of 12 months after surgery, 38% in the randomised surgical group (14% amongst those who had surgery) were taking reflux medication compared with 90% in the randomised medical group. There were substantial differences [one-third to one-half standard deviation (SD)] favouring the randomised surgical group across the health status measures, the size depending on assumptions about the proportion that actually had fundoplication. These differences were the same or somewhat smaller than differences observed at 3 months. The lower the REFLUX score the worse the symptoms at trial entry and the larger the benefit observed after surgery.

The preference surgical group had the lowest REFLUX scores at baseline. These scores improved substantially after surgery and by 12 months they were better than those in the preference medical group. The BMQ/BSQ and discrete choice experiment did distinguish the preference groups from each other and from the randomised groups. The latter indicated that the risk of serious complications was the most important single attribute of a treatment option.

A within-trial cost-effectiveness analysis suggested that the surgery policy was more costly (mean £2049) but also more effective [+0.088 quality-adjusted life-years (QALYs)]. The estimated incremental cost per QALY was £19,000–£23,000, with a probability between 46% (when 62% received surgery) and 19% (when all received surgery) of cost-effectiveness at a threshold of £20,000 per QALY. Modelling plausible longer-term scenarios (such as lifetime benefit after surgery) indicated a greater likelihood (74%) of cost-effectiveness at a threshold of £20,000, but applying a range of alternative scenarios indicated wide uncertainty. The expected value of perfect information was greatest for longer-term quality of life and proportions of surgical patients requiring medication.

Conclusions

Amongst patients requiring long-term medication to control symptoms of GORD, surgical management significantly increases general and reflux-specific health-related quality of life measures, at least up to 12 months after surgery. Complications of surgery were rare. A surgical policy is, however, more costly than continued medical management. At a threshold of £20,000 per QALY it may well be cost-effective, especially when putative longer-term benefits are taken into account, but this is uncertain.

Implications for health care

Extending the use of laparoscopic fundoplication to people whose GORD symptoms require long-term medication would provide health gain. However, it is more costly and so judgements are required about cost-effectiveness. The more troublesome the symptoms, the greater the potential benefit from surgery.

Recommendations for research

Uncertainty about cost-effectiveness would be greatly reduced by more reliable information about relative longer-term costs and benefits of surgical and medical policies. This could be through extended follow-up of the REFLUX trial cohorts or of other cohorts of fundoplication patients.

Trial registration

This trial is registered as ISRCTN15517081.

Chapter 1
Introduction

The NIHR Health Technology Assessment Programme identified the need to evaluate and compare the advent of minimal access surgery for gastro-oesophageal reflux disease (GORD) with medical management. This report describes the work commissioned to address this issue.

Gastro-oesophageal reflux disease

GORD causes some of the most frequently seen symptoms in both primary and secondary care; between 20% and 30% of a 'Western' adult population experience heartburn and/or reflux intermittently.[1–3] There is a clinical spectrum. The majority has only mild symptoms and requires little if any medication. A minority has severe reflux and develops overt complications, despite full medical therapy, and requires surgical intervention. Amongst the remainder, control of symptoms requires regular or continuous medical therapy, and it is from this intermediate group of patients with significant disease that most of the treatment costs for the health service arise.

Treatment of GORD includes a range of options, both medical and surgical. The simplest is self-administered antacids with advice to alter lifestyle factors such as dietary modification, smoking cessation and weight reduction. Many will require acid suppression therapy using either histamine receptor antagonists (H_2RAs) or proton pump inhibitors (PPIs). Initial high-dose therapy may be followed by maintenance treatment using these drugs either intermittently or continuously at reduced doses sufficient to suppress symptoms. The role of surgery has traditionally been confined to the treatment of those with severe symptoms not responding to medication in appropriate dosage and medically fit for surgery. There has, however, been a paradigm shift since the introduction of laparoscopic techniques, with surgery suggested as an alternative treatment to long-term medication. The NHS costs of GORD are considerable. The yearly drug budget for H_2RAs is in excess of £200M and for PPIs it is £300M. Of this budget, most of this prescribing occurs within the primary care setting.[4,5] Once started on PPIs, the majority of patients with significant GORD remain on long-term treatment,[6] and an estimated 4–5 patients (age 18–60) per 10,000 are taking maintenance PPIs for oesophagitis and reflux.

Although PPIs are increasingly assumed to be safe there is a spectrum of short-term symptoms caused by PPIs[7] and there are concerns regarding the impact of long-term use through profound acid suppression. PPIs cause hypergastrinaemia, the long-term significance of which is unknown but potentially important. Conditions associated with chronic hypergastrinaemia and low acid levels have been linked to a long-term increased risk of developing gastric cancer. There is some evidence of the formation of gastric carcinoid tumours in patients taking long-term PPIs[8] and also of vitamin B_{12} deficiency.[9] Adenocarcinoma of the lower oesophagus is a complication of long-term GORD,[10–13] and the incidence of this highly malignant disease has trebled in Western communities in the last 25 years. Whilst the overall incidence of gastric cancer is falling, adenocarcinoma of the gastro-oesophageal junction is now a common cause of death, especially in men. The reasons for this change are probably multifactorial, but there is a clear relationship between *Helicobacter pylori* infection with migration to the gastric fundus and acid suppression, whether naturally occurring or induced by drug therapy.[14,15]

Laparoscopic fundoplication

Interest in surgery as an alternative to long-term medical therapy for GORD has been considerable since the introduction of the minimal access approach in the early 1990s. The operative method, whether using an open or a laparoscopic approach, involves performing a fundoplication by wrapping the fundus of the stomach around the lower oesophagus to create a high-pressure zone, thus reducing gastro-oesophageal reflux. The wrap created can be either complete (360°) or partial. Many operative variants have been described. The commonest operation is a 1-cm complete wrap fashioned over a large bougie, the so-called 'short floppy Nissen'.[16,17] The use of a partial fundoplication has a number of potential advantages but several controlled studies have shown broad equivalence between the two

approaches.[18,19] For the purpose of this study they are therefore regarded as equivalent. Although fundoplication will produce resolution of reflux symptoms in upwards of 90% of patients, there is continuing debate regarding the risks, side effects and durability of surgical therapy.

Medical management

There is no doubt that PPIs, sometimes combined with prokinetic agents, are the most effective treatment for moderate to severe GORD. For the purpose of this study, medical therapy has been taken to mean long-term therapy with PPIs (or H_2RAs if intolerant to PPIs). Although fundoplication is highly effective for controlling GORD, there has been considerable uncertainty whether exchanging symptoms associated with the best medical management of GORD for those of the side effects of surgery is advantageous for the patient and cost-effective for the health-care provider.

The costs of laparoscopic fundoplication appear to be equivalent to those of 2–3 years of maintenance treatment with PPIs, although it is acknowledged that the costs of PPIs are falling.[20] The costs of surgery are related largely to two factors – the incidence of complications/length of hospital stay and the number of patients requiring long-term medical interventions after surgery.

Rationale for the study design

The study described in this report aimed to clarify the place of laparoscopic fundoplication in the belief that decisions about the management of GORD should be based on unbiased, statistically precise comparisons of alternative policies. All patients in this study fulfilled three criteria: they were on long-term acid suppression with PPIs; they had symptoms that were thought to be adequately controlled; and they were suitable in terms of fitness and co-morbidity for either surgical or continuing medical treatment for their GORD.

The most likely sources of bias were in the ways in which the groups being compared were selected, the ways in which their outcomes were assessed, and how the management was actually delivered. This is the basis for using a pragmatic randomised controlled trial design. Random allocation protects against selection bias. Confining the trial to those with no clear treatment preference limits biased patient-centred assessment of outcome, and pragmatic comparison of alternative policies (with intention to treat analysis) avoids bias introduced by non-compliance. This approach has limitations, however, and for this reason we chose to incorporate two parallel, non-randomised preference groups.

Excluding those with a clear preference for one policy or the other limits extrapolation and generalisation. Study of this group may give insights into the reasons for preference and hence give pointers to patient choices after the study.[21] Furthermore, preference may influence outcome and, if so, this may also help when making treatment decisions.[21,22] A third reason for including the parallel, non-randomised preference groups[23] is that the addition of data from the preference groups may reduce imprecision around the estimates from the randomised comparison and this may be particularly useful for rare events, such as complications, that can be confidently ascribed to one or other treatment. (The limitation is that these groups are not derived by random allocation and hence the comparisons are prone to the biases of non-randomised studies.)

The decisions about, and comparisons between, randomised and preference groups require valid measurement of treatment outcome. Although there are a number of quality of life tools available, none was sufficiently specific to assess the spectrum of gastrointestinal symptoms associated with the treatment of GORD, particularly surgery. For this reason the development and validation of a new outcome measure (the REFLUX questionnaire; see Chapter 4) was an essential component of the study.[24]

GORD and its management represent a very significant call on NHS resources. Although clinical effectiveness, acceptability and safety will be important determinants of future policy, the issues of cost and resource use may be over-riding. A prospective, multicentre study[25] found that the total cost for chronic PPI (omeprazole) therapy over 5 years was less than the cost of an open fundoplication; however, two other studies[26,27] found laparoscopic surgery to be less expensive in the long run than daily treatment with 20–40 mg of omeprazole. In one of these studies[27] laparoscopic fundoplication became more cost-effective at 1.4 years post procedure. A Canadian Markov model comparing medical management with laparoscopic fundoplication concluded that laparoscopic

fundoplication became cost-effective at 3.3 years post operation.[28]

A recent UK trial-based economic analysis comparing laparoscopic fundoplication with PPIs using data on 100 GORD patients[29] reported that the incremental cost per point improvement in combined gastrointestinal and psychological well-being scores at 12 months for laparoscopic fundoplication versus PPI was £293, and the incremental cost per additional patient returned to a physiologically normal acid score at 3 months was £5515.[29] There are, however, no existing studies in the UK that have compared laparoscopic fundoplication with PPIs using a generic measure of health, such as quality-adjusted life-years (QALYs). Expressing health benefits in terms of QALYs would provide decision-makers with a basis for comparison with other uses of health-care resources in a range of disease areas and specialties.

There is little doubt that PPIs are the most effective pharmacotherapy[30] for moderate to severe GORD and, for the purpose of this analysis, medical therapy will be taken to mean long-term therapy with PPIs. Although fundoplication is a highly effective therapy for controlling GORD, the question is whether surgery, which can alleviate GORD symptoms but may have unwanted side effects, is advantageous for the patient and cost-effective for the health-care provider.

This is the reason for the economic evaluation. Policy should be guided by both assessment of the relative cost-effectiveness of alternative policies and assessment of the impact that possible policy changes would have for the NHS and for patients with GORD.

Chapter 2
Methods

Study design

The study had two complementary components:

(a) a multicentre, pragmatic randomised trial (with parallel non-randomised preference groups) comparing a laparoscopic surgery-based policy with a continued medical management policy to assess their relative clinical effectiveness
(b) an economic evaluation of laparoscopic surgery for GORD comparing the cost-effectiveness of the two management policies to identify the most efficient provision of future care and describe the resource impact that various policies for fundoplication would have on the NHS.

Patients who consented to participate in the randomised trial were randomly allocated to either laparoscopic surgery or continued medical management. Those patients who had a strong preference for one or other of the two treatment options could be recruited to the preference study. Clinical history at trial entry was recorded on participants' entry forms (see Appendix 1). Participants completed health status questionnaires at the time of recruitment to the study and then at specified times equivalent to 3 and 12 months after surgery (see Appendix 2).

Approval for this study was obtained from the Scottish Multicentre Research Ethics Committee and the appropriate local research ethics committees.

Clinical centres

Clinical centres were based on local partnerships between surgeons with experience of laparoscopic fundoplication and the gastroenterologists with whom they shared the secondary care of patients with GORD. Centres were eligible if they included:

1. a surgeon who had performed at least 50 laparoscopic fundoplication operations
2. one or more gastroenterologists who agreed to collaborate with the surgeon(s) in the trial.

Study population

Potential participants, who were identified both retrospectively and prospectively, were invited to attend an outpatient appointment (see Appendix 3). The participating clinician reviewed each patient's symptoms and treatment regimen and assessed eligibility (see Appendix 4).

Eligible patients were those for whom care had been provided by a participating clinician who was uncertain which management policy (surgical or medical) was better. In addition, patients had to have documented evidence of GORD (based on endoscopy and/or manometry/24-hour pH monitoring) as well as symptoms for more than 12 months requiring maintenance PPI therapy for reasonable symptom control. Patients who were intolerant to PPIs and who therefore required H_2RA therapy to control their symptoms were also included. Patients who were morbidly obese [body mass index (BMI) > 40 kg/m^2], patients with Barrett's oesophagus of more than 3 cm or who had evidence of dysplasia, patients who had a para-oesophageal hernia and patients with an oesophageal stricture were all excluded.

If eligibility was confirmed the patient was invited to see the local research nurse who described the trial, giving supplementary information describing the operation (see Appendix 5) and answering any questions or concerns. This process is summarised in *Figure 1*.

Consent to participate

The randomised trial

Some potential participants made a decision about participation at this appointment. Those who wished to participate in the randomised trial were asked to sign a consent form (see Appendix 6). On this, they confirmed that they had been given the information they required and that the study had been explained to them. They also confirmed that they understood that they would be sent questionnaires at participant-specific time intervals after joining the study (this would be at times equivalent to around 3 months and 12

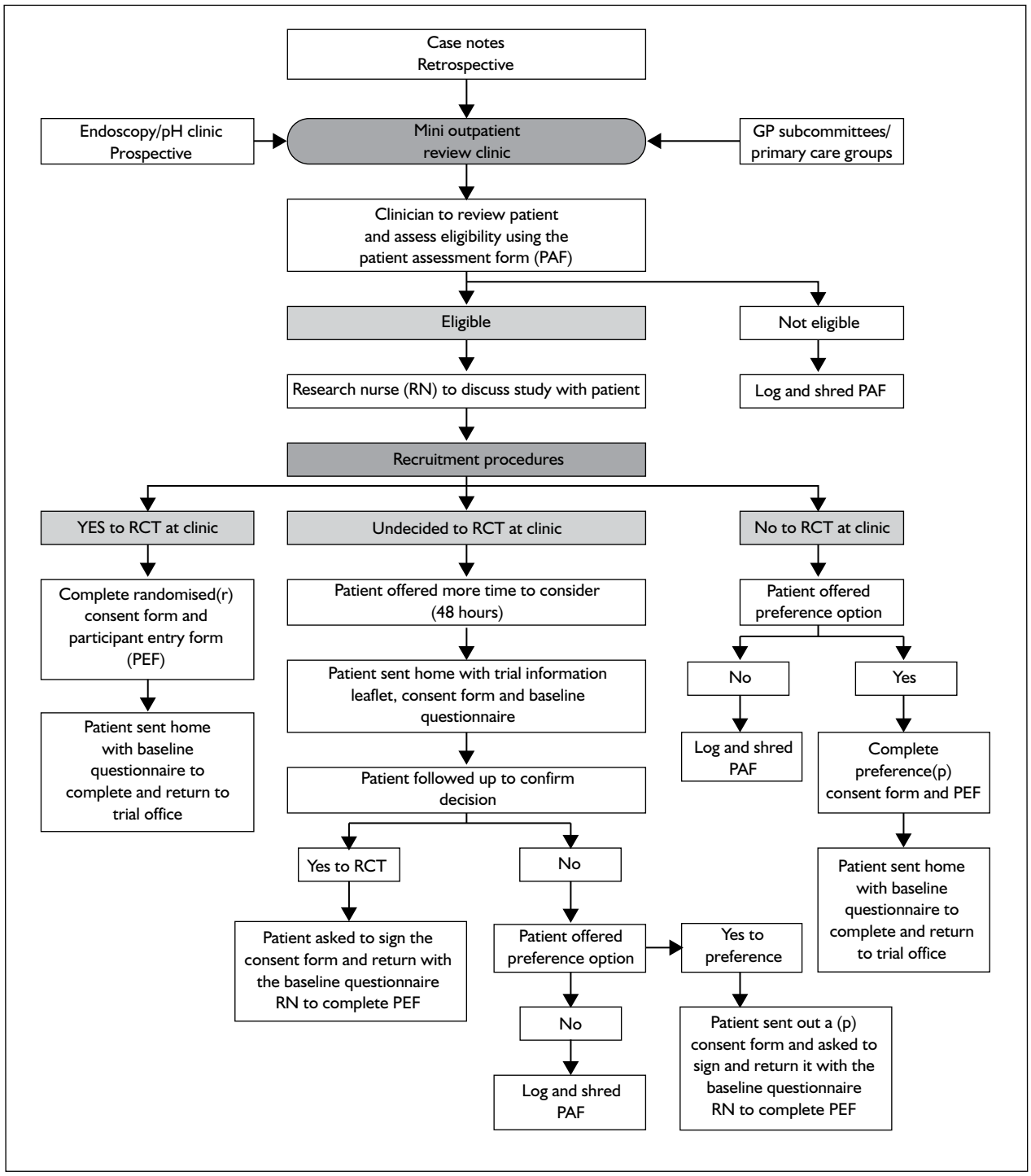

FIGURE 1 *Flow chart describing patient recruitment.*

months after surgery). They were also told that it was anticipated that further follow-up would be performed periodically thereafter for some years.

The preference study

A person who did not want to take part in the randomised trial because of a strong preference for one type of treatment management or the other was asked to take part in the preference arm of the study. Those who wished to participate in the preference study were given a preference information leaflet and asked to sign a consent form (see Appendix 7) confirming their preferred treatment allocation. For logistical reasons and to maintain a balance between the sizes of

randomised and preference groups, the numbers of participants recruited to preference arms was limited to 20 per arm in each centre.

Anyone who was uncertain was given at least 48 hours to consider participation.

Health technology policies being compared

Laparoscopic surgery policy

For those participants allocated or recruited to the surgical arms of the trial, subsequent deferring or declining of surgery, by either the participant or the surgeon, was always an option (i.e. even after trial entry), particularly amongst those recruited by a gastroenterologist and referred to a surgeon for consideration of surgery within the trial. Participants who had not had manometry/pH studies performed underwent these tests before surgery to exclude achalasia.

The surgery was performed either by a surgeon who had undertaken more than 50 laparoscopic fundoplications or by a less experienced surgeon working under the supervision of an experienced surgeon. It was recommended that crural repair be routine and that non-absorbable, synthetic sutures (not silk) be used for the repair. The type of fundoplication used was left to the discretion of the experienced surgeon. For the purposes of the main comparisons, the different surgical techniques for laparoscopic fundoplication were considered as part of a single policy. The study design, however, allowed for indirect comparisons between techniques.

Medical therapy policy

Those allocated to the medical therapy policy had their therapy reviewed and adjusted as necessary by the local gastroenterologist to be 'best medical management'. It was recommended that management conformed to the principles of the Genval Workshop Report.[31] These include stepping down anti-secretory medication in most patients to the lowest dose that maintains acceptable symptom control. However, patients with severe oesophagitis were not managed on the basis of symptoms alone. Although trial participants allocated to medical management were managed in this way, the protocol did include the option of surgery if a clear indication for it subsequently developed.

Study registration (and treatment allocation when randomised)

The entry procedure distinguished between those who agreed to randomisation and those who agreed to participate in the preference part of the study.

Once a participant had agreed to join the trial the research nurse recorded basic identifying and descriptive information on a standard form (see Appendix 1). A letter was sent to each participant, confirming their participation and whether they were taking part in the randomised or preference component of the trial. At this point the participant was also asked to complete a baseline questionnaire (see Appendix 2).

The treatment allocation for participants in the randomised component of the trial was computer generated in the trial office; it was stratified by centre, with balance in respect of other key prognostic variables – age (18–49 years or 50+ years), sex (male or female) and BMI (≤28 or > 29 kg/m^2) – by a process of minimisation. Randomisation was organised centrally at the Health Services Research Unit, Aberdeen, and was independent of all clinical collaborators.

Clinical management

The first 146 randomised participants (70 allocated surgery and 76 allocated medical management) were sent details of their allocation at the same time as the baseline questionnaires. This was changed for subsequent participants at the request of the Data Monitoring Committee (DMC; see page 10) such that the allocation was only generated once completed baseline forms had been returned. This was to ensure that there was no possibility that knowledge of the allocation might influence responses to the baseline questionnaire (as well as ensuring that a completed baseline questionnaire would be received from all randomised participants). A summary of the trial procedure pathways is illustrated in *Figure 2*.

Participants who were allocated to the surgical arm were invited to a consultation with the collaborating surgeon. During this consultation the surgeon confirmed that there were no

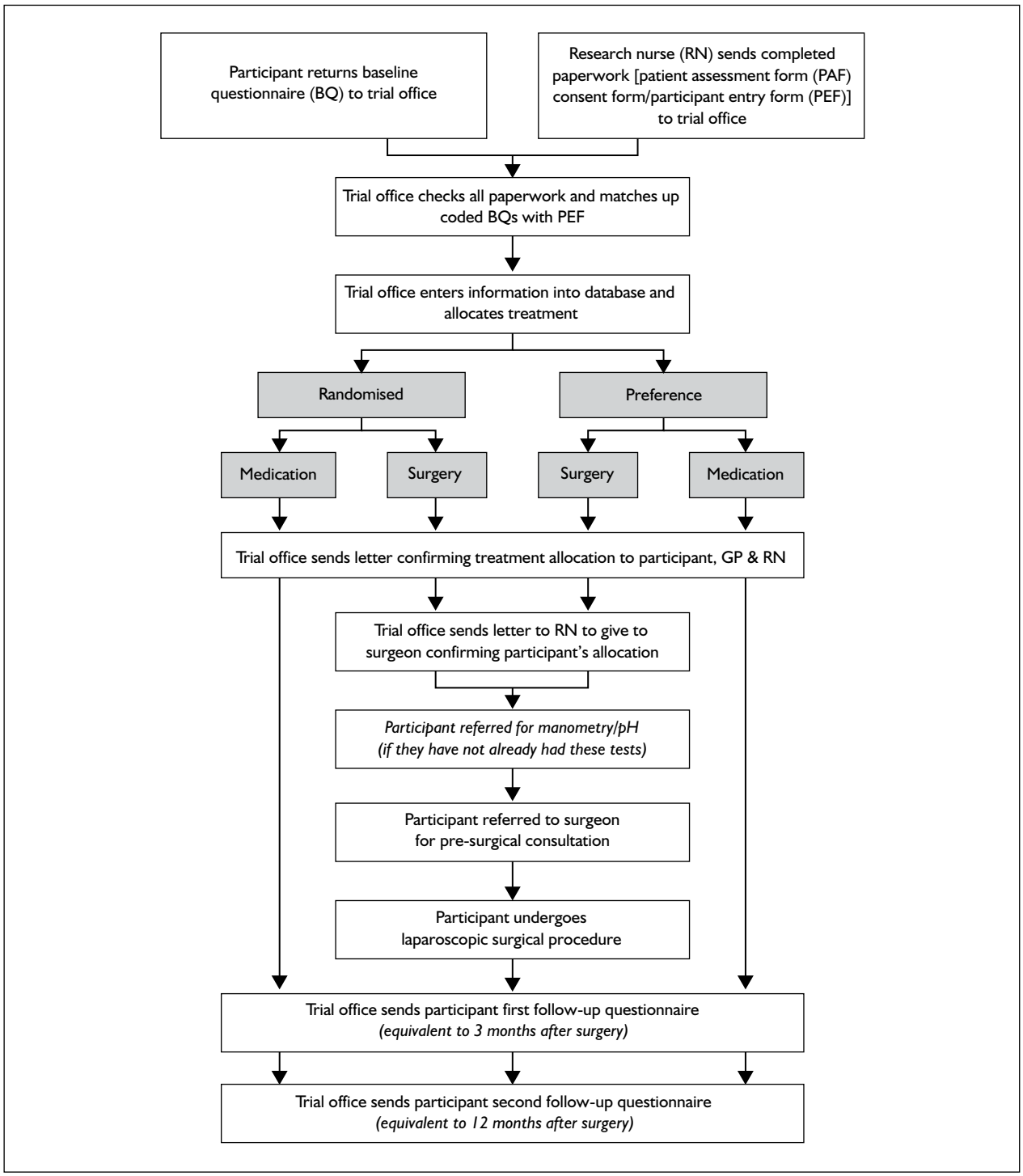

FIGURE 2 *Flow chart showing trial procedures post recruitment.*

contraindications to surgery and discussed the operation in more detail, before arranging an operation date. The intraoperative details were recorded by the surgeon on specially designed study forms (see Appendix 8). All other in-hospital data collection was the responsibility of the local research nurse. In all respects, other than the trial interventions, clinical management was left to the discretion of the clinician responsible for care.

Data collection

Follow-up by postal questionnaire was performed at least twice at participant-specific time intervals after joining the study. This was around 3 and 12 months after surgery or at an equivalent time amongst those who did not have surgery. The latter times were chosen through a process of matching participants in the various groups. Participants

received up to two reminder telephone calls or letters to encourage non-responders to return their postal questionnaires. On occasion, and at the convenience of participants, questionnaires were completed over the phone.

All data were sent to the trial office in Aberdeen for processing and staff in Aberdeen worked closely with participants' local research nurses to secure as complete and accurate data as possible. A random 10% sample of all data was double entered to check accuracy. Extensive range and consistency checks further enhanced the quality of the data.

The principal study outcome measures

The primary outcomes for measuring the differences in effects between medical and surgical treatment were:

- a 'disease-specific' measure incorporating assessment of reflux and other gastrointestinal symptoms and the side effects and complications of both therapies (the REFLUX questionnaire was developed specifically for this study as described in Chapter 4)
- NHS costs including treatments, investigations, consultations and other contacts with the health service.

The secondary outcome measures were:

- health-related quality of life (HRQoL) – EuroQol-5 Dimensions (EQ-5D) and Short Form with 36 Items (SF-36)
- patient costs including loss of earnings, reduction in activities, and the costs of prescriptions and travel for health care
- other serious morbidity, such as operative complications
- mortality.

The instruments for collecting this information are shown in Appendix 2.

Sample size

The original aim was to recruit 600 participants to the randomised trial to give 80% power to identify a difference between the two groups of 0.25 of a standard deviation in respect of the disease-specific instrument and other continuous variables such as EQ-5D or SF-36, using a significance level of 5%. Based on the same arguments it was planned that 300 people would be recruited to each arm of the preference study. The cost savings of a surgical policy largely depend on the number of patients managed surgically who no longer require PPI treatment, and a trial with 300 surgically managed patients would have estimated this proportion to within about 5% with 95% statistical confidence.

However, prompted by a lower rate of recruitment than expected, this target was revised in January 2003 in consultation with the DMC and representatives of the HTA programme. It was agreed that a larger benefit (0.3 of a standard deviation) was clinically plausible based on improvements seen after surgery amongst more severely affected people. This was calculated to require 196 in each group to give 80% power ($p = 0.05$). On this basis it was agreed that recruitment would be extended for an extra year, aiming for this revised sample size.

Statistical analysis

A single principal analysis of the randomised trial was planned when all participants had been followed up for 12 months after surgery (or an equivalent time if managed medically). The primary outcome measure [REFLUX quality of life (QoL) score at 12 months] and secondary outcome measures (REFLUX QoL score at 3 months; SF-36, EQ-5D, REFLUX symptom scores and use of reflux-related drugs at 3 months and 12 months) were analysed using general linear models that always adjusted for the minimisation covariates (age, BMI and sex) and where appropriate (defined by significant at the 5% significance level) also adjusted for baseline score and baseline score by treatment interaction. A secondary, pre-stated, subgroup analysis explored the differential effects of surgeons' preferred operative procedures on the primary outcome measure. All analyses used 95% confidence intervals.

The primary analysis of the randomised trial was by intention to treat. The intention to treat approach gives the least biased estimate of effectiveness of the two interventions. As a secondary comparison we were also interested in estimating the efficacy of the treatment received. Given that a relatively large proportion of the randomised surgical participants did not receive surgery, we used two approaches to estimate the efficacy of the treatment – a per protocol analysis and an adjusted treatment received analysis.[32] In the per protocol analysis, participants who were randomised to surgery and actually received

surgery were compared with participants who were randomised to medication and actually received medication (i.e. the compliers in the surgical group were compared with the compliers in the medical group). In an open trial design the per protocol estimate can have substantial selection bias. One way to estimate the effect when the allocation was complied with while adjusting for possible selection biases is to use a latent variable approach.[33] We used the method of adjusted treatment received as described by Nagelkerke *et al*.[32] The method used a two-stage least squares approach whereby treatment randomised was regressed onto treatment received and the residuals from that model were used as an independent variable in a second model together with the treatment received to estimate the effects on the various primary and secondary outcome measures.

For the preference group, only the primary outcome was analysed statistically. The analysis compared the preference surgical group with the preference medical group and adjusted for the minimisation factors. As described above, for logistical reasons and to maintain balance between the randomised and preference groups, we capped the number of preference participants at 20 per group per centre. The study design was not therefore a true comprehensive cohort. We did consider modelling differences between the randomised and preference groups; however, it is not universally accepted that formal modelling is appropriate in this context. In this case we knew from the randomised arms that there was a strong interaction with baseline reflux QoL, and in addition we also knew that there was a large difference in QoL between preference arms at baseline (and patient demographics). We therefore decided that formal modelling of the arms would not add much to the comparison given the large confounding between preference groups.

Missing items in the health-related outcome measures were treated as per the instructions for that particular measure. No further imputation for missing values was undertaken.

Data monitoring

In March 2003 an independent DMC met for the first time to review the overall conduct of the trial, patient accrual, data collection and an interim analysis of the data. They considered data available to them up to January 2003. At that time 146 participants had been recruited to the randomised trial, 76 allocated to the randomised medical group and 70 allocated to the randomised surgical group. Of the 177 preference participants, 77 chose the medical group and 100 chose the surgical group. On the basis of the data available to them they requested that the treatment allocation procedure be investigated. This led the DMC to instruct that the entry procedures be amended (as described on page 7) so that participants were only randomised once the trial office had received the baseline questionnaire and all of the other baseline paperwork (see Appendices 2, 4, and 6).

The DMC met on two further occasions (July 2003, January 2004) and were happy with the trial progress and interim analyses and saw no reason to recommend any further changes to the protocol.

Chapter 3

Preliminary economic modelling

A preliminary comparison of the cost-effectiveness of pharmacotherapy and surgery (laparoscopic fundoplication) in the treatment of gastro-oesophageal reflux disease

Background

Early in the study we chose to develop a preliminary economic model. Using the best evidence then available we developed a decision analytic model to provide preliminary estimates of costs and outcomes for medical and surgical management prior to the REFLUX trial reporting.[34,35] This chapter describes the preliminary economic model.

Methods

Description of the model

The model was probabilistic and took the perspective of the UK NHS. Health outcomes were expressed in terms of QALYs with a lifetime horizon. The model related to a 45-year-old patient as this is the peak age of presentation with GORD.[36] There proved to be very little difference between men and women; thus, only the results for males are presented here. Costs and QALYs have been discounted at a rate of 3.5% per annum.[37]

The structure of the model can be seen in *Figure 3*. Two strategies were compared: long-term medical management and immediate laparoscopic surgery for GORD. Medical management was assumed to be prescribed for the remainder of a patient's lifetime (30 years for a 45-year-old patient). Surgery was assumed to occur immediately following entry into the surgical arm of the model. The model was also split into short-term and long-term elements. The short-term model related to the period immediately following allocation to surgery or medical management. The longer-term element tracked the patient's progression through a series of states over the remainder of their lifetime. Patients were assumed to stay in a 'wait' state before surgery, during which they would have received a maintenance dose of PPIs. The effects of alternative waiting times for surgery were also explored using alternative scenarios (1 month and 1 year) to represent the possible length of delay. In these cases it was still assumed that surgery following relapse would occur immediately, that is there would be no delay. Monthly cycles represented the monthly transition probabilities between states in the model.

For patients receiving surgery a small mortality risk is associated with laparoscopic fundoplication (approximately 5 per 10,000 patients)[38–47] and this was included in the model. If patients survived surgery the outcomes could be success (cured) or failure (relapse). In addition, patients could relapse from a successful surgery each month. This rate was constant and lasted for only one cycle, during which a patient received a double dose of PPI. A scenario is also presented in which the risk of failure from surgery (and the need for revision) ended at 5 years after initial surgery. Patients could be given a reoperation following surgery failure. If the reoperation failed, surgery was deemed a total failure and patients were considered to have been prescribed long-term medical management with PPIs. For patients offered medical management following initial surgical failure, medical management was deemed a total failure if there was subsequent relapse from medical management, and patients were placed on a double dose of PPIs for the remainder of their lives.

Medical management patients had a risk of relapsing each month. They could be offered surgery or could receive a double dose of PPIs for a cycle, followed by a return to a stable (well) medical management state at a normal dose of PPIs. Patients receiving surgery following relapse on medical management faced the same transition probabilities as surgical patients post surgery. They could also receive one reoperation following surgery failure. Medical management following two operations was deemed a total failure and patients were placed on a double dose of PPIs for the remainder of their lives.

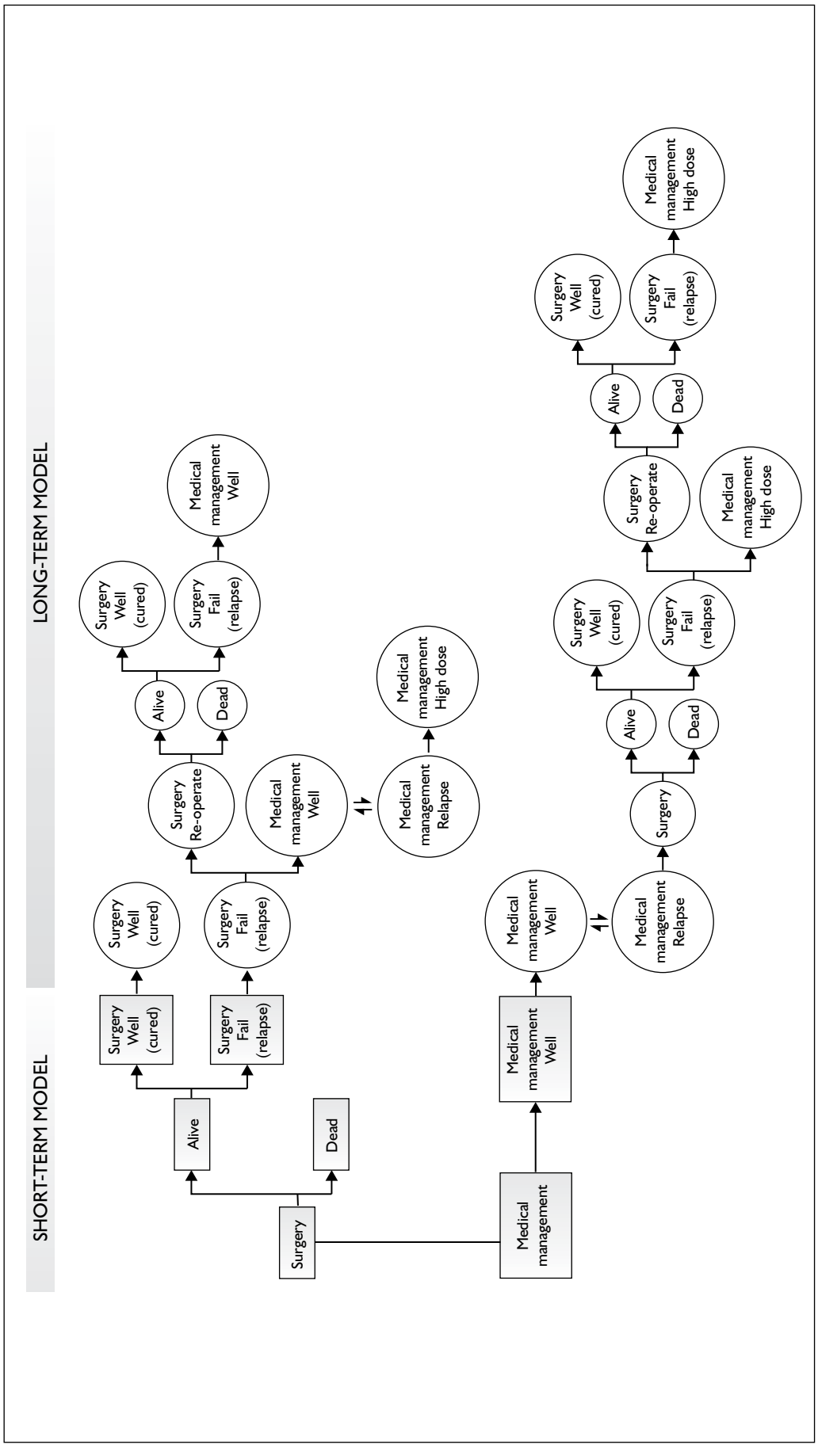

FIGURE 3 *Structure of the preliminary economic model.*

For both surgical and medical management patients there was a monthly risk of all-cause mortality. The age-specific death rate for men aged from 45 to 54 years was obtained from the UK Office of National Statistics (ONS)[48] and used to calculate the probability of death from natural causes from one cycle to the next.

Evidence to populate the model

Literature searches were undertaken to identify studies attempting to measure quality of life (measured by the EQ-5D) in relation to GORD or those providing information on the probability of movement between transition states during treatment. Searches were restricted to MEDLINE, EMBASE and internet sources, such as the Database of Abstracts of Reviews of Effectiveness (DARE). Studies carried out before 1995 were not included as medical and surgical treatments for GORD were expected to have advanced significantly in the past 10 years, particularly in relation to relapse rates from surgery. The search strategies are shown in Appendix 9. This research was conducted in December 2005.

Fixed-effects meta-analysis techniques were used to synthesise data from multiple sources. Further details of the studies identified in the review are available from the author on request. *Table 1* describes the probabilities and distributions of parameters used in the model.

TABLE 1 *Probabilities and distributions of parameters used in the model (probabilities are monthly unless stated otherwise)*

Parameter	Probability	Distribution	Sources
Probability of death from surgery (instantaneous risk)	0.0005	Beta (4–3997)	Multiple studies: Contini *et al*., 2002;[38] Gotley *et al*., 1996;[39] Dallemagne *et al*., 1998;[40] Kiviluoto *et al*., 1998;[41] Booth *et al*., 2002;[42] Landreneau *et al*., 1998;[43] Finley and McKernan, 2001;[44] Pessaux *et al*., 2002;[45] van der Peet *et al*. 1998;[46] Bais *et al*. 2000[47]
Probability of surviving surgery	(1–above)		
Probability of surgery failure	0.0044	Beta (78–1429)	Multiple studies: Contini *et al*., 2002;[38] Gotley *et al*., 1996;[39] Dallemagne *et al*., 1998;[40] Kiviluoto *et al*., 1998;[41] Booth *et al*., 2002;[42] Landreneau *et al*., 1998;[43] Pessaux *et al*., 2002;[45] Watson *et al*., 1995;[49] Lundell *et al*., 2001;[50] Lundell *et al*., 1996;[18] Anvari and Allen, 2003;[51] Ludemann *et al*., 2005;[52] Hunter *et al*., 1999;[53] Graziano *et al*., 2003;[54] Soper and Dunnegan, 1999[55]
Probability of surgery success	(1–above)		
Probability of reoperation after surgery failure (instantaneous risk)	0.1034	Beta (55–477)	Multiple studies: Contini *et al*., 2002;[38] Finley and McKernan, 2001;[44] Pessaux *et al*., 2002;[45] Anvari and Allen, 2003;[51] Soper and Dunnegan, 1999;[55] Eshraghi *et al*., 1998;[56] Bammer *et al*., 2001;[57] Jamieson *et al*.,1994[58]
Probability of medical management after surgery failure	(1–above)		
Probability of a relapse on medical management	0.0256	Beta (78.8–207)	Multiple studies: Lundell *et al*., 2001;[50] Hatlebakk and Berstad, 1997;[59] Festen *et al*.,1999;[60] Bate *et al*., 1995[61]
Probability of stable maintenance on medical management	(1–above)		
Probability of surgery to treat relapse on medical management (instantaneous risk)	0.1133	Beta (23–180)	Multiple studies: Lundell *et al*., 2001;[50] Myrvold *et al*., 2001[62]
Probability of returning to medical management after relapse	(1–above)		

Resource use

Resource use associated with surgery consisted of: (1) procedures for screening for the presence of GORD (endoscopy, manometry pH monitoring, etc); (2) theatre staff; (3) surgical disposables; (4) length of surgery; (5) length of hospital stay; (6) postoperative procedures; and (7) surgical revision or conversion to open fundoplication when needed. The resources used were estimated through a survey of five of the hospitals involved in the REFLUX trial. The lengths of surgery and of hospital stay were taken from the laparoscopic fundoplication baseline data for the REFLUX trial. An additional 15 minutes was added to the duration of operation to derive a total length of surgery, as the time from anaesthesia to recovery recorded in the REFLUX trial did not allow for preparation time.

Typical daily dosages of PPIs and other medicines used in medical maintenance of GORD were also obtained from the REFLUX trial baseline questionnaire using data for the month before study entry. An average daily dose was calculated for each drug and used to derive an average daily cost of medical treatment.

Costs

Table 2 shows the estimated monthly cost of drugs or surgery per patient and their associated distributions, which reflect the heterogeneity between centres and differences in pack sizes for medications.

Costs of all medicines were taken from the *British National Formulary* (2005)[63] and an assumption was made that lowest cost prescribing was used (e.g. generic formulations and tablets). The average daily cost of medical treatment was calculated and the model assumed that, in the event of a relapse on medical treatment, the dose would be doubled for a period of 1 month. Direct surgical treatment costs included the costs of preoperative screening for GORD, surgery and hospital stay. For theatre staff costs, salaries were taken as the mid-point on the relevant scale for each grade or professional.

Costs of perioperative procedures were taken from provider-to-provider tariffs for various hospitals or from published sources,[64,65] and the frequency of such procedures was calculated from the laparoscopic fundoplication baseline data in the REFLUX trial. Costs of surgical revision or conversion to open fundoplication were assumed to be the same as those of the original operation. In the case of open fundoplication, a hospital stay of 6 days was assumed and a cost loading (average cost was inflated to account for the expected number of high-cost rare events) applied based on a meta-analysis of published information.[45,51,58,66,67]

The cost of oesophageal dilatation for dysphagia (swallowing difficulties), the most commonly occurring postoperative corrective surgery encountered, was taken from Leeds General Infirmary and a cost loading was added to the total cost of surgery. Along with death, this was the only complication of surgery considered in these analyses. Costs of endoscopic disposables were obtained from a manufacturer, Ethicon Endo-Surgery. Costs of disposable drapes and gowns came from Kimberly-Clark Health Care, UK. Capital costs associated with standard laparoscopic surgery installations were obtained from Karl Storz GmbH and Ethicon Endo-Surgery. An assumption was made that the service life of a laparoscopic installation was 5 years and the capital costs were amortised (3.5% per annum) over that period. Furthermore, a capital cost for laparoscopic fundoplication was calculated assuming 200 operations were undertaken in that period in each centre.

Appendix 10 summarises the costs associated with surgery. Variation between centres largely reflects differing staff mix and variation in the use of disposables.

Health outcomes

Outcomes were expressed as QALYs with patients' HRQoL measured by the EQ-5D. This is a generic measure of health status in which health

TABLE 2 *Costs used in the preliminary economic model*

Parameter	Cost (£)	Distribution	Sources
Monthly cost of medications	18.25	Gamma (1.77–0.33)	REFLUX study baseline data and *British National Formulary*[63]
Cost of medications during months relapse (maintenance dose doubled)	36.50		
Cost of surgery	2787.39	Gamma (113.60–16.50)	Survey of REFLUX centres (see Appendix 10)

is characterised on five dimensions (mobility, self-care, ability to undertake usual activities, pain, anxiety/depression).[68] Each response to this instrument locates an individual into one of 245 mutually exclusive health states, each of which has previously been valued on the 0 (equivalent to dead) to 1 (equivalent to good health) 'utility' scale based on interviews with a sample of 3395 members of the UK public.[69]

EQ-5D values for patients who were on medical treatment were obtained from the available (as of December 2004) baseline data (surgical and medical management patients) collected in the REFLUX trial. EQ-5D values obtained for the UK general population (population norms) aged from 45 to 54 years were taken from Kind *et al.*[70] and were considered to represent a 'cured' state (successful surgery). HRQoL in the month immediately following laparoscopic fundoplication was taken from EQ-5D values as measured in patients following laparoscopic cholecystectomy.[71] Patients with unresolved symptoms of GORD (relapse) were assigned a utility based on the decrement between stable medical management and reflux symptoms estimated in a published expert opinion (0.53).[72] The utility values used and their sources are summarised in *Table 3*.

Analysis

The model was developed in Excel with the Crystal Ball 'add-on'. Monte Carlo simulation was used to propagate the prior distributions assigned to model inputs and estimate the expected costs and outcomes associated with each alternative therapy; incremental cost-effectiveness ratios (ICER) were calculated. Distributions for parameters were selected on the basis of the nature of the parameter concerned.[73] To conduct the simulations, the distributions reported in *Table 1* were assigned to the model inputs to characterise the current uncertainty surrounding their values. The simulation recalculated the results over 10,000 iterations. For each iteration, the value of each variable was sampled at random from the distributions specified. By repeating the calculations of expected costs and outcomes in this way, distributions of estimates are obtained, which allow estimation of the mean expected costs and QALYs and associated distributions.

The results of the model are presented in two ways. First, mean costs and QALYs for the various comparators are presented and their cost-effectiveness compared, using standard decision rules to estimate ICER as appropriate. Second, given that mean costs and QALYs gained are estimated with uncertainty, the output from the simulations have been used to generate cost-effectiveness acceptability curves. These curves illustrate the probability of surgery being more cost-effective than medical management given a range of values that an NHS decision-maker might attach to an additional QALY. Threshold values of cost-effectiveness ranging from £0 to £100,000 per additional QALY were used in the analysis. This is a Bayesian approach to the presentation of cost effectiveness, although this is not a full Bayesian analysis.[74,75]

The output of these simulations was also used to estimate the expected value of perfect information (EVPI).[76,77] The cost in terms of health benefits and resources forgone if a wrong decision is made can be described using the probability of making an error based on current knowledge and the consequences of a wrong decision. Thus, the expected costs of uncertainty can be interpreted as the EVPI, as perfect information would obviate decision error. The EVPI is, therefore, the maximum that the health-care system should be willing to pay for additional evidence to inform this decision in the future, that is, the maximum expenditure in relevant future research. Per patient EVPI was calculated and, in addition, an analysis of the EVPI associated with particular items of evidence used in the model was also conducted.

TABLE 3 *EQ-5D values, distributions and sources*

State	Utility	Distribution	Sources
QoL on stable medical maintenance	0.72	Gamma (0.02–8.38)	REFLUX study baseline data
QoL during relapse	0.56	Gamma (0.02–5.29)	REFLUX study baseline data; Heudebert *et al.*, 1997[72]
QoL following surgery	0.61	Fixed	Ainslie *et al.*, 2003[71]
QoL in cured post-surgical state	0.84	Gamma (0.25–11.29)	UK male (45–54 years) population norms (Kind *et al.*, 1999[70])

QoL, quality of life.

This can be used to focus research on those elements in the decision for which more precise estimates would be most valuable.[76–78]

Results

Base-case cost-effectiveness

The base-case estimates of costs and QALYs associated with surgery are shown in *Table 4*. Over a lifetime, medical management (£4890) was estimated to cost less than surgery (£5014) but it was associated with fewer QALYs than surgery: 12.36 compared with 13.04.

The lifetime ICER for surgery versus medical management is thus £180. Based on this, as long as decision-makers are willing to pay more than £180 for an additional QALY, surgery would be regarded as the more cost-effective treatment option. However, mean costs and QALYs were estimated with uncertainty. *Figure 4* shows the potential impact of the uncertainty in mean differences (surgery minus medical management) in costs and QALYs gained between the two groups (i.e. it shows mean costs and QALY differences based on the 1000 simulations). *Figure 5* represents this uncertainty in the form of a cost-effectiveness acceptability curve. The probability that surgery is cost-effective at a threshold of cost-effectiveness of £30,000 per QALY is 0.639.

Expected value of perfect information

The per patient EVPI for adults with GORD is illustrated in *Figure 6*. At a cost-effectiveness threshold of £30,000, EVPI is substantial at £15,106. At a threshold of £20,000, the EVPI is £10,081. EVPI for groups of parameters showed that all of the value of further research (£11,346 at a threshold of £30,000 for cost-effectiveness) is associated with the quality of life implications of medical or surgical therapies, indicating that this is where future research should focus.

Alternative model assumptions

Alternative assumptions regarding the model structure were explored, specifically the effect of any delay to receiving surgery (1 month and 1 year) and the risk of relapse from surgery 5 years postoperatively.

Assuming that there is no risk of surgical failure 5 years post operation reduces the total cost of surgery (to £4121) and increases QALYs (to 13.48). Although total costs (£4887) and QALYs (12.38) change for medical management, because of the small number of people receiving surgery following medical management relapse, the effect of this is only minor. Surgery now dominates medical management as it has lower costs and higher QALYs. Decision uncertainty is, however, relatively insensitive to this structural change, with the probability that surgery is cost-effective increased from 0.639 in the base-case model to 0.642 at a threshold of £30,000. As we are somewhat more certain about the decision to recommend surgery as the most cost-effective treatment, per patient EVPI decreases by a small amount from £15,106 in the base-case model to £15,078.

Incorporating any delays to surgery had very little effect on both the costs and the QALYs. This is because time spent in the 'wait' state was assigned a relatively small cost of medical management and the utility of stable management. Decision uncertainty and EVPI was also largely unaffected by delays to surgery.

Discussion

This was the first investigation of the cost-effectiveness of lifelong medical treatment compared with immediate laparoscopic fundoplication for the treatment of GORD. The results of this model suggest that, even when the risk of spontaneous failure of surgery exists for a patient's lifetime, surgery for GORD is more cost-effective than lifelong management with drugs.

TABLE 4 *Cost-effectiveness of surgery versus medical management for the treatment of gastro-oesophageal reflux disease*

	Total costs (£)	Total QALYs	ICER
Surgery	5014.17	13.04	£180.61
Medical management	4890.59	12.36	

ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life-years.

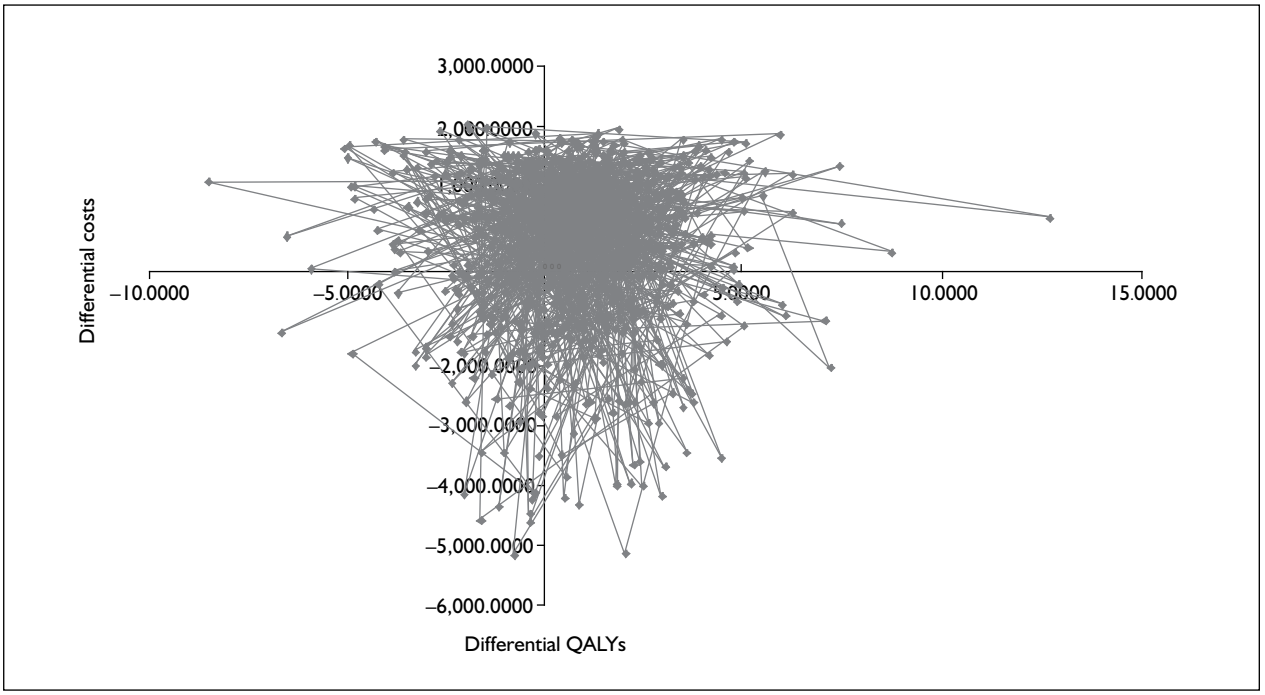

FIGURE 4 *Representation of the uncertainty in differential mean costs and quality-adjusted life-years (QALYs).*

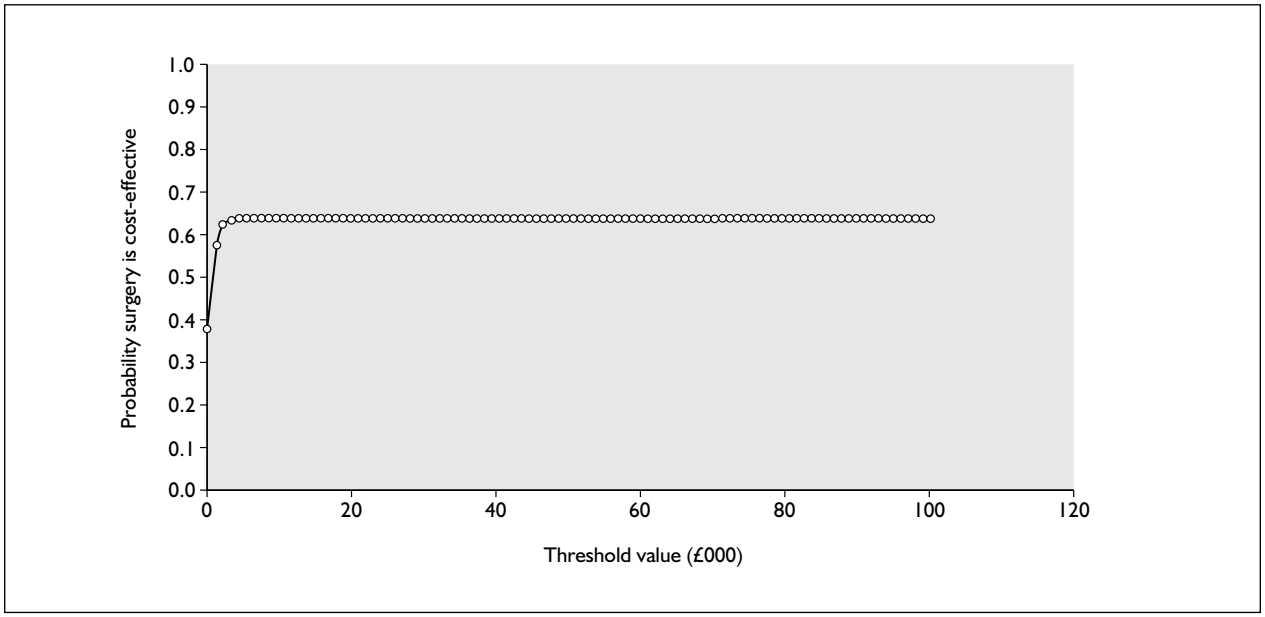

FIGURE 5 *Cost acceptability curve for surgery versus medical management.*

However, the true cost-effectiveness of surgery is uncertain and, at a threshold for cost-effectiveness of £30,000 per additional QALY, the value of information surrounding the decision problem is high. The number of people with GORD suitable for surgery is likely to be sizeable and therefore the EVPI of £15,106 at a threshold of £30,000 per QALY implies that the EVPI will exceed the cost of further investigation. This, in turn, suggests that further research will be potentially cost-effective.

EVPI analysis on groups of parameters suggested that further research should focus on collecting evidence relating to the HRQoL of patients on medical management and following surgery.

It was necessary to make a number of assumptions in the model. First, in the absence of applicable data, it was necessary to simplify the dosing adjustment used to deal with relapse. In clinical practice a more complicated titration of dose

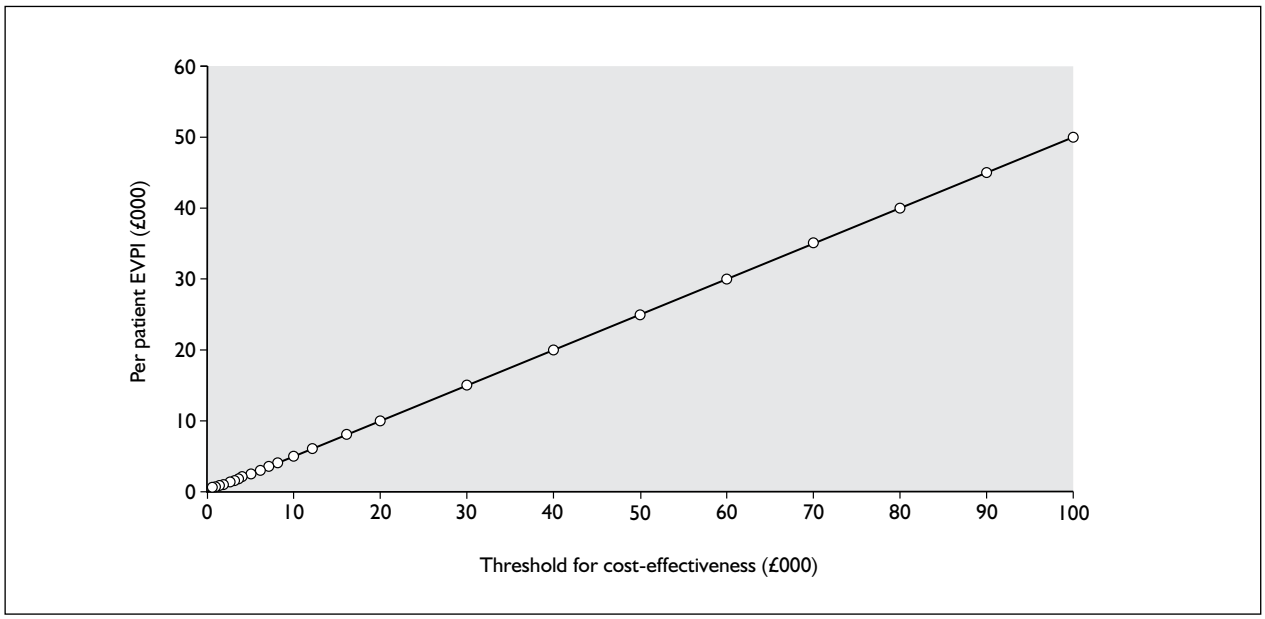

FIGURE 6 *Per patient expected value of perfect information (EVPI).*

and duration of step-up or step-down dosing would be used. The effect of this would probably be that patients in relapse spend more than 1 month on a higher dose (and at higher cost) and simultaneously experience lower HRQoL for longer than modelled here. At present, given that equal consequences of relapse have been applied to those patients relapsing on medical management or surgery, it is unlikely that applying a more complex relapse dosing structure would have a significant effect on the results of the model.

Second, the costs of surgery only partially capture true cost. Surgery may have unwanted side effects or may spontaneously fail at some point in the future. Treatment of side effects or surgical failure has costs both in monetary and quality of life terms. A common side effect, temporary difficulty with swallowing (dysphagia), has been considered in the model and a probabilised cost loading used to incorporate its treatment. However, no disutility of dysphagia, bloating, flatulence or other unwanted side effects following surgery has been included in the model because of a lack of data and consensus on the magnitude of effect. Related to this is the availability of data for other states in the model. In the absence of other suitable data, the utility values used to reflect the post-surgical state were based on patients measured following laparoscopic cholecystectomy,[71] which has some surgical similarities to laparoscopic fundoplication but may not have the same spectrum of postoperative discomfort or complications. The utility value associated with a surgical cure has been taken from UK age-specific population norms.[70] Also, it is unclear to what extent the post-surgical state can be likened to the utility of an average member of the UK population, that is, whether surgery actually generates a cure in utility terms.

Finally, because of the focus on those patients currently maintained on medical management, the analysis reported here did not consider management strategies other than medical management or surgery. In many clinical settings lifestyle management advice is being favoured as a first-line option, with medical management or surgery considered only as second-line therapies in patients who do not respond to lifestyle changes. This may limit the applicability of this model in certain settings.

Despite these necessary assumptions, the model presented here represents the first attempt to generate estimates of cost per QALY for surgical and medical management strategies for the treatment of GORD patients in the UK. The results of the model suggest that, on the basis of current evidence, laparoscopic fundoplication may well represent a cost-effective means of treating GORD rather than lifelong medical management. Coupled with the apparent safety of the surgical procedure (in experienced hands), patients and the health service may benefit from increased substitution of surgery for medical management. What this preliminary analysis confirmed was the need for more robust data, especially in respect of HRQoL, and these data were being generated in the REFLUX trial.

Chapter 4

REFLUX outcome measure

The development of a new measure of quality of life in the management of gastro-oesophageal reflux disease: the REFLUX questionnaire

Introduction

Although several GORD-specific or gastrointestinal-specific symptom scales and quality of life scales have been developed,[79–87] we found that none captures the experience of patients receiving alternative treatments in sufficient detail for evaluating outcomes in the REFLUX trial. Of particular concern was that these measures do not reflect patients' experiences of the side effects of surgery for GORD, which include general gastrointestinal symptoms as well as oesophageal reflux itself.[85] A new condition-specific outcome measure was therefore developed for use within the REFLUX trial. The aim of this measure was not only to assess the symptoms of GORD but also the side effects of both medical and surgical treatment for GORD and the effects that these have on HRQoL. There were two requirements for the new measure: it had to measure HRQoL and not merely symptom experience; and its content had to cover the effects of treatment for GORD as well as the symptoms of GORD. This chapter describes the development and assessment of the new measure.

Method

Questionnaire development

Between May and September 2000, a series of one-to-one interviews and focus groups were conducted with patients in two cities, Leeds and Aberdeen, to identify those themes and issues related to GORD and its treatment that were important to people affected by GORD. In total, 31 people were interviewed, 15 receiving medical treatment and 16 who had received surgery. In addition, two focus groups were conducted, each with six patients, one in Aberdeen and one in Leeds. Both focus groups included only patients who had received surgery for their GORD symptoms, identified via their gastroenterologist or surgeon.

Both the interviews and focus groups followed the same general format. Patients were asked questions about the types and severity of symptoms they experienced, how best to describe their symptoms, whether they felt that their symptoms were best described by their frequency, duration or level of distress, and about the impact that their symptoms had on their daily lives.

All interviews and focus groups were audiotaped and transcribed. These transcripts underwent thematic analysis by three members of the trial team. Emerging themes and issues suggested potential questionnaire items. Whenever possible the language used by patients was used when devising the questionnaire items. The transcripts showed that the frequency of symptoms and their effects on quality of life were the two most commonly reported themes by patients. This led to the development of 31 possible questions.

Piloting

The initial version of the questionnaire (with the 31 items) was piloted on a sample of 21 patients from Aberdeen, some of whom had taken part in the interview phase. The questionnaire was posted out to the patients asking them to complete it. At a later date they were interviewed about its readability and acceptability. Specifically, they were asked about whether they had any problems understanding the items, whether the response categories were appropriate for them and whether they thought that anything was missing from the questionnaire. The questionnaire was modified following the feedback from these interviews. At this stage a small number of items (three) were discarded as unsuitable or potentially ambiguous, others were reworded and three items that were not originally included in the initial version of the questionnaire, but were repeatedly mentioned by the patients and felt to be of importance, were added**.** The new version therefore also had 31 items.

Final questionnaire

The 31 items that were included in the formally evaluated version of the questionnaire were grouped into seven categories (heartburn; acid reflux; wind; eating and swallowing; bowel movements; sleep; and work, physical and social activities) describing symptoms relating to GORD or side effects of treatment (*Table 5*). For each category respondents were asked to show how often they had experienced problems with specified symptoms over the past 2 weeks, followed by how much they felt that those symptoms had affected their quality of life over the past 2 weeks. The symptom items offered five responses, from 'not at all' to 'every day', and the quality of life items offered five responses – 'not at all', 'a little', 'moderately', 'a lot' and 'extremely'. Items in the least clinical of the categories, work, physical and social activities, offered six responses including 'not applicable' (see the REFLUX questionnaire within Appendix 2).

Data

The new measure, along with two generic measures of HRQoL (EQ-5D[88] and SF-36[89]) and information on background, demographics and use of medicine, was included in a postal questionnaire, which was sent to all REFLUX trial participants. Trial participants were sent a questionnaire at baseline after they had agreed to take part in the trial, at first follow-up (3 months after surgery or its equivalent for non-surgical participants) and at second follow-up (12 months after surgery or equivalent). This chapter reports on data received by December 2004. Most of the analysis presented here was performed on the baseline data, but analysis of sensitivity to change also used the first follow-up data.

TABLE 5 *REFLUX categories*

Category	Number of items
Heartburn	3
Acid reflux	6
Wind	5
Eating and swallowing	3
Bowel movements	5
Sleep	4
Work, physical and social activities	5

Analysis

Developing a scoring system

We planned that the new measure would produce two different types of score:

- a REFLUX quality of life score (RQLS) summarising the extent to which respondents' symptoms affect their quality of life, where 0 is the worst quality of life and 100 is the best
- a series of seven REFLUX symptom scores that profile respondents' experiences of these groups of symptoms over the past 2 weeks.

Although it is possible to generate summary scores by merely summing the raw scores on each item, this assumes that all items in the measure are equally important. This disregards the possibility that some items are more important than others and should therefore have a larger emphasis in the final score. We chose to use two distinct methods of weighting the contribution of items to the total score.

The REFLUX questionnaire contains seven quality of life items, each relating to one of its seven categories, that require participants to indicate how much they feel their symptoms on a particular dimension in the past 2 weeks have affected their general quality of life. Weights for the RQLS were estimated by assessing the influence of these items on participants' assessments of their general quality of life. We used the seven baseline quality of life items as independent variables in an ordinary least squares (OLS) regression model with participants' assessments of their general HRQoL, as measured by the EQ-5D visual analogue scale (EQ-5D VAS), as the dependent variable. For modelling purposes we assumed that the data from these items were cardinal. EQ-5D VAS requires respondents to assess their current state of health on a 0–100 visual analogue scale, where 0 represents worst imaginable health and 100 best imaginable health. To remain in the model, regression coefficients did not have to be statistically significant but they did have to have the correct (negative) sign, i.e. a reported detrimental effect on quality of life should be associated with a decrease in EQ-5D VAS score. The resulting coefficients were used as weighting factors to calculate a general quality of life summary score.

In contrast, weights for the REFLUX symptom summary scores were generated by entering the 31 baseline symptom items into a principal components analysis (PCA) with a Varimax rotation. We judged how many components or factors to extract by using a combination of

the Kaiser criterion (include all factors with an eigenvalue greater than 1) and a scree plot of those eigenvalues. The resulting factor loadings were used as the item weights to calculate a number of symptom scores.

Reliability, validity and sensitivity to change

We assessed the reliability of the REFLUX quality of life and symptom scores by internal consistency, as measured by Cronbach's alpha. In contrast, our assessment of the validity and responsiveness or sensitivity to change concentrated on the quality of life score, as this was the main aim of the measure. The validity of the RQLS was assessed by comparing its performance against the SF-36. Sensitivity to change was assessed by the measure's ability to reflect changes in the condition of participants, as assessed by self-reported change in prescribed medication between baseline and first follow-up. Participants were asked to give details of their prescribed medication use (PPIs, H_2RAs and anti-emetics) at baseline and at first follow-up. This information was used to classify whether or not their medication use had changed between these times.

Results

Sample characteristics

Between March 2001 and June 2004 a total of 810 participants had been recruited into the REFLUX trial, of whom 799 had completed and returned their baseline questionnaires. By December 2004 602 participants out of 649 (93%) had returned a first follow-up questionnaire, and 418 out of 447 (94%) a second follow-up questionnaire. At baseline 64% of the sample was male, and the median age at trial entry was 46 years (range 18–74 years).

Scoring

Generating weights for the REFLUX quality of life score

All 727 participants with complete baseline data on the REFLUX quality of life items and EQ-5D VAS were included in the analysis. Although coefficients for three of the seven quality of life items were not statistically significant, we kept them in the regression model for completeness. In contrast, we excluded the wind item from the RQLS model as the coefficient consistently showed the wrong sign and was not statistically significant. In effect, the wind item will receive a weight of zero when calculating the final score. The work, physical and social activities item had the largest coefficient and thus had most effect on the EQ-5D VAS, and the sleep item had the smallest coefficient. The final model coefficients used to calculate the RQLS are given in *Table 6*.

The coefficients from this model were used as weights for calculating the quality of life score by multiplying the response to each quality of life item (coded from 0 'not at all' to 4 'extremely') by the corresponding weight (i.e. the coefficient from *Table 6*) and subtracting these values from the constant term as follows:

> Raw RQLS = 90 – (heartburn quality of life × 1.35) – (acid reflux quality of life × 1.70) – (wind quality of life × 0) – (eating quality of life × 1.10) – (bowel movement quality of life × 1.95) – (sleep quality of life × 0.35) – (activities quality of life × 2.15).

The score was then standardised to a scale from 0 (worst quality of life) to 100 (best quality of life) as follows:

> Standardised RQLS = (raw RQLS – 55.6) × 2.91.

TABLE 6 *Model coefficients used to calculate the REFLUX quality of life score (RQLS)*

REFLUX quality of life item	B	SE	Significance
Heartburn	–1.346	0.81	NS
Acid reflux	–1.700	0.70	< 0.05
Eating and swallowing	–1.103	0.68	NS
Bowel movements	–1.954	0.61	< 0.01
Sleep	–0.351	0.66	NS
Work, physical and social activities	–2.147	0.84	< 0.05
Constant	89.995	1.51	< 0.001

B, beta; NS, not significant; SE, standard error.

Adj $r^2 = 0.22$.

Figure 7 presents the frequency distribution of quality of life scores for patients at baseline. The mean score was 65.0 with a standard deviation of 24.3.

Generating weights for the REFLUX symptom scores

The PCA identified five components that accounted for 57% of the variance in the items (*Table 7*). In general, the component structure reflected the themes identified when the items were developed; however, component 1 grouped together heartburn-like symptoms and sleep disruption into general discomfort (*Table 7*). The first component after rotation explained 19% of the total variance and included seven items with loadings above 0.4. Component 2 explained 12% of the total variance and included six main items. The remaining three components accounted respectively for 10%, 9% and 8% of the total variance. Component loadings were used to construct a profile of five REFLUX symptom scores to summarise an individual's symptom experience. In the first instance we suggested the following labels for these components: 1 = general discomfort; 2 = wind and frequency; 3 = nausea and vomiting; 4 = activity limitation; and 5 = constipation and swallowing.

Each symptom score was calculated by multiplying the response to each of the symptom items in that score (coded from 0 'every day' to 4 'not at all') by the corresponding weight (i.e. the component loading for that item from *Table 7*) and then summing across the items. For the four items in activity limitation we grouped the response codes 'not applicable' and 'no, my symptoms do not affect me' as 4, and recoded the other categories from 0 'I no longer work/perform these activities because of my symptoms' to 3 'my symptoms have affected me but I still work/perform these activities'. Symptom scores were then standardised to a scale from 0 (worst symptom score) to 100 (best symptom score) as follows:

General discomfort = 5.24×[(item A1×0.674) + (item A2×0.643) + (item B1×0.654) + (item D2×0.421) + (item F1×0.777) + (item F2×0.814) + (item F3×0.791)].

Wind and frequency = 6.59×[(item C1×0.738) + (item C2×0.553) + (item C3×0.568) + (item C4×0.515) + (item E1×0.722) + (item E3×0.696)].

Nausea and vomiting = 9.84×[(item B2×0.734) + (item B3×0.556) + (item B4×0.541) + (item B5×0.709)].

Activity limitation = 9.58×[(item G1×0.695) + (item G2×0.571) + (item G3×0.755) + (item G4×0.588)].

Constipation and swallowing = 13.72×[(item D1×0.338) + (item E2×0.839) + (item E4×0.645)].

Table 8 presents the mean symptom scores at baseline. There were pronounced ceiling effects for nausea and vomiting, constipation and swallowing, and activity limitations: 26%, 25% and 17% respectively of the sample had a maximum score of 100. In contrast, wind and frequency showed a more normal distribution.

Both the RQLS and REFLUX symptom scores were calculated only for individuals with complete data.

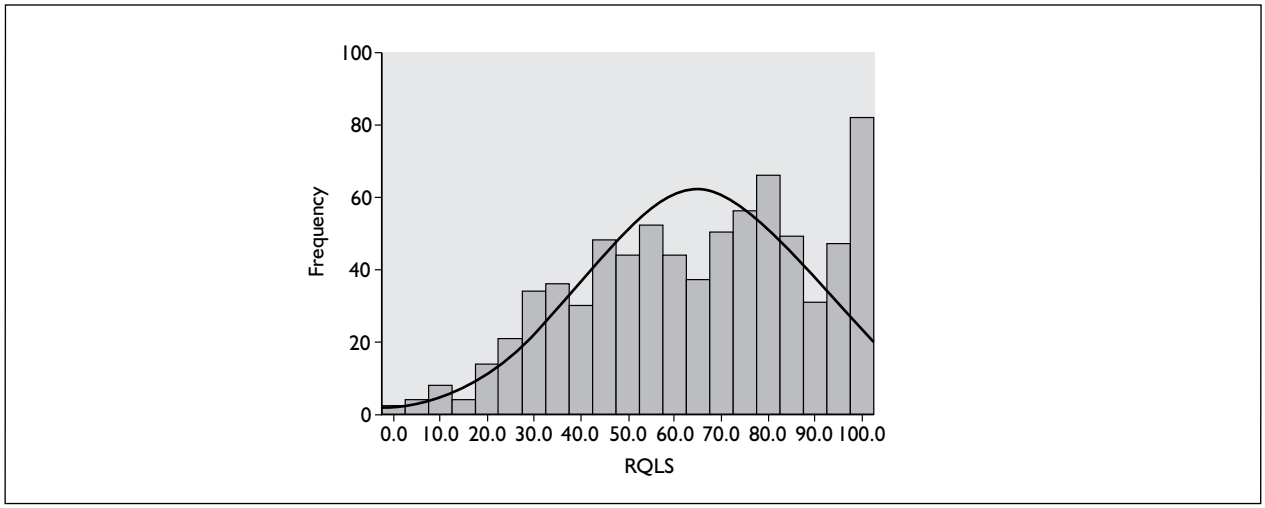

FIGURE 7 *Distribution of REFLUX quality of life scores (RQLS).*

TABLE 7 *Component loadings used to calculate the* REFLUX *symptom scores*

Item	Component 1	Component 2	Component 3	Component 4	Component 5
A1: Heartburn	0.674				
A2: Discomfort in chest	0.643				
B1: Acid reflux	0.654				
B2: Vomiting			0.734		
B3: Regurgitation			0.556		
B4: Nausea			0.541		
B5: Urge to be sick			0.709		
C1: Flatulence		0.738			
C2: Belching		0.553			
C3: Feeling bloated		0.568			
C4: Stomach gurgling		0.515			
D1: Difficulty swallowing					0.338
D2: Eating restricted	0.421				
E1: Diarrhoea		0.722			
E2: Constipation					0.839
E3: Urgent need to go		0.696			
E4: Feeling like bowels not emptied					0.645
F1: Difficulty sleeping lying down	0.777				
F2: Difficulty getting to sleep	0.814				
F3: Disrupted sleep	0.791				
G1: Paid/unpaid work				0.695	
G2: Less strenuous activities				0.571	
G3: Strenuous activities				0.755	
G4: Social activities				0.588	

Factor loadings < 0.3 have been suppressed.

TABLE 8 *Mean* REFLUX *symptom scores at baseline*

Reflux symptom dimension	Mean	SD	Median
General discomfort	59.4	25.6	60.3
Wind and frequency	50.7	22.1	49.6
Nausea and vomiting	81.7	19.6	89.0
Activity limitation	79.2	16.5	81.5
Constipation and swallowing	77.7	20.6	79.6

However, there were few missing data. REFLUX scores could be calculated for over 95% of patients at baseline. Missing data rates for symptom items ranged from 1% to 2%, and for quality of life items from 3% to 5%.

Reliability

The reliability coefficient (Cronbach's alpha) measuring the internal consistency of the RQLS was 0.90. For the REFLUX symptom scores, alphas were as follows: general discomfort 0.87; wind and

frequency 0.78; nausea and vomiting 0.75; activity limitations 0.68; and constipation and swallowing 0.56. Apart from the last two items all alphas are greater than 0.70, which is generally considered satisfactory.[90]

Validity

Table 9 presents the relationship (Pearson's *r*) between the RQLS and the eight SF-36 dimension scores. Social functioning and bodily pain showed the best relationships with the RQLS, and mental health the worst.

Table 10 presents the proportion of respondents who had a score of 100 (best health) on the SF-36 dimensions as a percentage of those who had a best score of 100 on the RQLS. Whereas 96% of those who had the maximum score on the SF-36 physical functioning dimension also had a score of 100 on the RQLS, only 31% of those who had a score of 100 on the SF-36 bodily pain dimension also had a score of 100 on the RQLS.

TABLE 9 *Relationship (Pearson's r) between RQLS and SF-36 dimension scores*

SF-36 dimension	RQLS
Physical functioning	0.42
Role limitations – physical	0.49
Bodily pain	0.56
General health perception	0.46
Energy/vitality	0.34
Social functioning	0.59
Role limitations – emotional	0.41
Mental health	0.18

TABLE 10 *Percentage (n) of respondents with the maximum REFLUX quality of life score (RQLS) with the maximum score on the SF-36 dimensions*

SF-36 dimension	% (*n*)
Physical functioning	96 (70)
Role limitations – physical	66 (48)
Bodily pain	31 (23)
General health perception	–
Energy/vitality	–
Social functioning	74 (54)
Role limitations – emotional	97 (71)
Mental health	–

Figure 8 plots the mean RQLS against the SF-36 mental component score (MCS) and physical component score (PCS) grouped into fifths. The mean RQLS increases steadily and significantly between successive PCS groups. There is a similar pattern for MCS groups except that respondents in the highest fifth have a lower mean RQLS than those in the next lower fifth.

Sensitivity to change

Participants reported whether they were being prescribed medication at baseline and first follow-up. This information was used to classify them into four groups: those prescribed medication at baseline and follow-up ($n = 293$); those prescribed medication at baseline but not follow-up ($n = 186$); those prescribed medication at follow-up but not baseline ($n = 3$); and those not prescribed medication at all ($n = 7$). As the last groups are reassuringly small, *Figure 9* presents mean change in RQLS (baseline score – follow-up score) for the first two groups.

A negative score indicates an improvement in quality of life. Although the RQLS improved for both groups (paired *t*-tests showed significant change), patients whose medication status changed between baseline and follow-up (medication at baseline but not at follow-up) showed a greater improvement in their RQLS than patients whose medication status stayed the same (medication at baseline and follow-up).

Discussion

Principal findings

This chapter describes a new outcome measure for use with patients being treated for GORD. The REFLUX questionnaire comprises 31 items and generates a single score (RQLS) measuring the extent to which individual participants feel that their GORD symptoms, and any side effects of treatment, affect their quality of life. The 31 items also generate five reflux symptom scores measuring the extent to which participants experienced clusters of symptoms over the previous 2 weeks. Thus, the RQLS provides a single index that can be used to record change for evaluation, whereas the symptom scores provide a descriptive profile that describes whether respondents experience problems in specific clusters. The data presented provide evidence that the new measure is valid, reliable and sensitive to change.

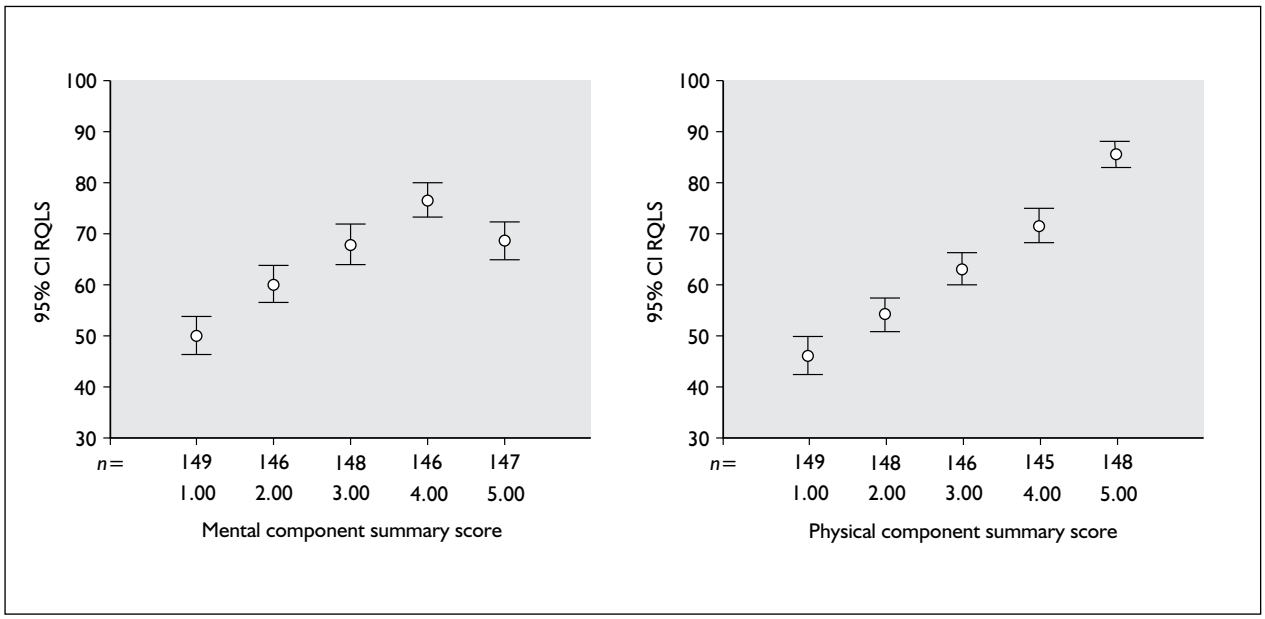

FIGURE 8 *REFLUX quality of life score (RQLS) by SF-36 mental component summary score and physical component summary score (grouped into fifths).*

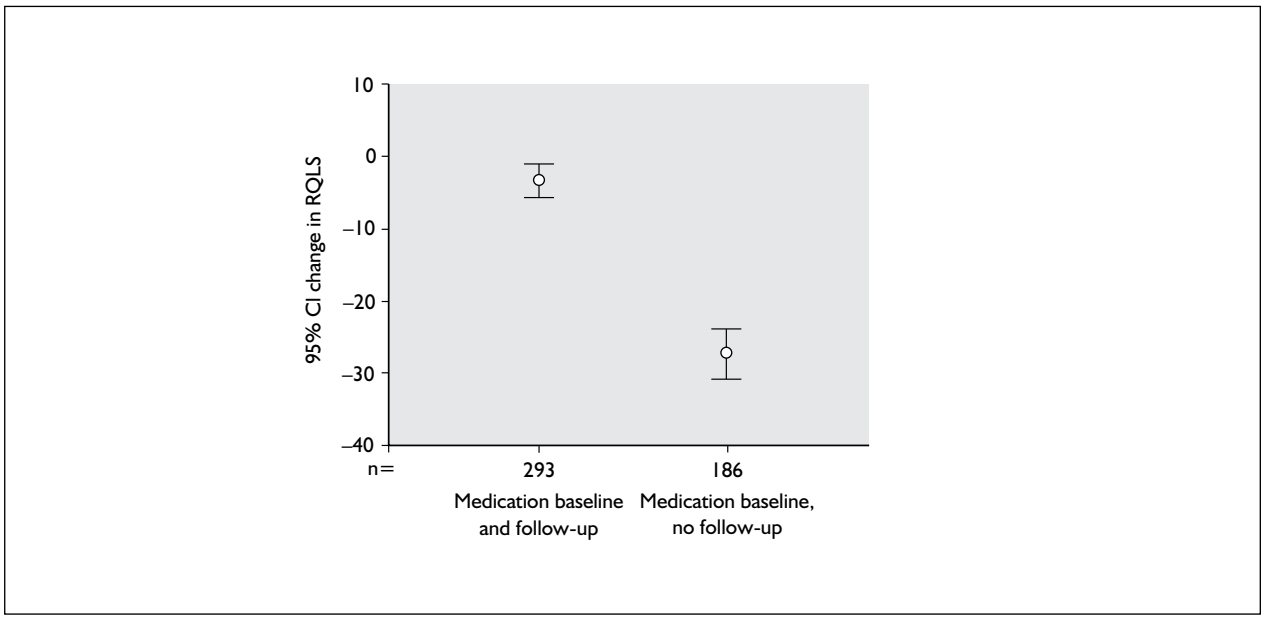

FIGURE 9 *Change in REFLUX quality of life score (RQLS) by change in prescribed medication (baseline to follow-up).*

Strengths of the study

The REFLUX questionnaire was designed as a patient-centred self-completed postal questionnaire. Items were generated by using GORD patients as key informants, rather than relying on the views of clinicians or other experts. Therefore the REFLUX questionnaire covers those elements of their illness that GORD patients indicated were important in determining their quality of life. A patient-centred approach also underlies the scoring system used to generate the RQLS. The weights used to create this score were based on the relationship between participants' reports of their scores on seven quality of life items and of their general health status on a visual analogue scale. The score takes account of patients' preferences through their self-reported effect on quality of life. In contrast, the REFLUX symptom scores, which were not intended as measures of HRQoL, used essentially statistical weights, generated from principal components analysis of symptom frequencies rather than patients' views.

The performance of a measure may also be assessed by its acceptability to respondents. Although the REFLUX questionnaire has 31 items, it suffered very few reported difficulties or missing item responses within the REFLUX trial. During the pilot, modifications were based on patient feedback on the acceptability and readability of items.

Weaknesses of the study

The most common method of establishing the validity of a measure is to analyse its association with a criterion of known validity that is accepted as a gold standard. However, there is no gold standard for quality of life, or disease severity, in GORD by which to determine validity. Nevertheless, the REFLUX trial does use SF-36 and EQ-5D, two reputable measures of generic HRQoL, although not designed for use with GORD patients. As we had used the EQ-5D VAS to generate the RQLS, we used the SF-36 to establish construct validity. The RQLS showed good correlations with the SF-36 dimensions of bodily pain and social functioning, topics common to both measures, and weaker correlations with mental health and energy, topics not included in the REFLUX questionnaire. We used self-reported change in medication to assess the sensitivity of the RQLS to change, which assumes that changing from being prescribed medication to not being prescribed medication necessarily shows improved health status.

The second issue in establishing the validity of the REFLUX questionnaire is that the analysis was based on patients with controlled symptoms, as one of the trial inclusion criteria was reasonable symptom control with medication. Thus, 10% of patients achieved the best possible RQLS at baseline, showing that their GORD was affecting quality of life 'not at all', probably because medication provided complete symptom control. There is scope to ameliorate these ceiling effects in future.

The final issue relates to the interpretability of the five REFLUX symptom scores, derived through multivariate statistical analysis. To interpret the resulting weights we have suggested five labels: general discomfort; wind and frequency; nausea and vomiting; activity limitation; and constipation and swallowing. Although the first four are easy to interpret, the fifth contains only three items – difficulty in swallowing and two items relating to constipation. Although these appear to be heterogeneous, this is a common consequence of multivariate analysis, which takes full account of correlations between items. Furthermore, these items play little part in the other four dimensions and have been identified as potential side effects of surgical treatment. We have therefore retained this fifth dimension, more to assess changes after treatment than status at baseline.

Unanswered questions

The aim of this component of the study was to validate a new measure of the HRQoL of patients being treated for GORD. Further evidence about the performance of the measure will be available through detailed analysis of the REFLUX trial, some of which is described later in this report. Although our principal aim was to develop and validate an outcome measure for use in the REFLUX trial, we hope that the REFLUX questionnaire will prove more widely applicable.

Chapter 5

Beliefs about medicines and surgery

Background

This chapter describes a study that was conducted in addition to the research activities described in the trial protocol. It is the result of discussion among the trial team in which it was decided that it would be wise to check the validity of a questionnaire measure that was devised specifically for, and used for the first time in the context of, the REFLUX trial. We have called this measure the Beliefs about Surgery questionnaire (BSQ). It has the potential to be further developed as a tool for use by consultants and surgical teams. In the sections below we describe the initial analyses that were carried out to determine the validity of the measure. In the final section we suggest further work that could result in the development of a tool to support communication between consultants and patients with GORD as they discuss treatment preferences and decisions.

Introduction

Current health-care policy and practice acknowledge the importance of offering choice across the spectrum of health care to users of the health-care system.[91] It is plausible that people's choices about treatment will be influenced by their beliefs about the risks and benefits of various treatments, which in turn will be shaped by their experiences or anticipated experiences of treatment processes. Indeed, this link between beliefs (cognitions) and action is represented in Leventhal's common sense model of self-regulation in the face of a threat to health[92] as follows. People appraise a health threat situation with reference to cognitions about the illness and then implement coping procedures to restore their physical or emotional equilibrium. The model specifies the cognitive components of this appraisal process in terms of factors that have become known as the illness representations framework.[93] The dimensions of this framework include beliefs about effective treatment or control of the illness (e.g. 'taking medication will be effective'; 'surgery may be more effective than medication'; 'recovery from surgery could take a long time'). A questionnaire measure about illness representations has been developed and is frequently used to investigate people's cognitions about illness in the context of Leventhal's model.[92] This chapter reports the development and validation of a measure relating to beliefs about surgical treatments.

The treatment beliefs component of the Leventhal model has been investigated by Horne,[94] who proposed that behaviour relating to treatment (e.g. adherence) is determined by perceptions about treatment rather than, or in addition to, perceptions about illness. There are two broad classes of treatments: those involving professional intervention (e.g. medicine, surgery, therapy) and those involving the adoption of different lifestyle behaviours (e.g. exercise, diet, stress management). The Beliefs about Medicines questionnaire (BMQ)[93] developed by Horne and colleagues assesses perceptions about one form of treatment. The BMQ has been validated using a chronic illness sample ($n = 524$), including people diagnosed with asthma, diabetes, renal disease and psychiatric illness, and cardiac and general medicine inpatients. On the basis of principal components analysis and confirmatory factor analysis, four subscales were identified relating to beliefs about medications specific to the diagnosed condition ('concerns' about taking the medication and 'necessity' of taking the medication) and beliefs about medication in general ('harmfulness' of medication in general and 'overuse' of medication in general). The psychometric properties of these scales have been reported by Horne *et al*.[93] and demonstrate high levels of discriminant validity, criterion-related validity and stability of the factor structure across the different illness groups. This chapter investigates the measure of beliefs about medicine amongst people with GORD and also a parallel measure of beliefs about surgery, in the context of the REFLUX trial.

Because the REFLUX trial involved non-randomised preference groups, it was felt important from the start to include a measure that would investigate the process of patients' decision-making about their treatment choices. Thus, this trial provided the opportunity to answer three questions relating to beliefs about treatment. First, would baseline measures provide support for the validity of the BMQ for individuals in a chronic illness group that was different from the groups investigated

in the original validation study, namely people suffering GORD? Second, if participants were asked to answer questions relating to beliefs about surgery (in the form of a BSQ), would their answers suggest that these beliefs relate to professional interventions in general (i.e. would the dimensions of the BSQ converge with dimensions of the BMQ) or would distinguishable factors emerge? The answer to this question could be important when treatment options include both medical and surgical interventions. Third, would data from the BMQ and the BSQ, administered at baseline, provide evidence of criterion-related validity? Such evidence would be provided if the profile of scores on the BMQ and BSQ distinguished between the surgery group and the medication group in the preference groups (the 'criterion') but not in the randomised groups.

Methods

Item development

During the development of the new GORD-specific outcome measure (the REFLUX questionnaire)[24] for use within the REFLUX trial as described in Chapter 4, a series of one-to-one interviews and focus groups were conducted involving a total of 43 people (15 of whom were receiving medical treatment and 28 who had had surgery). In addition to the relevance of these discussions for the outcome measure, the feedback also suggested that patients had a range of views about medical and surgical treatments and that they invoked these views when discussing the decision about whether to have surgery to treat their GORD. This suggested that it would be informative to ask trial participants to report their beliefs about taking medications and about having surgery. We decided to use the previously validated measure of beliefs about medication[93] referred to above, but no measure has been developed to assess beliefs about surgery. We decided therefore that additional items to assess patients' beliefs about surgery should be added.

Items for a BSQ were generated in two ways. First, some questions from the BMQ lent themselves to a directly parallel version referring to surgery (e.g. 'Doctors place too much trust in medicines': 'Doctors place too much trust in surgery'). Second, additional items were included as a result of analysis of the interview data. Eight items were judged to be acceptable, answerable and relevant by this group. Similar to the BMQ, the response format for these items was from 1 (strongly agree) to 5 (strongly disagree).

Trial context

All 810 participants in the REFLUX trial were asked to complete the study baseline questionnaire. As described in detail in Chapter 6, 357 were recruited to the randomised component of the trial and 453 to the preference study (261 of these choosing surgery and 192 medical management).

In addition to the REFLUX questionnaire[24] the baseline questionnaire contained the EQ-5D[88] and the SF-36,[89] and the BMQ and BSQ.

Analytic strategy

To achieve a clear replication of the original validation study by Horne *et al*.,[93] the same analytic procedures were used. That is, an exploratory PCA was conducted on the BMQ items and confirmatory factor analysis was performed by computing Pearson's correlations for factor loadings against: (1) the theoretical model of predicted factor loadings; and (2) the empirical model of factor loadings reported by Horne *et al*.[93] As described by Horne *et al*.,[93] the theoretical model was defined by assigning a factor loading of 1 to all items expected to load on the factor, with all other items assigned a loading of 0. This strategy permitted a comparison of the expected pattern of factor loadings with the pattern derived from the REFLUX sample.

To assess the level of discrimination between beliefs about medication and beliefs about surgery, a further exploratory PCA was conducted on the combined items from the BMQ and BSQ using a non-orthogonal (direct oblimin) method of rotation. The factor scree plot and eigenvalues were used to select the number of factors.

Finally, discriminant function analysis was used to test the criterion-related validity of the combined BMQ/BSQ. This form of validity would be demonstrated if the profile of scores from the questionnaire enabled correct classification of cases to the surgery and medication groups in the preference groups but not in the randomised groups.

Results

Of the people recruited to the trial, 329 (92.12%) in the randomised groups and 419 (91.48%) in the preference groups completed the baseline questionnaire. Data from these 748 participants were analysed in this validation study.

Distributions of scores on the BMQ and BSQ items were generally acceptable. Skewness was greater than 1 for only two variables: 'My health, at present, depends on my medicines' (sk = 1.48); 'I would be willing to have an uncomfortable test' (sk = 1.09). Kurtosis was greater than 1 for six variables: 'My health at present depends on my medicines' (ku = 2.20, modal value = 1); 'Natural remedies are safer than medicines' (ku = 1.48, modal value = 3); 'Medicines do more harm than good' (ku = 1.81, modal value = 4); 'I would be willing to have an uncomfortable test' (ku = 1.74, modal value = 2); 'Surgery does more harm than good' (ku = 1.10, modal value = 4); 'Doctors are too quick to suggest surgery' (ku = 1.40, modal value = 4).

Exploratory principal components analysis on BMQ items

Based on the structure of the instrument, as reported by Horne *et al*.,[93] the BMQ was expected to comprise four factors (corresponding to the two subscales for each of the item pools relating to beliefs about general medicine and specific medicine). Using an eigenvalue cut-off of 1.1,[95] the REFLUX data yielded three factors that together accounted for 48.99% of the variance in the scores. Using a cut-off of 0.4 for item inclusion, every item in the item pool loaded on to a factor and none of the 18 items had diffuse loading. Factor 1 corresponded to the combined 'general harm' and 'general overuse' scales of Horne *et al*.,[93] and factors 2 and 3 corresponded exactly to their 'specific necessity' and 'specific concerns' factors respectively. *Table 11* presents the item loadings reported by Horne *et al*.[93] and the item loadings derived from the REFLUX BMQ data.

Confirmatory factor analysis on BMQ items

To test the consistency between the factor solution derived from the REFLUX sample and that of the chronic illness groups reported by Horne *et al*.,[93] a confirmatory factor analysis was conducted by computing the correlations between all of the factor loadings derived from the REFLUX data set and (1) a theoretical model, defined by assigning factor loadings of 1 to items expected to load on a factor, or else 0; and (2) the empirically derived factor loadings of Horne *et al*.[93] The confirmatory factor analysis was based on three factors (general overuse/harm, specific necessity, specific concerns). Results of the confirmatory factor analysis are presented in *Table 12*.

Exploratory principal components analysis on BMQ/BSQ items

A PCA (with oblimin rotation) was conducted on all BMQ and BSQ items together. Based on the structure of the BMQ for this sample, the combined BMQ/BSQ was expected to comprise up to six discriminable factors (corresponding to the two subscales for each of general medicine, specific medicine and general surgery). The scree plot (*Figure 10*) suggested that it was appropriate to extract five factors, which together accounted for 50.95% of the variance in the scores. Using a cut-off of 0.4 for item inclusion, only one item in the item pool did not load on to a factor and none of the 26 items had diffuse loading. *Table 13* presents the item loadings reported by Horne *et al*.[93] and the item loadings derived from the REFLUX data.

In the solution for the combined BMQ/BSQ, beliefs about medicines in general again formed one factor; the two factors relating to beliefs about medicines specific to the reflux condition mapped perfectly on to the solution reported by Horne *et al*.,[93] and beliefs about surgery also corresponded exactly to the pattern that was expected, based on the findings of Horne *et al*.[93] Beliefs about surgery appeared to be clearly discriminable from beliefs about medicines, as all between-factor correlations were less than 0.3 (*Table 14*).

Discriminant function analysis

The next question concerned the capacity of the BMQ/BSQ scores to discriminate between participants who chose to undergo surgery and those who chose to remain on medical treatment. Five composite belief scores were computed for each participant, corresponding to the five factors in the combined BMQ/BSQ factor solution. The five variables were entered as independent variables in a discriminant function analysis of data from the preference groups. This profile of scores resulted in the correct classification of 76% of the cases into surgery or medication groups. This was significantly greater than chance ($\chi^2(5) = 178.93$, $p < 0.001$). In contrast, discriminant function analysis of data from the randomised groups resulted in correct classification of 58% of the cases into surgery or medication groups. This was not significantly greater than chance ($\chi^2(5) = 6.68$, $p > 0.05$). *Table 15* presents classification results for (a) the preference groups and (b) the randomised groups.

TABLE 11 *Item loadings for the BMQ (four-factor solution) reported by Horne* et al.[94] *and the BMQ (three-factor solution) derived from the* REFLUX *baseline data (cut-off for inclusion 0.4)*

	Loadings							
	Horne *et al.*[94] (*n* = 524)				**REFLUX baseline (*n* = 750)**			
Items	**F1: Specific concerns**	**F2: Specific necessity**	**F3: General harm**	**F4: General overuse**	**F1: General overuse/ harm**	**F2: Specific necessity**	**F3: Specific concerns**	**Item mean[a] (SD)**
Having to take medicines [this medicine][b] worries me	0.80						0.82	2.64 (1.14)
I sometimes worry about becoming too dependent on my medicines	0.78						0.72	2.47 (1.16)
I sometimes worry about the long-term effects of my medicines	0.76						0.84	2.06 (0.97)
My medicines disrupt my life	0.60						0.54	3.61 (1.06)
My life would be impossible without my medicines		0.81				0.81		2.21 (1.12)
My health, at present, depends on my medicines		0.76				0.82		1.68 (0.88)
Without my medicines I would be very ill		0.74				0.77		2.53 (1.12)
My health, in the future, will depend on my medicines		0.70				0.79		2.26 (0.93)
My medicines protect me from becoming worse		0.65				0.61		1.95 (0.86)
If doctors had more time they would prescribe fewer medicines			0.81		0.80			2.92 (0.98)

Items	Loadings							
	Horne et *al.*[94] (*n* = 524)				REFLUX baseline (*n* = 750)			
	F1: Specific concerns	F2: Specific necessity	F3: General harm	F4: General overuse	F1: General overuse/ harm	F2: Specific necessity	F3: Specific concerns	Item mean[a] (SD)
Doctors place too much trust in medicines			0.75		0.81			3.34 (0.88)
Doctors use too many medicines			0.71		0.72			3.11 (0.86)
Natural remedies are safer than medicines			0.47	0.45	0.42			3.07 (0.74)
Most medicines are addictive				0.71				3.37 (0.74)
Medicines do more harm than good				0.67	0.52			3.79 (0.67)
All medicines are poisons				0.58	0.47			3.96 (0.84)
My medicines are a mystery to me				0.55				3.48 (1.00
People who take medicines should stop their treatment every now and again				0.51	0.31			3.11 (0.92)
Eigenvalue	3.38	2.92	1.60	1.44	4.13	3.08	1.61	
Percentage variance explained	18.8	16.2	8.9	8.0	22.96	17.10	8.94	

a Item mean (SD) for REFLUX items, where 1 = strongly agree and 5 = strongly disagree.

b Square brackets indicate original BMQ wording.

TABLE 12 *Confirmatory factor analysis for the BMQ scales, testing factor loadings (on three factors) from the* REFLUX *data set against the theoretical and the empirically derived models*

	Pearson correlation of items with predicted factor loadings	
Factor label	**Theoretical model**	**Empirically derived model**
General overuse/harm	0.90	0.92
Specific necessity	0.96	0.98
Specific concerns	0.90	0.92

For the merged factor 'general overuse/harm' the empirically derived factor loadings from the Horne *et al*.[93] study were the highest loadings for items loading on the separate factors 'general overuse' and 'general harm' and the loadings closest to zero for the items loading on the other factors. This afforded the most stringent test of the REFLUX model against the empirically derived model.

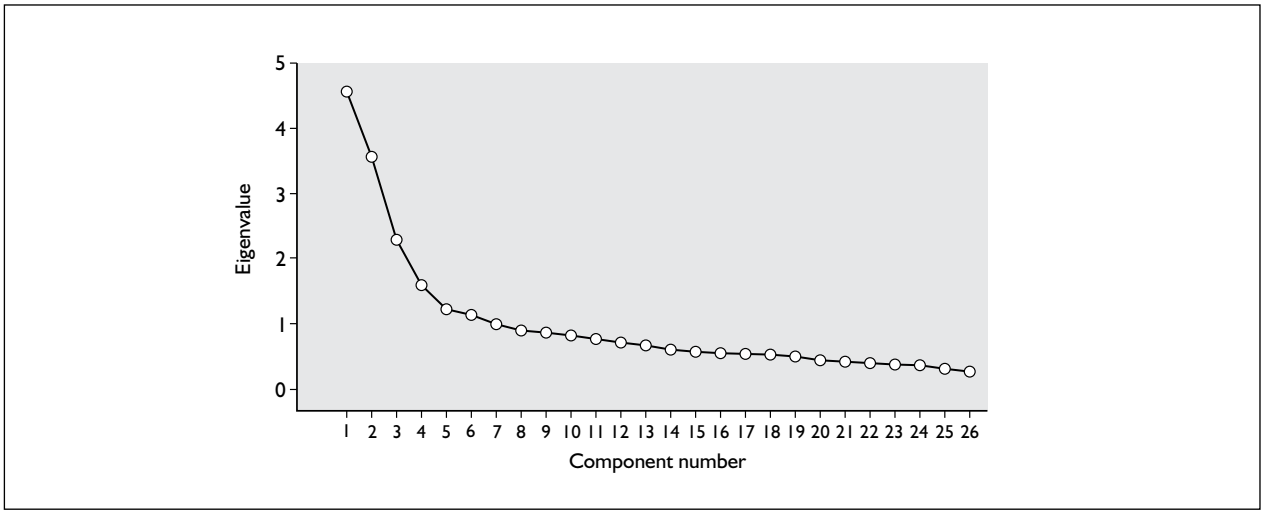

FIGURE 10 *Scree plot indicating that a five-factor solution would be appropriate.*

Discussion

Baseline measures in the REFLUX trial provided support for the validity of the BMQ for individuals suffering from GORD. However, the two general medicine scales (labelled harm and overuse) merged in this factor solution. It is possible that specific characteristics of the sample may explain this. For example, GORD is a condition for which medication is taken symptomatically whereas the original validation study was conducted with people experiencing chronic illnesses in which medications are taken continuously. This could have increased the tendency of the GORD sample to discriminate between items relating to medications specific to the illness and correspondingly decreased the tendency to discriminate between the items in the general medicine scales. Furthermore, all of the current sample were trial participants and their involvement in the recruitment and informed consent processes of the trial may have made the GORD-specific items more salient and therefore more discriminable than the items about medicines in general.

Importantly, when participants were asked to answer questions relating to beliefs about surgery, their answers yielded factors that were discriminable from those relating to beliefs about medications, suggesting that these participants held distinctive patterns of beliefs about these two kinds of treatment, rather than about professional interventions in general. Furthermore, data from the BMQ and the BSQ provided evidence of criterion-related validity of the BMQ and the BSQ in that the profile of scores on the BMQ and the BSQ distinguished between the surgery group and the medication group in the preference arm of the trial but not in the randomised arm. In other words, knowing nothing about the participants other than their BMQ/BSQ scores allowed a reasonably good prediction of their treatment choices.

Beliefs about treatment have previously been investigated in relation to adherence to medication regimens but little research in this area has explored the issue of patient choices about treatment. The addition of a measure of beliefs

TABLE 13 *Item loadings for the BMQ (four-factor solution) reported by Horne* et al.*[94] and the BMQ/BSQ (five-factor solution) derived from the* REFLUX *baseline data (cut-off for inclusion 0.3)*

	Loadings								
	Horne *et al.*[94] (*n* = 524)				**REFLUX baseline (*n* = 739)**				
Items	**F1: Specific concerns**	**F2: Specific necessity**	**F3: General harm**	**F4: General overuse**	**F1: General medicine overuse**	**F2: Specific medicine necessity**	**F3: Surgery overuse/ harm**	**F4: Specific medicine concerns**	**F5: Surgery concerns**
Having to take medicines [this medicine][a] worries me	0.80							0.81	
I sometimes worry about becoming too dependent on my medicines	0.78							0.76	
I sometimes worry about the long-term effects of my medicines	0.76							0.80	
My medicines disrupt my life	0.60							0.60	
My life would be impossible without my medicines		0.81				0.84			
My health, at present, depends on my medicines		0.76				0.82			
Without my medicines I would be very ill		0.74				0.79			
My health, in the future, will depend on my medicines		0.70				0.79			
My medicines protect me from becoming worse		0.65				0.59			
If doctors had more time they would prescribe fewer medicines			0.81		0.74				
Doctors place too much trust in medicines			0.75		0.80				
Doctors use too many medicines			0.71		0.75				

continued

TABLE 13 *Item loadings for the BMQ (four-factor solution) reported by Horne* et al.[94] *and the BMQ/BSQ (five-factor solution) derived from the* REFLUX *baseline data (cut-off for inclusion 0.3) (continued)*

	Loadings								
	Horne *et al.*[94] (*n* = 524)				**REFLUX baseline (*n* = 739)**				
Items	**F1: Specific concerns**	**F2: Specific necessity**	**F3: General harm**	**F4: General overuse**	**F1: General medicine overuse**	**F2: Specific medicine necessity**	**F3: Surgery overuse/ harm**	**F4: Specific medicine concerns**	**F5: Surgery concerns**
Natural remedies are safer than medicines			0.47	0.45	0.50				
Most medicines are addictive				0.71	0.48				
Medicines do more harm than good				0.67	0.61				
All medicines are poisons				0.58	0.51				
My medicines are a mystery to me				0.55	(0.36)				
People who take medicines should stop their treatment every now and again				0.51	0.47				
Doctors rely on surgery too much							0.75		
Surgery does more harm than good							0.74		
Doctors place too much trust in surgery							0.73		
Doctors are too quick to suggest surgery							0.71		
I would be willing to have an uncomfortable test							–0.44		
I worry about the risks of surgery							0.40		0.64
Surgery can result in new health problems									0.51
Surgery should only be taken as a last resort							0.40		0.51
Eigenvalue	3.38	2.92	1.60	1.44	4.56	3.57	2.31	1.59	1.22
Percentage variance explained	18.8	16.2	8.9	8.0	17.54	13.73	8.87	6.10	4.70

a Square brackets indicate original BMQ wording.

TABLE 14 *Component correlation matrix for the BMQ/BSQ five-factor solution*

Factor	F1	F2	F3	F4	F5
F1: Medication in general: overuse/harm	–				
F2: Specific medication: necessity	0.014	–			
F3: Surgery in general: overuse/harm	0.274	–0.053	–		
F4: Specific medication: concerns	0.296	0.160	0.035	–	
F5: Surgery in general: concerns	–0.048	–0.051	0.119	–0.116	–

TABLE 15 *Discriminant function analysis: classification results as frequencies (percentages) for participants in (a) the preference groups and (b) the randomised groups, based on scores for BMQ/BSQ*

		Predicted group membership		
		Surgical	**Medical**	**Total**
(*a*) *Preference groups*				
Actual group membership	Surgical	184 (75.7)	59 (24.3)	243 (100)
	Medical	42 (23.9)	134 (76.1)	176 (100)
75.9% of original grouped cases correctly classified.				
(*b*) *Randomised groups*				
Actual group membership	Surgical	99 (59.6)	67 (40.4)	166 (100)
	Medical	72 (44.2)	91 (55.8)	163 (100)
57.8% of original grouped cases correctly classified.				

about surgery to the existing measure of beliefs about medication provided the opportunity to explore such decisions. In addition, it may be that a patient's score on the BSQ can provide important clinically relevant information. It is possible that people with less negative beliefs about surgery experience less anxiety associated with the surgery and, as there is evidence that anxiety is associated with poorer clinical outcomes post surgery,[96] this could be important information for surgeons to be aware of. Furthermore, it may be that knowing the scores on these two questionnaires could help clinicians to counsel patients who have higher levels of concern or to help patients make better decisions about their treatment. It could be helpful to explore these possibilities in future research.

In terms of the common sense self-regulation model more generally, there is ample evidence that people's illness perceptions influence their emotional and behavioural responses to an illness threat.[92] Perceptions and beliefs about how an illness may be controlled – including the treatment options of medication and surgery – are potentially important factors that may link with other behaviours such as altered lifestyle. The development of additional measures that relate to other ways of controlling the symptoms of chronic illness could be useful in identifying people's preferred ways of coping with illness.

In conclusion, the perceptions of people with chronic illness about potential treatments can be measured validly and reliably. Core elements of the factor structure of the BMQ (in particular the distinction between specific and general classes of beliefs) were replicated in this study. Furthermore, responses to the BSQ indicate that beliefs about surgery form a distinct pattern of treatment representations and there is no redundancy between these two scales. Used together, the two measures can significantly distinguish between groups of individuals who choose one form of treatment over the other.

Implications for future research

As proposed above, there is potentially important follow-up work to be carried out in this field. Some possibilities that could be followed up using the REFLUX data set are:

1. Can the correct classification rate be improved further by the addition of other patient characteristics, for example severity of symptoms at baseline, sociodemographic factors, co-morbidities?
2. Can the recruitment of participants into the randomised groups of the trial be predicted by using a discriminant function analysis as described above to classify those who chose (a) surgery, (b) continued medication, and (c) to be randomised?
3. Do underlying treatment beliefs modify treatment effects? If so, can subgroups be identified who are more likely or less likely to respond well to alternative approaches to treatment, such as surgery or medical management?
4. Can the length of the questionnaire be reduced without reducing its predictive power, for example by using item response theory[97] to identify the discriminating items?
5. Are these treatment beliefs stable or do they change over time or as a function of changes in symptom severity?
6. Could the questionnaire be adapted for use as a communication tool by consultants and surgical teams?

In conclusion, this work has thus generated a number of possibilities for continued work in this field. It appears that the BSQ is a valid instrument that has a number of potential applications in surgical practice and research.

Chapter 6
Trial results

This chapter describes the partially randomised patient preference trial that was the cornerstone of this project. The chapter starts with an explanation of how the trial groups were derived. It then describes the study groups at trial entry and the management that they actually received. The results at the two follow-up points are then reported, followed by a formal statistical analysis of the data for the principal measures of outcome.

Recruitment to the trial

Participants were recruited in 21 clinical centres, all within the UK (*Table 16*). Recruitment to the trial was open from March 2001 until the end of June 2004, although not all centres enrolled over the total period because of the staggered introduction of centres and early closure for logistical reasons in a few places.

Initial recruitment was limited to two centres (Aberdeen Royal Infirmary; St Mary's Hospital, London) and these acted as pilot centres whilst systems for recruitment were developed. Roll-out of the trial to other centres started after 6 months

TABLE 16 *Number of participants by centre*

	Randomised participants		Preference participants	
Clinical centre	**Surgical, *n* (%)**	**Medical, *n* (%)**	**Surgical, *n* (%)**	**Medical, *n* (%)**
Aberdeen: Aberdeen Royal Infirmary	38 (21.3)	40 (22.3)	20 (7.7)	21 (10.9)
Belfast: Royal Victoria Hospital	15 (18.4)	14 (7.8)	4 (1.5)	20 (10.4)
Bournemouth: Royal Bournemouth Hospital	4 (2.2)	3 (1.7)	20 (7.7)	3 (1.6)
Bristol: Bristol Royal Infirmary	12 (6.7)	11 (6.1)	18 (6.9)	20 (10.4)
Bromley: Princess Royal Infirmary	3 (1.7)	3 (1.7)	20 (7.7)	17 (8.9)
Edinburgh: Royal Infirmary of Edinburgh	11 (6.2)	11 (6.1)	1 (0.4)	15 (7.8)
Guildford: Royal Surrey County Hospital	10 (5.6)	10 (5.6)	17 (6.5)	10 (5.2)
Hull: Hull Royal Infirmary	7 (3.9)	7 (3.9)	1 (0.4)	2 (1.0)
Inverness: Raigmore Hospital	7 (3.9)	8 (4.5)	2 (0.8)	8 (4.2)
Leeds: Leeds General Infirmary	1 (0.6)	2 (1.1)	10 (3.8)	3 (1.6)
Leicester: Leicester Royal Infirmary	0 (0.0)	0 (0.0)	3 (1.1)	1 (0.5)
London: St Mary's Hospital	8 (4.5)	7 (3.9)	4 (1.5)	10 (5.2)
London: Whipps Cross Hospital	4 (2.2)	3 (1.7)	16 (6.1)	5 (2.6)
Poole: Poole Hospital	10 (5.6)	10 (5.6)	25 (9.6)	13 (6.8)
Portsmouth: Queen Alexandra Hospital	10 (5.6)	10 (5.6)	15 (5.7)	1 (0.5)
Salford: Hope Hospital	0 (0.0)	1 (0.6)	6 (2.3)	3 (1.6)
Stoke-on-Trent: North Staffordshire Hospital	5 (2.8)	6 (3.4)	20 (7.7)	9 (4.7)
Swansea: Morriston Hospital	8 (4.5)	8 (4.5)	14 (5.4)	9 (4.7)
Telford: Princess Royal Hospital	11 (6.2)	12 (6.7)	24 (9.2)	8 (4.2)
Yeovil: Yeovil District Hospital	9 (5.1)	8 (4.5)	18 (6.9)	8 (4.2)
York: York District Hospital	5 (2.8)	5 (2.8)	3 (1.1)	6 (3.1)
Total	178 (100)	179 (100)	261 (100)	192 (100)

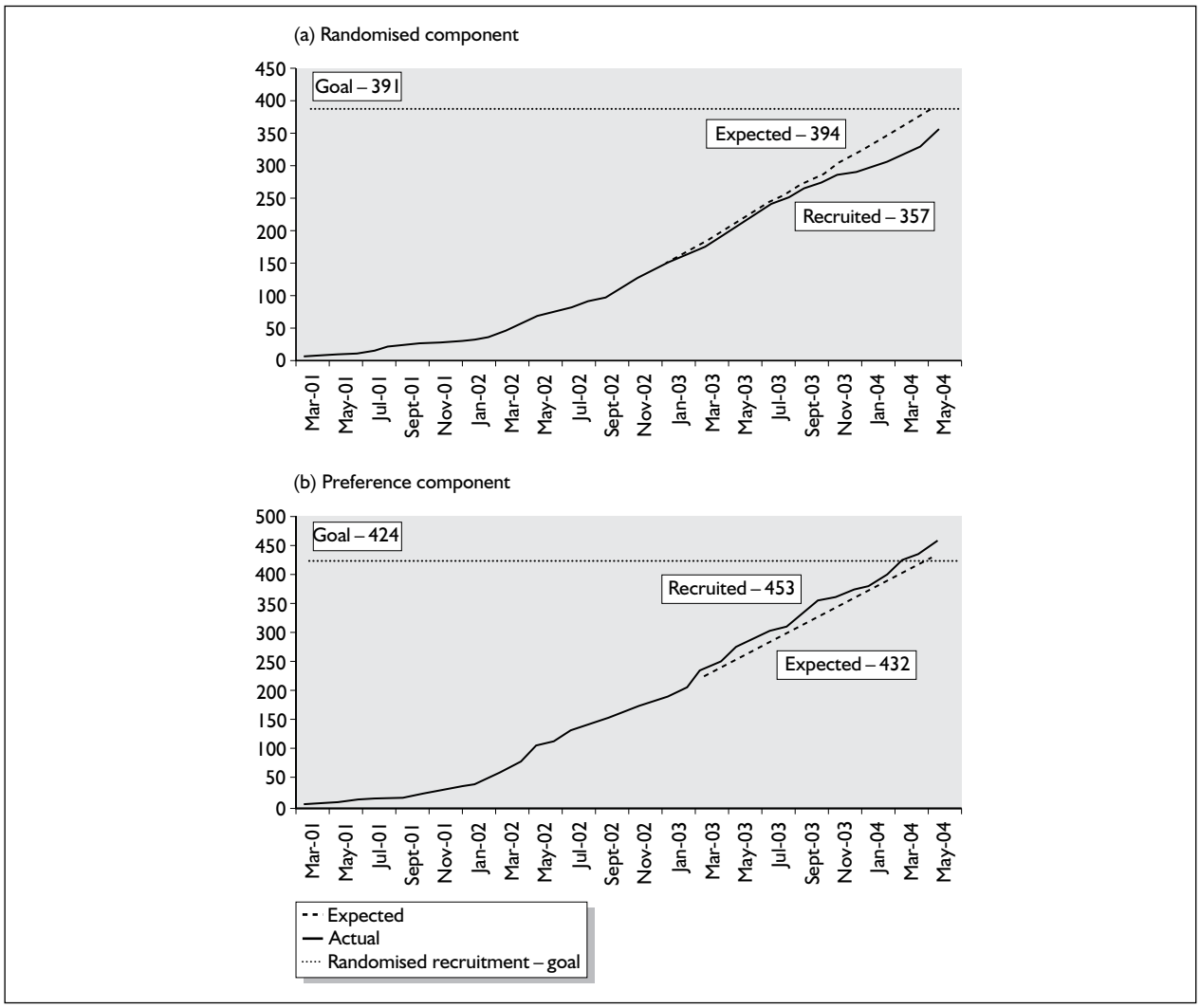

FIGURE 11 *Actual versus expected recruitment rates: (a) randomised component; (b) preference component.*

with gradual extension to all remaining centres over the following 3 years. *Figure 11* shows the total recruitment: the dotted line was the expected rate of recruitment over the last 16 months of the trial based on earlier recruitment. As can be seen, it proved difficult to sustain recruitment to the randomised component, although there was evidence for an increase in recruitment towards the time of recruitment closing.

A total of 357 participants were recruited to the randomised component, with 178 allocated to surgery and 179 allocated to medical management. In total, 453 participants agreed to join the preference component, 261 choosing surgery and 192 choosing medical management. *Table 16* shows recruitment by centre. Around 20% of the randomised participants were enrolled in Aberdeen; no centre contributed more than 11% of participants in the preference component.

Analysis populations

Throughout the analyses presented later in this chapter the participants in the randomised component are kept separate from those in the preference component (other than for rare surgical events). Primary analyses of the comparisons between surgical and medical management in both of these components are based on the allocated management at trial entry, that is, they are based on the intention to treat (ITT) principle. This sustains the integrity of the randomisation in particular. However, as described later in this chapter, a sizeable minority of participants did not actually receive their allocated management. To allow exploration of the impact ('blunting effect') that this might have on any observed differences, secondary analyses based on those who actually received their allocated management – per protocol (PP) analyses – were also undertaken and are presented alongside the ITT analyses.

The number of participants in each of the four main analysis populations is shown in *Table 17*. All 357 who joined the randomised component are in the randomised intention to treat (RITT) population whereas only the 280 within this group who actually received their allocated management are in the randomised per protocol (RPP) population. Similarly, all 453 participants who joined the preference component are in the preference intention to treat (PITT) population, and the 407 of these who were managed as originally chosen are in the preference per protocol (PPP) population.

Trial conduct

The derivation of the main study groups and their progress through the trial is shown in *Figure 12*. This is in the form of a CONSORT (Consolidated Standards of Reporting Trials) flow diagram. In total, 1078 patients were considered for trial

TABLE 17 *Number of participants in each analysis population*

	Surgical, *n* (%)	Medical, *n* (%)	Total, *n*
Randomised intention to treat (RITT)	178 (49.9)	179 (50.1)	357
Randomised per protocol (RPP)	111 (39.6)	169 (60.4)	280
Preference intention to treat (PITT)	261 (57.6)	192 (42.4)	453
Preference per protocol (PPP)	218 (53.6)	189 (46.4)	407

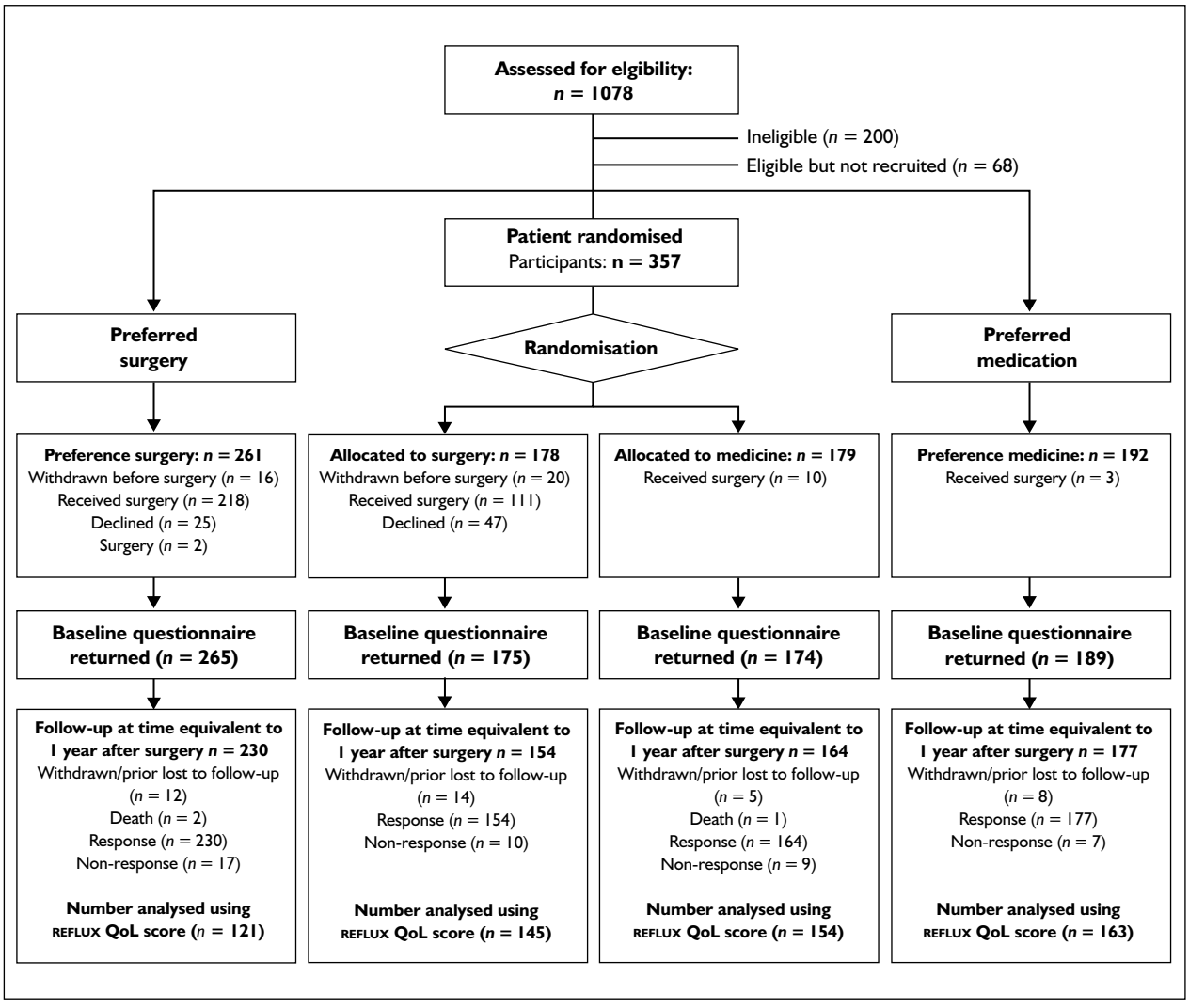

FIGURE 12 *CONSORT diagram.*

entry. Of these, 200 were found not to meet one or more of the eligibility criteria. Of the 68 patients eligible for the study but not recruited, 51 declined to participate, 6 were subsequently deemed inappropriate for the study by the surgeon responsible for care, and the remaining 11 were missed.

In total, 357 participants were recruited to the randomised component, with 178 randomly allocated to surgery and 179 to best medical management. A further 453 patients who wished to have one or other of the alternative approaches to management agreed to join the preference component – 261 to the surgical group and 192 to the medical management group.

In the early stages of the trial a few participants failed to return baseline questionnaires. After the first meeting of the Data Monitoring Committee, procedures were changed to prevent this, such that formal entry to the study (and random allocation if appropriate) occurred only after full baseline questionnaires had been received. The 1-year follow-up questionnaires were received from approximately 90% of the study participants. There were no substantive differences in response rates between the groups.

Three participants died before the 1-year follow-up was reached, two in the preference surgery group and one in the randomised medical group. None of these participants actually had surgery.

Description of the groups at trial entry

Sociodemographic and clinical factors

Randomised arms

Table 18 shows a description of the groups at trial entry. The table is first divided into whether participants were in the randomised or preference component, then divided according to their allocation, and finally subdivided according to intention to treat or per protocol. Within the randomised groups there were no apparent imbalances between the medical and surgical intervention arms. On average the patients were 46 years old, 66% were men and around two-thirds were in full employment; participants had been on GORD medication for a median of 32 months. The baseline characteristics in the randomised per protocol groups were similar.

Preference arms

The sociodemographic characteristics of the preference participants were broadly similar to those of the randomised groups. However, preference medical participants tended to be older (mean 50 years) and were more likely to be female, fewer were in full-time employment, and participants had been on GORD medication for a shorter period (approximately 6 months less than RCT participants).

Prescribed medications

The prescribed medications at the time of trial entry are shown in *Table 19*. There was a similar profile of prescribed medications across the randomised and preference groups. As would be expected, nearly all participants reported taking a reflux-related drug in the previous 2 weeks. Over 90% had taken a PPI, of which lansoprazole was the most common.

Health status

Randomised arms

The HRQoL scores at study entry are displayed in *Table 20*. The scores were broadly similar in the randomised surgical and randomised medical groups, although they were slightly higher (better health) in the randomised medical group. As described in Chapter 2, after the Data Monitoring Committee first met after the first 143 participants had been recruited to the randomised component, we were asked to change the enrolment procedure to ensure that baseline questionnaires were completed *before* formal entry and randomisation. We understand that this is because the committee were concerned about an apparent imbalance between the randomised groups in baseline health status at that time. After satisfying themselves that this was not due to a breakdown in the randomisation procedure, the committee surmised that this might be due to prior knowledge of the treatment allocation affecting questionnaire responses (with those allocated surgery tending to project worse health status than those allocated medical management). Certainly, the groups based on the first 143 participants were well balanced in other respects, and there was subsequently good balance in health status as well. The apparent small imbalance between the total randomised groups in health status measures is therefore likely to be a reflection of the imbalance in the first 143 participants.

TABLE 18 *Description of groups at trial entry*

	Randomised participants				Preference participants			
	Surgical		Medical		Surgical		Medical	
	ITT ($n = 178$)	PP ($n = 111$)	ITT ($n = 179$)	PP ($n = 169$)	ITT ($n = 261$)	PP ($n = 218$)	ITT ($n = 192$)	PP ($n = 189$)
Baseline questionnaire returned, *n* (%)	175 (98.3)	111 (100.0)	174 (97.2)	165 (97.6)	256 (98.1)	216 (99.1)	189 (98.4)	186 (98.4)
Mean age, years (SD)	46.7 (10.3)	46.3 (10.2)	45.9 (11.9)	45.9 (11.9)	44.4 (12.0)	44.5 (12.2)	49.9 (11.8)	50.0 (11.7)
Male, *n* (%)	116 (65.2)	68 (61.3)	120 (67.0)	115 (68.0)	170 (65.1)	139 (63.8)	111 (57.8)	110 (58.2)
Mean BMI (SD)	28.5 (4.3)	28.7 (4.1)	28.4 (4.0)	28.3 (4.0)	27.7 (4.0)	27.5 (3.7)	27.4 (4.1)	27.4 (4.1)
Duration in months (median) of prescribed medication for GORD – (IQR)	33 (15–83)	30 (16–76)	31 (16–71)	30 (15–71)	35 (14–71)	36 (14–65)	27 (13–60)	26.5 (13–60)
Employment status, *n* (%)								
Employed full-time	116 (66.3)	72 (65.5)	110 (61.8)	104 (61.9)	168 (65.1)	138 (64.2)	100 (52.4)	97 (51.6)
Employed part-time	13 (7.4)	12 (10.9)	16 (9.0)	15 (8.9)	35 (13.6)	29 (13.5)	20 (10.5)	20 (10.6)
Student	5 (2.9)	3 (2.7)	3 (1.7)	3 (1.8)	2 (0.8)	2 (0.9)	3 (1.6)	3 (1.6)
Retired	12 (6.9)	9 (8.2)	22 (12.4)	20 (11.9)	18 (7.0)	16 (7.4)	35 (18.3)	35 (18.6)
Housework	11 (6.3)	6 (5.5)	10 (5.6)	10 (6.0)	17 (6.6)	15 (7.0)	15 (7.9)	15 (8.0)
Seeking work	6 (3.4)	1 (0.9)	3 (1.7)	2 (1.2)	5 (1.9)	5 (2.3)	2 (1.0)	2 (1.1)
Other	12 (6.9)	7 (6.4)	14 (7.9)	14 (8.3)	13 (5.0)	10 (4.7)	16 (8.4)	16 (8.5)
Age left full-time education, *n* (%)								
16 years or under	110 (62.5)	68 (62.4)	108 (60.7)	102 (60.7)	151 (58.5)	128 (59.3)	105 (55.3)	104 (55.6)
17–19 years	38 (21.6)	24 (22.0)	40 (22.5)	40 (23.8)	63 (24.4)	51 (23.6)	45 (23.7)	43 (23.0)
20 years or over	28 (15.9)	17 (15.6)	30 (16.9)	26 (15.5)	44 (17.1)	37 (17.1)	40 (21.1)	40 (21.4)
Current smoker, *n* (%)	46 (25.8)	29 (26.1)	40 (22.3)	36 (21.3)	71 (27.2)	61 (28.0)	39 (20.3)	39 (20.6)
Erosive oesophagitis, *n* (%)	85 (54.8)	48 (50.0)	97 (62.2)	91 (62.3)	104 (46.4)	80 (43.2)	87 (50.9)	86 (51.2)
Co-morbidity – *H. pylori* status, *n* (%)								
Positive (subsequently treated)	12 (9.0)	5 (6.1)	14 (10.4)	13 (10.3)	18 (8.4)	14 (7.9)	15 (10.5)	15 (10.7)
Positive (subsequently untreated)	1 (0.8)	0 (0.0)	3 (2.2)	3 (2.4)	8 (3.7)	8 (4.5)	2 (1.4)	2 (1.4)
Negative	75 (56.4)	48 (58.5)	73 (54.1)	67 (53.2)	118 (54.9)	101 (56.7)	74 (51.7)	72 (51.4)
Uncertain	45 (33.8)	29 (35.4)	45 (33.3)	43 (34.1)	71 (33.0)	55 (30.9)	52 (36.4)	51 (36.4)
Hiatus hernia present, *n* (%)	94 (57.3)	64 (61.0)	102 (60.4)	94 (59.1)	168 (68.9)	146 (71.2)	101 (59.8)	99 (59.6)
Asthma, *n* (%)	21 (11.9)	14 (12.7)	21 (11.8)	19 (11.3)	30 (11.5)	23 (10.6)	36 (18.8)	36 (19.0)

BMI, body mass index; GORD, gastro-oesophageal reflux disease; IQR, interquartile range; ITT, intention to treat; PP, per protocol.

TABLE 19 *Description of groups at trial entry – prescribed medications*

	Randomised participants				Preference participants			
	Surgical		Medical		Surgical		Medical	
	ITT (*n* = 178)	PP (*n* = 111)	ITT (*n* = 179)	PP (*n* = 169)	ITT (*n* = 261)	PP (*n* = 218)	ITT (*n* = 192)	PP (*n* = 189)
Any reflux-related drug, *n* (%)	170 (97.1)	108 (97.3)	169 (97.1)	160 (97.0)	235 (91.8)	198 (91.7)	184 (97.4)	181 (97.3)
Proton pump inhibitors, *n* (%)								
Any proton pump inhibitor	161 (92.0)	105 (94.6)	162 (93.1)	153 (92.7)	225 (87.9)	191 (88.4)	173 (91.5)	170 (91.4)
Omeprazole (Losec®[b])	46 (26.3)	32 (28.8)	46 (26.4)	43 (26.1)	49 (19.1)	36 (16.7)	61 (32.3)	61 (32.8)
Lansoprazole (Zoton®[b])	77 (44.0)	47 (42.3)	72 (41.4)	69 (41.8)	100 (39.1)	92 (42.6)	69 (36.5)	66 (35.5)
Pantoprazole (Protium®[b])	6 (3.4)	6 (5.4)	11 (6.3)	11 (6.7)	21 (8.2)	17 (7.9)	11 (5.8)	11 (5.9)
Rabeprazole (Pariet®[b])	12 (6.9)	6 (5.4)	13 (7.5)	13 (7.9)	21 (8.2)	16 (7.4)	14 (7.4)	14 (7.5)
Esomeprazole (Nexium®[b])	20 (11.4)	14 (12.6)	20 (11.5)	17 (10.3)	37 (14.5)	33 (15.3)	18 (9.5)	18 (9.7)
Histamine receptor antagonists, *n* (%)								
Any histamine receptor antagonist	14 (8.0)	6 (5.4)	12 (6.9)	9 (5.5)	22 (8.6)	16 (7.4)	13 (6.9)	13 (7.0)
Ranitidine (Zantac®[b])	13 (7.4)	6 (5.4)	8 (4.6)	6 (3.6)	11 (4.3)	7 (3.2)	11 (5.8)	11 (5.9)
Famotidine (Pepcid®[b])	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.5)	1 (0.5)	1 (0.5)
Cimetidine (Tagamet®[b])	1 (0.6)	0 (0.0)	1 (0.6)	0 (0.0)	1 (0.4)	1 (0.5)	0 (0.0)	0 (0.0)
Nizatidine (Axid®[b])	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.2)	3 (1.4)	0 (0.0)	0 (0.0)
Over-the-counter histamine receptor antagonist	0 (0.0)	0 (0.0)	4 (2.3)	3 (1.8)	7 (2.7)	4 (1.9)	2 (1.1)	2 (1.1)
Prokinetics, *n* (%)								
Any prokinetics	12 (6.9)	7 (6.3)	8 (4.6)	6 (3.6)	11 (4.3)	10 (4.6)	5 (2.6)	4 (2.2)
Domperidone (Motilium®[b])	8 (4.6)	5 (4.5)	4 (2.3)	3 (1.8)	7 (2.7)	6 (2.8)	4 (2.1)	3 (1.6)
Metoclopramide (Maxolon®[b])	4 (2.3)	2 (1.8)	4 (2.3)	3 (1.8)	4 (1.6)	4 (1.9)	1 (0.5)	1 (0.5)
Other prescribed drugs, *n*[a]								
Alginates (Gaviscon, etc., Topal®[b])	22	12	21	18	37	33	14	13
Anti-spasmodics (e.g. dicycloverine)	0	0	2	2	3	3	0	0
Chelates (sucralfate)	1	1	0	0	0	0	0	0
Other ulcer healing drugs	0	0	0	0	1	1	0	0
Antacids: Mucogel®[b]	0	0	1	1	1	1	1	1
Antacids: Asilone®[b]	0	0	1	1	0	0	0	0
Non-gastrointestinal	7	2	4	4	5	4	6	6
Anti-nausea	0	0	1	1	1	1	1	1

ITT, intention to treat; PP, per protocol

a Number of prescriptions; more than one prescription per person possible.

b Losec®, AstraZeneca; Zoton®, Wyeth; Protium®, Atlanta; Pariet®, Janssen-Cilag; Nexium®, AstraZeneca; Zantac®, GlaxoSmithKline; Pepsid®, Merck Sharp & Dohme; Tagamet®, Chemidex; Axid®, Flynn; Motilium®, Sanofi-Synthelabo; Maxolon®, Shire; Topal®, Ceuta; Mucogel®, Forest; Asilone®, Thornton & Ross.

TABLE 20 *Description of groups at trial entry – health status*

	Randomised participants				Preference participants			
	Surgical		Medical		Surgical		Medical	
	ITT (*n* = 178)	PP (*n* = 111)	ITT (*n* = 179)	PP (*n* = 169)	ITT (*n* = 261)	PP (*n* = 218)	ITT (*n* = 192)	PP (*n* = 189)
REFLUX QoL, mean (SD)	63.6 (24.1)	61.9 (24.5)	66.8 (24.5)	68.2 (24.2)	55.8 (23.2)	55.9 (23.2)	77.5 (19.7)	78.0 (19.1)
REFLUX symptom score, mean (SD)								
General discomfort symptom score	58.5 (24.5)	57.1 (25.1)	61.3 (25.8)	62.4 (25.7)	49.1 (24.4)	48.7 (25.2)	73.1 (21.3)	73.6 (20.9)
Wind and frequency symptom score	48.1 (20.9)	46.2 (20.9)	49.3 (21.4)	49.5 (21.7)	47.1 (21.4)	47.5 (21.2)	59.6 (22.7)	59.8 (22.7)
Nausea and vomiting symptom score	81.5 (19.5)	81.6 (18.8)	80.7 (21.9)	81.6 (21.7)	76.9 (19.9)	77.5 (19.5)	89.7 (13.6)	90.1 (12.9)
Activity limitation symptom score	78.5 (16.9)	77.6 (16.3)	78.9 (17.3)	79.5 (17.1)	74.4 (16.1)	73.9 (16.2)	86.8 (13.0)	87 (13.0)
Constipation and swallowing symptom score	77.5 (19.9)	77.3 (20.3)	74.8 (21.0)	75.6 (20.4)	75.8 (22.0)	74.8 (22.6)	83 (17.7)	83.3 (17.6)
SF-36 scores, mean (SD)								
Norm-based physical functioning	46.8 (10.2)	46.1 (10.3)	47.5 (10.5)	47.7 (10.5)	46.3 (9.4)	46.1 (9.3)	47.1 (10.8)	47.0 (10.9)
Norm-based role physical	46.9 (10.7)	46.6 (10.8)	46.8 (10.6)	47.0 (10.4)	44.7 (10.9)	44.6 (10.7)	46.7 (10.9)	46.6 (10.9)
Norm-based bodily pain	44.4 (10.1)	44.1 (9.9)	44.6 (10.4)	44.9 (10.3)	41.8 (9.5)	41.9 (9.6)	47.1 (9.8)	47.2 (9.8)
Norm-based general health	40.9 (9.9)	40.2 (9.6)	41.1 (10.6)	41.4 (10.6)	40.6 (10.2)	40.8 (10.0)	42.4 (10.0)	42.4 (9.9)
Norm-based vitality	43.5 (10.5)	43.9 (10.3)	44.0 (11.7)	44.4 (11.4)	42.8 (11.1)	42.8 (11.3)	45.5 (10.7)	45.6 (10.7)
Norm-based social functioning	44.4 (11.1)	44.1 (10.6)	44.7 (11.7)	45.2 (11.5)	42.2 (11.6)	42.1 (11.5)	46.8 (10.2)	46.7 (10.2)
Norm-based role emotional	46.6 (11.5)	47.2 (11.5)	45.8 (12.9)	46.3 (12.6)	45.9 (12.2)	46.1 (12.1)	46.9 (11.8)	46.8 (11.8)
Norm-based mental health	46.0 (11.6)	46.9 (11.0)	46.7 (11.6)	47.1 (11.3)	44.6 (11.4)	44.6 (11.6)	46.4 (10.7)	46.3 (10.8)
EQ-5D, mean (SD)	0.71 (0.26)	0.72 (0.24)	0.72 (0.25)	0.73 (0.25)	0.68 (0.26)	0.68 (0.26)	0.75 (0.22)	0.75 (0.22)
EQ-5D VAS, mean (SD)	68.6 (17.1)	69.2 (15.9)	70.5 (18.1)	71.2 (17.6)	67.2 (18.5)	67.0 (18.5)	71.3 (16.7)	71.5 (16.6)

ITT, intention to treat; PP, per protocol; QoL, quality of life; VAS, visual analogue scale.

The most prevalent reflux symptoms (those with lowest scores) were general discomfort and wind and frequency. The participants had lower SF-36 and EQ-5D scores than a normal UK population with the same average age and sex characteristics (SF-36 population norm approximately 50 for all domains, and EQ-5D norm 0.88).

Preference arms

The preference for surgery participants reported worse REFLUX quality of life scores and worse health in general than the preference for medicine participants. It can be seen that the randomised participants reported quality of life measures in between these two extremes.

Surgical management

Table 21 gives details of the surgical management of those randomly allocated or in the preference for surgery group. For 47 allocated surgery there was subsequently a definite decision not to have surgery. For 25 of these, this was a clinical decision, most commonly the surgeon deciding that surgery was not appropriate. Most of the others changed their minds about having surgery for a variety of work- or home-related reasons, because of worries about the risks of surgery, because of a wish to avoid the preoperative tests, or because their symptoms had improved. A further 20 withdrew for uncertain reasons. There is no doubt, however, that a number of these participants suffered long delays before being formally offered surgery, and this was an important factor in their eventual decision to choose not to have surgery after all. The trial was conducted at a time when there was great pressure on surgical services in the NHS, with long delays for elective surgery for non-life-threatening benign conditions being common. Indeed, the average time between trial entry and surgery in the trial was 8–9 months (see *Table 23*).

In total, 111 (62.4%) of those randomised to surgery and 218 (83.5%) of the preference participants actually received surgery. Amongst the randomised participants, about 50% had a total wrap and 50% a partial wrap fundoplication. A total wrap was, however, the predominant procedure in the preference group (72.8%). The difference between the randomised and preference group fundoplication procedures was a reflection of the surgeon's preferred procedure and not any systematic surgeon bias between a surgeon's randomised and preference participants. This is illustrated in *Figure 13*, which shows that, within a given centre, the surgeon(s) performed the same procedures on their randomised and preference patients. The majority of operations were performed by a consultant and took around 2 hours to complete.

Intra- and postoperative surgical outcomes

Table 22 shows the intra- and postoperative surgical outcomes in the randomised and preference surgical participants who actually had a fundoplication. Two (0.6%) participants out of the total of 329 participants who had surgery required conversion to an open procedure (95% CI 0.2%–2.2%), and 8 (2.4%) had a visceral injury (95% CI 1.2%–4.7%). One participant had a blood transfusion. Three were admitted to a high dependency unit, but none to an intensive care unit. Nearly all were discharged to their homes after a median length of stay of 2 days. Three participants (0.9%) required a reoperation (95% CI 0.3%–2.6%) – all in the preference group – and three had dilatation of an oesophageal stricture or food disimpaction within 12 months of their initial surgery.

Follow-up at the time equivalent to 3 months after surgery

Patient flow

As mentioned earlier, around 90% of all participants returned completed questionnaires. As shown in *Table 23*, by the time of the first follow-up, some participants had formally withdrawn, and so were not sent questionnaires, and others had lost contact with the study office. Of the participants for whom it was appropriate to send a follow-up questionnaire, approximately 95% returned it (*Table 23*). For the surgical participants, the median and interquartile range (IQR) time from surgery to the first questionnaire was approximately 90 days. However, given that there were substantial waiting times for surgical participants, the median time from randomisation to sending the 3-month follow-up questionnaire was approximately 300 days (and this implied a waiting list time of 8–9 months). The median lag time from randomisation to follow-up was similar across all of the groups suggesting that our intention of pairing follow-up times between participants during the conduct of the trial (as described in Chapter 2) was successful.

TABLE 21 *Management received by those actually receiving surgery*

	Surgical participants	
	Randomised (*n* = 178)	**Preference (*n* = 261)**
Number declined surgery, *n* (%)	47 (26.4)	25 (9.6)
Number on waiting list, *n* (%)	0 (0.0)	2 (0.8)
Number withdrawn/lost to follow-up before surgery, *n* (%)	20 (11.2)	16 (6.1)
Number who received surgery, *n* (%)	111 (62.4)	218 (83.5)
Endoscopy before surgery, *n* (%)	97 (87.4)	196 (89.9)
pH monitoring before surgery, *n* (%)	77 (69.4)	158 (72.5)
Manometry before surgery, *n* (%)	73 (65.8)	164 (75.2)
Type of fundoplication, *n* (%)		
Total wrap	52 (46.8)	158 (72.8)
Partial – anterior	51 (45.9)	35 (16.1)
Partial – posterior	8 (7.2)	24 (11.1)
Short gastric arteries divided, *n* (%)	38 (34.2)	98 (45.0)
Left hepatic from left gastric artery, *n* (%)	13 (11.7)	13 (6.0)
If present, left hepatic artery divided, *n* (%)	4 (3.6)	6 (2.8)
Hepatic branch vagus divided, *n* (%)	30 (27.0)	40 (18.3)
Hiatus hernia present, *n* (%)	50 (45.0)	101 (46.3)
Bougie used, *n* (%)	25 (22.5)	67 (30.7)
Crural repair, *n* (%)	87 (78.4)	167 (76.6)
Grade of operating surgeon, *n* (%)		
Consultant	100 (91.7)	174 (80.6)
Staff grade, associate specialist	5 (4.6)	10 (4.6)
SPR	3 (2.8)	30 (13.9)
Other	1 (0.9)	2 (0.9)
Operation time in minutes (mean) (SD)	113 (38.0)	123 (64.4)

SPR, specialist registrar.

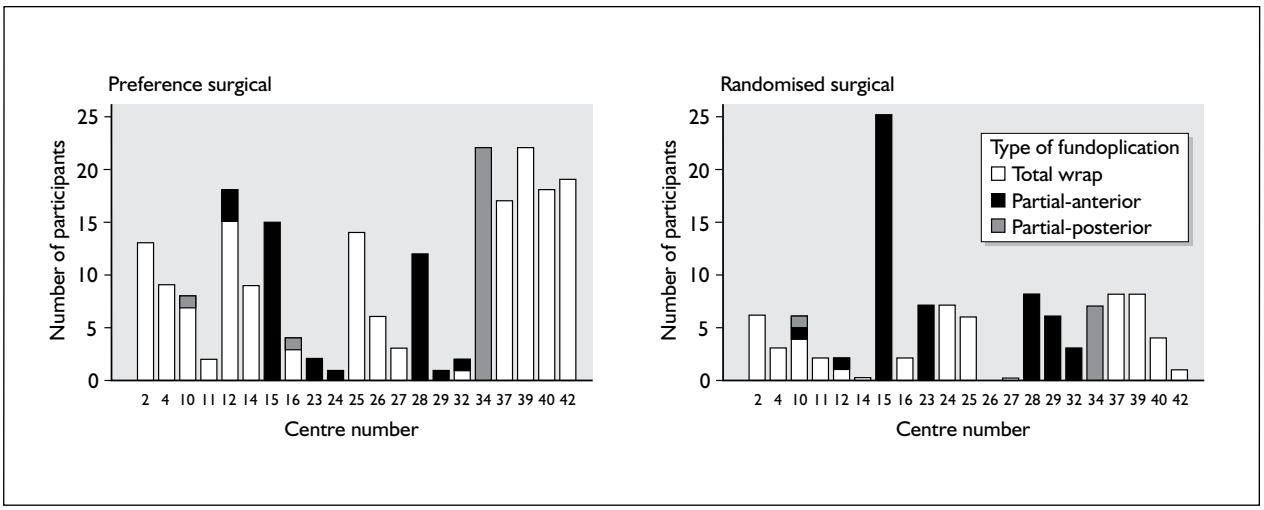

FIGURE 13 *Type of fundoplication performed by centre.*

TABLE 22 *Intra- and postoperative surgical outcomes*

	Surgical participants	
	Randomised (*n* = 111)	**Preference (*n* = 218)**
Conversion, *n* (%)	2 (1.8)	0 (0.0)
Liver injury, *n* (%)	1 (0.9)	1 (0.5)
Splenic injury, *n* (%)	0 (0.0)	1 (0.5)
Pleural injury, *n* (%)	1 (0.9)	2 (0.9)
Oesophageal injury, *n* (%)	0 (0.0)	0 (0.0)
Other visceral injury, *n* (%)	0 (0.0)	0 (0.0)
Haemorrhage, *n* (%)	1 (0.9)	1 (0.5)
Pneumothorax, *n* (%)	0 (0.0)	2 (0.9)
Blood transfusion, *n* (%)	0 (0.0)	1 (0.5)
Number of units transfused, mean (SD)	–	3 (–)
Other postoperative event, *n* (%)	3 (2.7)	5 (2.3)
ICU admission, *n* (%)	0 (0.0)	0 (0.0)
HDU admission, *n* (%)	1 (0.9)	2 (0.9)
Reoperation within 12 months, *n* (%)	0 (0.0)	3 (1.4)
Stricture dilatation or food disimpaction required within 12 months, *n* (%)	1 (0.9)	2 (0.9)
Ward only, *n* (%)	104 (93.7)	206 (94.5)
Discharged status		
Home, *n* (%)	107 (96.4)	213 (97.7)
Other, *n* (%)	4 (3.6)	5 (2.3)
Length of stay in days (median) (IQR)	2 (2–3)	2 (2–3)

HDU, high dependency unit; ICU, intensive care unit; IQR, interquartile range; SD, standard deviation.

Medications

The medications that participants were taking at the time of the 3-month follow-up are shown in *Table 24*. For the RITT surgery group, 33.3% were on a reflux-related drug compared with 92.4% of those randomised to medical management. When considering only randomised participants who received the intended management (the RPP groups), 9.2% of surgical participants and 92.7% of medical participants were on a reflux-related drug. The preference surgical and preference medical participants had a broadly similar proportion on medications as the randomised surgical and randomised medical groups respectively, although use of anti-reflux drugs was lower in the preference surgical ITT group than in the randomised surgical ITT group (as would be expected given that a higher proportion actually went on to have surgery).

Health status

The health status measures at the 3-month follow-up are shown in *Table 25*. Within the randomised component (RITT groups) there were clear differences across all measures, with the surgery group having better scores than the medical group. The differences were larger when only the per protocol participants were considered (RPP groups). Details of the formal statistical testing of these differences are described in the section on statistical analyses.

The health status scores of the two preference groups were more similar, although they tended to slightly favour the preference surgical group. Overall levels were equivalent to those of the randomised surgical group. (It is important to bear in mind, however, that the baseline levels were clearly lowest in the preference surgical group – see *Table 20*.)

TABLE 23 *Follow-up at the time equivalent to 3 months after surgery – patient flow*

	Randomised participants				Preference participants			
	Surgical		Medical		Surgical		Medical	
	ITT (*n* = 178)	PP (*n* = 111)	ITT (*n* = 179)	PP (*n* = 169)	ITT (*n* = 261)	PP (*n* = 218)	ITT (*n* = 192)	PP (*n* = 189)
Loss to follow-up, *n*	10	0	8	8	5	4	0	0
Formally withdrawn, *n*	11	0	2	2	9	1	2	2
Questionnaire sent, *n*	157	111	169	159	247	213	190	187
Questionnaire returned, *n* (%)	150 (95.5)	109 (98.2)	158 (93.5)	150 (94.3)	230 (93.1)	202 (94.8)	182 (95.8)	179 (95.7)
Lag in days (median) between surgery and 3-month follow-up (IQR)	86 (85–90)				86 (85–98)			
Lag in days (median) between randomisation and 3-month follow-up (IQR)	325 (266–435)		278 (215–314)		319 (210–455)		287 (214–342)	

IQR, interquartile range; ITT, intention to treat; PP, per protocol.

TABLE 24 *Follow-up at the time equivalent to 3 months after surgery – medications*

	Randomised participants				Preference participants			
	Surgical		Medical		Surgical		Medical	
	ITT (n = 178)	PP (n = 111)	ITT (n = 179)	PP (n = 169)	ITT (n = 261)	PP (n = 218)	ITT (n = 192)	PP (n = 189)
Any reflux-related drug, *n* (%)	50 (33.3)	10 (9.2)	146 (92.4)	139 (92.7)	45 (19.6)	17 (8.4)	176 (96.7)	161 (89.9)
Proton pump inhibitors, *n* (%)								
Any proton pump inhibitor	47 (31.3)	8 (7.3)	140 (88.6)	133 (88.7)	41 (17.8)	13 (6.4)	167 (91.8)	152 (84.9)
Omeprazole (Losec)	16 (10.7)	5 (4.6)	45 (28.5)	45 (30.0)	15 (6.5)	3 (1.5)	57 (31.3)	57 (31.8)
Lansoprazole (Zoton)	19 (12.7)	3 (2.8)	55 (34.8)	54 (36.0)	13 (5.7)	7 (3.5)	67 (36.8)	64 (35.8)
Pantoprazole (Protium)	1 (0.7)	0 (0.0)	9 (5.7)	8 (5.3)	3 (1.3)	2 (1.0)	14 (7.7)	14 (7.8)
Rabeprazole (Pariet)	4 (2.7)	1 (0.9)	9 (5.7)	9 (6.0)	3 (1.3)	0 (0.0)	13 (7.1)	13 (7.3)
Esomeprazole (Nexium)	7 (4.7)	1 (0.9)	22 (13.9)	21 (14.0)	7 (3.0)	3 (1.5)	21 (11.5)	21 (11.7)
Histamine receptor antagonists, *n* (%)								
Any histamine receptor antagonist	1 (0.7)	0 (0.0)	12 (7.6)	10 (6.7)	4 (1.7)	2 (1.0)	14 (7.7)	13 (7.3)
Ranitidine (Zantac)	0 (0.0)	0 (0.0)	8 (5.1)	8 (5.3)	2 (0.9)	1 (0.5)	10 (5.5)	9 (5.0)
Famotidine (Pepcid)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.6)
Cimetidine (Tagamet)	1 (0.7)	0 (0.0)	1 (0.6)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Nizatidine (Axid)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.6)
Over-the-counter histamine receptor antagonist	0 (0.0)	0 (0.0)	4 (2.5)	4 (2.7)	2 (0.9)	1 (0.5)	3 (1.7)	3 (1.7)
Prokinetics, *n* (%)								
Any prokinetics	7 (4.7)	3 (2.8)	6 (3.8)	5 (3.3)	7 (3.0)	6 (3.0)	5 (2.7)	4 (2.2)
Domperidone (Motilium)	3 (2.0)	1 (0.9)	6 (3.8)	5 (3.3)	3 (1.3)	2 (1.0)	4 (2.2)	3 (1.7)
Metoclopramide (Maxolon)	4 (2.7)	2 (1.8)	0 (0.0)	0 (0.0)	4 (1.7)	4 (2.0)	1 (0.5)	1 (0.6)
Other prescribed drugs, *n*[a]								
Alginates (Gaviscon, etc., Topal)	0	0	4	4	0	0	2	2
Anti-spasmodics (e.g. dicycloverine)	0	0	1	1	2	2	0	0
Chelates (sucralfate)	0	0	0	0	0	0	0	0
Other ulcer-healing drugs	0	0	0	0	0	0	0	0
Antacids: Mucogel	0	0	0	0	0	0	1	1
Antacids: Asilone	0	0	0	0	0	0	0	0
Non-gastrointestinal	1	1	0	0	2	1	1	1
Anti-motility	0	0	0	0	1	1	0	0

ITT, intention to treat; PP, per protocol.

a Number of prescriptions; more than one prescription per person possible

TABLE 25 *Follow-up at the time equivalent to 3 months after surgery – health status*

	Randomised participants				Preference participants			
	Surgical		Medical		Surgical		Medical	
	ITT (*n* = 178)	PP (*n* = 111)	ITT (*n* = 179)	PP (*n* = 169)	ITT (*n* = 261)	PP (*n* = 218)	ITT (*n* = 192)	PP (*n* = 189)
REFLUX QoL, mean (SD)	83.9 (19.4)	85.9 (19.0)	70.6 (24.6)	70.8 (24.4)	80.4 (21.6)	82.5 (20.3)	80.2 (18.2)	80.6 (17.7)
REFLUX symptom score, mean (SD)								
General discomfort symptom score	84.8 (17.3)	89.4 (14.0)	66.9 (26.2)	66.5 (26.0)	84.1 (19.6)	87.2 (16.6)	75.7 (19.6)	76.0 (19.5)
Wind and frequency symptom score	58.1 (19.7)	55.9 (19.7)	53.7 (22.6)	54.4 (22.5)	52.2 (21.1)	52.6 (20.7)	60.7 (22.2)	60.9 (22.3)
Nausea and vomiting symptom score	91.5 (15.7)	93.1 (15.7)	82.1 (20.7)	82.3 (20.2)	90.2 (15.2)	91.6 (13.7)	89.5 (12.9)	90.0(11.9)
Activity limitation symptom score	88.2 (17.0)	89.9 (16.7)	81.6 (19.6)	81.9 (19.0)	88.4 (18.0)	89.7 (17.5)	87.9 (13.2)	88.0 (13.3)
Constipation and swallowing symptom score	79.2 (20.0)	78.7 (20.7)	75.8 (20.9)	77.0 (19.8)	77.1 (21.2)	76.9 (21.3)	84.2 (16.9)	84.6 (16.5)
SF-36 scores, mean (SD)								
Norm-based physical functioning	49.2 (10.0)	49.3 (10.4)	46.5 (11.5)	46.6 (11.6)	49.9 (9.7)	50.4 (9.4)	47.6 (10.3)	47.5 (10.4)
Norm-based role physical	47.7 (11.8)	47.4 (12.1)	44.8 (12.1)	45.0 (12.1)	48.1 (11.3)	48.7 (10.7)	47.1 (10.4)	47.1 (10.4)
Norm-based bodily pain	48.5 (10.3)	48.8 (10.8)	45.3 (11.4)	45.3 (11.3)	48.4(11.3)	49.0 (11.2)	46.5 (10.2)	46.5 (10.3)
Norm-based general health	46.3 (11.0)	47.4 (11.0)	40.7 (11.2)	40.7 (11.2)	47.2 (11.3)	48.2 (11.1)	42.5 (10.5)	42.6 (10.4)
Norm-based vitality	47.1 (11.9)	48.0 (12.1)	43.9 (12.4)	44.3 (12.2)	48.0 (11.9)	48.4 (11.9)	44.7 (11.4)	44.8 (11.4)
Norm-based social functioning	47.2 (11.5)	47.5 (12.1)	43.6 (12.7)	43.8 (12.6)	46.8 (12.3)	47.6 (12.0)	46.9 (10.5)	46.9 (10.5)
Norm-based role emotional	48.3 (12.3)	48.4 (12.5)	43.9 (14.2)	44.1 (14.2)	47.0 (12.6)	48.9 (11.7)	47.0 (11.4)	46.9 (11.4)
Norm-based mental health	48.7 (12.0)	49.7 (11.9)	44.5 (12.2)	44.7 (11.9)	48.3 (12.2)	49.2 (11.8)	47.1 (10.6)	47.1 (10.7)
EQ-5D, mean (SD)	0.79 (0.23)	0.81 (0.24)	0.69 (0.30)	0.70 (0.30)	0.81 (0.25)	0.82 (0.24)	0.76 (0.23)	0.77 (0.23)
EQ-5D VAS, mean (SD)	74.8 (19.7)	77.0 (18.4)	67.8 (20.8)	68.1 (20.7)	75.1 (18.6)	76.3 (18.3)	70.8 (17.6)	70.9 (17.5)

ITT, intention to treat; PP, per protocol; QoL, quality of life; VAS, visual analogue scale.

Follow-up at the time equivalent to 12 months after surgery

Patient flow

As with the 3-month follow-up, of the participants for whom it was appropriate to send a follow-up questionnaire at 12 months, approximately 95% returned it (*Table 26*). The median lag time from randomisation to this second follow-up was similar across all of the groups. It was also approximately 270 days after the 3-month follow-up questionnaire, further demonstrating that the pairing of follow-up times between participants had been successful.

Medications

The medications that participants had taken during the previous 2 weeks at the time of the 12-month follow-up are shown in *Table 27*. In the RITT groups, 38.3% of the randomised surgical participants had taken a reflux-related drug compared with 89.6% of the randomised medical participants (and nearly all of these were PPIs). When considering only randomised participants who received their intended management (the RPP groups), 14.4% of surgical participants and 92.9% of medical participants had been taking reflux-related drugs. As at 3 months, the preference medical groups reported similar patterns of drug use to the randomised medical groups; however, the rate of drug use in the preference surgical ITT group was about one-half of that in the randomised surgical ITT group. Omeprazole and lansoprazole were equally commonly reported and this contrasts with the findings at study entry when lansoprazole was the predominant PPI used.

Health status

The health status measures at the 12-month follow-up are shown in *Table 28*. Within the randomised trial (RITT groups) there were still substantial differences across all measures (of the order of magnitude of one-third or one-half of a standard deviation of the score), with the surgery group having better scores than the medical group. The differences were larger when only the per protocol participants were considered (RPP groups). Details of statistical testing of the health status scores can be found in the next section of this chapter. For the reflux symptoms, although there were improvements across all symptom groups for surgical participants, the largest improvement in symptom score was for the general discomfort dimension. A detailed description of the responses to each symptom question is given in the REFLUX questionnaire (see Appendix 2). These improvements were also reflected in the SF-36 scores where the biggest differences were observed in the general health and bodily pain dimensions.

For preference participants the health status measure scores tended to favour the surgical group. However, the differences between the preference groups were less marked than the differences between the randomised groups, mainly because the preference medical group had better scores than the randomised medical group.

Graphical displays of the changes in REFLUX QoL scores and EQ-5D scores for all study groups are displayed in *Figures 14* and *15* respectively.

Three participants died, one in the randomised medical group (road traffic accident) and two in the preference surgical group, neither of whom had surgery (alcoholic liver disease and cause unknown).

Statistical analyses

Primary outcome

The pre-chosen primary outcome was the REFLUX QoL score at the time equivalent to 12 months after surgery. The mean and standard deviation of the score for each group at this follow-up are shown in *Table 28*. The differences between groups with corresponding 95% confidence intervals are shown in *Table 29*. Three types of analysis are presented for the randomised participants – intention to treat, per protocol and adjusted treatment received. *Table 29* also displays the impact of including adjustment for baseline score and randomised group × baseline score interaction terms.

Intention to treat

For the intention to treat analysis there was a mean difference in favour of surgery of 11.2 between the groups when only the minimisation variables were adjusted for ($p < 0.001$). This was not the most parsimonious model – there was strong evidence of an interaction effect between the randomised group and baseline REFLUX QoL score (interaction term was –0.35; 95% CI –0.53 to 0.17; $p < 0.001$). This implied that as baseline REFLUX QoL score increased the treatment effect decreased. Estimating the treatment difference at the trial baseline mean REFLUX QoL score of 65.4 resulted in a trial effect size of 14.0 (95% CI 9.6–18.4). If the average patient had a lower mean REFLUX QoL

TABLE 26 *Follow-up at the time equivalent to 12 months after surgery – patient flow*

	Randomised participants				Preference participants			
	Surgical		Medical		Surgical		Medical	
	ITT (*n* = 178)	PP (*n* = 111)	ITT (*n* = 179)	PP (*n* = 169)	ITT (*n* = 261)	PP (*n* = 218)	ITT (*n* = 192)	PP (*n* = 189)
Formally withdrawn/loss to follow-up, *n*	14	1	6	5	14	3	8	8
Questionnaire sent, *n*	164	110	173	164	247	215	184	181
Questionnaire returned, *n* (%)	154 (93.9)	104 (94.5)	164 (94.8)	155 (94.5)	230 (93.1)	203 (94.4)	177 (96.2)	174 (96.1)
Lag in days (median) between surgery and 12-month follow-up (IQR)	359 (358–361)				360 (359–362)			
Lag in days (median) between randomisation and 12-month follow-up (IQR)	580 (540–683)		541 (467–571)		574 (460–708)		546 (480–607)	

IQR, interquartile range; ITT, intention to treat; PP, per protocol.

TABLE 27 *Follow-up at the time equivalent to 12 months after surgery – medications*

	Randomised participants				Preference participants			
	Surgical		Medical		Surgical		Medical	
	ITT (*n* = 178)	PP (*n* = 111)	ITT (*n* = 179)	PP (*n* = 169)	ITT (*n* = 261)	PP (*n* = 218)	ITT (*n* = 192)	PP (*n* = 189)
Any reflux-related drug, *n* (%)	59 (38.3)	15 (14.4)	147 (89.6)	144 (92.9)	46 (20.0)	22 (10.8)	165 (93.2)	163 (93.7)
Proton pump inhibitors, *n* (%)								
Any proton pump inhibitor	56 (36.4)	13 (12.5)	142 (86.6)	139 (89.7)	42 (18.3)	19 (9.4)	156 (88.1)	154 (88.5)
Omeprazole (Losec)	19 (12.3)	6 (5.8)	47 (28.7)	45 (29.0)	14 (6.1)	4 (2.0)	61 (34.5)	60 (34.5)
Lansoprazole (Zoton)	21 (13.6)	2 (1.9)	51 (31.1)	50 (32.3)	17 (7.4)	12 (5.9)	56 (31.6)	5 (31.6)
Pantoprazole (Protium)	2 (1.3)	1 (1.0)	9 (5.5)	9 (5.8)	3 (1.3)	1 (0.5)	16 (9.0)	16 (9.2)
Rabeprazole (Pariet)	3 (1.9)	1 (1.0)	12 (7.3)	12 (7.7)	2 (0.9)	0 (0.0)	9 (5.1)	9 (5.2)
Esomeprazole (Nexium)	11 (7.1)	3 (2.9)	25 (15.2)	25 (16.1)	8 (3.5)	3 (1.5)	15 (8.5)	15 (8.6)
Histamine receptor antagonists, *n* (%)								
Any histamine receptor antagonist	4 (2.6)	3 (2.9)	9 (5.5)	9 (5.8)	5 (2.2)	2 (1.0)	13 (7.3)	13 (7.5)
Ranitidine (Zantac)	3 (1.9)	2 (1.9)	7 (4.3)	7 (4.5)	2 (0.9)	0 (0.0)	8 (4.5)	8 (4.6)
Famotidine (Pepcid)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.6)
Cimetidine (Tagamet)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Nizatidine (Axid)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Over-the-counter histamine receptor antagonist	1 (0.6)	1 (1.0)	2 (1.2)	2 (1.3)	3 (1.3)	2 (1.0)	5 (2.8)	5 (2.9)
Prokinetics, *n* (%)								
Any prokinetics	6 (3.9)	2 (1.9)	4 (2.4)	4 (2.6)	5 (2.2)	4 (2.0)	6 (3.4)	5 (2.9)
Domperidone (Motilium)	4 (2.6)	1 (1.0)	4 (2.4)	4 (2.6)	1 (0.4)	0 (0.0)	5 (2.8)	4 (2.3)
Metoclopramide (Maxolon)	2 (1.3)	1 (1.0)	0 (0.0)	0 (0.0)	4 (1.7)	4 (2.0)	1 (0.6)	1 (0.6)
Other prescribed drugs, *n*[a]								
Alginates (Gaviscon, etc., Topal)	3	0	4	4	1	0	5	5
Anti-spasmodics (e.g. dicycloverine)	1	1	4	4	1	1	1	1
Chelates (sucralfate)	0	0	0	0	0	0	0	0
Other ulcer-healing drugs	0	0	0	0	0	0	0	0
Antacids: Mucogel	0	0	1	1	0	0	0	0
Antacids: Asilone	0	0	0	0	0	0	0	0
Non-gastrointestinal	2	2	6	5	4	4	3	3
Anti-motility	0	0	0	0	0	0	0	0

ITT, intention to treat; PP, per protocol.

a Number of prescriptions; more than one prescription per person possible.

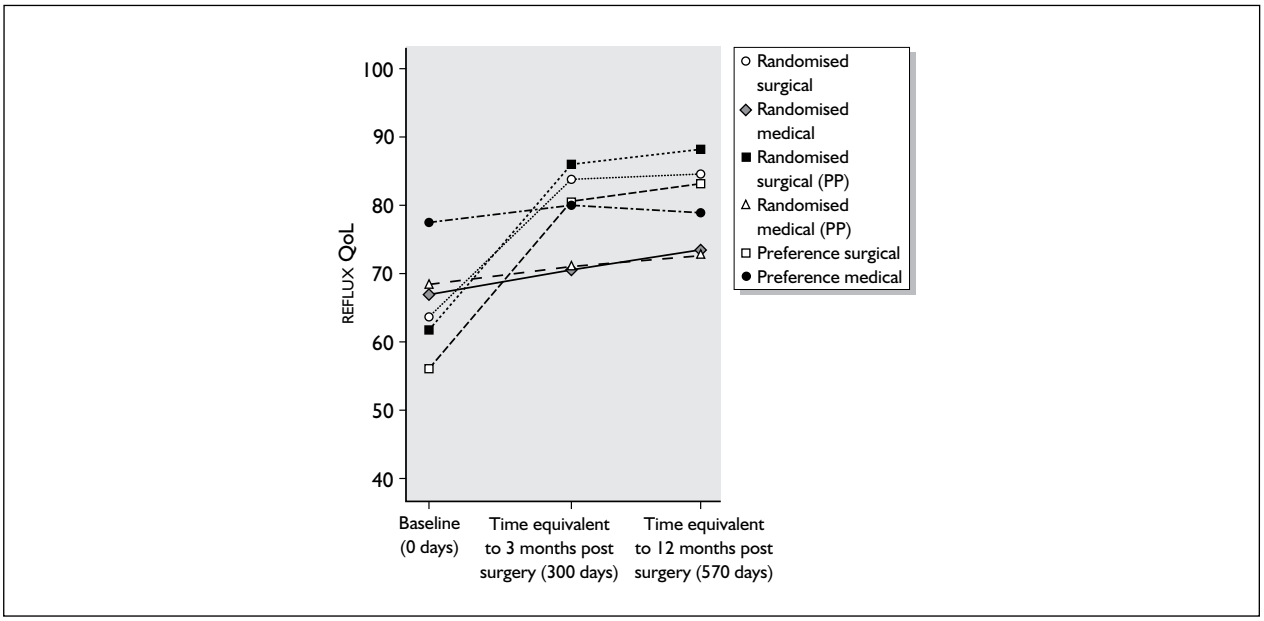

FIGURE 14 *REFLUX quality of life (QoL) scores at baseline and follow-up. Scores ranged from 0 to 100; the higher the score the better the patient felt.*

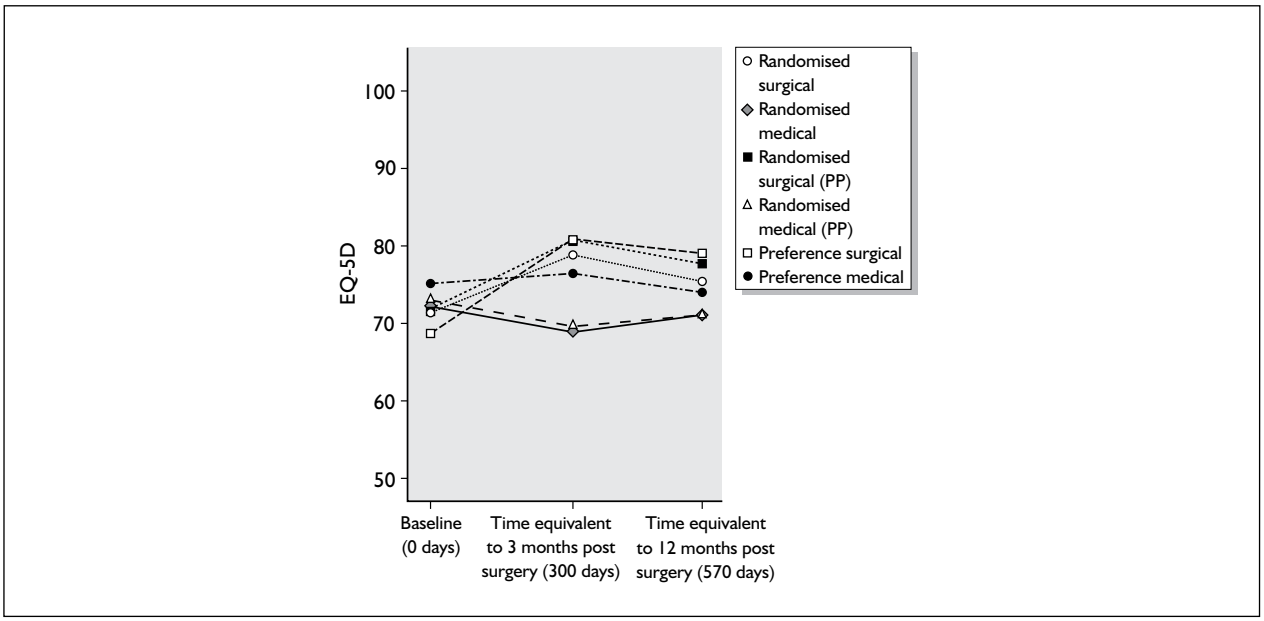

FIGURE 15 *EQ-5D scores at baseline and follow-up. Scores ranged from 100 (perfect health) to 0 (equivalent to death).*

score at baseline of 56.0, the effect size increased to 17.2 (95% CI 12.6–21.9). If the patient had a higher baseline score of 78.0, the treatment effect decreased to 9.5 (95% CI 4.5–14.5). All results, however, showed strong evidence of increases in REFLUX QoL scores, favouring surgery.

Per protocol

The per protocol analysis in *Table 29* estimated the difference between the randomised groups using only participants who received their allocated GORD management. This provided an estimate of the efficacy of the treatments. The per protocol

TABLE 28 *Follow-up at the time equivalent to 12 months after surgery – health status*

	Randomised participants				Preference participants			
	Surgical		Medical		Surgical		Medical	
	ITT (*n* = 178)	PP (*n* = 111)	ITT (*n* = 179)	PP (*n* = 169)	ITT (*n* = 261)	PP (*n* = 218)	ITT (*n* = 192)	PP (*n* = 189)
REFLUX QoL, mean (SD)	84.6 (17.9)	88.3 (15.6)	73.4 (23.3)	73.1 (23.7)	83.3 (20.7)	86.0 (17.9)	79.2 (19.2)	79.4 (19.0)
REFLUX symptom score, mean (SD)								
General discomfort symptom score	84.7 (17.5)	90.2 (14.0)	67.4 (25.8)	66.7 (25.8)	85.0 (19.4)	87.7 (16.5)	73.9 (20.7)	74.0 (20.8)
Wind and frequency symptom score	56.7 (21.0)	56.9 (21.7)	52.6 (23.3)	52.7 (23.5)	56.9 (22.5)	57.5 (22.1)	61.4 (21.9)	61.5 (22.0)
Nausea and vomiting symptom score	91.9 (14.4)	94.7 (11.8)	84.0 (18.6)	83.3 (18.8)	91.1 (16.5)	93.3(13.8)	88.6 (15.4)	88.9 (14.4)
Activity limitation symptom score	90.7 (12.8)	93.3 (11.5)	82.2 (19.2)	81.6 (19.4)	90.8 (16.8)	92.4 (14.8)	87.3 (14.7)	87.4 (14.8)
Constipation and swallowing symptom score	79.3 (19.1)	80.2 (19.6)	74.5 (22.8)	75.2 (22.3)	78.5 (20.2)	79.1 (19.7)	83.6 (17.6)	83.8 (17.4)
SF-36 scores, mean (SD)								
Norm-based physical functioning	48.9 (10.3)	49.6 (10.3)	47.2 (11.0)	47.2 (10.9)	49.7 (10.8)	50.3 (10.5)	47.4 (10.5)	47.4 (10.6)
Norm-based role physical	46.7 (11.4)	47.4 (11.3)	45.8 (11.8)	46.0 (11.7)	49.0 (11.2)	49.6 (10.5)	46.8 (10.7)	46.8 (10.7)
Norm-based bodily pain	47.7 (10.4)	48.5 (10.7)	44.5 (10.9)	44.5 (10.9)	49.1 (11.3)	49.9 (11.1)	47.4 (9.9)	47.4 (10.0)
Norm-based general health	45.2 (11.1)	46.2 (11.8)	40.7 (11.2)	40.5 (11.1)	46.4 (10.8)	47.2 (10.6)	42.3 (10.1)	42.3 (10.1)
Norm-based vitality	46.9 (11.5)	47.6 (11.6)	44.2 (11.9)	44.4 (11.7)	47.3 (12.0)	48.0 (11.7)	45.1 (10.3)	45.2 (10.3)
Norm-based social functioning	46.9 (11.6)	47.8 (11.7)	45.2 (12.2)	45.4 (12.1)	46.9 (12.5)	47.8 (12.1)	46.6 (10.6)	46.6 (10.6)
Norm-based role emotional	46.4 (13.5)	47.2 (12.9)	44.2 (14.4)	44.4 (14.2)	47.3 (13.3)	48.1 (12.7)	46.2 (12.0)	46.1 (12.0)
Norm-based mental health	47.2 (11.7)	48.5 (11.6)	46.4 (12.1)	46.5 (12.2)	46.9 (12.0)	47.4 (12.0)	46.5 (10.9)	46.6 (10.9)
EQ-5D, mean (SD)	0.75 (0.25)	0.78 (0.23)	0.71 (0.27)	0.71 (0.27)	0.79 (0.26)	0.80 (0.25)	0.74 (0.24)	0.74 (0.24)
EQ-5D VAS, mean (SD)	74.3 (18.0)	75.9 (17.8)	69.3 (20.1)	69.2 (20.0)	75.6 (16.7)	76.5 (16.1)	71.5 (18.1)	71.7 (17.8)

ITT, intention to treat; PP, per protocol; QoL, quality of life; VAS, visual analogue scale.

TABLE 29 *Primary outcome – REFLUX quality of life score at the time equivalent to 12 months after surgery*

	Randomised participants								
	Intention to treat			Per protocol			Adjusted treatment received		
	Difference[a]	(95% CI)	*p*-value	Difference[a]	(95% CI)	*p*-value	Difference[a]	(95% CI)	*p*-value
REFLUX QoL score, mean (SD)									
Adjusted for minimisation variables	11.2	(6.4–16.0)	< 0.001	15.4	(10.0–20.9)	< 0.001	16.7	(9.7–23.6)	< 0.001
Adjusted for minimisation variables and baseline REFLUX QoL score	14.1	(9.6–18.6)	< 0.001	19.1	(14.0–24.1)	< 0.001	20.3	(13.8–26.8)	< 0.001
Adjusted for minimisation variables, baseline score and treatment × baseline REFLUX QoL score interaction	14.0	(9.6–18.4)	< 0.001	18.4	(13.6–23.2)	< 0.001	19.4	(13.0–25.8)	< 0.001

CI, confidence interval; QoL, quality of life; SD, standard deviation.

a Difference is surgery group minus medical group.

analyses demonstrated larger effects in favour of surgery than the corresponding intention to treat analyses. Addition of the baseline score and interaction with the randomised group provided the best model fit resulting in a difference in favour of surgery of 18.4 (95% CI 13.6–23.2). Selection bias is to be expected in these estimates and indeed those who did not receive surgery in the randomised surgical group had higher (better) REFLUX QoL scores at baseline than those who did have surgery (69.0 versus 61.8).

Adjusted treatment received

The adjusted treatment received analyses attempted to reduce the selection bias effect inherent in the per protocol analyses. The effect sizes using the adjusted treatment received approach produced slightly larger estimates of differences than the per protocol estimates (see *Table 29*); however, the confidence interval widths increased. Nevertheless, the estimates and confidence intervals of the efficacy of the treatments suggested large benefits of surgery.

Preference groups

The preference for surgery participants reported considerably worse mean REFLUX QoL scores at baseline than the preference for medicine participants (55.8 versus 77.5; *Table 20*). Despite starting from a much lower baseline score, at follow-up at the time equivalent to 12 months after surgery, the REFLUX QoL score favoured the surgical group using an intention to treat analysis (difference = 3.9; 95% CI –0.2 to 8.0; $p = 0.064$) and using a per protocol analysis (difference = 6.3; 95% CI 2.4–10.2; $p = 0.002$).

Secondary outcomes

The secondary outcomes were the health status measures (EQ-5D, SF-36 and symptom scores) at the times equivalent to 3 and 12 months after surgery. The use of reflux medication at 12 months after surgery was also analysed.

At time equivalent to 12 months after surgery

Table 30 shows the health status measures at the time equivalent to 12 months after surgery described by the same three analyses as for the primary outcome (intention to treat, per protocol and adjusted treatment received).

Intention to treat

There were statistically significant improved REFLUX symptom category scores in favour of surgery across all domains (with the exception of the constipation and swallowing domain, which non-significantly favoured surgery). The bodily pain and general health scores had the largest SF-36 changes ($p \leq 0.001$); there were relatively small, non-statistically significant changes in SF-36 role physical, role emotional and mental health scores, although the directions of difference all favoured surgery. The EQ-$5D_{index}$ score was also higher in the surgery group, although the difference did not reach conventional levels of statistical significance ($p = 0.07$).

Per protocol and adjusted treatment received

All the per protocol analyses had larger differences than the corresponding intention to treat analyses, but the differences in SF-36 role physical, role emotional and mental health scores were still not statistically significant. The adjusted treatment received estimates were broadly similar to those derived from the per protocol analyses.

Use of medication

There were large differences between the groups in the numbers of participants requiring any reflux medication at the 12-month follow-up (*Table 27*). For the intention to treat analysis, the odds ratio of requiring any reflux medication in the surgical group was 0.07 (95% CI 0.04–0.125; $p < 0.001$) compared with the medical group (absolute difference 38.3% versus 89.6%). The odds ratios for the per protocol analysis and adjusted treatment received were 0.012 (95% CI 0.005–0.029; $p < 0.001$) and 0.017 (95% CI 0.006–0.048; $p < 0.001$) respectively. This is related to an absolute difference of 14.4% versus 92.9%. Across the 312 participants (randomised and preference) who received surgery and completed follow-up, 37 (11.9%; 95% CI 8.7–15.9%) required any reflux medication and 21 (6.7%) required PPIs.

At time equivalent to 3 months after surgery

Table 31 shows the health status measures at the time equivalent to 3 months after surgery described by the three analyses (intention to treat, per protocol and adjusted treatment received). In general, the scores were higher at 3 months than at 12 months. The differences in EQ-5D, in particular, were about twice as big at 3 months and were clearly statistically significant at that time.

TABLE 30 *Secondary outcomes at the time equivalent to 12 months after surgery – health status*

	Randomised participants								
	Intention to treat			Per protocol			Adjusted treatment received		
	Difference[a]	(95% CI)	*p*-value	Difference[a]	(95% CI)	*p*-value	Difference[a]	(95% CI)	*p*-value
REFLUX symptom score, mean (SD)									
General discomfort symptom score	18.3	(13.8–22.9)	< 0.001	25.0	(20.2–29.8)	< 0.001	26.1	(19.6–32.5)	< 0.001
Wind and frequency symptom score	4.9	(0.8–9.1)	0.019	6.1	(1.5–10.8)	0.01	6.7	(0.6–12.8)	0.033
Nausea and vomiting symptom score	7.8	(4.6–10.9)	< 0.001	11.7	(8.4–14.9)	< 0.001	11.5	(7.0–16.0)	< 0.001
Activity limitation symptom score	8.4	(5.2–11.7)	< 0.001	12.3	(8.7–16.0)	< 0.001	12.0	(7.3–16.7)	< 0.001
Constipation and swallowing symptom score	3.5	(–0.5 to 7.5)	0.085	4.8	(0.1–9.4)	0.045	5.0	(–0.9 to 10.9)	0.099
SF-36 scores, mean (SD)									
Norm-based physical functioning	2.3[b]	(0.6–4.0)	0.007	3.4[b]	(1.5–5.4)	0.001	3.4[b]	(0.9–5.9)	0.008
Norm-based role physical	0.9	(–1.1 to 3.0)	0.383	1.7	(–0.6 to 3.9)	0.145	1.2	(–1.8 to 4.3)	0.434
Norm-based bodily pain	3.4[b]	(1.4–5.5)	0.001	5.0[b]	(2.8–7.2)	< 0.001	5.1[b]	(2.1–8.0)	0.001
Norm-based general health	4.8[b]	(2.7–6.8)	< 0.001	6.9[b]	(4.6–9.3)	< 0.001	7.0b	(4.0–10.0)	< 0.001
Norm-based vitality	2.5	(0.4–4.6)	0.018	3.6	(1.2–6.0)	0.003	3.7	(0.6–6.8)	0.019
Norm-based social functioning	2.3	(0.1–4.5)	0.040	3.5	(1.0–6.0)	0.006	3.3	(0.04–6.6)	0.047
Norm-based role emotional	1.8	(–0.8 to 4.4)	0.177	2.1	(–0.7 to 5.0)	0.142	2.7	(–1.1 to 6.5)	0.168
Norm-based mental health	1.0[b]	(–1.0 to 3.1)	0.312	2.2[b]	(–0.1 to 4.5)	0.055	1.5[b]	(–1.5 to 4.5)	0.324
EQ-5D index, mean (SD)	0.047[b]	(–0.004 to 0.097)	0.07	0.076[b]	(0.021–0.131)	0.007	0.068[b]	(–0.006 to 0.142)	0.072

CI, confidence interval.

a Difference is surgery group minus medical group. All analyses adjusted for body mass index, age, sex, baseline score and baseline × group interaction.

b Adjusted for body mass index, age, sex and baseline score; baseline × group interaction term not fitted.

TABLE 31 *Secondary outcomes at the time equivalent to 3 months after surgery – health status*

	Randomised participants								
	Intention to treat			Per protocol			Adjusted treatment received		
	Difference[a]	(95% CI)	*p*-value	Difference[a]	(95% CI)	*p*-value	Difference[a]	(95% CI)	*p*-value
REFLUX QoL, mean (SD)	15.0	(10.5–19.4)	< 0.001	17.7	(12.9–22.5)	< 0.001	20.7	(13.9–27.5)	< 0.001
REFLUX symptom score, mean (SD)									
General discomfort symptom score	19.2	(14.9–23.6)	< 0.001	24.5	(20.1–28.9)	< 0.001	26.0	(19.6–32.4)	< 0.001
Wind and frequency symptom score	4.6	(0.5–8.6)	0.027	2.9	(–1.6 to 7.4)	0.202	5.1	(–1.0 to 11.3)	0.101
Nausea and vomiting symptom score	8.8	(5.8–11.9)	< 0.001	10.9	(7.6–14.2)	< 0.001	12.4	(7.7–17.1)	< 0.001
Activity limitation symptom score	7.1	(3.2–11.0)	< 0.001	9.2	(4.9–13.5)	< 0.001	9.1	(3.2–15.1)	0.003
Constipation and swallowing symptom score	2.0	(–1.9 to 6.0)	0.318	1.3	(–2.9 to 5.6)	0.536	2.1	(–3.9 to 8.2)	0.486
SF-36 scores, mean (SD)									
Norm-based physical functioning	3.1[b]	(1.3–4.9)	0.001	3.7[b]	(1.6–5.8)	< 0.001	4.4[b]	(1.5–7.2)	0.003
Norm-based role physical	2.7	(0.5–4.9)	0.018	2.6	(0.1–5.0)	0.043	3.4	(–0.04 to 6.8)	0.053
Norm-based bodily pain	3.2[b]	(1.1–5.3)	0.003	4.3[b]	(2.0–6.7)	< 0.001	4.1[b]	(0.9–7.2)	0.012
Norm-based general health	5.8[b]	(3.8–7.8)	< 0.001	7.9[b]	(5.6–10.1)	< 0.001	7.8[b]	(4.8–10.7)	< 0.001
Norm-based vitality	3.0	(0.9–5.1)	0.006	3.9	(1.5–6.2)	0.001	3.9	(0.7–7.1)	0.018
Norm-based social functioning	3.6	(1.3–5.8)	0.002	4.6	(2.1–7.1)	< 0.001	4.6	(1.1–8.1)	0.010
Norm-based role emotional	3.3	(0.7–5.8)	0.012	3.7	(0.9–6.6)	0.010	4.1	(0.2–8.0)	0.042
Norm-based mental health	4.2[b]	(2.1–6.2)	< 0.001	5.5[b]	(3.3–7.7)	< 0.001	5.5[b]	(2.4–8.6)	0.001
EQ-5D index, mean (SD)	0.099[b]	(0.048– 0.150)	< 0.001	0.130[b]	(0.074– 0.185)	< 0.001	0.129[b]	(0.051– 0.207)	0.001

CI, confidence interval.

a Difference is surgery group minus medical group. All analyses adjusted for body mass index, age, sex, baseline score and baseline × group interaction.

b Adjusted for body mass index, age, sex and baseline score; baseline × group interaction term not fitted.

Subgroup analyses

Removal of data from the single largest clinical centre (Aberdeen)

No formal exploration of centre effects was undertaken because of the small numbers of participants recruited in many of the clinical centres. However, a sensitivity analysis removing the data from the Aberdeen centre, the centre where the largest number of participants were recruited, did not significantly change the conclusions (adjusted difference in REFLUX score +15.4; 95% CI 10.2–20.6).

Partial versus total wrap procedure

In an observational analysis there was no evidence of a difference between a total wrap procedure and a partial wrap procedure. The difference in the REFLUX QoL score between these procedures at the time equivalent to 12 months post surgery was –1.3 (95% CI –7.9 to 5.2; $p = 0.687$).

Discussion

The trial provides strong evidence of improvement in GORD symptoms following laparoscopic fundoplication as judged by the REFLUX quality of life score and its constituent domains. There were large differences between the randomised groups in these respects at 3 months post surgery, which were broadly sustained 9 months later. Also, scores in the preference surgical group were somewhat higher than those in the preference medical group despite starting from much lower baseline levels. The estimated sizes of differences varied depending on the assumptions being made. However, significant differences were observed even in the most conservative of the three main analyses – that based on intention to treat – where about one-third of those randomised to surgery did not actually receive it. Similar differences were also seen in most of the other measures of health status. There is, however, some evidence of a narrowing of the differences when the 3-month and 12-month follow-up results are compared. This was most marked for the EQ-5D, in which the surgical values had decreased and the medical values had increased somewhat (most easily seen in *Figure 15*).

We anticipated that this would be a difficult trial to deliver and so it proved. Trials comparing strikingly different interventions (such as surgery versus medical management) are often a challenge to recruit to. The explanation of such a trial needs to encompass a range of considerations and it is not unusual for some people, both clinicians and patients, to have strong views on the alternative procedures. As expected, many potential participants did have preferences for one approach or the other, and it was partly because we anticipated this that we included preference groups alongside the randomised core of the study. By enrolling surgeon/gastroenterologist pairs who were uncertain about the place of minimal access surgery in this context, we aimed to avoid clinician preferences. However, the differential recruitment to the preference groups in the clinical centres, in part reflecting which clinician actually first saw a potential participant, showed that there were differences in clinical perspective. This became a problem within the randomised comparison on the (relatively few) occasions in which a patient recruited by one clinician was deemed unsuitable for surgery by another clinician in the same centre.

To make the study more attractive to potential participants, those allocated medical management underwent a review of their medication to 'optimise this', rather than just carrying on with their existing regimen. This may be the reason why the types of PPI taken at follow-up differed from those at the time of trial entry (predominantly lansoprazole at entry, but omeprazole or lansoprazole equally at follow-up).

People suitable for the trial were not easy to identify. Most patients on long-term PPI treatment are managed in general practice, often through a repeat prescription system. We used a combination of three approaches: retrospective case note review to identify potentially eligible patients who had been seen in a participating hospital; prospectively, especially through endoscopy clinics; and (in selected centres) advertisements to the general public. All potentially eligible people had to be assessed clinically and they were only then formally approached about the trial. This was extra work over and above normal clinical duties, often through specially established monthly clinics. As described in Chapter 2, the numbers enrolled in individual centres tended to be small, reflecting all of these constraints. In the event, we found that those who agreed to join the randomised trial had characteristics mid-way between those of the two preference groups.

What we did not predict were the long waiting times for surgery in many centres. This was due to ambiguity about the responsibilities of participating hospitals in terms of the extra treatment costs of surgery. The intention had been that surgical slots would be pre-booked for

the trial and that participants randomised to surgery would take the next available of these slots. In the event, emergencies such as cancer cases were given precedence, sometimes with repeated postponements of REFLUX trial patients. Anecdotally, long delays were an important factor in the decision of some of those participants allocated surgery ultimately not to have surgery. Delays became intractable in a few centres to the extent that special subvention funds were eventually found to allow the operations to be performed without any impact on normal clinical services. The availability of such funds to all centres from the start of the trial would almost certainly have overcome much of the waiting list problem.

In retrospect, given the long waits for surgery, it might have been better following enrolment to delay random allocation until there was a definite operation appointment. However, the likely impact would have been significant uncertainty amongst those enrolled about what they had agreed to, and greatly reduced numbers actually randomised (with some operations still postponed).

The standard rule in most trials is to time follow-up from randomisation. This was not appropriate in this trial because of the variable time between randomisation and surgery, exacerbated by the waiting list problem. The protocol specified follow-up at times equivalent to 3 and 12 months after surgery. It was important to have follow-up in the medical groups at equivalent times. We arranged this by pairing surgical and medical participants such that follow-up was linked and at (about) the same time after randomisation. The success of this manoeuvre can be assessed in *Tables 23* and *26*.

The large number of participants who did not get the management that they had been allocated to did have an impact on the results. For example, only 20% (10/50) of those allocated surgery who were taking reflux-related drugs at the 3-month follow-up had actually had surgery. As discussed earlier in this chapter, we have gone to some lengths to explore the likely impact of this non-adherence to the trial allocation. One way is through per protocol analyses limited to those randomised who received their allocated management. The second way is through an adjusted approach as a way of attempting to circumvent the likely selection bias of per protocol analyses. In this study the direction of effects was so clear, irrespective of the way that the analysis was performed, that the main issue became the size of effects. These did vary substantially (see, for example, *Table 29*) and this could be very important when policy decisions are being made, for example in the context of an economic evaluation. The approach that we took to address this in our economic analyses is described in the next two chapters.

One reason why we elected to have parallel non-randomised preference groups was to get more experience of the two forms of management. This particularly applied to surgery. Complications amongst the 319 participants who actually had fundoplication were rare (*Table 22*). Two operations were converted to open procedures, there were six visceral injuries and two pneumothoraces, and there were three admissions to a high dependency unit with no admissions to an intensive care unit. Patients stayed in hospital for a median of only 2 days. Three had reoperations and three had operations related to oesophageal stenosis.

As discussed in the following two chapters, an important measure of outcome is the proportion of patients continuing to take reflux-related drugs, especially after surgery. Rates did go up somewhat between the 3-month and 12-month assessment. Our rate of 11–14% at 12 months is higher than that in some other studies although estimates do vary both above and below this. Funding for this project was for follow-up to the time equivalent to 12 months after surgery. We have, however, instituted further annual follow-ups using similar questionnaires to those used at 3 and 12 months. Further follow-up will be important for assessing whether the benefits of surgery are sustained or whether differences in health status further narrow over time. We expect to report this after 5 years of follow-up are available for all participants.

The next two chapters on the economic evaluation reflect the position that we are in currently, having only 1 year of follow-up data, while recognising that long-term lifetime effects are likely to determine whether laparoscopic fundoplication is cost-effective. First, the within-trial cost-effectiveness analyses reported in Chapter 7 are developed within an economic framework. Then, an economic model is used to explore and extrapolate cost-effectiveness over a longer-term perspective.

Chapter 7

Within-trial cost-effectiveness results

Introduction

This chapter presents the within-trial cost-effectiveness analysis comparing laparoscopic fundoplication with medical management. Mean costs and health outcomes per patient are evaluated over 1 year using data from the REFLUX trial. The analysis is conducted from the perspective of the health and social care services. Costs are at 2006 prices and include the use of reflux-related health-care resources. Costs and outcomes are not discounted for this 1-year analysis.

Methods

Patients included

We compare the treatment strategies of immediate laparoscopic fundoplication with continued medical management on an intention to treat basis. The analysis includes data from 318 REFLUX patients (154 in the surgery group and 164 in the medical management group) who were randomised to a treatment strategy and who were followed up for a time equivalent to at least 1 year after surgery. We do not model the wait for surgery, that is, we model a best practice situation.

Because, as described in Chapter 6, the management of a high proportion of patients did not comply with their randomised treatment allocation, we also conducted a secondary analysis of the use of resources, costs and HRQoL for patients who received randomised per protocol treatment. However, it should be noted that these data are potentially biased, as described in Chapter 6.

Resource use

The use of the following health-care resources was collected retrospectively from clinical questionnaires for patients receiving randomised surgery: the use of endoscopy, pH monitoring and manometry prior to surgery; the length of time in surgery; and length of stay in wards, high dependency units and intensive therapy units post surgery. The trial also recorded whether patients had revision of surgery or non-randomised surgery, but did not collect detailed use of health-care resources or length of stay for these patients.

The use of anti-reflux medication taken in the previous 2 weeks was recorded at baseline and at each follow-up by questionnaires completed by the patients. There was a small amount of missing data for use of medication, which was handled as follows. If the patient confirmed that they were using an anti-reflux medication but did not report the dose, the median dose for other patients using that medication was imputed. All patients were assumed to be on medication at baseline as this was an inclusion criterion for entry into the REFLUX trial. If no medication was declared the missing data were imputed as the mean cost per day. We assume that all patients randomised to surgery undergo their procedure immediately and discontinue medication at that point unless they declare use of medication at a subsequent follow-up. The total cost per patient of anti-reflux medication was calculated using the trapezium rule using linear interpolation between follow-up points.[98,99]

The REFLUX trial recorded use of the following health services for the previous 3 months at first follow-up (at a time equivalent to 3 months after surgery) and second follow-up (at a time equivalent to 12 months after surgery): visits to and from general practitioners; visits to outpatient clinics; and admissions to hospital during follow-up. These questionnaires did not record use of health services between the third month and the ninth month. To capture these data a postal survey of patients was undertaken in May 2006 asking patients about the use of health services at any time during the first year. The cost of use of hospital and community health services for each patient during the first year was estimated as the greater of the sum of the first and second follow-ups compared with the use of resources reported in the postal survey.

Unit costs

Costs per patient were calculated by multiplying use of health-care resources as collected in the trial by unit costs taken from surveys and published data sources (*Table 32*).

TABLE 32 *Mean (SE) use of health-care resources and costs for patients according to intention to treat and followed up for 1 year*

				Medical (*n* = 164)				Surgical (*n* = 154)			
	Unit cost (£)	**Source[a]**	**Unit of measure**	**Any use (%)**	**Mean use**	**Mean cost (£)**	**SE (£)**	**Any use (%)**	**Mean use**	**Mean cost (£)**	**SE (£)**
Randomised surgery											
Endoscopy	172	1	Tests					59	0.59	102	7
pH tests	64	1	Tests					47	0.47	30	3
Manometry	61	1	Tests					45	0.45	27	2
Operation time	4	1	Minutes					68	77.34	284	18
Consumables	825	1								558	31
Ward	213	2	Days					68	1.91	407	22
ICU	1470	2	Days					0	0.00	0	0
HDU	628	2	Days					2	0.03	20	20
Total surgery										1428	74
Visit to GP	24	3	Visits	45	1.21	29	4	44	1.18	28	4
Visit from GP	69	3	Visits	1	0.01	1	1	1	0.01	1	1
Outpatient	142	2	Visits	15	0.30	43	9	35	0.46	65	9
Day case	460	2	Admit	12	0.17	79	19	32	0.38	173	24
Inpatient	1378	2	Admit	2	0.02	34	17	3	0.03	36	18
Non-randomised surgery	2596	2	Admit	5	0.05	142	46	0	0.00	0	0
Visit costs						328	63			304	38
Medication costs		4				179	10			55	7
Total costs						506	63			1786	88

HDU, high dependency unit; ICU, intensive care unit; SE, standard error.

a Sources of unit costs used in the analysis: (1) mean unit costs of a survey of five participating centres 2003, updated for inflation;[100] (2) published national mean reference costs 2005/2006;[103] (3) published national mean estimates 2005;[64] (4) *British National Formulary* 2006.[20]

The use and costs of consumable items and laparoscopic surgical equipment was collected by a survey in 2003 of five centres participating in the trial, described in detail in Chapter 3 of this report.[100] This survey also estimated the mean cost per hour in surgical theatre in each centre, based on the use of staff in each centre and national salary scales.[64] The mean unit costs estimated by this survey were then applied to all centres in the within-trial cost analysis, updated for inflation.[64]

Quality-adjusted life-years

The outcome used in the cost-effectiveness analysis was the difference in mean QALYs between the treatment groups. HRQoL was assessed at baseline and at each follow-up using the EQ-5D instrument. QALYs for each patient over the year of follow-up were calculated as the area under the curve using the trapezium rule, that is, assuming linear interpolation between follow-up points. The difference in mean QALYs per patient between the treatment groups was estimated using ordinary least squares regression, adjusting for baseline differences in EQ-5D between individuals. Bootstrap methods (resampling with replacement)[101] were used to estimate confidence intervals for the differences in mean costs and QALYs and the correlation between them. Uncertainty regarding the treatment decision was represented using cost-effectiveness acceptability curves.[74] These show the proportion of samples from the data in which each therapy is the more cost-effective across a range of alternative threshold values that the health-care system may be willing to pay for a QALY.[102]

Results

Use of health-care resources

Table 32 shows the average use of reflux-related health-care resources in the two groups at 1 year according to intention to treat. Nine patients randomised to medical management underwent laparoscopic surgery and 50 patients randomised to the surgical group did not receive surgery. Although the intention to treat analysis is unbiased, it is not very informative for describing the use of health-care resources, which depend on the treatment actually received.

Table 33 shows the average use of health-care resources according to the randomised per protocol analysis. Patients randomised to and who received laparoscopic fundoplication spent an average of 115 minutes in theatre and 2.4 days in wards postoperatively. Only one patient out of 104 required the use of a high dependency unit. During the year of follow-up similar numbers of patients in each group required use of general practitioner services but patients who had surgery tended to require more outpatient visits and day-case admissions. At the 12-month follow-up, 14 out of 104 (13%) in the surgical arm (who had surgery) had used anti-reflux medications in the past 2 weeks compared with 144 out of 155 (93%) in the medical arm who did not have surgery. A proportion of those not reporting use of prescription medications, however, were missing data, were using over-the-counter pharmaceuticals, had stopped temporarily or had stopped for non-reflux-related reasons such as pregnancy. No patients randomised to surgery required revision of the fundoplication procedure during the year.

Costs

Total mean costs per patient over the year on an intention to treat basis were £1786 for patients randomised to surgery and £506 for patients randomised to medical management (*Table 32*), a difference of £1280 (95% CI £1054–£1468) (*Table 34*). The mean cost per patient of the surgical procedure and hospital admission for those randomised to and who underwent surgery was £2012 (SE £41) (*Table 33*).

Quality-adjusted life-years

The HRQoL of patients, measured using the EQ-5D, tended to improve on average in the surgical group over the year of the analysis but not in the medical management group (*Tables 35 and 36*). After adjusting for baseline differences in HRQoL, patients gained 0.066 more QALYs (95% CI 0.026–0.107) during the trial period compared with medical management using an intention to treat analysis.

Cost-effectiveness

The estimated mean ICER is around £19,000 per QALY using intention to treat (*Table 34*). Bootstrap simulations were undertaken to estimate the uncertainty around the treatment decision. At a cost-effectiveness threshold ICER of £20,000 per QALY, surgery has a probability of 46% of being cost-effective, and at a threshold of £30,000 per QALY surgery is 86% likely to be cost-effective (*Figure 16*). This indicates that there is considerable uncertainty about whether surgery is cost-effective using the REFLUX trial data.

TABLE 33 *Mean (SE) use of health-care resources and costs for patients receiving their randomised treatment per protocol and followed up for 1 year*

				Medical (*n* = 155)				Surgery (*n* = 104)			
	Unit cost (£)	Source[a]	Unit of measure	Any use (%)	Mean use	Mean cost (£)	SE (£)	Any use (%)	Mean use	Mean cost (£)	SE (£)
Endoscopy	172	1	Tests					88	0.88	151	6
pH tests	64	1	Tests					70	0.70	45	3
Manometry	61	1	Tests					66	0.66	40	3
Operation time	4	1	Minutes					100	114.50	420	14
Consumables	825	1								825	0
Ward	213	2	Days					100	2.34	500	28
ICU	1470	2	Days					0	0.00	0	0
HDU	628	2	Days					1	0.05	30	29
Total surgery										2012	41
Visit to GP	24	3	Visits	44	1.16	28	5	44	1.14	27	5
Visit from GP	69	3	Visits	1	0.01	1	1	2	0.02	1	1
Outpatient	142	2	Visits	14	0.30	43	7	43	0.54	76	9
Day case	460	2	Admit	10	0.14	65	8	42	0.47	217	15
Inpatient	1378	2	Admit	3	0.03	36	6	4	0.04	53	7
Visit costs						173	38			375	49
Medication costs		4				183	10			18	5
Total costs						356	40			2405	69

HDU, high dependency unit; ICU, intensive care unit; SE, standard error.

a Sources of unit costs used in the analysis: (1) mean unit costs of a survey of five participating centres 2003, updated for inflation;[100] (2) published national mean reference costs 2005/2006;[103] (3) published national mean estimates 2005;[64] (4) *British National Formulary* 2006.[20]

TABLE 34 *Cost-effectiveness results for patients according to intention to treat and followed up for 1 year*

	Mean (95% CI)
Difference in mean costs (£)	1280 (1054–1468)
Difference in mean QALYs	0.066 (0.026–0.107)
ICER (£/QALY)	19,288
Probability surgery is cost-effective when threshold = £20,000	46%
Probability surgery is cost-effective when threshold = £30,000	86%

ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.

TABLE 35 *Predicted unadjusted HRQoL and QALY and adjusted QALY for baseline differences in HRQoL for patients according to intention to treat and followed up for 1 year*

	Medical (*n* = 164)		Surgical (*n* = 154)	
	Mean	SE	Mean	SE
Baseline EQ-5D index	0.723	0.020	0.721	0.020
First follow-up EQ-5D	0.693	0.024	0.781	0.020
Second follow-up EQ-5D	0.709	0.021	0.754	0.020
Unadjusted QALY	0.704	0.020	0.773	0.017
QALY adjusted for baseline differences in EQ-5D	0.703	0.014	0.770	0.015

QALY, quality-adjusted life-years; SE, standard error.

TABLE 36 *Predicted unadjusted HRQoL and QALY and adjusted QALY for baseline differences in HRQoL for patients receiving randomised treatment per protocol and followed up for 1 year*

	Medical (*n* = 155)		Surgical (*n* = 104)	
	Mean	SE	Mean	SE
Baseline EQ-5D index	0.736	0.020	0.722	0.023
First follow-up EQ-5D	0.700	0.024	0.800	0.024
Second follow-up EQ-5D	0.710	0.022	0.777	0.023
Unadjusted QALY	0.710	0.019	0.786	0.020
QALY adjusted for baseline differences in EQ-5D	0.706	0.014	0.793	0.017

QALY, quality-adjusted life-years; SE, standard error.

Sensitivity analyses

Whether a hospital visit was classified as a day-case admission or an outpatient visit could differ between providers even if similar procedures were undertaken. As a sensitivity analysis, if all of the visits classified as day-case admissions in the trial incurred the average cost of an outpatient visit, this would reduce the incremental mean cost by £90, from £1280 to £1190. If all visits incurred the average cost of a day-case admission, this would increase the incremental cost by £76 to £1356.

A cost-effectiveness analysis was also undertaken for patients who received randomised treatment per protocol and who were followed up for 1 year (*Table 37*). This estimated a greater mean difference in health benefit than the intention to treat analysis (0.088 QALYs) but a greater difference in mean

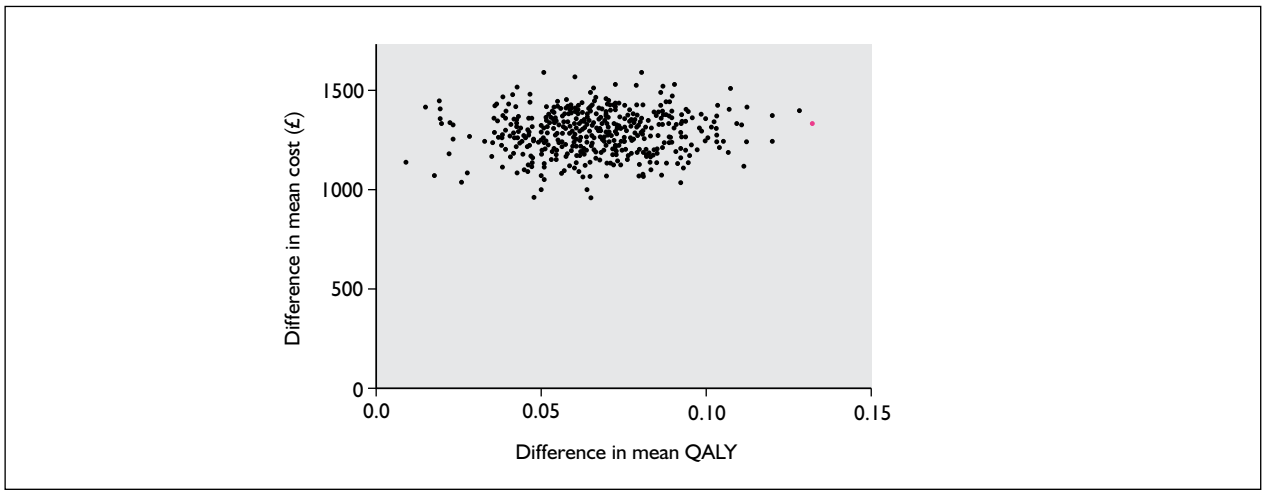

FIGURE 16 *Cost-effectiveness plane for laparoscopic surgery versus medical management using an intention to treat analysis. This figure shows the difference in mean cost and difference in mean quality-adjusted life-years (QALYs) per patient in 1000 bootstrap simulations of the data.*

TABLE 37 *Cost-effectiveness results for patients receiving randomised treatment per protocol and followed up for 1 year*

	Mean (95% CI)
Difference in mean costs (£)	2049 (1907–2198)
Difference in mean QALYs	0.088 (0.046–0.130)
ICER (£/QALY)	23,284
Probability surgery is cost-effective when threshold = £20,000	19%
Probability surgery is cost-effective when threshold = £30,000	80%

ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-years.

cost per patient (£2049), and found surgery to be slightly less cost-effective with an ICER of £23,284.

Further sensitivity analyses were undertaken and are described in the cost-effectiveness modelling chapter (Chapter 8).

Discussion

Cost-effectiveness analysis is intended to inform two separate decisions. First, which strategy (medical management or laparoscopic fundoplication) is most cost-effective for the management of patients with reflux who are stable on medication from the perspective of the NHS and, second, what value there is in acquiring further information about these strategies.

This chapter presented the expected differences in costs and health outcomes between laparoscopic surgery and medical management over 1 year using the REFLUX trial data only. Surgery was on average more effective (in terms of QALYs gained over 1 year) but more costly. The ICER of £19,000 suggests that laparoscopic fundoplication might be cost-effective given that the threshold value in England and Wales is between £20,000 and £30,000.[102] However, there is still considerable uncertainty about this result (probability that surgery is cost-effective between 46% and 86%). The main limitation, however, is that the within-trial analysis ignores events, costs and health benefits that accrue after 1 year. The benefits of surgery are likely to be experienced by patients over the longer term,[104] and the costs of medical management, even with widespread use of generics, are considerable when continued over a patient's lifetime. Conversely, although no revisions of laparoscopic fundoplication were observed in the randomised surgical group over 1 year in this trial, the procedure may fail in the longer term.[105]

More generally, new trials have to be placed in the context of existing evidence. Other randomised trials, and observational studies, have evaluated these strategies in the United Kingdom and elsewhere. A modelling framework can be used to

extrapolate events, costs and health outcomes over a longer time horizon and to synthesise data from different sources to evaluate cost-effectiveness.[106] A modelling framework can also inform decisions about whether, and with what purpose, further research is needed. Value of information analysis can help to identify which variables contribute most to the overall uncertainty in the treatment decision and to quantify the benefits that would arise from having further information about these parameters.[107] To address these questions, a revised version of the decision model described in Chapter 3, updated with the evidence from the first year of the REFLUX trial, is described in the next chapter of this report.

Chapter 8
Cost-effectiveness analysis

Introduction

The REFLUX trial compared a strategy of laparoscopic surgery with one of continued medical management for patients with reasonable symptom control on anti-reflux medications. Data are now available from the clinical trial for at least 1 year after surgery for all patients. However, as discussed in the preceding chapter, as reflux is a chronic disease, an analysis that considers only events, costs and health benefits accruing over 1 year is too restricted. To accurately determine cost-effectiveness, and the value of conducting further research, a modelling approach is required that extrapolates costs and health benefits over an appropriate time horizon and allows the synthesis of evidence from different sources. This chapter describes a long-term decision-analytic model including evidence from the REFLUX trial and other sources.

The model presented here differs somewhat from the preliminary model described in Chapter 6. The preliminary model required evidence of the underlying disease process, that is, knowledge of whether treatment failure was temporary or permanent. Further treatment, such as dose adjustment, withdrawal of medication or revision of surgery, was then carried out conditional on the type of failure that occurred. However, in the reports from clinical trials, including the REFLUX trial, the follow-up points are infrequent and/or the underlying disease is rarely observed or described consistently. On the other hand, the treatments administered during follow-up are usually well recorded in these reports. Therefore, the model has been revised to define treatment failure in terms of change in treatment rather than return of symptoms.

Methods

Model structure

In the model patients follow a strategy of either immediate laparoscopic surgery or continuation of medical management (without an option of surgery following failure of medical management). In principle, immediate open surgery is feasible in this patient group but it is not considered here because it is widely considered to have been superseded by laparoscopic surgery, although conversion to open surgery is an option when laparoscopic surgery fails. Patients are assumed to be male and aged 45 when entering the model, which is the median age and commoner gender of patients in the REFLUX trial. Costs and health benefits are discounted at 3.5% per year and the price year is 2006.

The model structure is represented by *Figure 17*. As mentioned above, we define treatment failure following surgery as a change of treatment. Two options are considered for patients who fail surgery: patients may return to the use of anti-reflux medication or they may undergo a revision of surgery.

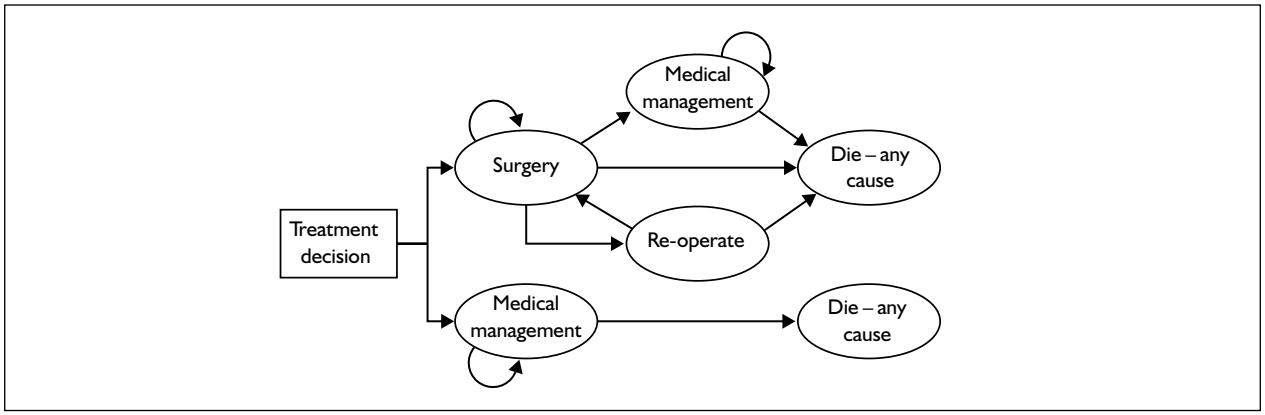

FIGURE 17 *Model structure diagram.*

It is assumed that patients randomised to receive surgery who are found to be using medication at the end of a clinical trial are doing so to control reflux symptoms or symptoms related to surgery. It is further assumed that such patients will incur costs of medication indefinitely.

Although, in practice, patients who fail surgery may recommence anti-reflux drugs followed by revision of surgery, data on sequences of therapies were not available and so these events are treated as mutually exclusive competing risks in the model. Patients are assumed to have the same prognosis following revision as surgical patients who were not reoperated on.

To estimate the rates of return to medical management and revision of surgery, all of the available studies, whether randomised or not, are treated as observational data. The rates of failures could simply be estimated as the total number of events divided by the total patient years of exposure (*Tables 38* and *39*), which would estimate the rate of return to medical management as 4.8 per 100 patient-years. This estimate ignores any between-study heterogeneity, which might arise from patient selection, definition of outcomes, study design, surgical technique or other sources.

To assess the assumption of homogeneity we also estimated the rate using a random effects Poisson regression using the statistical package WinBUGS® (see Appendix 11 for code).[113] We also explored whether any observed factors (length of follow-up, study design) might explain some of the heterogeneity, but these variables were not found to be statistically significant and were omitted from the final model.

A state of treatment failure for patients following medical management is not defined because there is no feasible alternative treatment, that is, in this model (unlike the preliminary model), surgery is not an option for patients following medical management. The estimates of mean HRQoL after successful surgery and after medical management, and the standard errors, are those observed in the randomised REFLUX trial at 1 year as there are no other randomised trials comparing surgery with medication that have used a preference-based utility instrument (see Chapter 6 for details of HRQoL data collected in the trial). HRQoL following treatment failure is estimated by the mean EQ-5D of all surgical patients (preference or randomised to surgery) who returned to medical management or required revision of surgery by 1 year. The base-case assumption in the model is

TABLE 38 *Surgical patients requiring medical management: results of laparoscopic surgery arms of randomised trials or observational studies*

Study	Number of subjects	Years of follow-up	Exposure (person-years)	Number of failures	Rate of failure per person-year	Proportion of failures at end of study (%)
Mahon *et al.*, 2005[108]	109	1	109	2	0.018	1.8
Booth *et al.*, 2002[42]	179	4	716	19	0.027	10.6
Bammer *et al.*, 2001[57]	171	6.3	1094	24	0.022	14.0
Contini *et al.*, 2002[38]	103	1	103	5	0.049	4.9
Pessaux *et al.*, 2002[45]	1470	3	4410	60	0.014	4.1
Papasaras *et al.*, 2005 [109]	289	2	578	150	0.260	51.9
Granderath *et al.*, 2002[110]	27	4	108	2	0.019	7.4
Dassinger *et al.*, 2004[111]	52	5	260	11	0.042	21.2
Bloomston *et al.*, 2003[112]	100	1	100	19	0.190	19.0
Bloomston *et al.*, 2003[112]	84	4	336	31	0.092	36.9
Vidal *et al.*, 2006[105]	124	4.3	533.2	10	0.019	8.1
Madan and Minocha, 2006[104]	100	3	300	80	0.267	80.0
Laine *et al.*, 1997[67]	18	1	18	0	0.000	0.0
REFLUX trial, 2006	104	1	104	14	0.135	13.5
All studies			8769	427	0.049	

TABLE 39 *Surgical patients requiring re-operation during follow-up: results of single arms of randomised trials or observational studies*

Study	Number of subjects	Exposure (years)	Number of failures	Rate of failure
Mahon *et al.*, 2005[108]	50	50	2	0.040
Booth *et al.*, 2002[42]	179	716	11	0.015
Bammer *et al.*, 2001[57]	171	1094	5	0.005
Contini *et al.*, 2002[38]	103	103	0	0.000
Pessaux *et al.*, 2002[45]	1470	4410	35	0.008
Laine *et al.*, 1997[67]	18	18	0	0.000
REFLUX trial, 2006	104	104	0	0.000
All studies		6495	53	0.008

that, although HRQoL decreases with age at the same rate as that in the age- and sex-matched general population, proportionate differences in HRQoL between health states are maintained over time.

To account for the decline in HRQoL with age, the HRQoL for each outcome observed at the end of the trial was compared with the average HRQoL of the general population aged from 45 to 55 years.[70] It was assumed that this proportionate decrement of HRQoL was constant as the cohort aged (*Table 40*). The age- and sex-stratified rate of death was taken from life tables,[115] assuming that this patient group has a similar life expectancy to the UK general population after surgery. There is a small risk of operative mortality, estimated in a literature review as 4 deaths in 4000 procedures (see Chapter 3).

During the first year of follow-up, 35% of patients require an outpatient visit and 35% a day-case or hospital admission following surgery compared with 15% who require an outpatient visit and 14% a day-case or hospital admission following medical management (see *Table 32*; Chapter 7). The Nordic GORD study[62] found that only a small proportion of patients required endoscopy after 12 months in either group, and here it is assumed that no further hospital admissions or outpatient visits are needed after 1 year other than revisions of surgery.

TABLE 40 *Mean (SE) HRQoL parameters used in the model*

Parameter	Mean	SE	Source
HRQoL following medical management	0.711	0.018	REFLUX trial EQ-5D in randomised medical arm at 1 year
Additional HRQoL following successful laparoscopic surgery compared with medical management	0.071	0.028	REFLUX trial EQ-5D in randomised surgery arm at 1 year (off drugs)
HRQoL following unsuccessful laparoscopic surgery (on medication)	0.686	0.048	REFLUX trial EQ-5D in all patients who failed surgery at 1 year
Average HRQoL during year if undergoing re-intervention	0.686	0.048	As for unsuccessful surgery
HRQoL for general population aged 45–55: men; women	0.84; 0.85		Kind *et al.*, 1999[71]
HRQoL for general population aged 55–65: men; women	0.78; 0.81		Kind *et al.*,1999[71]
HRQoL for general population aged 65–75: men; women	0.78; 0.78		Kind *et al.*, 1999[71]
HRQoL for general population aged 75+: men; women	0.75; 0.71		Kind *et al.*, 1999[71]
Prevalence of GORD in population aged 18–60	0.0045		McDougall *et al.*, 1996;[30] Trimble *et al.*, 1995[114]

GORD, gastro-oesphageal reflux disease; HRQoL, health-related quality of life; SE, standard error.

The model time horizon is a patient's lifetime. However, there are significant sources of uncertainty surrounding several model parameters given that the main source of data in the model, the REFLUX trial, has reported only 1 year of follow-up. To provide a point of reference, the model analysis starts from a set of assumptions that are similar to those used in the within-trial cost-effectiveness analysis presented in Chapter 7, which assumed that there were no differences in cost or health benefits beyond 1 year. This is unlikely to be the case and so a series of scenarios that relax these assumptions is explored, described in *Box 1*.

One way of proceeding with this analysis might be to vary the time horizon over which the model is run, from 1 year up to a lifetime, in a series of scenarios; however, this would be naïve. Reflux is a chronic disease and, therefore, the only reasonable analysis is over a lifetime. The role of scenario analysis is to explore different assumptions about HRQoL, costs and clinical events over this time horizon. The sources for the alternative assumptions are presented in Chapter 3.

Analysis

The model was implemented in R, a programming language,[116] as a discrete-time Markov model with a cycle length of 1 year. The model outputs were mean costs and QALYs in each treatment cohort. A probabilistic sensitivity analysis was used to represent the uncertainties in the model inputs.[117] Gamma distributions were assigned to the decrements in utility compared with perfect health and the costs used in the model. Log-normal distributions were assigned to the rates of surgical failure. Values were randomly sampled from these distributions in 1000 Monte Carlo simulations and these were used as inputs to the model to give 1000 calculations of costs and QALYs for the cohort. The ICER was calculated as the ratio of the difference in expected costs to the difference in expected QALYs. The overall uncertainty in the treatment decision arising from uncertainty in the model inputs is represented by the proportion of iterations in which laparoscopic surgery is cost-effective, given a threshold value for the ICER.

Results

Base-case analysis

The base-case analysis assumed that the relative treatment benefit from surgery endured for a lifetime, provided patients did not experience treatment failure. A summary of the assumptions used in the base-case analysis, and in alternative scenarios, is shown in *Box 1*.

Under base-case assumptions, surgery had an additional mean cost of £847 and additional mean QALYs of 0.37 over the lifetime of the patients (*Table 41*), which generates an incremental cost

BOX 1 *Assumptions used in the within-trial analysis and alternative scenarios explored using a series of sensitivity analyses (see Chapter 3 for data sources for assumptions)*

	Assumption			
Scenario number	Duration of cost of medication	Duration of relative health benefit of surgery	Annual rate of conversion from surgery to medical	Annual rate of reoperation
11 (within-trial analysis)	1 year	1 year	13% convert year 1, 0.0% thereafter	0.0%
15 (temporary QoL advantage)	Lifetime	5 years	13% per year up to year 2, 4.9% thereafter	0.0% year 1, 0.8% thereafter
16 (low rate of surgical failure)	Lifetime	Lifetime	4.9%	0.8%
17 (base-case)	Lifetime	Lifetime	13% per year up to year 2, 4.9% thereafter	0.0% year 1, 0.8% thereafter
18 (very high rate of surgical failure)	Lifetime	Lifetime	13% per year	0.8%
19 (high rate of surgical failure)	Lifetime	Lifetime	8% per year	0.8%

TABLE 41 *Results of sensitivity analyses. The numbered scenarios are described in Box 1*

Scenario	Cost M (£)	Cost S (£)	Cost difference (£)	QALY M	QALY S	QALY difference	ICER (£/QALY)	*p* (20k)	*p* (30k)
11 (within-trial analysis)	275	2302	2027	12.48	12.526	0.046	44,065	0.02	0.41
15 (temporary QoL advantage)	3933	4780	847	12.48	12.51	0.03	28,233	0.53	0.56
16 (low rate of surgical failure)	3933	4433	500	12.48	13.039	0.559	894	0.87	0.87
17 (base-case)	3933	4780	847	12.48	12.848	0.369	2295	0.74	0.77
18 (very high rate of surgical failure)	3933	5245	1312	12.48	12.596	0.116	11,310	0.56	0.57
19 (high rate of surgical failure)	3933	4870	938	12.48	12.805	0.325	2886	0.73	0.74

ICER, incremental cost-effectiveness ratio; M, medical management; QALY, quality-adjusted life-year; S, laparoscopic surgery; *p* (20k), probability surgery is cost-effective at a threshold ICER of £20,000; *p* (30k), probability surgery is cost-effective at a threshold ICER of £30,000.

per additional QALY of about £3000. Uncertainty arising from imprecision of estimates of mean parameter values using base-case assumptions was characterised using a probabilistic sensitivity analysis. This showed that, at a threshold ICER of £20,000, surgery was about 74% likely to be cost-effective. However, this underestimates the uncertainty because the base-case model assumes the same imprecision about mean values of parameters for all years in the model, whereas the data on HRQoL is available only for the first year.

Alternative scenarios

Under the base-case assumptions, laparoscopic fundoplication is cost-effective compared with medical management at a relatively low threshold ICER. This is because we assume that, although the annual costs of treatment on medical management are relatively modest, these costs accrue over a lifetime and offset much of the upfront cost of surgery. Furthermore, there is an HRQoL advantage of surgery over medical management that is assumed to persist in the long term. We explored how alternative assumptions would affect these conclusions using different scenarios (*Table 41*). Surgery is not likely to be cost-effective if HRQoL after successful surgery is similar to that on medical management after 5 years (scenario 15) or if the annual percentage of patients who restart anti-reflux medication after surgery is similar to that observed in the first year of the REFLUX trial (13%) (scenario 18).

Value of information analysis

The value of conducting additional research that, in principle, would reduce parameter uncertainty can be estimated using value of information analysis. The expected value of perfect information (EVPI) is the amount that a decision-maker should be willing to pay to eliminate all uncertainty that arises because of imprecision in the parameters of the model. The partial EVPI represents the amount a decision-maker should be willing to pay to eliminate all uncertainty in individual parameters or a subset of parameters, given the uncertainties elsewhere in the model.

To illustrate this we estimated the EVPI and partial EVPI for five sets of parameters: (1) the HRQoL of patients who fail surgery; (2) the estimates of HRQoL for all other model states; (3) the estimates of the annual rates of failure of surgery; (4) the estimates of unit costs used in the model; and (5) the rate of return to medical management post surgery together with the HRQoL of patients who fail. The analysis requires an estimate of the percentage of the population who would be eligible for surgery if it were cost-effective. A Spanish population survey (both sexes, ages 40–79 years) found that 287 out of 2500 (11%) interviewees used anti-reflux drugs, and 119 (4.8%) were stable (not having had reflux symptoms in the past year), although 43 (1.7%) acknowledged taking anti-reflux drugs to prevent symptoms.[118] This might be considered a conservative estimate of patients who could be considered for surgery. If we assume that about one-half of these might be excluded because of age, preference or co-morbidity, then prevalence is estimated at 1% of this population, equivalent to about 160,000 people in the UK.[115] *Figure 18* shows an estimate of population EVPI at a range of values of the threshold ICER. EVPI in this case is increasing with the threshold ICER because at higher values of the ICER we are more willing to pay for the health benefits associated with surgery (and therefore more certain that surgery is the correct decision), but the consequences of a wrong decision are also greater (in terms of loss of health and wasted resources) and we are willing to pay more to avoid the possibility of these losses. Because the population is large, the model indicates that the EVPI is £300 million at a threshold ICER of £30,000, indicating that we would be willing to pay up to this to eliminate all of the uncertainty in the decision.

Figure 18 also shows the partial EVPI for selected sets of parameters. Partial EVPI is greatest for the rate of return to medical management post surgery together with the HRQoL of patients who fail. This indicates that almost all of the variation affecting the treatment decision is due to the interaction of these two parameters. Relatively little information is available on the HRQoL of patients who fail surgery; this could be captured in a longer follow-up but does not necessarily require a randomised trial. *Figure 18* shows relatively little value of information in other parameters. However, this analysis does not on its own capture all of the uncertainty in the decision for two reasons. First, we have used mean estimates of HRQoL collected in a short-term trial to extrapolate over the longer term, without adjusting standard errors to take account of this additional uncertainty. There is, therefore, additional uncertainty over long-term differences in HRQoL, which is not captured in this value of information analysis. Second, we have assumed that the pooled rates of failure from observational studies of between 1 and 6 years are generalisable to our population, and that these rates will continue over the long term. We have attempted to represent this uncertainty as a series

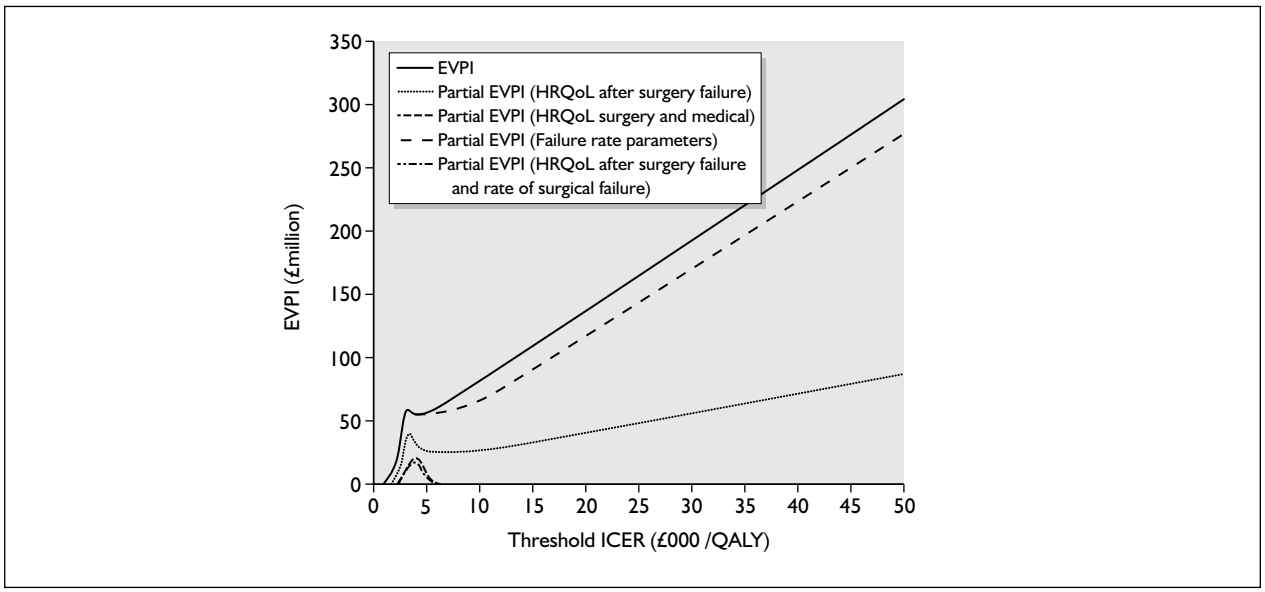

FIGURE 18 *Expected value of perfect information (EVPI) assuming a population of 160,000 patients in England and Wales, and partial EVPI for three sets of parameters: (1) all HRQoL parameters; (2) HRQoL after surgery failure; and (3) failure rates for surgery.*

of scenario analyses. Taken together, this implies value in a continuing long-term follow-up to the randomised trial. The question remains, however, over how long this follow-up should optimally be.

Discussion

This chapter has presented a decision-analytic model comparing laparoscopic surgery with medical management, using data from the REFLUX trial and other sources to estimate cost-effectiveness over a lifetime. The results of this model are similar to those of the preliminary model presented in Chapter 6, which indicated that surgery was cost-effective but with a high degree of uncertainty. Other authors have examined the cost-effectiveness of laparoscopic surgery versus medical management. Cookson *et al.*[29] found that laparoscopic surgery broke even compared with medical management after 8 years and was cost saving thereafter. Romagnuolo *et al.*[28] evaluated cost-effectiveness over 5 years in a Canadian setting, in which both surgery and medical therapy is on average more expensive (generic formulations were not used in that model) than that found in the REFLUX trial and by Cookson in a UK setting. They concluded that there was little difference in HRQoL between the treatments and that surgery broke even relative to medical management after 3 years. Arguedas *et al.*[119] evaluated the strategies in a US setting with costs similar to Canada, assuming a relatively higher rate of symptom recurrence and failure of surgery, and relatively lower differences in HRQoL between the treatments, and concluded that medical therapy dominated surgery using a 10-year time horizon.

Although surgery seems likely to be cost-effective in terms of expected (mean) costs and health effects, there remains considerable uncertainty about this conclusion. Balances between risks and benefits and between costs and health gain will depend on patient characteristics such as age, the presence of serious co-morbidity and the severity of GORD symptoms. Furthermore, there are a number of practical issues to consider before the NHS could consider offering surgery to a wider range of patients who are currently stable on medical management. In particular, surgical capacity and availability of trained surgeons are potential barriers to implementation and should be addressed.

We have estimated the value of reducing some of the model uncertainty in the analysis of EVPI and partial EVPI, and through a series of scenario analyses. These have indicated that continued follow-up of the randomised trial would be valuable, particularly to obtain more information on HRQoL following surgery failure and the long-term difference in HRQoL between strategies. Further research to obtain more information on the long-term HRQoL and prognosis of patients would be valuable.

Chapter 9

Discrete choice experiment to measure preferences for treatment options

Introduction

This chapter reports an application of a discrete choice experiment (DCE) to measure patient preferences for treatment options for GORD. DCEs are increasingly recognised as an important method in health services research for measuring the strength of patients' preferences (utility) for treatments and methods of delivery of care.[120]

The aims of this work were to identify the strength of the trial participants' preferences for the different treatments and outcomes of GORD; to investigate whether these preferences differ between the different arms of the trial; and finally to identify whether the mean benefits associated with each treatment vary. It should be noted that the utilities produced by the DCE reflect the preferences of people with GORD for the treatment and outcomes of GORD. As such, they are different from the utilities used to generate QALYs, which were based on the responses to the EQ-5D questionnaire and reflect the public preferences for the outcomes following treatment of GORD. It is these latter utilities that are arguably most useful for priority setting within the NHS.[102]

In the following section a brief description of the DCE approach is provided. This is followed by the methods used to achieve the aims stated above and the subsequent results. Finally, a brief discussion is presented outlining the strengths and limitations of the approach and the implications of the findings.

The discrete choice experiment approach

DCEs are based on random utility theory,[121] which defines a set of assumptions about desires and transforms them into a demand function describing the actions of a consumer under a defined set of circumstances. The following five stages are undertaken when a DCE is performed:

- Identification of attributes (i.e. different dimensions of the process or outcome of care) that are potentially important to the people with the condition under study. This is performed by using literature reviews, group discussions, interviews and direct questioning of individual subjects. Sometimes there is a predefined policy question, in which case the dimensions may already be predefined,[122] although that is not the case in this study.
- Assigning plausible, actionable levels that are capable of being traded off. Again, these may be defined from the literature or by using any of the mechanisms mentioned above.
- Identification of the profiles to present to potential respondents. These profiles describe all of the possible configurations of the dimensions and levels identified in the first two stages. As the number of dimensions and levels increases, the number of possible profiles increases. Because of the potentially very large number of profiles that might exist, it is not desirable to present each profile to potential respondents. Various methods, for example computer software, catalogues (e.g. Hahn and Shapiro), websites and expert advice, are used to reduce the number of profiles for inclusion in the questionnaire to a manageable number while still allowing utilities to be inferred for all possible profiles. Within the DCE the scenarios must then be placed in choice sets. A number of approaches have been used to do this that vary in the extent to which they meet specific statistical design criteria (orthogonality, balance, minimum overlap and balanced utilities).
- Presentation of the choice sets to study participants. In the DCE, respondents are presented with the choice sets and asked to state which intervention they prefer. They make a series of choices and each choice indicates which scenario in a choice set would lead to the higher level of utility (or satisfaction or benefit).
- Data input and analysis using regression techniques and interpretation. This stage of the DCE helps establish the overall importance of dimensions, their relative importance, willingness of respondents to trade between them, and benefits (or utility scores) for the different combinations of levels of dimensions.

In addition to these five standard stages for a DCE, a sixth stage, specific to this study, was also added. In this stage the results of the DCE are combined with data from the trial on the actual level observed for each dimension for each treatment group. This provides a summary score for each treatment group, the treatment group with the highest score being associated with the greatest benefit.

Methods

The study was performed in two stages: a methodological stage to develop the questionnaire and an applied stage to derive the utility estimates for the different treatments and outcomes for GORD.

Identification of dimensions and levels

As reported earlier, a qualitative study was performed to identify the potential issues related to GORD and its treatment that are important to patients (Chapter 4). The dimensions selected, therefore, represent those issues that are concerns to patients undergoing treatment for GORD. Some of the identified factors were combined into themes and, from these, four dimensions were eventually defined. These dimensions are frequency of troublesome symptoms, chance of serious complications, chance of undergoing surgery and chance of needing lifelong medication. Several considerations were taken into account when identifying the levels of the dimensions. They had to be realistic and they had to be set up in such a way that individuals could consider trade-off between improvements. The levels of the dimensions were derived from the trial data and discussions with gastroenterology experts. *Table 42* provides a detailed description of the dimensions and levels that were used to develop the questionnaire.

Which scenarios to present

Once the dimensions and levels have been identified they are combined to generate combinations of dimension levels referred to as profiles. The four dimensions and four levels yield 246 possible profiles, too many to present to individuals. Therefore, a fractional factorial design was used to reduce the profiles to a manageable level while still being able to infer utilities for all possible profiles. Existing literature suggests that individuals can manage between 9 and 16 pairwise comparisons before they become bored or tired.[123] The identified design had 16 profiles and they were randomly split into two different questionnaires containing 8 questions (see Appendix 12). The design was derived from a web-based catalogue.[124–126]

Although profiles from fractional factorial designs have statistical properties for the estimation of parameters of general linear models, we needed to ensure that the choice sets generated from these profiles were statistically efficient. Therefore, tests for the properties of an efficient design were performed. The properties of an efficient design include:

- *Level balance* – this occurs when the levels of a dimension occur with equal frequency.
- *Orthogonality* – this is satisfied when dimension levels are not correlated, that is, the joint occurrence of any two levels of different dimensions appears in profiles with a frequency that is equal to the product of their marginal frequencies (Addelman 1962, cited in Zwerina *et al.*, 1996[126]). Therefore, the levels of dimensions appear in choice sets with equal frequency to each level of each other dimension.
- *Minimum overlap* – this means that the probability that a dimension level repeats itself in each choice set should be as small as possible, especially in instances when there is more than one choice, e.g. choice A and choice B. This is an important issue as the differences in dimension levels are only useful within a choice set if the respondents trade these levels. When this property is violated the choice sets provide no information on the dimension's value.

The set of alternatives is typically the same for all subjects and the explanatory variables are all choice specific. Individuals were asked to make a number of such choices, and using the responses from these the preferences for alternative profiles could be elicited.

Eliciting preferences

Once the scenarios to be presented to patients were identified, preferences for these scenarios were obtained by using a forced choice approach. An example of the choices presented to participants is shown in *Figure 19*; respondents were asked which option they would choose, 'A' or 'B'.

TABLE 42 *Dimensions and levels used to develop the questionnaire for the discrete choice experiment*

Dimension and description	Level of difficulty
Frequency of troublesome symptoms This aspect describes the frequency with which you may experience troublesome symptoms of GORD. These symptoms could include heartburn (a burning sensation that moves up the chest), acid reflux (an acid taste in mouth), excessive wind in lower bowel or trapped in stomach, difficulty eating and swallowing food, troublesome bowel movements (diarrhoea/constipation), and experiencing difficulty with lying down or getting to sleep	Not at all Once a week Two or three times a week Most days or every day
Chance of serious complications requiring hospitalisation This aspect refers to the possibility that you may experience complications/side effects as a result of your GORD treatment. These complications/side effects could lead to you spending a few days in hospital. They could include bleeding that could lead to anaemia, scarring of the oesophagus, or difficulty or pain when swallowing	1 in 800 (0.1%) people 1 in 500 (0.2%) people 1 in 300 (0.3%) people 1 in 100 (1%) people
Chance of undergoing surgery This aspect describes the chance that you might have to undergo any surgery to treat your GORD symptoms	1 in 20 (5%) people 1 in 3 (33%) people 2 in 3 (66%) people 5 in 6 (83%) people
Chance of needing lifelong medication This aspect describes the chance that you might have to take medication (e.g. PPIs) over a long period of time (months or years) for GORD	1 in 20 (5%) people 1 in 3 (33%) people 2 in 3 (66%) people 5 in 6 (83%) people

GORD, gastro-oesophageal reflux disease; PPI, proton pump inhibitor.

One important issue in preference elicitation is whose preferences should be elicited. Patients with the experience of both disease and treatment were considered appropriate for this study and therefore the completed questionnaire was sent to all active participants in the REFLUX trial during August 2006.

Piloting the questionnaire

The sample for piloting the questionnaire was obtained from individuals attending a gastroenterology clinic in Aberdeen. Patients were screened by a clinician and those assessed as having GORD were asked to complete the DCE

Choice 1 Which option would you choose?

	Option A	Option B
Frequency of troublesome symptoms	Most days or every day	Not at all
Chance of serious complications requiring hospitalisation	1 in 500	1 in 300
Chance of undergoing surgery	1 in 3	2 in 3
Chance of needing lifelong medication	5 in 6	1 in 20
(Tick one box only)	☐ option A	☐ option B

FIGURE 19 *Example of discrete choice experiment question presented to trial participants.*

questionnaire with a researcher (LV). The aim of the pilot work was to ensure that the guidance notes provided with the questionnaire were clear and that patients could understand them and that they were able to perform the task of making choices. The respondents were asked to complete the questionnaire using the guidance information provided and they were then asked about its readability and acceptability. They indicated that the guidance notes were clear and easy to understand and that they were able to answer the questions without much difficulty.

Consistency of responses

An important aspect of a DCE is that respondents should behave in a rational manner when making choices. Rationality within DCEs is mainly tested using non-satiation (dominance) tests. These tests are, however, perceived as easy to satisfy.[120] For this reason more sophisticated expansion property tests were conducted.[127] This involved adding two consistency questions to the questionnaire.

Respondents were first asked to choose the worse of two situations (A or B). In the consistency question, which was presented as a non-consecutive question, this choice was widened to a set of three situations (A, B or C). As with the simple two situation question, respondents were asked to choose one of the three situations (see example of both questionnaires in Appendix 12). A respondent was believed to behave rationally if the choice they made in the two situation question did not conflict with the choice they made when faced with the three situation question. For example, if the respondent choose situation B in the first choice set, then they should not choose situation A in the expanded choice set. Similarly, if the respondent chose situation A in the first choice set, then they should not choose situation B in the expanded choice set.

A sensitivity analysis was performed that excluded those respondents who failed the consistency test (i.e. they gave an inconsistent response in both consistency questions).

Estimating utilities

To establish the importance of the various dimensions, the relationship between the dimensions and utility must be specified. The linear additive model assumes that the overall valuation or utility derived from any combination of dimensions is given by the sum of the values of the separate dimensions. In this model the reference group for the modelling analysis was the best level of each dimension. This means that the results from the DCE will be able to illustrate how the different combinations of dimensions and levels compare with the best possible combination of dimensions and levels from the DCE.

The linear additive model for a simple model was specified as:

$$U = \beta_1 \text{frequency} + \beta_2 \text{frequency} + \beta_3 \text{frequency} + \beta_4 \text{serious complications} + \beta_5 \text{surgery} + \beta_6 \text{lifelong medication}$$

where 'U' is the utility or preference score for an outcome with a given level of each dimension; 'frequency' is the occurrence of troublesome symptoms and, as it was a categorical variable, dummy values were used for the analysis for each level; 'serious complications' is the chance of complications requiring hospitalisation; 'surgery' is the chance of undergoing surgery; and 'lifelong medication' is the chance of needing lifelong medication. The parameters β_1–β_6 are the coefficients of the model to be estimated.

The coefficients indicate the relative importance, or weight, of a unit change in that dimension in terms of overall benefit. The rate at which respondents are willing to trade between these dimensions (i.e. how much of the dimension they are willing to give up for improvements in other dimensions) is shown by the ratio of the coefficients (i.e. the marginal rate of substitution). For example, β_5/β_6 indicates how much of a change in the chance of having lifelong medication would be required if there was a 10% change in the chance of having surgery so that overall utility remains constant.

The internal validity (the extent to which the results are consistent with economic theory or a priori expectations) of the DCE can be determined by the results from the regression analysis. Given that the higher the chance an episode will be experienced, the less it will be preferred, we anticipated that the dimensions would have a negative sign in the regression equation.

Econometric techniques were used to analyse the DCE responses and to estimate a value such that the utility weights could be estimated for all of the outcomes in the instrument. As described above, the best level was used as the comparator for all dimensions. As participants provided multiple responses, a conditional fixed-effects logistic regression model was used to analyse the response data. Two models were estimated: a main model

that measured preferences across the whole group and a further model that was used to establish whether the responses of individuals differed based upon the trial group to which they belonged. Although it would be possible to estimate a regression model for each arm of the study (i.e. to estimate four separate models), it would not be appropriate to make comparisons between the models. A more appropriate way of considering the effect that people's initial preferences for a particular treatment have on the choices they make when responding to the DCE is to include interaction terms to explore the extent to which the preferences of those in the two preference arms differed. Interaction terms were included to explore whether the preferences of specific groups (e.g. preferred medicine, preferred surgery, randomised surgery, randomised medicine) for each dimension included in the model differed from the preferences of the whole model.

Sensitivity analyses

The analyses described above included all responses, even those for which there was evidence that the responses were not consistent. Therefore, in a first sensitivity analysis the effect of excluding the inconsistent responses from the main model was investigated.

The methods described above involve making the assumption that preferences for a unit change in risk are independent of the scale of that risk (i.e. a 10% change in risk from 4% to 14% would be valued the same as a 10% change in risk from 70% to 80%). To investigate whether it was appropriate to assume a linear relationship between the levels of each dimension, a quadratic variable (surgery 1, lifelong medicines 1, and serious complications 1) was included for each dimension.

Calculation of utilities for each treatment group

The results of the econometric analyses can be used to estimate a utility score. This can be accomplished by combining the information on the levels for each dimension, which was derived directly from the trial, with the coefficient for that dimension. *Table 43* gives an example of how a utility might be calculated for hypothetical levels and coefficients.

Similar scores can be calculated for data taken from each arm of the trial. The scores from the different arms could be compared relative to each other (i.e. the ratio of the scores from two groups), but, to aid this comparison, a score has been estimated for both the worst possible and the best case situation (which is by definition 0). Using the coefficient values from *Table 43*, and assuming that people experienced the worst level of each dimension (i.e. symptoms most days/every day, 100% chance of surgery, lifelong medications and a hypothetical maximum of 10% for complications), the worst case scenario would be associated with a score of –210. Therefore, if the worst case scenario was rescaled to 0, then the best case scenario would equal +210 and the state described in *Table 43* would have a score of 175 (i.e. 210–35). As a consequence it can be seen that the state described in *Table 43* is equivalent to 0.833 (i.e. 175/210) of the utility of the hypothetical best case scenario.

Selection of respondents

The sample of respondents used in this DCE was made up of REFLUX trial participants. They were considered to be the appropriate group as they had already undergone treatment. As described in earlier chapters, the trial was composed of four arms: two arms involved the randomisation of

TABLE 43 *Example of the calculation of a utility score from the results of a discrete choice experiment*

Dimension	Coefficient	Actual level (%)	Utility
Troublesome symptoms			
None	0.00 (baseline)	60	0.00
Once a week	–0.05	20	–1.00
Two/three times a week	–0.20	15	–3.00
Most days/every day	–0.40	5	–2.00
Serious complications	–1.00 per 0.1% change	0.1	–1.00
Surgery	–5.00 per 10% change	40	–20.00
Lifelong medication	–2.00 per 10% change	40	–8.00
Total score			–35.00

individuals to either medical or surgical treatment and the other two arms included those who had expressed a preference for either medical management or surgical treatment.

Results

Of the 705 questionnaires sent out, 441 (63%) were returned; 17(3%) were returned uncompleted and 424 (60%) were fully or partially completed. Of these 424 questionnaires, 87 (21%) were from the randomised surgical group, 103 (24%) were from the randomised medical group, and 109 (26%) and 125 (29%) were from the preference medical and preference surgical groups respectively.

Consistency of responses

Ten (2%) people failed to answer the two consistency test questions consistently and so were excluded when the sensitivity analysis was performed.

Econometric analysis

The conditional logistic regression analysis was based on all of the respondents who returned completed questionnaires. Out of a possible 6784 (424×16) observations from the 424 completed and partially completed questionnaires, there were 6434 observations and 350 missing responses. Of these 6434 observations, 1392 (21%) were from the randomised surgical group, 1648 (24%) were from the randomised medical group, and 1744 (26%) and 2000 (29%) were from the preference medical and preference surgical groups respectively.

A sensitivity analysis performed after excluding the ten respondents who had failed both consistency tests was based on 6274 observations from 414 respondents.

Analysis based on the whole sample including inconsistent responses

The sign of the coefficient indicates the direction of the influence of preferences. All other things being equal, a higher negative coefficient indicates a higher negative influence on the overall preference (see Appendix 13). The regression coefficients all had the expected sign (negative) and decreased as expected (i.e. as more difficulty is experienced, the coefficient becomes larger). There was no statistically significant difference between the first two levels for the first dimension, frequency of troublesome symptoms. Therefore, in subsequent analyses these two levels were combined.

The results of the regression model in which the first two levels for frequency of troublesome symptoms were combined are presented in *Table 44*, and the results of the initial regression model in which the levels for frequency of troublesome symptoms were not combined are presented in Appendix 13.

The absolute importance of the parameters included in the analysis can be established by comparing the sizes of the regression coefficients. As *Table 44* illustrates, the most important factor was serious complications with a coefficient of –5.454, indicating that respondents experienced greater disutility for a unit increase (i.e. a 0.1% increase) in the probability of occurrence of serious complications than for a unit change in any other factor. The chance of undergoing surgery (–5.212 per 10% change), the chance of having lifelong medications (–4.797 per 10% change) and the chance of having troublesome symptoms most days/every day (–1.130 per 10% change) were the next largest dimensions.

TABLE 44 *The regression model for the whole sample with the first two levels for frequency of troublesome symptoms combined*

Dimension	Coefficient	Standard error	*p*-value	95% CI
Troublesome symptoms				
Two or three times a week	–0.397	0.061	0.000	–0.516 to –0.277
Most days/every day	–1.130	0.065	0.000	–1.258 to –1.001
Serious complications	–5.454	0.661	0.000	–6.750 to –4.158
Surgery	–5.212	0.845	0.000	–6.868 to –3.556
Lifelong medication	–4.797	0.685	0.000	–6.139 to –3.455

CI, confidence interval.

Conditional (fixed-effects) logistic regression: number of obs = 6434, LR $\chi^2(5) = 491$, prob > $\chi^2 = 0.0000$.

Log likelihood = –1984.3546, pseudo $r^2 = 0.1101$.

The relative importance of the coefficients was estimated by investigating the marginal rates of substitution between coefficients. In absolute terms (i.e. ignoring the sign of the coefficient) the smallest coefficient was that for experiencing troublesome symptoms two or three time per week. Experiencing symptoms most days was over 2.8 times as important, whereas a 0.1% change in the risk of experiencing serious complications was 13.7 times more important. Similar rates were calculated for a 10% change in the risks of surgery and lifelong medication, which were 1.3 times and 1.2 times as important respectively (a full description of marginal rates of substitution between all coefficients is provided in Appendix 13).

Analysis to investigate whether preferences differ between the four groups of the REFLUX trial

Further analysis was performed to establish the effect of the treatment group that patients were assigned to, either through their own preferences or through randomisation. There was no evidence of any differences in preferences in the four treatment groups for either troublesome symptoms or serious complications. However, as would be anticipated, preferences did differ for surgery and lifelong medications. The exception to this was that there was no evidence of a statistically significant difference in the preferences for lifelong medication amongst those people that had expressed a preference for medication compared with the preferences from the whole sample.

The results of the analysis investigating whether preferences varied between treatment groups is reported in *Table 45* (interaction terms for troublesome symptoms or serious complications have been omitted as they were not statistically significant).

As would be expected, the results of this analysis indicate that people who expressed a preference for one treatment would experience a further loss of utility if they received the other treatment (indicated by the negative signs for 'surgery for those that preferred medicine' and 'lifelong medication for those that preferred surgery'). Similarly, individuals who received the treatment that they preferred would experience less loss of utility (indicated by the positive signs for 'lifelong medication for those that preferred medicine' and 'surgery for those that preferred surgery').

Sensitivity analyses

Analysis based on the whole sample but excluding inconsistent responses

The econometric analysis was repeated for the whole sample, this time omitting those individuals

TABLE 45 *The regression model including interaction terms for surgery and lifelong medication*

Dimension	Coefficient	Standard error	*p*-value	95% CI
Troublesome symptoms				
Two or three times a week	–0.406	0.062	0.000	–0.526 to –0.285
Most days/every day	–1.146	0.066	0.000	–1.275 to –1.016
Serious complications	–5.525	0.664	0.000	–6.826 to –4.224
Surgery	–5.573	1.255	0.000	–8.034 to –3.112
Lifelong medication	–3.495	1.009	0.001	–5.473 to –1.516
Interactions				
Surgery for those that preferred medicine	–5.017	2.143	0.019	–9.218 to –0.816
Surgery for those that preferred surgery	5.491	2.008	0.006	1.555–9.427
Lifelong medication for those that preferred surgery	–5.258	1.632	0.001	–8.457 to –2.059
Lifelong medication for those that preferred medicine	0.772	1.695	0.649	–2.549 to 4.094

CI, confidence interval.

Conditional (fixed-effects) logistic regression: number of obs = 6434, LR $\chi^2(10) = 525.48$, prob > $\chi^2 = 0.0000$.

Log likelihood = –1967.1124, pseudo $r^2 = 0.1178$.

TABLE 46 *The regression model for the whole sample omitting the inconsistent responses*

Dimension	Coefficient	Standard error	*p*-value	95% CI
Troublesome symptoms				
Two or three times a week	–0.415	0.062	0.000	–0.537 to –0.415
Most days/every day	–1.166	0.067	0.000	–1.297 to –1.166
Serious complications	–5.649	0.673	0.000	–6.967 to –5.648
Surgery	–4.754	0.858	0.000	–6.435 to –3.072
Lifelong medication	–5.060	0.696	0.000	–6.425 to –3.696

CI, confidence interval.
Conditional (fixed-effects) logistic regression: number of obs = 6274, LR $\chi^2(5) = 497.95$, prob > $\chi^2 = 0.0000$.
Log likelihood = –1925.4265, pseudo $r^2 = 0.1145$.

TABLE 47 *The regression model for the whole sample but including quadratic functions for continuous variables*

Dimension	Coefficient	Standard error	*p*-value	95% CI
Troublesome symptoms				
Two or three times a week	–0.398	0.061	0.000	–0.518 to –0.278
Most days/every day	–1.127	0.065	0.000	–1.256 to –0.999
Serious complications	–27.853	4.142	0.000	–35.971 to –19.736
Quadratic function	1948.761	353.906	0.000	1255.118–2642.404
Surgery	–12.868	3.921	0.001	–20.554 to –5.182
Quadratic function	9.109	4.390	0.038	0.505–17.713
Lifelong medication	–4.828	2.858	0.091	–10.430 to 0.774
Quadratic function	–0.046	0.3133	0.988	–6.187 to 6.095

CI, confidence interval.
Conditional (fixed-effects) logistic regression: number of obs = 6434, LR $\chi^2(8) = 525.85$, prob > $\chi^2 = 0.0000$.
Log likelihood = –1966.929, pseudo $r^2 = 0.1179$.

who failed the consistency tests (*Table 46*). As reported above, this had the effect of reducing the sample size by ten respondents and 160 observations. The results of this analysis are reported in *Table 46*, although the values for all attributes are higher except for the chance of undergoing surgery.

Analysis based on the whole sample but including quadratic functions

Quadratic functions were used in the model to establish the linear relationships in the continuous variables. All coefficients, except the chance of having lifelong medication and its associated quadratic function, were significant at the 5% level (*Table 47*). The quadratic functions for serious complications and chance of surgery are both positive and this indicates that, as these risks increase, the disutility still increases, but at a decreasing rate. However, these results should only be used to indicate that there may not be a linear relationship for serious complications and surgery. This is because the quadratic function is only a simple method and can provide estimates of utility that are counterintuitive for some levels of risk, for example utility increases as risk increases.

Estimation of utility scores for each treatment group

Table 48 reports the trial findings for the dimensions included in the DCE. Using these data and the results of the DCE regression model reported in *Table 45* it is possible to calculate utility

TABLE 48 *Data on dimension levels for each group from the trial*

Dimension	Randomised surgical	Randomised medical	Preference surgical	Preference medical
Frequency of troublesome symptoms (heartburn only, %)				
Not at all	63	29	73	32
Once a week	12	22	11	29
Two or three times a week	14	23	7	21
Most days or every day	10	26	9	19
Chance of serious complications requiring hospitalisation (%)				
Reflux related (obtained from different source)	1	0.12	1	0.12
Chance of undergoing surgery (%)	62.3	5.6	84.0	1.6
Chance of needing lifelong medication at 12 months (%)	33.8	84.8	19.6	85.9

TABLE 49 *Utility scores for each group in the trial and for the worst case scenario*

Dimension	Randomised surgical	Randomised medical	Preference surgical	Preference medical	Worst case
Frequency of troublesome symptoms (heartburn only)					
Not at all	0.00	0.00	0.00	0.00	0.00
Once a week	0.00	0.00	0.00	0.00	0.00
Two or three times a week	–5.68	–9.34	–2.84	–8.53	0.00
Most days or every day	–11.46	–29.80	–10.31	–21.77	–114.60
Chance of serious complications requiring hospitalisation					
Reflux related (obtained from different source)	–55.25	–6.63	–5.52	–6.63	–552.48
Chance of undergoing surgery	–34.72	–3.12	–46.81	–0.89	–55.73
Chance of needing lifelong medication at 12 months	–11.81	–29.64	–6.85	–29.92	–34.95
Interactions					
Surgery for those who preferred medicine				–0.80	
Surgery for those who preferred surgery			46.12		
Lifelong medication for those who preferred surgery			–17.77		–52.58
Lifelong medication for those who preferred medicine					
Total utility	–118.92	–78.52	–43.99	–68.54	–810.4

scores for each of the four groups (*Table 49*). Also included in *Table 49* are the utility scores for the worst case scenario (by default the utility score for the best case scenario is 0). Using the approach outlined in the methods section, the relative weight of each of the four trial groups relative to the best case scenario was estimated from these data (*Table 50*).

As *Table 49* illustrates, the largest component of total utility comes from serious complications. The data presented in this table also serve to illustrate

the importance of patients' preferences for utility. For example, the utility gained by a person who prefers surgery receiving the treatment they prefer (46.1) is just less than the disutility associated with surgery (46.8).

As indicated above, the comparisons between the four treatment groups are best informed by considering their relative weights. As there are several different relative weights that could be calculated, it was decided to compare the mean total utility for each arm with the total utility that is implied for the best possible combination of attributes and levels (the last column of *Table 50*). As the data in this table illustrate, relative to the best case, the preference surgical group has the highest weight and the randomised surgical group has the lowest weight. In this situation the preference arms are associated with higher mean utilities than the randomised arms.

Discussion

The aim of this chapter was to use a DCE to explore the strength of preference for the treatment and outcomes of GORD. This approach has been used to measure preferences of GORD patients previously[128,129] but this earlier work sought to establish willingness to pay for complete symptom relief of GORD and for diagnostic uncertainty. The DCE reported in this chapter was different in that it attempted to explore preferences for the outcomes of treatment (e.g. troublesome symptoms and serious complications) and preferences for the process by which these outcomes were obtained.

The results of the DCE indicate that the most important single dimension is serious complications, followed by a 10% change in the chance of having surgery or receiving lifelong medication. Suffering troublesome symptoms most days was less important, although the unit of analysis was a 1% chance of this event occurring. There was no evidence that respondents placed any importance on suffering troublesome symptoms once a week in comparison with no symptoms.

The group that was associated with the highest utility relative to a best case situation was the preference surgical group, and the group that was associated with the lowest utility was the randomised surgical group. If the effect of serious complications is removed from the consideration of utility, then the preference groups are associated with higher levels of utility relative to the best case than the randomised groups. Furthermore, the surgical group is associated with higher utility than the medical group.

The exclusion of serious complications from the consideration of utility might be considered contentious. However, an analysis was conducted to explore whether the preferences for the continuous variables (risk of serious complications, risk of surgery and risk of receiving lifelong medication) in the econometric analysis were linear. The results of this analysis indicated that, although utility fell as risk increased, it fell at a decreasing rate for both the risk of serious complications and surgery (there was no evidence of this effect for lifelong medication). The implication of this is that it is possible that there is little or no difference in the loss of utility caused by serious complications

TABLE 50 *Relative utility of each trial arm relative to the utility of the best case scenario*

Situation	Loss of utility from the best possible combination of attributes and levels[a]	Gain in utility from the worst possible combination of attributes and levels	Relative weight compared with the best case
Best case	0	810	1.000
Worst case	–810	0	0.000
Randomised surgical	–119	691	0.853
Randomised medical	–79	732	0.903
Preference surgical	–44	766	0.946
Preference medical	–69	742	0.915

[a] Estimated from Table 49.

between groups. Research is required to further investigate how this non-linearity in preferences might be most appropriately modelled, as the quadratic function would result in implausible utility estimates for higher risks of serious complications than were considered in the DCE questionnaire.

The results of the analysis presented in this chapter also provide some insight into the importance of people's preferences for treatment with respect to utility. For example, people who have a preference for medicine but who actually undergo surgery experience almost twice the loss of utility (1.059 or –0.557 + –0.502) as those people in the randomised arm who receive surgery (–0.557) for a 1% increase in the risk of surgery. Similarly, people who preferred surgery and received surgery lost less utility (–0.008 or –0.557 + 0.549). This result indicates the importance of patient choice when decisions are made about which type of treatment to provide.

Some of the limitations of the analysis reported in this chapter have already been described but one further limitation relates to how the information derived by the DCE could have been used in the economic model reported earlier. It was not possible, nor was it planned, for these two 'economic' elements to be integrated. Indeed, methods to integrate DCEs into a trial remain relatively undeveloped. However, future work should consider how a DCE and an economic model conducted as part of a trial analysis can be developed in an integrated fashion. It is likely that this will involve the attributes and levels of the DCE being reflected in the model structure, with the values of attribute levels being produced by the model and fed into the estimation of utilities as part of the DCE analysis. Any attempt to integrate these approaches would be facilitated by the use of a common continuous measure, such as willingness to pay, so that all dimensions could be valued in terms of this numeraire.

The methods used to analyse and present the results of the DCE have limitations. One of the main limitations is the limited handling of uncertainty in the analysis. In economic studies it is expected that an extensive sensitivity analysis would be conducted to assess how robust the conclusions are. Increasingly, as exemplified by the economic evaluation presented in Chapter 7, it is becoming expected that a probabilistic sensitivity analysis will be used to develop credible intervals around mean estimates. Although sensitivity analysis has been performed as part of the work reported in this chapter, probabilistic sensitivity analysis has not been conducted. Probabilistic sensitivity analysis would also help overcome a further limitation of the DCE. When analysing the DCE, we followed the common econometric convention of combining levels of dimensions when there was no evidence of a statistically significant difference and of dropping parameters from an analysis when the coefficients were not statistically significant. There is some debate about how appropriate this approach is as it reduces the information available to decision-makers. However, with probabilistic sensitivity analysis a full model, including both statistically significant and insignificant coefficients, can be used to develop both mean utility scores and credible intervals. Therefore, further work might focus on conducting a probabilistic sensitivity analysis.

DCEs use hypothetical questions and, as such, they have been criticised. This is because it is unclear whether people would pick these scenarios if they were faced with these choices in real life. Nevertheless, the respondents to the DCE all had experience of GORD and its treatment (either medical, surgical or both); hence, it was hoped that the respondents would be able to consider the choices and trade-offs involved in each choice question.

A final concern relates to the number of choice questions to present to potential respondents. The greater the number of dimensions and levels that are considered relevant the greater the number of possible scenarios that individuals could potentially be presented with. Experimental design techniques were used to reduce the number of scenarios that were presented to individuals while still allowing for utilities to be inferred for all possible scenarios. However, even after the use of these techniques it was felt that the number of questions to be presented ($n = 16$) was too great. As a consequence, the questions were randomly split into two questionnaires, each containing eight questions. It was hoped that this would increase the completion rate of the questionnaire, although it did have the effect of reducing our ability to detect important differences in preferences. Overall, the completion rate achieved was quite high for a DCE questionnaire (which are thought to be cognitively demanding on respondents) and this may be attributed to the relatively short length of the questionnaire.

Conclusions

The results of the DCE presented in this chapter complement the evidence reported in earlier chapters. The results also aid the interpretation of the clinical evidence by indicating the importance placed on type of treatment and the ability of a treatment to resolve symptoms. The most important single dimension is serious complications, followed by changes in surgery, lifelong medication and troublesome symptoms most days. There was no statistically significant evidence that respondents placed any importance on suffering troublesome symptoms once a week in comparison with no symptoms. Relative to a best case situation the trial arm associated with the highest mean utility was the preference surgical group and that associated with the lowest mean utility was the randomised surgical group. The utility associated with surgery is dependent upon the risk of serious complications, which was assumed to be greater than that for lifelong medical treatment. If the effect of serious complications is removed from the consideration of utility, the preference arms are associated with higher levels of utility than the randomised groups. Furthermore, the surgical arms are associated with higher utility than the medical arms. Thus, the results of the analysis indicate the importance of quantifying the risk of serious complications and of considering patient choice when decisions are made about which types of treatment to provide and the type of treatment to recommend.

Additional further research is also indicated. Part of this research should focus on how approaches such as DCEs can be made more useful to trials-based research. A more specific research need is to consider how best to describe the imprecision surrounding the mean estimates of utilities that are generated.

Chapter 10

Conclusions

Implications for health care and recommendations for research

The advent of less invasive fundoplication performed laparoscopically opened up new possibilities for the management of people with chronic symptoms of GORD. Good results obtained amongst people whose symptoms were not satisfactorily controlled by medical management raised questions about the place of relatively early surgery in people with GORD whose symptom control from long-term medical management was reasonably acceptable. Would surgery be more effective than continuing medical management? Would surgery be sufficiently safe? And would widening the use of laparoscopic fundoplication to such patients be cost-effective? These are the principal questions addressed in this study.

The study had two main components: a pragmatic randomised controlled trial to assess clinical effectiveness and an economic evaluation to explore cost-effectiveness and the wider implications for efficient health-care provision.

The trial provided clear evidence of effectiveness in respect of reflux-related quality of life. Even though the number of participants in the trial was not as large as originally intended, the sizes of differences observed in the condition-specific reflux quality of life measure were so large that they were highly statistically significant. As with other disease-specific measures, the magnitude of these differences is hard to conceptualise. However, broadly similar differences were also observed in most components of the more accessible generic health status measures, SF-36 and EQ-5D.

As described in Chapter 6, clear differences were observed even though as many as one-third of those allocated surgery did not have fundoplication. Extra analyses explored how much of a blunting effect this might have had on the results and, arguably, these adjusted analyses provide better estimates of the true effects of surgery in this type of population as it might be used in normal clinical practice.

Current follow-up is to the equivalent of 12 months after surgery. In comparison with the results obtained at 3 months there were sustained better scores but with some evidence of attenuation of the differences. For example, the number taking reflux-related drugs after surgery went up from around 9% to 14%. Narrowing of differences was most marked for the EQ-5D health status measure. It is possible that some of the 'improvement' is due to a placebo effect of surgery and one explanation of any attenuation of difference is that the placebo effect has diminished over time. This could be clarified by further follow-up to find out if differences are sustained or whether there is more narrowing of the differences.

In addition to the randomised groups the trial also had two preference groups, which aid interpretation of the randomised trial results. As a group, the preference surgical participants had the lowest baseline REFLUX scores (worst symptoms) and the preference medical group the highest (with the randomised groups between them (see *Figure 14*). After surgery the preference surgical group had scores that rose to the level of the preference medical group and by 12 months they were the better of the two groups. The preference groups give an indication of likely behaviour if surgery were to become more freely available. In addition to having the least well-controlled symptoms at baseline, the preference surgical group had been on medication longer and were less concerned about possible adverse effects of surgery (described in Chapter 5).

The preference groups also add extra information about clinical events, in particular rare serious adverse events. Taken at face value, laparoscopic fundoplication appears to be a relatively safe procedure; however, even the experience of all of the 329 participants who had surgery is too little to provide sufficiently precise estimates of uncommon events. So, questions still remain about the extent of possible adverse effects of surgery and their frequency.

The within-trial (i.e. up to 12 months of follow-up) cost-effectiveness analysis related the extra mean costs associated with the surgical policy with the increase in mean QALYs that followed surgery to generate an incremental cost-effectiveness ratio. This was around £19,000 when the intention to treat approach to analysis was used. Taking into account uncertainties around the various estimates, it was calculated that the chances that the surgical policy would be cost-effective at a threshold of £20,000 per QALY was 46%. When a per protocol approach was used, the incremental cost per QALY increased to around £23,000, with a probability that this would be cost-effective at a threshold of £20,000 of only 19%. These results indicate considerable uncertainty at thresholds that are currently commonly applied to costs per QALY.

The within-trial analyses have significant limitations, however, as discussed in Chapters 7 and 8. The most important is that they ignore events, costs and benefits that accrue after 1 year. It is likely that surgery will continue to bestow benefits after 1 year, although there could also be relapse of symptoms, and medical management may require lifelong medication with significant costs. For this reason, the REFLUX trial data were synthesised with other data to develop an extended cost-effectiveness model. This explored a number of possible scenarios. Assuming that the benefits of surgery persist throughout a lifetime, that without surgery mediation use would continue for a lifetime, that there would be a 4.8% annual rate of additional uptake of medication in the surgery group, and that there would be an annual 0.8% reoperation rate led to an estimated incremental cost per QALY of around only £2000, with a 74% probability of surgery being considered cost-effective at a threshold of £20,000 per QALY. Applying other plausible assumptions, however, gave a range of incremental costs per QALY of between £1000 and £44,000, again indicative of wide uncertainty. The factors most contributing to the uncertainty were the projected HRQoL parameters and the long-term rate of uptake of medication following surgery.

The DCE was performed to provide an alternative way of assessing the weights that people with GORD place on their outcome and treatment. The results were broadly in line with the other economic evaluation in this project, based on the EQ-5D. The DCE did show, however, that respondents put considerable weight on avoiding rare but serious risks. The economic analysis found that these risks have little impact on QALYs on average and that the uncertainty in the clinical results about their incidence does not affect the treatment decision at the population level, all other things being equal. Nevertheless, the DCE highlights that these risks may be important when patients choose whether to accept surgery if it is offered.

Currently available evidence from the REFLUX trial indicates that surgery could be cost-effective at the thresholds (£20,000–£30,000) currently applied by the National Institute for Health and Clinical Excellence (NICE) but with considerable uncertainty. The extended model suggests that the true cost-effectiveness, when lifetime costs and benefits are taken into account, is likely to be more favourable. But this, too, is prone to major uncertainty.

Questions also remain about the generalisability of the study's results. The economic model was based on a 45-year-old man, whereas many people receiving PPIs for GORD are older than this and can have significant co-morbidities.

The most urgent need for further research, therefore, is to acquire improved estimates of longer-term benefits and costs. This could be accomplished relatively easily by continuing annual follow-up in the REFLUX trial, and indeed arrangements for this have been put in place. Funds have recently been awarded by the HTA Programme to support follow-up to 5 years after surgery. Our analyses of cost-effectiveness will then be updated to take these results and other changes (such as in the costs of PPIs) into account. In the meantime it may be worth exploring whether there are other longer-standing non-randomised cohorts that could be useful in this respect. Perceptions of the risks of rare adverse events may play a major role in decision-making about surgery. Such cohorts could also be useful for getting more precise estimates of uncommon events associated with both surgical and medical management.

Acknowledgements

Contributions of authors

Adrian Grant (Director, HSR trialist) was the principal grant applicant and contributed to the development of the trial protocol and the preparation of the report and was responsible overall for the conduct of the trial.

Samantha Wileman (Trial Co-ordinator, HSR trialist) contributed to the development of the trial design, was responsible for the day-to-day management of the trial, monitored data collection and assisted in the preparation of the report.

Craig Ramsay (Senior Research Fellow, Health Statistics) contributed to the grant application and the trial design and conducted the statistical analysis.

Mark Sculpher (Senior Health Economist, Health Economics) was responsible for the economic evaluation section of the grant application and protocol, and Laura Bojke (Research Fellow, Health Economics) and David Epstein (Research Fellow, Health Economics) conducted the analysis of the economic models for the report.

Sue Macran (Research Fellow, Health Outcomes) led the development of the REFLUX outcome measure.

Luke Vale (Senior Research Fellow, Health Economics) and Mary Kilonzo (Research Fellow, Health Economics) conducted the discrete choice experiment (DCE) and assisted in the preparation of the DCE for the report.

Jill Francis (Senior Research Fellow, Health Psychology) conducted the analysis of the belief questionnaires and wrote the report for this part of the study.

Zygmunt Krukowski (Surgeon, Gastroenterology) and Ashley Mowat, Robert C Heading and Mark Thursz (Physicians, Gastroenterology) advised on clinical aspects of the trial design and the conduct of the trial and commented on the draft report.

Ian Russell (Director, HSR, Health Outcomes) contributed to the development of the trial design.

Marion Campbell (Programme Director, HSR statistician/trialist) contributed to the development of the trial design, commented on all aspects of the conduct of the trial and contributed to the preparation of the report.

Other members of the Trial Steering Group were as follows (those marked with an asterisk were independent of the trial): Wendy Atkin* (Chair), John Bancewicz, Garry Barton (1999–2002), Ara Darzi, Janusz Jankowski*, Richard Lilford*, Iain Martin (1997–2000).

Members of the independent Data Monitoring Committee were as follows: Jon Nicholl, Chris Hawkey, Iain MacIntyre.

The authors wish to thank the following researchers for their assistance in nurse co-ordination and patient recruitment and follow-up: Maureen GC Gillan, Marie Cameron, Christiane Pflanz-Sinclair; Sharon McCann who was involved in the piloting of the practical arrangements of this trial; Allan Walker for database and programming support; and Janice Cruden and Pauline Garden for their magnificent secretarial support and data management.

Members of the REFLUX trial group responsible for recruitment in the clinical centres are shown in the table below.

Finally, the authors are indebted to the referees for reading the report and for the quality of their comments.

The Health Services Research Unit is funded by the Chief Scientist Office of the Scottish Government Health Directorates.

Aberdeen: Aberdeen Royal Infirmary	A Mowat, Z Krukowski, E El-Omar, P Phull, T Sinclair, L Swan
Belfast: Royal Victoria Hospital	B Clements, J Collins, A Kennedy, H Lawther
Bournemouth: Royal Bournemouth Hospital	D Bennett, N Davies, S Toop, P Winwood
Bristol: Bristol Royal Infirmary	D Alderson, P Barham, K Green, R Mittal
Bromley: Princess Royal University Hospital	M Asante, S El Hasani
Edinburgh: Royal Infirmary of Edinburgh	A De Beaux, RC Heading, L Meekison, S Paterson-Brown, H Barkell
Guildford: Royal Surrey County Hospital	G Ferns, M Bailey, N Karanjia, TA Rockall, L Skelly
Hull: Hull Royal Infirmary	M Dakkak, C Royston, P Sedman
Inverness: Raigmore Hospital	K Gordon, LF Potts, C Smith, PL Zentler-Munro, A Munro
Leeds: Leeds General Infirmary	S Dexter, P Moayeddi
Leicester: Leicester Royal Infirmary	DM Lloyd
London: St Mary's Hospital	V Loh, M Thursz, A Darzi
London: Whipps Cross Hospital	A Ahmed, R Greaves, A Sawyerr, J Wellwood, T Taylor
Poole: Poole Hospital	S Hosking, S Lowrey, J Snook
Portsmouth: Queen Alexandra Hospital	P Goggin, T Johns, A Quine, S Somers, S Toh
Salford: Hope Hospital	J Bancewicz, M Greenhalgh, W Rees
Stoke-on-Trent: North Staffordshire Hospital	CVN Cheruvu, M Deakin, S Evans, J Green, F Leslie
Swansea: Morriston Hospital	JN Baxter, P Duane, MM Rahman, M Thomas, J Williams
Telford: Princess Royal Hospital	D Maxton, A Sigurdsson, MSH Smith, G Townson
Yeovil: Yeovil District Hospital	C Buckley, S Gore, RH Kennedy, ZH Khan, J Knight
York: York District Hospital	D Alexander, G Miller, D Parker, A Turnbull, J Turvill,

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Appendix 1

Patient entry form

Participant Study No

(for completion by co-ordinating centre in Aberdeen)

Study Centre No

The REFLUX Trial

PARTICIPANT ENTRY FORM

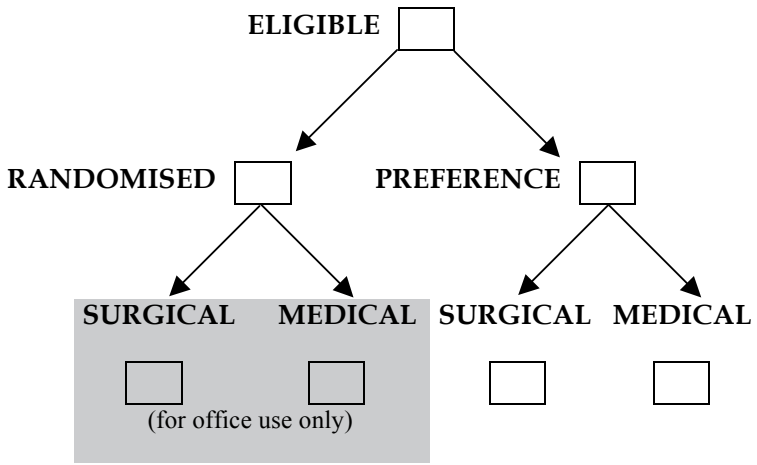
CONFIDENTIAL

This study is funded by the NIHR
Health Technology Assessment Programme

ELIGIBILITY

Please mark relevant box as to whether participant has chosen to be randomised OR has declined and has opted for the preference arm.

Please put an X in the relevant boxes



PERSONAL INFORMATION

Instruction for completion:
if you make any errors while completing this form, please score through the incorrect data with a horizontal line and initial and date any changes

Please put an x in the relevant boxes

PERSONAL INFORMATION

Title *(Mr, Mrs etc)*

Surname

First Names

ADDRESS

House Name

House Number

Street Name

Town/City

County

Postcode

Telephone No
(including code)

Maiden name (if female and ever married)

NHS Number *(if known)*

Hospital Number *(if known)*

CHI Number *(if known - Scotland only)*

DESCRIPTIVE INFORMATION ABOUT THE PARTICIPANT

Date of Birth **Day** ☐☐ / **Month** ☐☐ / **Year** ☐☐☐☐

Sex
Male ☐ Female ☐

Height ☐.☐☐ m *or* ☐☐ ft ☐☐ inches

Weight ☐☐.☐☐ kg *or* ☐☐ st ☐☐ lbs

1. **Date of Recruitment** **Day** ☐☐ / **Month** ☐☐ / **Year** ☐☐☐☐

	Yes	No
2. **Does the participant take prescribed reflux medication daily?**	☐	☐

3. **When was the participant first prescribed medicine for their reflux symptoms?**

Month ☐☐ / **Year** ☐☐☐☐

	Yes	No	Don't know
4. **Is the participant a current smoker?**	☐	☐	☐

	Yes	No	Don't know
5. **Does the participant suffer from asthma?**	☐	☐	☐

6. **Please tick the box which accurately describes when the participant first finished full time education?**

16 years or less	☐
17-19 years old	☐
20 years or over	☐

7. **Since leaving, have they undertaken any more full-time or part-time education?**

Yes	☐
No	☐

Participant Study No ☐☐☐☐☐
(for completion by co-ordinating centre in Aberdeen)

Study Centre No ☐☐

8. Please tick the box, which best describes the participant's current employment status.

Full time employment	☐	Housework	☐
Part time employment	☐	Seeking work	☐
Student	☐	Other	☐
Retired	☐		

GENERAL PRACTITIONER

Initials **Surname**

Practice Name

Street Number

Street Name

Town/City

County

Postcode

Telephone No *(including code)*

COLLABORATING CLINICIAN

Title *(Mr, Mrs, Professor, Dr)* **Surname**

First Name(s) *(if known)*

Hospital

Clinic name

Thank you for completing this information. Please return it in a reply-paid envelope to:
The REFLUX Trial Office, Health Services Research Unit (Flea),
University of Aberdeen, Foresterhill, ABERDEEN AB25 2ZD
Tel: 01224 000000 Fax: 01224 554580 E-mail: reflux@hsru.abdn.ac.uk

Appendix 2

Baseline questionnaire

Participant Study No

(for completion by co-ordinating centre in Aberdeen)

The REFLUX Trial

BASELINE QUESTIONNAIRE

A questionnaire for people participating in the REFLUX trial, which aims to find out whether taking medication or having an operation is the best form of treatment for gastro-oesophageal reflux disease

CONFIDENTIAL

This study is funded by the NIHR Health Technology Assessment Programme

PLEASE READ ALL THE INSTRUCTIONS BEFORE COMPLETING THE QUESTIONNAIRE

Thank you for agreeing to take part in the study. The responses you give in this questionnaire will help us find out if the treatments you get are helpful for your condition.

The information you provide will be completely confidential.

HOW TO FILL IN THE QUESTIONNAIRE

For each section please put a cross in the appropriate box like this:

Do you drive a car? **Yes** ☐

No ☒

If you make any errors while completing this questionnaire, shade out the incorrect box completely and put a cross in the correct box like this:

Do you drive a car? **Yes** ☒

No ☒

The intended answer above is No

PLEASE USE A BLUE OR BLACK PEN TO FILL IN YOUR ANSWERS

REFLUX QUESTIONNAIRE

For the questions in section A - F, please tick the box which best describes how often your symptoms have occurred and the effect they have had on your quality of life.

SECTION A - HEARTBURN

A1. In the last two weeks, how often have you experienced heartburn (a burning sensation which moves up from your chest to your throat)?

Not at all ☐
Once a week ☐
Two or three times a week ☐
Most days ☐
Everyday ☐

A2. In the last two weeks, how often have you experienced any discomfort or pain in your chest?

Not at all ☐
Once a week ☐
Two or three times a week ☐
Most days ☐
Everyday ☐

A3. In the last two weeks, how much has the heartburn or discomfort/pain in your chest affected your quality of life?

Not at all ☐
A little ☐
Moderately ☐
A lot ☐
Extremely ☐

Participant Study No

(for completion by co-ordinating centre in Aberdeen)

SECTION B - ACID REFLUX

B1. In the last two weeks, how often have you experienced acid reflux and/or had an acid taste in your mouth?

- Not at all ☐
- Once a week ☐
- Two or three times a week ☐
- Most days ☐
- Everyday ☐

B2. In the last two weeks, how often have you been sick (vomited)?

- Not at all ☐
- Once a week ☐
- Two or three times a week ☐
- Most days ☐
- Everyday ☐

B3. In the last two weeks, how often have you regurgitated (brought up) quantities of liquid or solids into your mouth?

- Not at all ☐
- Once a week ☐
- Two or three times a week ☐
- Most days ☐
- Everyday ☐

B4. In the last two weeks, how often have you experienced a feeling of nausea (without actually being sick or regurgitating)?

- Not at all ☐
- Once a week ☐
- Two or three times a week ☐
- Most days ☐
- Everyday ☐

B5. In the last two weeks, how often have you wanted to be sick but physically been unable to?

- Not at all ☐
- Once a week ☐
- Two or three times a week ☐
- Most days ☐
- Everyday ☐

B6. In the last two weeks, how much have these reflux symptoms affected your quality of life?

- Not at all ☐
- A little ☐
- Moderately ☐
- A lot ☐
- Extremely ☐

Participant Study No

(for completion by co-ordinating centre in Aberdeen)

SECTION C – WIND

C1. In the last two weeks, how often have you experienced a lot of wind from the lower bowel?

- Not at all ☐
- Once a week ☐
- Two or three times a week ☐
- Most days ☐
- Everyday ☐

C2. In the last two weeks, how often have you experienced a lot of burping/belching?

- Not at all ☐
- Once a week ☐
- Two or three times a week ☐
- Most days ☐
- Everyday ☐

C3. In the last two weeks, how often have you experienced bloatedness and/or a feeling of trapped wind, in your stomach?

- Not at all ☐
- Once a week ☐
- Two or three times a week ☐
- Most days ☐
- Everyday ☐

C4. In the last two weeks, how often have you experienced loud gurgling noises from your stomach?

Not at all ☐
Once a week ☐
Two or three times a week ☐
Most days ☐
Everyday ☐

C5. In the last two weeks, how much have these wind problems affected your quality of life?

Not at all ☐
A little ☐
Moderately ☐
A lot ☐
Extremely ☐

SECTION D - EATING AND SWALLOWING

D1. In the last two weeks, how often have you experienced difficulty swallowing food or have you actually choked on food?

Not at all ☐
Once a week ☐
Two or three times a week ☐
Most days ☐
Everyday ☐

Participant Study No

(for completion by co-ordinating centre in Aberdeen)

D2. In the last two weeks, how often have your eating habits been restricted because of your condition? Examples might be eating more slowly, having smaller portions or eating different foods.

Not at all ☐
Once a week ☐
Two or three times a week ☐
Most days ☐
Everyday ☐

D3. In the last two weeks, how much have these problems with eating affected your quality of life?

Not at all ☐
A little ☐
Moderately ☐
A lot ☐
Extremely ☐

SECTION E – BOWEL MOVEMENTS

E1. In the last two weeks, how often have you experienced diarrhoea and/or loose stools?

Not at all ☐
Once a week ☐
Two or three times a week ☐
Most days ☐
Everyday ☐

E2. In the last two weeks, how often have you experienced constipation and/or hard stools?

Not at all ☐

Once a week ☐

Two or three times a week ☐

Most days ☐

Everyday ☐

E3. In the last two weeks, how often have you felt an urgent need to have a bowel movement?

Not at all ☐

Once a week ☐

Two or three times a week ☐

Most days ☐

Everyday ☐

E4. In the last two weeks, how often have you had a feeling of not emptying your bowels?

Not at all ☐

Once a week ☐

Two or three times a week ☐

Most days ☐

Everyday ☐

Participant Study No

(for completion by co-ordinating centre in Aberdeen)

E5. In the last two weeks, how much have these bowel problems affected your quality of life?

Not at all ☐
A little ☐
Moderately ☐
A lot ☐
Extremely ☐

SECTION F – SLEEP

F1. In the last two weeks, how often have you experienced difficulty in lying down to sleep?

Not at all ☐
Once a week ☐
Two or three times a week ☐
Most nights ☐
Every night ☐

F2. In the last two weeks, how often have you experienced difficulty getting to sleep because of your reflux symptoms?

Not at all ☐
Once a week ☐
Two or three times a week ☐
Most nights ☐
Every night ☐

F3. In the last two weeks, how often have you been woken up because of your reflux symptoms?

Not at all ☐
Once a week ☐
Two or three times a week ☐
Most nights ☐
Every night ☐

F4. In the last two weeks, how much have these sleep related problems affected your quality of life?

Not at all ☐
A little ☐
Moderately ☐
A lot ☐
Extremely ☐

Participant Study No

(for completion by co-ordinating centre in Aberdeen)

SECTION G – WORK, PHYSICAL AND SOCIAL ACTIVITIES

For the following section, please tick the box which best applies to you.

G1. In the last two weeks, have your reflux symptoms affected you at work (paid or voluntary)?

- Not applicable (I do not do paid or voluntary work) ☐
- No, my symptoms do not affect me ☐
- Yes, my symptoms have affected me but I still work ☐
- Yes, I have worked less often because of my symptoms ☐
- Yes, I have not worked in the last two weeks because of my symptoms ☐
- I no longer work because of my symptoms ☐

G2. In the last two weeks, have your reflux symptoms affected your ability to perform less strenuous activities (such as going for a gentle walk, shopping or housework)?

- Not applicable (I do not perform these activities, though this is not due to my reflux symptoms) ☐
- No, my symptoms do not affect me ☐
- Yes, my symptoms have affected me but I still perform these activities as often as ever ☐
- Yes, I perform these activities less often because of my symptoms ☐
- Yes, I have not performed these activities in the last two weeks ☐
- I no longer perform these activities at all because of my symptoms ☐

G3. In the last two weeks, have your reflux symptoms affected your ability to perform strenuous activities (such as brisk walking or swimming)?

- Not applicable (I do not perform these activities, though this is not due to my reflux symptoms) ☐
- No, my symptoms do not affect me ☐
- Yes, my symptoms have affected me but I still perform these activities as often as ever ☐
- Yes, I perform these activities less often because of my symptoms ☐
- Yes, I have not performed these activities in the last two weeks ☐
- I no longer perform these activities at all because of my symptoms ☐

G4. In the last two weeks, have you found that your reflux symptoms have affected any of your social activities (such as going out for meals, going out for drinks or socialising with other people)?

- Not applicable (I do not perform these activities, though this is not due to my reflux symptoms) ☐
- No, my symptoms do not affect me ☐
- Yes, my symptoms have affected me but I still perform these activities as often as ever ☐
- Yes, I perform these activities less often because of my symptoms ☐
- Yes, I have not performed these activities in the last two weeks ☐
- I no longer perform these activities at all because of my symptoms ☐

G5. In the last two weeks, how much has the effect of your reflux symptoms on your work, physical or social activities affected your quality of life?

- Not at all ☐
- A little ☐
- Moderately ☐
- A lot ☐
- Extremely ☐

Participant Study No

(for completion by co-ordinating centre in Aberdeen)

SECTION H - YOUR VIEWS ABOUT MEDICINES PRESCRIBED TO YOU FOR YOUR REFLUX

- We would like to ask you about your personal views about medicines prescribed for your reflux symptoms, now or in the past.
- Below are statements other people have made about their medicines.
- Please indicate the extent to which you agree or disagree with them by putting a cross in the appropriate box.
- **There are no right or wrong answers.** We are interested in your personal views.

	Strongly agree	**Agree**	**Uncertain**	**Disagree**	**Strongly disagree**
My health, at present, depends on my medicines	☐	☐	☐	☐	☐
Having to take medicines worries me	☐	☐	☐	☐	☐
My life would be impossible without my medicines	☐	☐	☐	☐	☐
Without my medicines I would be very ill	☐	☐	☐	☐	☐
I sometimes worry about the long term effects of my medicines	☐	☐	☐	☐	☐
My medicines are a mystery to me	☐	☐	☐	☐	☐
My health in the future depends on my medicines	☐	☐	☐	☐	☐
My medicines disrupt my life	☐	☐	☐	☐	☐
I sometimes worry about becoming too dependent on my medicines	☐	☐	☐	☐	☐
My medicines protect me from becoming worse	☐	☐	☐	☐	☐

SECTION I - YOUR VIEWS ABOUT MEDICINES IN GENERAL

- We would like to ask you about your personal views about medicines in general.
- Below are statements other people have made about medicines in general.
- Please indicate the extent to which you agree or disagree with them by putting a cross in the appropriate box.
- **There are no right or wrong answers.** We are interested in your personal views.

	Strongly agree	**Agree**	**Uncertain**	**Disagree**	**Strongly disagree**
Doctors use too many medicines	☐	☐	☐	☐	☐
People who take medicines should stop their treatment for a while every now and again	☐	☐	☐	☐	☐
Most medicines are addictive	☐	☐	☐	☐	☐
Natural remedies are safer than medicines	☐	☐	☐	☐	☐
Medicines do more harm than good	☐	☐	☐	☐	☐
All medicines are poisons	☐	☐	☐	☐	☐
Doctors place too much trust on medicines	☐	☐	☐	☐	☐
If doctors had more time with patients they would prescribe fewer medicines	☐	☐	☐	☐	☐

SECTION J - YOUR VIEWS ABOUT SURGERY IN GENERAL

- We would like to ask you about your personal views about surgery in general.
- Below are statements other people have made about surgery in general
- Please indicate the extent to which you agree or disagree with them by putting a cross in the appropriate box.
- **There are no right or wrong answers.** We are interested in your personal views.

	Strongly agree	**Agree**	**Uncertain**	**Disagree**	**Strongly disagree**
I would be willing to have an uncomfortable test to assess my suitability for surgery	☐	☐	☐	☐	☐
Surgery does more harm than good	☐	☐	☐	☐	☐
Doctors rely on surgery too much	☐	☐	☐	☐	☐
I worry about the risks of surgery	☐	☐	☐	☐	☐
Doctors place too much trust in surgery	☐	☐	☐	☐	☐
Doctors are too quick to suggest surgery	☐	☐	☐	☐	☐
Surgery should only be undertaken as a last resort	☐	☐	☐	☐	☐
Surgery can result in new health problems	☐	☐	☐	☐	☐

SECTION K - OTHER HEALTH PROBLEMS

1. In the last two weeks, how many times have you experienced any of the following problems?

	Not at all	Once a week	2 or 3 times a week	Most days	Every day
Headaches (or migraine)	☐	☐	☐	☐	☐
Rashes	☐	☐	☐	☐	☐
Itching	☐	☐	☐	☐	☐
Lack of concentration	☐	☐	☐	☐	☐
Sweating	☐	☐	☐	☐	☐
Breathlessness	☐	☐	☐	☐	☐
Pains in stomach	☐	☐	☐	☐	☐
Lack of motivation	☐	☐	☐	☐	☐
Frustration	☐	☐	☐	☐	☐
Temperature	☐	☐	☐	☐	☐
Hot flushes	☐	☐	☐	☐	☐
Feeling low	☐	☐	☐	☐	☐
Shoulder pain	☐	☐	☐	☐	☐
Teeth problems	☐	☐	☐	☐	☐
Hunger pains	☐	☐	☐	☐	☐

	Not at all	Once a week	2 or 3 times a week	Most days	Every day
Dizziness	☐	☐	☐	☐	☐
Tired/Fatigued	☐	☐	☐	☐	☐
Dry mouth	☐	☐	☐	☐	☐
Sore throat	☐	☐	☐	☐	☐
Pins and needles	☐	☐	☐	☐	☐
Drowsiness	☐	☐	☐	☐	☐

2. In the last two weeks, have you experienced any change in weight?

	Yes	No
Weight loss	☐	☐
Weight gain	☐	☐

3. In the last two weeks, how much have the other health problems listed above affected your quality of life?

- Not at all ☐
- A little ☐
- Moderately ☐
- A lot ☐
- Extremely ☐

SECTION L – DESCRIBING YOUR OWN HEALTH TODAY

By placing a cross in one box in each group below, please indicate which statements best describe your own health state today

Mobility	I have no problems in walking about	☐
	I have some problems in walking about	☐
	I am confined to bed	☐
Self-care	I have no problems with self-care	☐
	I have some problems washing or dressing myself	☐
	I am unable to wash or dress myself	☐
Usual Activities *(e.g. work, study, housework, family or leisure activities)*	I have no problems with performing my usual activities	☐
	I have some problems with performing my usual activities	☐
	I am unable to perform my usual activities	☐
Pain/Discomfort	I have no pain or discomfort	☐
	I have moderate pain or discomfort	☐
	I have extreme pain or discomfort	☐
Anxiety/Depression	I am not anxious or depressed	☐
	I am moderately anxious or depressed	☐
	I am extremely anxious or depressed	☐

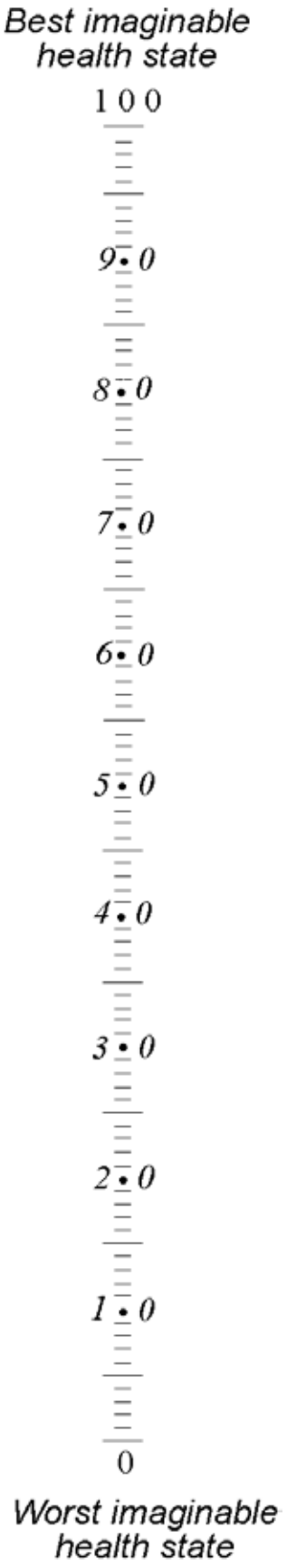
DESCRIBING YOUR OWN HEALTH TODAY

Please indicate on this scale how good or bad your own health state is today.

The best health state you can imagine is marked 100 and the worst health state you can imagine is marked 0.

Please draw a line from the box below to the point on the scale that best indicates how good or bad your health state is today.

Your own health state today



SECTION M – GENERAL HEALTH

Please fill in all the questions again by crossing the relevant box of the answer that applies to you.

These questions ask for your views about your health and how you feel about life in general. Do not spend too much time in answering as your immediate response is likely to be the most accurate, but please make sure you answer every question.

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

Excellent	Very good	Good	Fair	Poor
☐	☐	☐	☐	☐

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

Much better now than one year ago	Somewhat better now than one year ago	About the same as one year ago	Somewhat worse now than one year ago	Much worse now than one year ago
☐	☐	☐	☐	☐

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

	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 sport	☐	☐	☐
b) **Moderate activities**, such as moving a table, pushing a vacuum cleaner, bowling or playing golf	☐	☐	☐
c) Lifting or carrying groceries	☐	☐	☐
d) Climbing **several** flights of stairs	☐	☐	☐
e) Climbing **one** flight of stairs	☐	☐	☐
f) Bending, kneeling or stooping	☐	☐	☐
g) Walking **more than one mile**	☐	☐	☐
h) Walking **several hundred yards**	☐	☐	☐
i) Walking **one hundred yards**	☐	☐	☐
j) Bathing or dressing yourself	☐	☐	☐

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

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a) Cut down on the **amount of time** you spent on work or other activities	☐	☐	☐	☐	☐
b) **Accomplished less** than you would like	☐	☐	☐	☐	☐
c) Were limited in the **kind** of work or other activities	☐	☐	☐	☐	☐
d) Had **difficulty** performing the work or other activities (for example, it took extra effort)	☐	☐	☐	☐	☐

5. During the past 4 weeks, how much of the time 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)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a) Cut down on the **amount of time** you spent on work or other activities	☐	☐	☐	☐	☐
b) **Accomplished less** than you would like	☐	☐	☐	☐	☐
c) Did work or other **activities less carefully than usual**	☐	☐	☐	☐	☐

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

Not at all	Slightly	Moderately	Quite a bit	Extremely
☐	☐	☐	☐	☐

7. How much <u>bodily</u> pain have you had during the past 4 weeks?

None	Very mild	Mild	Moderate	Severe	Very severe
☐	☐	☐	☐	☐	☐

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

Not at all	A little bit	Moderately	Quite a bit	Extremely
☐	☐	☐	☐	☐

9. These questions are about how you feel and how things have been with you 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**	**Some of the time**	**A little of the time**	**None of the time**
a) Did you feel full of life?	☐	☐	☐	☐	☐
b) Have you been very nervous?	☐	☐	☐	☐	☐
c) Have you felt so down in the dumps that nothing could cheer you up?	☐	☐	☐	☐	☐
d) Have you felt calm and peaceful?	☐	☐	☐	☐	☐
e) Did you have a lot of energy?	☐	☐	☐	☐	☐
f) Have you felt downhearted and depressed?	☐	☐	☐	☐	☐
g) Did you feel worn out?	☐	☐	☐	☐	☐
h) Have you been happy?	☐	☐	☐	☐	☐
i) Did you feel tired?	☐	☐	☐	☐	☐

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 friends, relatives etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐	☐	☐	☐	☐

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 sick a little easier than other people	☐	☐	☐	☐	☐
b)	I am as healthy as anybody I know	☐	☐	☐	☐	☐
c)	I expect my health to get worse	☐	☐	☐	☐	☐
d)	My health is excellent	☐	☐	☐	☐	☐

SECTION N – HEALTH CARE RELATED QUESTIONS

In the following questions, we are trying to find out about some of the costs you incur as a result of your health problems.

If you are not sure or cannot remember exact details, please give the best answer you can.

1. PRESCRIBED MEDICATION FOR REFLUX

Are you currently being PRESCRIBED medication for your reflux symptoms?

YES ☐ **NO** ☐ → *If NO, please go to question 2 on the next page*

If YES, please put a cross in the box against the current dose you are being prescribed and write in the number of tablets you have taken in the last two weeks.

(Please note the dose can be found on the side of your tablet bottle or packet)

	Dose (mg)			Number of tablets taken in the last 2 weeks
Omeprazole (Losec)	10mg ☐	20mg ☐	40mg ☐	☐
Lansoprazole (Zoton)	15mg ☐	30mg ☐		☐
Pantoprazole (Protium)	20mg ☐	40mg ☐		☐
Rabeprazole (Pariet)	10mg ☐	20mg ☐		☐
Esomeprazole (Nexium)	20mg ☐	40mg ☐		☐
Rantidine (Zantac)	150mg ☐	300mg ☐		☐
Famotidine (Pepcid)	20mg ☐	40mg ☐		☐
Nizatidine (Axid)	150mg ☐	300mg ☐		☐
Cimetidine (Tagamet)	400mg ☐	800mg ☐		☐
Domperidone (Motilium)	10mg ☐	20mg ☐		☐
Metoclopramide (Maxolon)	10mg ☐	20mg ☐		☐

If you are prescribed any other medication (tablets or liquid) for your reflux symptoms that are not listed above, please list below the name(s) of the medicine(s) and include the number of times you have taken it in the last two weeks.

Names of medication	Number of times taken in last 2 weeks
e.g. Gaviscon	

2. NON PRESCRIBED MEDICATION FOR REFLUX

Please list below the names of any NON PRESCRIBED (over the counter) medication (tablets/liquid) you take for your reflux symptoms and include the number of times you have taken it in the last two weeks.

Names of medication	Number of times taken in last 2 weeks
e.g Rennies	

IF YOU HAVE ANY OTHER COMMENTS about your gastro-oesophageal reflux symptoms, your reflux treatment or this study, please write them below.

THANK YOU FOR YOUR HELP IN COMPLETING THIS QUESTIONNAIRE

Once you have completed the form, please return it in the pre-paid envelope provided or to the following address:

REFLUX Trial Office
Health Services Research Unit (Flea)
Polwarth Building
Foresterhill
Aberdeen AB25 2ZD
Tel: 01224 000000
Fax: 01224 554580
E-Mail: reflux@hsru.abdn.ac.uk

Appendix 3

Patient letter of invitation and patient information leaflets 1 and 2

Patient letter of invitation

Date as postmark

Dear

You are invited to attend a review appointment at my outpatient clinic (see enclosed appointment card) for your reflux (heartburn/regurgitation) symptoms.

I am writing to let you know that **<<*Hospital*>>** is part of a large national study funded by the NHS to look at the different types of treatment for reflux. As someone who is taking medication for their reflux symptoms, you may be eligible for the study.

I have included two patient information leaflets about the study. The first explains in further detail why the study is being done and the second explains what would happen if you were eligible to join the study. I would be most grateful if you would take the time to read through the information. There will be the opportunity to discuss the study in more detail during your appointment.

If you would like any further information about the trial please call the trial office directly on 01224 000000.

Yours sincerely

<<*Consultants name*>>
<<*Consultants position*>>
Enc.

The REFLUX Trial

A STUDY OF GASTRO-OESOPHAGEAL REFLUX DISEASE

PATIENT INFORMATION LEAFLET

1. WHAT IS THE STUDY ABOUT?

This hospital is one of several centres throughout the UK that are taking part in a study to find out the best way to treat people who suffer from heartburn and reflux. This problem is usually refereed to as gastro-oesophageal reflux disease (GORD).

What is gastro-oesophageal reflux?

Gastro-oesophageal reflux is the term used to describe a back-flow of acid from the stomach into the swallowing tube, the oesophagus. Gastro-oesophageal reflux occurs when the valve at the lower end of the oesophagus (next to the stomach) does not work properly. Almost everyone experiences gastro-oesophageal reflux at some time. The usual symptom is heartburn, an uncomfortable burning sensation behind the breast bone that often occurs after a meal. For some people, reflux can become frequent and serious enough to be regarded as a disease. It is when it reaches this point that it is recognised as being the medical condition known as gastro-oesophageal reflux disease (GORD).

What is the purpose of the study?

The two main treatments routinely used in the National Health Service (NHS) to treat GORD are medication and surgery.

At present we do not know whether medical treatment (drugs in the form of tablets) or surgical treatment is better for treating persistent symptoms of reflux. The main purpose of this study is to find out which form of treatment is best.

This hospital is one of several centres throughout the UK taking part in this study. As a person who is taking medication for their GORD symptoms, you may be eligible for the study. We plan to involve around 1200 people who suffer from persistent symptoms of reflux.

What are the advantages and disadvantages of the two types of treatments being compared?

*The advantages of **medical treatment** are:*

- it is effective in reducing symptoms, if there are any
- it does not require hospitalisation or time off work.

*The disadvantages of **medical treatment** are:*

- it has to be given indefinitely, and may occasionally cause side-effects such as headaches, rash, muscle and joint pain and stomach upsets
- it may impair the normal functions of stomach acid in digesting food and controlling bacteria. It should be remembered that in GORD, acid production by the stomach is usually normal; it simply gets into the wrong place, i.e. the oesophagus.

*The advantages of the **surgical operation** are:*

- it corrects the underlying cause of the problem, namely the faulty valve
- it preserves the normal acid production of the stomach
- it greatly reduces the need for lifelong medication.

*The disadvantages of the **surgical operation** are:*

- it requires one to three days in hospital and approximately two to six weeks off work
- it may cause temporary difficulty in swallowing solids, a feeling of fullness after eating and a change in bowel habits
- it may occasionally fail to abolish the symptoms of reflux
- as with all surgery, it is associated with a risk, albeit a very low risk, of operative death or serious complications.

What happens next?

Your doctor(s) will assess whether you are eligible for the study. If so, he/she will give you further information and ask if you would like to take part.

Who is organising the study?

The study is being funded by the NIHR Health Technology Assessment Programme.

Contact for Further Information

REFLUX Trial Office
Health Services Research Unit
University of Aberdeen
Foresterhill
Aberdeen
AB25 2ZD
Tel. 01224 000000 Fax: 01224 554580
Email: reflux@hsru.abdn.ac.uk

Thank you for reading this

Consumers for Ethics in Research (CERES) publish a leaflet entitled 'Medical Research and You'. This leaflet gives more information about medical research and looks at some questions you might want to ask. A copy may be obtained from CERES, PO Box 1365, London N16 0BW

The REFLUX Trial

A STUDY OF GASTRO-OESOPHAGEAL REFLUX DISEASE

PATIENT INFORMATION LEAFLET

2. WHAT HAPPENS IF I JOIN THE STUDY?

Before you decide whether to take part, it is important for you to understand why the study is being done and what it will involve. Please take time to read the following information carefully and discuss it with friends or relatives if you wish. Ask us if there is anything you don't understand or if you would like more information. Take time to decide whether or not you wish to take part.

What is the purpose of the study?

The two main forms of treatment routinely used in the NHS to treat GORD are medication and surgery. At present we do not know whether medical treatment (drugs in the form of tablets) or surgical treatment is better for treating persistent symptoms of reflux. The main purpose of this study is to find out which form of treatment is best.

To find out which is the best way of treating people with GORD we need to make comparisons between groups of people receiving medication or surgery. In this study, people are allocated, by a computer, to one of two different treatment groups: (1) medical treatment, or (2) surgery. The computer selects people to these two groups by chance (this is called randomisation). This is done so that we can be sure that both groups will include the same mix of people – male or female, older or younger – and the only difference between the groups is the treatment they will receive.

Half the people participating will receive long-term medical treatment and the other half will receive an operation. Those in the medical treatment group will continue with medication to control their symptoms. For many this is likely to be the same type of tablets as prescribed previously, but for some people, other tablets may be tried to improve symptom control. Those in the surgery group will have an operation performed by an experienced surgeon, using 'key-hole' surgery. In this, the upper part of the stomach is wrapped around the lower end of the oesophagus. This reinforces the 'valve' between them aiming to stop the reflux.

What will happen if I join the study?

- It is up to you to decide whether or not you would like to take part in the study. If you do decide to take part you will be asked to sign a consent form and fill in a questionnaire.
- You will be sent questionnaires by post, one after about 6 months and another 9 months later, which will take about half an hour to complete. Contact may continue for some years after that. You are free to decline to answer any of our questions without giving a reason at any time.
- Information relating to the treatment of your reflux symptoms may be collected from your medical notes.

What are the advantages and disadvantages of the two types of treatments being compared?

*The advantages of **medical treatment** are:*

- it is effective in reducing symptoms, if there are any
- it does not require hospitalisation or time off work.

*The disadvantages of **medical treatment** are:*

- it has to be given indefinitely, and may occasionally cause side-effects such as headaches, rash, muscle and joint pain and stomach upsets
- it may impair the normal functions of stomach acid in digesting food and controlling bacteria. It should be remembered that in GORD, acid production by the stomach is usually normal; it simply gets into the wrong place, i.e. the oesophagus.

*The advantages of the **surgical operation** are:*

- it corrects the underlying cause of the problem, namely the faulty valve
- it preserves the normal acid production of the stomach
- it greatly reduces the need for lifelong medication.

*The disadvantages of the **surgical operation** are:*

- it requires one to three days in hospital and approximately two to six weeks off work
- it may cause temporary difficulty in swallowing solids, a feeling of fullness after eating and a change in bowel habits
- it may occasionally fail to abolish the symptoms of reflux
- as with all surgery, it is associated with a risk, albeit a very low risk, of operative death or serious complications.

What are the possible benefits of taking part?

We hope that the treatment you receive will control your GORD symptoms. However, this cannot be guaranteed. The information we will get from this study may help in the future to provide better treatment for patients with GORD.

We want to reassure you that:

- Your involvement in the study is entirely voluntary.
- You are free to withdraw at any time and this would not affect your current of future medical treatment. Although we do not expect participation to affect private medical insurance, if you do have insurance, please check with the company before agreeing to take part in the study.
- All information collected for the study will be treated as confidential and used only for the purpose of the study.
- All people taking part will be kept informed about the study and will be sent a summary of the results. The results of the study will be published in medical journals. Participants will not be identifiable in any of the study reports.
- Both forms of treatment are in common use in the NHS. You will not have to undergo any tests or procedures that are not part of the routine management of GORD.

What if something goes wrong?

If you are harmed by taking part in this study, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds for a legal action but you may have to pay for it. Regardless of this, if you have any cause to complain about any aspect of the way you have been approached or treated during the course of this study, the normal NHS complaints mechanisms are available to you.

Contact for Further Information

REFLUX Trial Office
Health Services Research Unit
University of Aberdeen
Foresterhill
Aberdeen
AB25 2ZD
Tel. 01224 000000 Fax: 01224 554580
Email: reflux@hsru.abdn.ac.uk

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Appendix 4

Patient assessment form

The REFLUX Trial

Patient Details (or affix stamp)

Name: _____

Address: _____

_____

_____

Sex: _____ DoB: _____

Hosp ID: _____

Patient Assessment Form

Participant Study No

Hospital: _____

Date: _____/_____/_____

Consultant's Details

Name: _____

Signature: _____

Please tick the box which best describes the patient:-

Eligibility Criteria		**Yes**	**No**
1	Evidence of GORD (endoscopy and/or pH monitoring)		
2	Symptoms > 12 months		
3	Currently requiring maintenance PPI symptom control		
4	Suitable for either policy (ASA Grade I or II)		

Reasons for Exclusion		**Yes**	**No**
5	BMI > 40 kg/m^2		
6	Barrett's oesophagus (≥3cm)		
7	Paraoesophageal hernia		
8	Oesophageal strictures		
9	One type of management is clinically indicated for another reason		
10	Other (state)		

If there is a tick in **every** shaded box the patient is eligible

↓

Has the patient had erosive oesophagitis? (please circle**)** **Yes** **No**

↓

Please pass on this form with the patient to the research nurse

Recruitment and Co-morbidity Information *(to be completed by the **research nurse**)*

Source of recruitment Retrospective ☐ Prospective ☐

Reasons for non-recruitment

Clinician chose not to recruit ☐ Patient declined ☐ Patient not approached/missed ☐

H.Pylori test **(CLO test)**

Positive (subsequently treated) ☐ Positive (subsequently untreated) ☐ Negative ☐ Uncertain ☐

Hiatus Hernia Yes ☐ No ☐

pH monitoring Yes ☐ No ☐

Height _____ m / ft

Weight _____ kg / st

Appendix 5

Surgical patient information leaflet

The REFLUX Trial

PATIENT INFORMATION LEAFLET

LAPAROSCOPIC SURGERY FOR GASTRO-OESOPHAGEAL REFLUX DISEASE

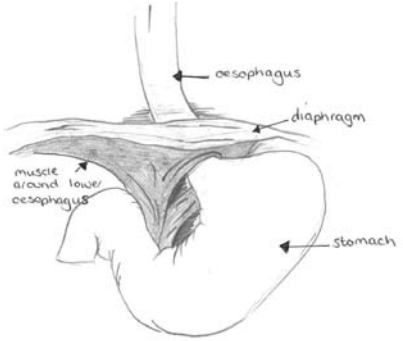
Please take time to read the following information carefully and discuss it with friends or relatives if you wish. It is important for you to understand what the operation involves. Ask us if there is anything you don't understand or if you would like more information. Take time to decide whether or not you wish to take part.

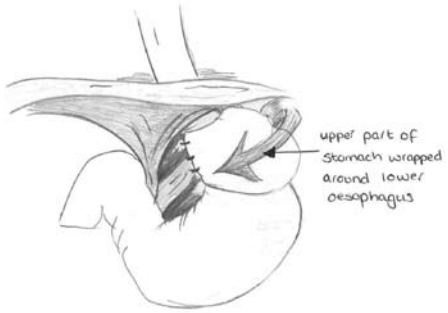
What is laparoscopic surgery?

Laparoscopic (key-hole) surgery is an established technique for treating the symptoms caused by excessive reflux from the stomach back into the oesophagus. Most patients with this problem (usually referred to as GORD – Gastro-oesophageal Reflux Disease) are aware of heartburn, pain and reflux of acid and fluid. This is usually worse on bending and lying down.

What does the operation involve?

Laparoscopic surgery involves strengthening the 'valve' between the oesophagus and the stomach by wrapping the upper part of the stomach around the lowest part of the oesophagus – much the way a bun fits around a hot dog (about 2cm long).





The operation usually involves making five small punctures through which special surgical instruments are passed into the upper part of the abdomen. The surgeon uses a laparoscope, a form of telescope with a miniature video camera attached to it, to give a magnified view on a television screen of the inside of the body. This lets the surgeon carry out the operation from outside the body. The benefits of key-hole surgery are that patients recover more quickly from the operation, have less scarring and suffer less pain.

As in all key-hole operation there is a small chance that the operation will have to change to a standard open operation with a long incision. This is usually only required for reasons of safety because it has not been possible to carry out the operation as a key-hole procedure or to deal with a problem which could not be managed with the laparoscopic approach. The risk of being changed to an open operation is probably less than one in fifty operations.

What happens before the operation?

Before you have been considered for an operation you will have undergone investigations; a gastroscopy to look at the extent of inflammation in the lower oesophagus, normally a test involving the passage of tubes into the oesophagus to measure the pressures and the amount of acid refluxing, and sometimes a barium meal.

What happens after the operation?

Patients usually need to stay in hospital for two or three days and should be able to return to work after about a month. After the operation it is normal to experience some pain. The small incisions may be sore but in addition some patients feel quite sharp pain in their shoulders. Occasionally this persists for a few days and rarely for a few weeks after the operation. Pain alleviating medication is routinely prescribed for post-operative pain.

Some difficulty in swallowing is also routine after the operation and normally improves on its own over a few weeks. Avoiding dry food, bread and meat is the best way of avoiding problems until you are sure that your swallowing is back to normal.

A degree of abdominal bloating and discomfort is also common and may persist in some patients. Improving the valve at the top of the stomach will change the way you belch or vomit and some patients find it difficult to do either of these after surgery.

A significant number of patients are aware that they pass more wind from the back passage after the operation and some patients notice a change in their bowel movements. It is normal to notice a change in the first few months but this usually settles. A small number of patients may have diarrhoea which can take several months to settle.

Recurrence of reflux symptoms is possible after these operations particularly as years go by. If symptoms do recur they are normally milder and more easily treated than before surgery.

Contact for Further Information

REFLUX Trial Office
Health Services Research Unit
University of Aberdeen
Foresterhill
Aberdeen
AB25 2ZD
Tel. 01224 000000 Fax: 01224 554580
Email: reflux@hsru.abdn.ac.uk

Thank you for reading this

Consumers for Ethics in Research (CERES) publish a leaflet entitled 'Medical Research and You'. This leaflet gives more information about medical research and looks at some questions you might want to ask. A copy may be obtained from CERES, PO Box 1365, London N16 0BW

Appendix 6

Trial consent form

The REFLUX Trial

Participant Study No

Trial Consent Form

Copy 1
Participant's Copy to Keep

I have:

- Discussed the study with

	Yes	No
• Been given the Information Leaflets about the study	☐	☐
• Received satisfactory answers to questions	☐	☐
• Been given satisfactory information about the study	☐	☐

I understand that:

- I have chosen to be randomly allocated to either having surgery or continuing with medication for the treatment of my reflux symptoms
- I will be sent questionnaires at specified time intervals after starting the study
- I may be approached to find out how I am, for some years after starting the study
- Information related to treatment of reflux may be collected from my medical notes
- My family doctor will be notified that I am taking part in the study
- I am free to withdraw from the study at any time without having to give a reason
- If I withdraw, this will not affect my future care

I agree to take part in the study

Signature of participant

Name (in block capitals)

Date

I confirm that I have explained to the person named above, the nature and purpose of the study and the procedures involved

Signature of researcher

Date

REFLUX Trial Office, Health Service Research Unit (Flea), University of Aberdeen, Foresterhill, ABERDEEN AB25 2ZD
Tel: 01224 000000 Fax: 01224 554580 Email: REFLUX@abdn.ac.uk

RCFV3/02/01

The REFLUX Trial

Participant Study No

Trial Consent Form

Copy 2
To Return to The REFLUX Trial Office

I have:

- Discussed the study with

	Yes	No
• Been given the Information Leaflets about the study	☐	☐
• Received satisfactory answers to questions	☐	☐
• Been given satisfactory information about the study	☐	☐

I understand that:

- I have chosen to be randomly allocated to either having surgery or continuing with medication for the treatment of my reflux symptoms
- I will be sent questionnaires at specified time intervals after starting the study
- I may be approached to find out how I am, for some years after starting the study
- Information related to treatment of reflux may be collected from my medical notes
- My family doctor will be notified that I am taking part in the study
- I am free to withdraw from the study at any time without having to give a reason
- If I withdraw, this will not affect my future care

I agree to take part in the study

Signature of participant

Name (in block capitals)

Date

I confirm that I have explained to the person named above, the nature and purpose of the study and the procedures involved

Signature of researcher

Date

REFLUX Trial Office, Health Service Research Unit (Flea), University of Aberdeen, Foresterhill, ABERDEEN AB25 2ZD
Tel: 01224 000000 Fax: 01224 554580 Email: REFLUX@abdn.ac.uk

Appendix 7

Preference study: patient information leaflet and consent form

The REFLUX Trial

A STUDY OF GASTRO-OESOPHAGEAL REFLUX DISEASE

PATIENT INFORMATION LEAFLET

3. WHAT HAPPENS IF I CHOOSE MY TREATMENT WITHIN THE STUDY?

- THE PREFERENCE STUDY -

Before you decide whether to take part in the preference study, it is important for you to understand why the study is being done and what it will involve. Please take time to read the following information carefully and discuss it with friends or relatives if you wish. Ask us if there is anything you don't understand or if you would like more information. Take time to decide whether or not you wish to take part.

What is the purpose of the study?

The main purpose of this study is to find out which of the two main forms of treatment routinely used in the NHS to treat Gastro-oesophageal Reflux Disease, GORD (taking medication or having an operation) is better for treating persistent symptoms of reflux.

Comparisons can be made about these treatments in two different ways. The first, which was described in the second patient information leaflet, compares groups of people who have no strong preference for the two treatment groups and are willing to be allocated at random to one of the groups. The second is to look at comparisons between groups of people who **choose** their own preferred treatment from one of the two treatments being studied.

If you have chosen to continue with medication, it is likely that you will continue taking the same type of tablets you have previously been prescribed, although other tablets may be tried to help improve symptom control.

If you have chosen to have surgery, you will have an operation using 'key-hole' surgery. In this, the upper part of the stomach is wrapped around the lower end of the oesophagus. This reinforces the 'valve' between them aiming to stop the reflux.

Including eligible people who have a strong preference for a particular treatment, allows the study to be completely representative of all people who suffer with GORD.

What will happen if you join the preference study?

- If you decide to take part you will be asked to sign a consent form and fill in a questionnaire.
- You will be sent questionnaires by post, at specific time intervals after joining the study, which will take about half an hour to complete. Contact may continue for some years after that. You are free to decline to answer any of the questions without giving a reason at any time.
- If you do join the study, you are still free to withdraw from it any time without giving a reason.
- Information relating to the treatment of your reflux symptoms may be collected from your medical notes.

We want to reassure you that:

- Your involvement in the study is entirely voluntary.
- You are free to withdraw at any time and this would not affect your current of future medical treatment.
- All information collected for the study will be treated as confidential and used only for the purpose of the study.
- We will inform your GP that you are taking part.
- All people taking part will be kept informed about the study and will be sent a summary of the results. The results of the study will be published in medical journals. Participants will not be identifiable in any of the study reports.
- Both forms of treatment are in common use in the NHS. You will not have to undergo any tests or procedures that are not part of the routine management of GORD.

What if something goes wrong?

If you are harmed by taking part in this study, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds for a legal action but you may have to pay for it. Regardless of this, if you have any cause to complain about any aspect of the way you have been approached or treated during the course of this study, the normal NHS complaints mechanisms are available to you.

Contact for Further Information

REFLUX Trial Office
Health Services Research Unit
University of Aberdeen
Foresterhill
Aberdeen
AB25 2ZD
Tel. 01224 554196 Fax: 01224 554580
Email: reflux@hsru.abdn.ac.uk

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The REFLUX Trial

Participant Study No

Preference Consent Form

Copy 1
Participant's Copy to Keep

I have:

- Discussed the study with

	Yes	No
• Been given the Information Leaflets about the study	☐	☐
• Received satisfactory answers to questions	☐	☐
• Been given satisfactory information about the study	☐	☐

I understand that:

- I have chosen to have surgery / continue with medication* for the treatment of my reflux symptoms (*delete as appropriate)
- I will be sent questionnaires at specified time intervals after starting the study
- I may be approached to find out how I am, for some years after starting the study
- Information related to treatment of reflux may be collected from my medical notes
- My family doctor will be notified that I am taking part in the study
- I am free to withdraw from the study at any time without having to give a reason
- If I withdraw, this will not affect my future care

I agree to take part in the study

Signature of participant

Name (in block capitals)

Date

I confirm that I have explained to the person named above, the nature and purpose of the study and the procedures involved

Signature of researcher

Date

REFLUX Trial Office, Health Service Research Unit (Flea), University of Aberdeen, Foresterhill, ABERDEEN AB25 2ZD
Tel: 01224 000000 Fax: 01224 554580 Email: REFLUX@abdn.ac.uk

PCFV3/02/01

The REFLUX Trial

Participant Study No

Preference Consent Form

Copy 2
To Return to The REFLUX Trial Office

I have:

- Discussed the study with

	Yes	No
• Been given the Information Leaflets about the study	☐	☐
• Received satisfactory answers to questions	☐	☐
• Been given satisfactory information about the study	☐	☐

I understand that:

- I have chosen to have surgery / continue with medication* for the treatment of my reflux symptoms (*delete as appropriate)
- I will be sent questionnaires at specified time intervals after starting the study
- I may be approached to find out how I am, for some years after starting the study
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Date

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Tel: 01224 000000 Fax: 01224 554580 Email: REFLUX@abdn.ac.uk

Appendix 8

Laparoscopic fundoplication operative data form

Patient Details (or affix stamp to both copies)

Name: _____

Address: _____

_____

_____

Sex: _____ DoB: _____

Hosp ID: _____

The REFLUX Trial

Laparoscopic Fundoplication Operative Data

Participant Study No

Date of admission _____/_____/_____

Date of operation _____/_____/_____

Date of discharge _____/_____/_____

PREOPERATIVE DETAILS

1) Tests before surgery (tick against tests performed)

Endoscopy ☐ pH monitoring ☐ Manometry ☐

Other (state) _____

2) Previous abdominal surgery (state) _____

OPERATIVE DETAILS

1) Operating surgeon's name _____

2) Grade of operating surgeon (tick against grade)

Consultant ☐ Staff, Assoc. Spec ☐ SpR ☐

Other (state) _____

3) Operation times (24 hour)

Time into anaesthetic room ☐☐:☐☐

Time into recovery room ☐☐:☐☐

4) Type of fundoplication (tick against type)

Total wrap ☐

Partial - anterior ☐

- posterior ☐

Other (state) _____

5) Operative (tick if yes)

Liver injury ☐

Splenic injury ☐

Pleural injury ☐

Oesophageal injury ☐

Other visceral injury ☐

Haemorrhage (requiring change to normal procedure) ☐

6) Technical (tick if yes)

Short gastric arteries divided ☐

Left hepatic from left gastric artery ☐

If present, left hepatic artery divided ☐

Hepatic branch vagus divided ☐

Hiatus Hernia present ☐

Bougie used ☐

7) Crural repair (tick if yes) ☐

8) Conversion to open (tick if yes) ☐

Reason (state) _____

POSTOPERATIVE DETAILS (*to be completed by the **Research Nurse***)

1) Post-op level of care (tick if yes)

Ward only ☐

HDU admission ☐

ICU admission ☐

Re-operation (describe below) ☐

_____

2) Early post operative event (tick if yes)

Pneumothorax (requiring intervention) ☐

Blood transfusion required ☐

Number of units transfused (state) ☐

Other (state) ☐

3) Outcomes (tick if yes)

Discharged - home ☐

- other ☐

Died ☐

Appendix 9

Search strategies for literature searches

Search strategies

1. fundoplication or fundiplication or fundoplast$or stretta).mp.
2. (euroqol or EQ-5D or eq-5d or (eq adj 5d) or hui or qwb or utility or utilities).mp.
3. quality of life/
4. 1 and (2 or 3)

Reference manager/ MEDLINE

(SF-36) OR (sf 36)

(EQ-5D) OR (eq 5d) OR (euroqol) OR (euro qol)

(short form 36) OR (shortform 36) OR (sf thirtysix) OR (sf thirty six) OR (short form thirty six)

(hrql) OR (hrqol) OR (h qol) OR (hql) OR (hqol)

or (hye) OR (hyes) OR (health$year$equivalent$) OR (health util$)

or rosser

or (quality of life) OR (quality adjusted life year) OR (health status indicator) OR (qaly) OR (quality adjusted life) OR (life quality)

(ppi) OR (omeprazole) OR (pantoprazole) OR (lansoprazole) OR (esomeprazole) OR (rabeprazole)

(SF-36) OR (sf 36)

(EQ-5D) OR (eq 5d) OR (euroqol) OR (euro qol)

(short form 36) OR (shortform 36) OR (sf thirtysix) OR (sf thirty six) OR (short form thirty six)

or (64) OR (hrqol) OR (h qol) OR (hql) OR (hqol)

or (hye) OR (hyes) OR (health$year$equivalent$) OR (health util$)

or rosser

or (quality of life) OR (quality adjusted life year) OR (health status indicator) OR (qaly) OR (quality adjusted life) OR (life quality)

and (H2-blocker) OR (ranitidine) OR (famotidine) OR (cimetidine) OR (nizatidine)

Appendix 10

Costs of surgery and cost loadings

	Total surgical costs (£)				
	Centre 1	**Centre 2**	**Centre 3**	**Centre 4**	**Centre 5**
Preoperative procedures	£314.66	£299.42	£314.66	£321.66	£364.66
Theatre staff	£545.20	£289.92	£455.06	£441.46	£520.39
Disposables	£725.30	£853.52	£1051.08	£635.93	£816.46
Capital equipment	£9.22	£9.22	£9.22	£9.22	£9.22
Bed costs	£1140.72	£1140.72	£1140.72	£1140.72	£1140.72
Consumables	£47.57	£47.57	£47.57	£47.57	£47.57
Total/centre	£2782.67	£2640.37	£3018.31	£2596.56	£2899.02
Mean cost of LNF	£2787.39				
SD	£175.95				

Cost loadings (for complications)	
Cost of open fundoplication (conversion) allowing for longer LOS	£4490.67
Probability of conversion being required	0.05
Cost of dilatation	£165
Probability of dilatation being performed	0.021
Total cost of surgery	£3015.39

LNF, laparoscopic Nissen fundoplication; LOS, length of stay.

Appendix 11

Programming code using the WinBUGS® statistical package to estimate the pooled rate of surgery patients requiring medical management, using a random study effect

Model

```
#filename "poisson6.odc"
{
for (i in 1:N) {
#likelihood poisson family
n_cases[i] ~ dpois(mu[i])
#beta0 = intercept
#no covariates
#total is the offset term (coefficient forced to = 1)
#estimate random effects b[i]
#log (multiplicative) link function
log(mu[i]) <–log(total[i]) + b[i]
#prior for random study effect
b[i] ~ dnorm(beta0,tau)
}
#prior for log(pooled rate)
beta0 ~ dnorm(0,1.0E-6)
#various priors are possible for precision
#eg (gamma(0.001,0.001) on tau,uniform(0,10) on
sigma)
sigma ~ dunif(0,10)
#recalculate intercept on natural scale
rate <–exp(beta0)
tau <–1/(sigma × sigma)
}
inits
#list(beta0 = 0, tau = 1,
b = c(0,0,0,0,0
0,0,0,0,0,
0,0,0,0,0
))
list(beta0 = 0, sigma = 0.5,
b = c(0,0,0,0,0,   0,0,0,0,0,
0,0,0,0,0
))
data
list(N = 15,
n_cases = c(2,14,19,24,5,
10,60,150,2,11,
19,31,10,80,0
),
total = c(109,104,716,1094,103,
411,4410,578,108,260,
100,336,533,300,18
))

END
```

Results of WinBUGS regression model

Node	Mean	SD	MC error	2.5%	Median	97.5%	Start	Sample
b[1]	–3.890	0.5914	0.005063	–5.184	–3.836	–2.87	10001	20000
b[2]	–2.096	0.2738	0.001975	–2.666	–2.083	–1.593	10001	20000
b[3]	–3.631	0.2259	0.001579	–4.094	–3.624	–3.21	10001	20000
b[4]	–3.815	0.2013	0.001423	–4.224	–3.808	–3.439	10001	20000
b[5]	–3.113	0.4303	0.003166	–4.032	–3.085	–2.343	10001	20000
b[6]	–3.709	0.3049	0.001992	–4.342	–3.695	–3.154	10001	20000
b[7]	–4.291	0.1289	8.542E-4	–4.551	–4.287	–4.044	10001	20000
b[8]	–1.361	0.08253	6.599E-4	–1.525	–1.360	–1.203	10001	20000
b[9]	–3.890	0.5920	0.004299	–5.199	–3.844	–2.871	10001	20000
b[10]	–3.197	0.2945	0.002113	–3.817	–3.181	–2.663	10001	20000
b[11]	–1.747	0.2347	0.001692	–2.224	–1.738	–1.309	10001	20000
b[12]	–2.417	0.1799	0.001345	–2.781	–2.412	–2.078	10001	20000
b[13]	–3.955	0.3002	0.002147	–4.579	–3.944	–3.407	10001	20000
b[14]	–1.345	0.1133	8.246E-4	–1.574	–1.343	–1.129	10001	20000
b[15]	–3.890	1.0070	0.008261	–6.141	–3.798	–2.213	10001	20000
beta0	–3.086	0.3382	0.002570	–3.774	–3.077	–2.433	10001	20000
rate	0.04833	0.01689	1.232E-4	0.02297	0.04608	0.08779	10001	20000
sigma	1.208	0.2936	0.003329	0.7787	1.159	1.919	10001	20000
tau	0.7991	0.3561	0.003369	0.2717	0.744	1.65	10001	20000

MC error, Monte Carlo error.

Appendix 12

Discrete choice experiment questionnaires

Participant Study No

(for completion by co-ordinating centre in Aberdeen)

For office use only

A	

GASTRO-OESOPHAGEAL REFLUX DISEASE (GORD) TREATMENT CHOICE QUESTIONNAIRE

CONFIDENTIAL

This study is funded by the NIHR Health Technology Assessment Programme

THE FOLLOWING TWO PAGES ARE FOR INFORMATION ONLY

Thank you for taking part in this survey.

The responses you give will help us find out which reflux treatment option has the biggest impact on overall health and quality of life. The information you provide will be completely confidential.

HOW TO FILL IN THE QUESTIONNAIRE

In this questionnaire, you are presented with 10 questions relating to different GORD treatment choices, each describing two or three treatment options: Option A or Option B and sometimes Option C.

When answering these questions, we would like you to imagine that your gastroenterologist is offering you the choice of treatment options (A or B or C) and that (s)he would like you to pick the option you prefer. You would do this by putting a tick in the appropriate box.

Although, you may not like either treatment option, please choose the one that is most preferable to you.

Please tick just **ONE** box for every question.

PLEASE REFER TO THE GUIDANCE NOTES ENCLOSED WITH THIS QUESTIONNAIRE TO HELP YOU MAKE YOUR DECISIONS

Here is an **EXAMPLE QUESTION** to help you fill out the following questions:

Example question Which option would you choose?

	Option A	Option B
Frequency of troublesome symptoms	None at all	Once a week
Chance of serious complications requiring hospitalisation	1 in 500	1 in 800
Chance of undergoing surgery	2 in 3	1 in 20
Chance of needing lifelong medication	1 in 20	2 in 3

(Tick one box only)	☑ **Option A**	☐ **Option B**

IN THIS CASE YOU WOULD PREFER TO:

Have the option of no symptoms, having a 1 in 500 chance of serious complications, having a 2 in 3 chance of undergoing surgery, and a 1 in 20 chance of needing lifelong medication.

RATHER THAN:

The option of having symptoms once a week, having a 1 in 800 chance of serious complications, having a 1 in 20 chance of undergoing surgery, and a 2 in 3 chance of needing lifelong medication.

Please remember, **there is no right or wrong answer**.
We just want to know what **YOU** think.

Choice 1 Which option would you choose?

	Option A	Option B
Frequency of troublesome symptoms	Once a week	Two or three times a week
Chance of serious complications requiring hospitalisation	1 in 500	1 in 100
Chance of undergoing surgery	1 in 20	1 in 3
Chance of needing lifelong medication	5 in 6	1 in 3

(Tick one box only) ☐ **Option A** ☐ **Option B**

Choice 2 Which option would you choose?

	Option A	Option B
Frequency of troublesome symptoms	Two or three times a week	Most days/everyday
Chance of serious complications requiring hospitalisation	1 in 100	1 in 500
Chance of undergoing surgery	1 in 3	2 in 3
Chance of needing lifelong medication	1 in 20	2 in 3

(Tick one box only) ☐ **Option A** ☐ **Option B**

Choice 3 Which option would you choose?

	Option A	Option B
Frequency of troublesome symptoms	Two or three times a week	Most days/everyday
Chance of serious complications requiring hospitalisation	1 in 500	1 in 100
Chance of undergoing surgery	5 in 6	1 in 20
Chance of needing lifelong medication	2 in 3	1 in 20

(Tick one box only) ☐ **Option A** ☐ **Option B**

Choice 4 Which option would you choose?

	Option A	Option B
Frequency of troublesome symptoms	Most days/everyday	Not at all
Chance of serious complications requiring hospitalisation	1 in 300	1 in 800
Chance of undergoing surgery	1 in 3	2 in 3
Chance of needing lifelong medication	5 in 6	1 in 3

(Tick one box only) ☐ **Option A** ☐ **Option B**

Choice 5 Which option would you choose?

	Option A	Option B	Option C
Frequency of troublesome symptoms	Two or three times a week	Most days/everyday	Two or three times a week
Chance of serious complications requiring hospitalisation	1 in 100	1 in 500	1 in 100
Chance of undergoing surgery	1 in 3	2 in 3	2 in 3
Chance of needing lifelong medication	1 in 20	2 in 3	1 in 3

(Tick one box only) ☐ **Option A** ☐ **Option B** ☐ **Option C**

Choice 6 Which option would you choose?

	Option A	Option B
Frequency of troublesome symptoms	Once a week	Two or three times a week
Chance of serious complications requiring hospitalisation	1 in 100	1 in 500
Chance of undergoing surgery	2 in 3	5 in 6
Chance of needing lifelong medication	1 in 3	5 in 6

(Tick one box only) ☐ **Option A** ☐ **Option B**

Choice 7 Which option would you choose?

	Option A	Option B
Frequency of troublesome symptoms	Not at all	Once a week
Chance of serious complications requiring hospitalisation	1 in 800	1 in 300
Chance of undergoing surgery	1 in 20	1 in 3
Chance of needing lifelong medication	1 in 20	2 in 3

(Tick one box only) ☐ **Option A** ☐ **Option B**

Choice 8 Which option would you choose?

	Option A	Option B
Frequency of troublesome symptoms	Most days/everyday	Not at all
Chance of serious complications requiring hospitalisation	1 in 800	1 in 300
Chance of undergoing surgery	5 in 6	1 in 20
Chance of needing lifelong medication	1 in 3	5 in 6

(Tick one box only) ☐ **Option A** ☐ **Option B**

Choice 9 Which option would you choose?

	Option A	Option B
Frequency of troublesome symptoms	Not at all	Once a week
Chance of serious complications requiring hospitalisation	1 in 300	1 in 800
Chance of undergoing surgery	2 in 3	5 in 6
Chance of needing lifelong medication	2 in 3	1 in 20

(Tick one box only) ☐ **Option A** ☐ **Option B**

Choice 10 Which option would you choose?

	Option A	Option B	Option C
Frequency of troublesome symptoms	Most days/everyday	Not at all	Most days/everyday
Chance of serious complications requiring hospitalisation	1 in 300	1 in 800	1 in 100
Chance of undergoing surgery	1 in 3	2 in 3	2 in 3
Chance of needing lifelong medication	5 in 6	1 in 3	5 in 6

(Tick one box only) ☐ **Option A** ☐ **Option B** ☐ **Option C**

IF YOU HAVE ANY OTHER COMMENTS about your gastro-oesophageal reflux symptoms, your reflux treatment or this study, please write them below.

THANK YOU FOR YOUR HELP IN COMPLETING THIS QUESTIONNAIRE

Once you have completed the form, please return it in the pre-paid envelope provided or to the following address:

REFLUX Trial Office
Health Services Research Unit
Polwarth Building
Foresterhill
Aberdeen AB25 2ZD
Tel: 01224 000000
Fax: 01224 554580
E-mail: reflux@hsru.abdn.ac.uk

Participant Study No

(for completion by co-ordinating centre in Aberdeen)

For office use only

B	

The REFLUX Trial

GASTRO-OESOPHAGEAL REFLUX DISEASE (GORD) TREATMENT CHOICE QUESTIONNAIRE

CONFIDENTIAL

This study is funded by the NIHR Health Technology Assessment Programme

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Thank you for taking part in this survey.

The responses you give will help us find out which reflux treatment option has the biggest impact on overall health and quality of life. The information you provide will be completely confidential.

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When answering these questions, we would like you to imagine that your gastroenterologist is offering you the choice of treatment options (A or B or C) and that (s)he would like you to pick the option you prefer. You would do this by putting a tick in the appropriate box.

Although, you may not like either treatment option, please choose the one that is most preferable to you.

Please tick just **ONE** box for every question.

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Here is an **EXAMPLE QUESTION** to help you fill out the following questions:

Example question Which option would you choose?

	Option A	Option B
Frequency of troublesome symptoms	None at all	Once a week
Chance of serious complications requiring hospitalisation	1 in 500	1 in 800
Chance of undergoing surgery	2 in 3	1 in 20
Chance of needing lifelong medication	1 in 20	2 in 3

(Tick one box only)

☑ **Option A** ☐ **Option B**

IN THIS CASE YOU WOULD PREFER TO:

Have the option of no symptoms, having a 1 in 500 chance of serious complications, having a 2 in 3 chance of undergoing surgery, and a 1 in 20 chance of needing lifelong medication.

RATHER THAN:

The option of having symptoms once a week, having a 1 in 800 chance of serious complications, having a 1 in 20 chance of undergoing surgery, and a 2 in 3 chance of needing lifelong medication.

Please remember, **there is no right or wrong answer**.
We just want to know what **YOU** think.

Choice 1 Which option would you choose?

	Option A	Option B
Frequency of troublesome symptoms	Once a week	Two or three times a week
Chance of serious complications requiring hospitalisation	1 in 800	1 in 300
Chance of undergoing surgery	1 in 3	2 in 3
Chance of needing lifelong medication	2 in 3	1 in 20

(Tick one box only) ☐ **Option A** ☐ **Option B**

Choice 2 Which option would you choose?

	Option A	Option B
Frequency of troublesome symptoms	Two or three times a week	Most days/everyday
Chance of serious complications requiring hospitalisation	1 in 300	1 in 800
Chance of undergoing surgery	1 in 20	1 in 3
Chance of needing lifelong medication	1 in 3	5 in 6

(Tick one box only) ☐ **Option A** ☐ **Option B**

Choice 3 Which option would you choose?

	Option A	Option B
Frequency of troublesome symptoms	Two or three times a week	Most days/everyday
Chance of serious complications requiring hospitalisation	1 in 800	1 in 300
Chance of undergoing surgery	2 in 3	5 in 6
Chance of needing lifelong medication	5 in 6	1 in 3

(Tick one box only) ☐ **Option A** ☐ **Option B**

Choice 4 Which option would you choose?

	Option A	Option B
Frequency of troublesome symptoms	Most days/everyday	Not at all
Chance of serious complications requiring hospitalisation	1 in 100	1 in 500
Chance of undergoing surgery	1 in 20	1 in 3
Chance of needing lifelong medication	2 in 3	1 in 20

(Tick one box only) ☐ **Option A** ☐ **Option B**

Choice 5 Which option would you choose?

	Option A	Option B	Option C
Frequency of troublesome symptoms	Once a week	Two or three times a week	Two or three times a week
Chance of serious complications requiring hospitalisation	1 in 800	1 in 300	1 in 100
Chance of undergoing surgery	1 in 3	2 in 3	5 in 6
Chance of needing lifelong medication	2 in 3	1 in 20	1 in 20

(Tick one box only) ☐ **Option A** ☐ **Option B** ☐ **Option C**

Choice 6 Which option would you choose?

	Option A	Option B
Frequency of troublesome symptoms	Once a week	Two or three times a week
Chance of serious complications requiring hospitalisation	1 in 300	1 in 800
Chance of undergoing surgery	5 in 6	1 in 20
Chance of needing lifelong medication	1 in 20	2 in 3

(Tick one box only) ☐ **Option A** ☐ **Option B**

Choice 7 Which option would you choose?

	Option A	Option B
Frequency of troublesome symptoms	Not at all	Once a week
Chance of serious complications requiring hospitalisation	1 in 500	1 in 100
Chance of undergoing surgery	1 in 3	2 in 3
Chance of needing lifelong medication	1 in 3	5 in 6

(Tick one box only) ☐ **Option A** ☐ **Option B**

Choice 8 Which option would you choose?

	Option A	Option B
Frequency of troublesome symptoms	Most days/everyday	Not at all
Chance of serious complications requiring hospitalisation	1 in 500	1 in 100
Chance of undergoing surgery	2 in 3	5 in 6
Chance of needing lifelong medication	1 in 20	2 in 3

(Tick one box only) ☐ **Option A** ☐ **Option B**

Choice 9 Which option would you choose?

	Option A	Option B
Frequency of troublesome symptoms	Not at all	Once a week
Chance of serious complications requiring hospitalisation	1 in 100	1 in 500
Chance of undergoing surgery	5 in 6	1 in 20
Chance of needing lifelong medication	5 in 6	1 in 3

(Tick one box only) ☐ **Option A** ☐ **Option B**

Choice 10 Which option would you choose?

	Option A	Option B	Option C
Frequency of troublesome symptoms	Most days/everyday	Not at all	Most days/everyday
Chance of serious complications requiring hospitalisation	1 in 500	1 in 100	1 in 300
Chance of undergoing surgery	2 in 3	5 in 6	5 in 6
Chance of needing lifelong medication	1 in 20	2 in 3	1 in 3

(Tick one box only) ☐ **Option A** ☐ **Option B** ☐ **Option C**

IF YOU HAVE ANY OTHER COMMENTS about your gastro-oesophageal reflux symptoms, your reflux treatment or this study, please write them below.

THANK YOU FOR YOUR HELP IN COMPLETING THIS QUESTIONNAIRE

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Health Services Research Unit
Polwarth Building
Foresterhill
Aberdeen AB25 2ZD
Tel: 01224 000000
Fax: 01224 554580
E-mail: reflux@hsru.abdn.ac.uk

Appendix 13

Further results of the discrete choice experiment (DCE)

The regression model for the whole sample

Dimension	Coefficient	Standard error	*p*-value	95% confidence interval
Troublesome symptoms				
Once a week	–0.068	0.066	0.299	–0.197 to 0.061
Two or three times a week	–0.445	0.077	0.000	–0.596 to –0.295
Most days/every day	–1.156	0.071	0.000	–1.295 to –1.018
Serious complications	–5.471	0.661	0.000	–6.767 to –4.174
Surgery	–5.176	0.844	0.000	–6.830 to –3.521
Lifelong medication	–4.815	0.685	0.000	–6.159 to –3.472

Conditional (fixed-effects) logistic regression: number of obs = 6434; LR $\chi^2(6) = 492.08$; prob > $\chi^2 = 0.0000$.
Log likelihood = –1983.8155; pseudo $r^2 = 0.1103$.

Relative importance of dimensions

	Troublesome symptoms				
	Two or three times	Most days	Serious complications	Surgery	Lifelong medication
Troublesome symptoms					
Two or three times	1.00	2.85	13.74	13.13	–12.08
Most days	0.35	1.00	4.83	4.61	–4.25
Serious complications	0.07	0.21	1.00	0.96	–0.88
Surgery	0.08	0.22	1.05	1.00	–0.92
Lifelong medication	–0.08	–0.24	–1.14	–1.09	1.00

Example: having symptoms most days is 2.85 times as important as having symptoms two or three times a week, whereas having a 0.1% chance of a serious complication is 13.7 times more important than having symptoms two or three times per week.

Health Technology Assessment reports published to date

Volume 1, 1997

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By Richards DM, Deeks JJ, Sheldon TA, Shaffer JL.

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Diagnosis, management and screening of early localised prostate cancer.
A review by Selley S, Donovan J, Faulkner A, Coast J, Gillatt D.

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We look forward to hearing from you.

The NIHR Coordinating Centre for Health Technology Assessment
Alpha House, Enterprise Road
Southampton Science Park
Chilworth
Southampton SO16 7NS, UK
Email: hta@hta.ac.uk
www.hta.ac.uk

ISSN 1366-5278