THE PLACE OF MINIMAL ACCESS SURGERY AMONGST PEOPLE WITH GASTRO-OESOPHAGEAL REFLUX DISEASE (GORD)

A UK COLLABORATIVE STUDY FUNDED BY THE NHS R&D HTA PROGRAMME

PROTOCOL

VERSION 6a - November 2003

THE PLACE OF MINIMAL ACCESS SURGERY AMONGST PEOPLE WITH GASTRO-OESOPHAGEAL REFLUX DISEASE (GORD) A UK COLLABORATIVE STUDY

(Known as the REFLUX Trial)

PROTOCOL SUMMARY

AIM	To identify the optimal place within the NHS for minimal access surgery amongst people with GORD, whose symptoms would otherwise be managed with long-term medical therapy.
DESIGN	Multicentre, pragmatic randomised trial (with parallel non-randomised preference groups).
PATIENT ELIGIBILTY	• Documented evidence of GORD (endoscopy and/or manometry/24h pH monitoring) • Symptoms for more than 12 months and currently requiring maintenance proton pump inhibitor (PPI) therapy for reasonable symptom control • Received care from a participating clinician • Suitable for either policy (ASA grade I or II) • Recruiting doctor uncertain which management policy is better • Give informed consent to either random allocation of management or follow-up after preferred management
RECRUITMENT	Based on surgeon-physician 'partnership' in at least 15 centres.
INTERVENTIONS	A laparoscopic surgery based policy compared with a continued medical management policy.
OUTCOME MEASUREMENT	**Primary –** Disease specific outcome and NHS costs **Secondary –** Patient costs and Health-related quality of life (EQ5D, SF36)
ORGANISATION	• All whole-hearted contributors part of the GORD Trialist Group (with group authorship of main reports) • Conduct overseen by Steering Group • Trial Office in Aberdeen responsible for day-to-day non-clinical co-ordination • Sessional research nurses in each clinical centre • Health economic evaluation and outcome measure assessment jointly led from York and Aberdeen
FUNDING	NHS R&D Health Technology Assessment Programme

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See Grant *et al*.[1] for details of appendices.

1. OUTLINE OF THE TRIAL

Aim

The aim is to identify the optimal place within the NHS of minimal access surgery amongst people with gastro-oesophageal reflux disease (GORD). Its focus is people whose symptoms would otherwise be managed with long-term medical therapy. The background and justification are summarised in Appendix I.

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.
- To explore factors which may influence the relative performance of the two policies, such as patient preference, surgeon experience, pre-enrolment symptoms and signs, underlying pathology, type of operative procedure used or choice of therapy, and time since surgery.
- To explore the impact that various policies for using laparoscopic surgery would have on the NHS and society in respect of the costs or savings that they would imply for (a) those providing surgical care (in secondary care settings), (b) those providing long-term medical management (usually in primary care settings), and (c) those with GORD.

Design

The study will have two complementary components:

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 to compare the cost-effectiveness of the two management policies, to identify the most efficient provision of future care, and to describe the resource impact that various policies for fundoplication would have on the NHS.

The rationale for the study design is described in Appendix II.

2. THE RANDOMISED TRIAL (WITH PARALLEL PREFERENCE GROUPS)

Centre eligibility

Clinical centres will be based on local partnerships between surgeons with experience of laparoscopic fundoplication and the gastroenterologists, with whom they share the secondary care of patients with GORD. Centres will be eligible if they include:

1. a surgeon who has performed at least 50 laparoscopic fundoplication operations
2. one or more gastroenterologists who agree to collaborate with the surgeon in the trial.

Patient eligibility

Inclusion criteria

1. Documented evidence of GORD (based on endoscopy and/or manometry/24hr pH monitoring)
2. Symptoms for more than 12 months and currently requiring maintenance proton pump inhibitor (PPI) therapy for reasonable symptom control (Patients who are intolerant to PPIs and therefore require Histamine Receptor Antagonists (H_2RAs) therapy to control their symptoms will also be included)
3. Care provided by a participating clinician
4. Suitable for either policy (including ASA grade I or II)
5. Recruiting doctor uncertain which management policy is better
6. Informed consent either to random allocation of management or to follow-up after preferred management

Exclusion criteria

1. Morbidly obese (BMI >40 kg/m^2)
2. Barrett's oesophagus of more than 3 cm or have evidence of dysplasia
3. Paraoesophageal hernia
4. Oesophageal stricture

Although there is no formal age limit, it will be younger patients with GORD who will be eligible, who are expected to be aged between 18 and 65 years .

Health technology policies being compared

Laparoscopic surgery policy:

Most of those allocated to this policy will have surgery. Deferring or declining will remain an option, however, 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 have not had manometry/pH studies will undergo these tests before surgery to exclude achalasia.

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

It is expected that local policies for thromboembolism prophylaxis will include a suitable anticoagulant (such as heparin or tinzaparin) plus surgical stockings or pneumatic compression.

Medical therapy policy:

Most of those allocated to the medical therapy policy will continue 'best medical management' (appropriate PPI), as recommended by the clinician responsible for care. Management should conform to the principles of the Genval Workshop Report (see Appendix III). While all the recommendations of this workshop cannot be summarised here, they include stepping down antisecretory medication in most patients to the lowest dose that maintains acceptable symptom control. Patients who have had severe oesophagitis should not be managed on the basis of symptoms alone, however. While it is expected that most trial participants allocated medical management will continue to be managed in this way, surgery should be considered if a clear indication for it subsequently develops.

Outcome measurements

Primary:

a 'Disease-specific' outcome to include the need for changes in treatment, reflux and other gastro-intestinal symptoms, and the side effects and complications of both therapies.

b NHS costs including treatments, investigations, consultations and other contacts with the health service.

Secondary:

c Health-related quality of life – EQ5D and SF36.

d Patient costs including loss of earnings, reduction in activities, and the cost of prescriptions and travel to health care.

Other:

e Other serious morbidity, such as operative complications

f Mortality

The instrument for collecting this information are in Appendix IV. The ways in which these data will be displayed in the final report are illustrated in Appendix V.

Sample size and statistical analysis

A sample size of 600 will identify a difference between the two randomised groups of less than 0.25 of the standard deviation of the disease-specific instrument, EQ5D or SF36 with 80% power using a significance level of 5%. Based on the same arguments, about 300 people will be recruited to each arm of the preference study.

The cost savings of a surgical policy will largely depend on the number of patients managed surgically who no longer require PPI treatment. A trial with 300 surgically managed patients will estimate this proportion to within about 5% with 95% statistical confidence.

A single principal analysis is planned within the current time frame when all participants have been followed-up for at least 12 months after surgery (or an equivalent time if managed medically). Standard statistical techniques will be used with analysis by intention to treat and 95% confidence intervals. Secondary analyses will explore differential effects within pre-stated sub-groups, characterised by initial symptom severity and surgeon's preferred operative procedure; 99% confidence intervals will be

generated for such analyses to reflect their exploratory nature. The issue of continued surgeon 'learning' will also be investigated using curve fitting techniques.

3. THE ECONOMIC EVALUATION

The economic evaluation is described in detail in Appendix VI. It will have three components: a within-trial cost-effectiveness study; a detailed assessment of the preferences of patients with GORD; and an outside-trial cost-effectiveness analysis based on decision modelling.

4. PRACTICAL ARRANGEMENTS

Each clinical centre will be supported by a part-time research nurse.

Identification of potential participants

Potential participants will be identified in three ways:

- Retrospective case-note review
- Prospective identification of current case
- Referral from general practice

These are summarised in Figure 1. The actual approach used will vary between centres, but case note review is likely to be the principal method.

As a general rule, potentially eligible participants will be booked for an outpatient appointment. They will be sent a brief letter, together with a copy of the information leaflets in advance, letting them know that the trial is likely to be discussed with them (Appendix VII). At the appointment, the clinician will review the person's symptoms and current treatment regimen, and assess eligibility for the trial following the completion of a Patient Assessment Form (Appendix VIII). If eligibility is confirmed, the person will be invited to see the research nurse who will describe the study and discuss any issues that arise. This is summarised in Figure 2. The nurse will also give a supplementary information leaflet that describes the operation in more detail (Appendix IX). Information will also be sent to the general practitioner (GP) in case the participant consults them to discuss the trial (Appendix X); a specific clinic letter will follow from the consultant.

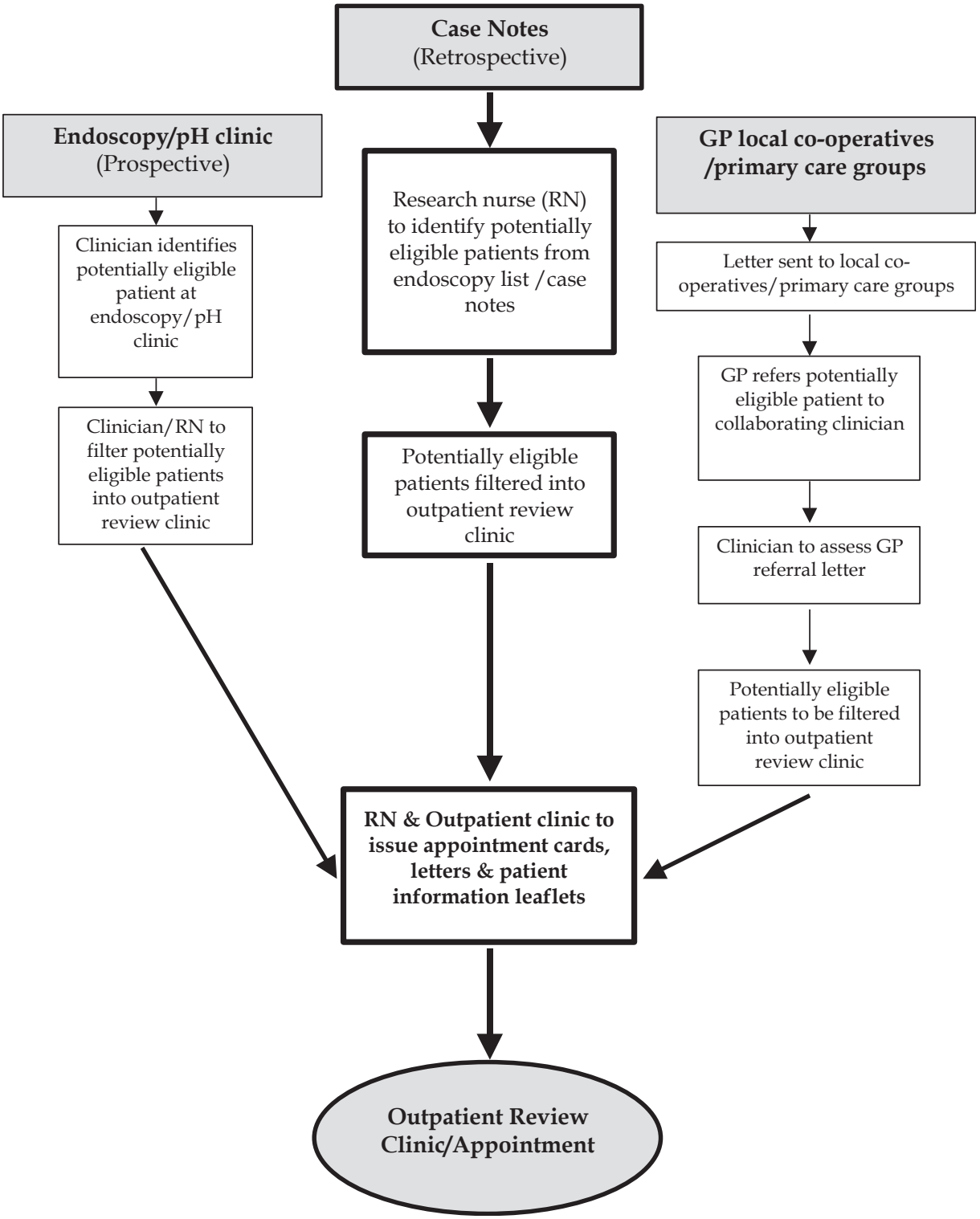

Figure 1. Flowchart describing sources for patient identification

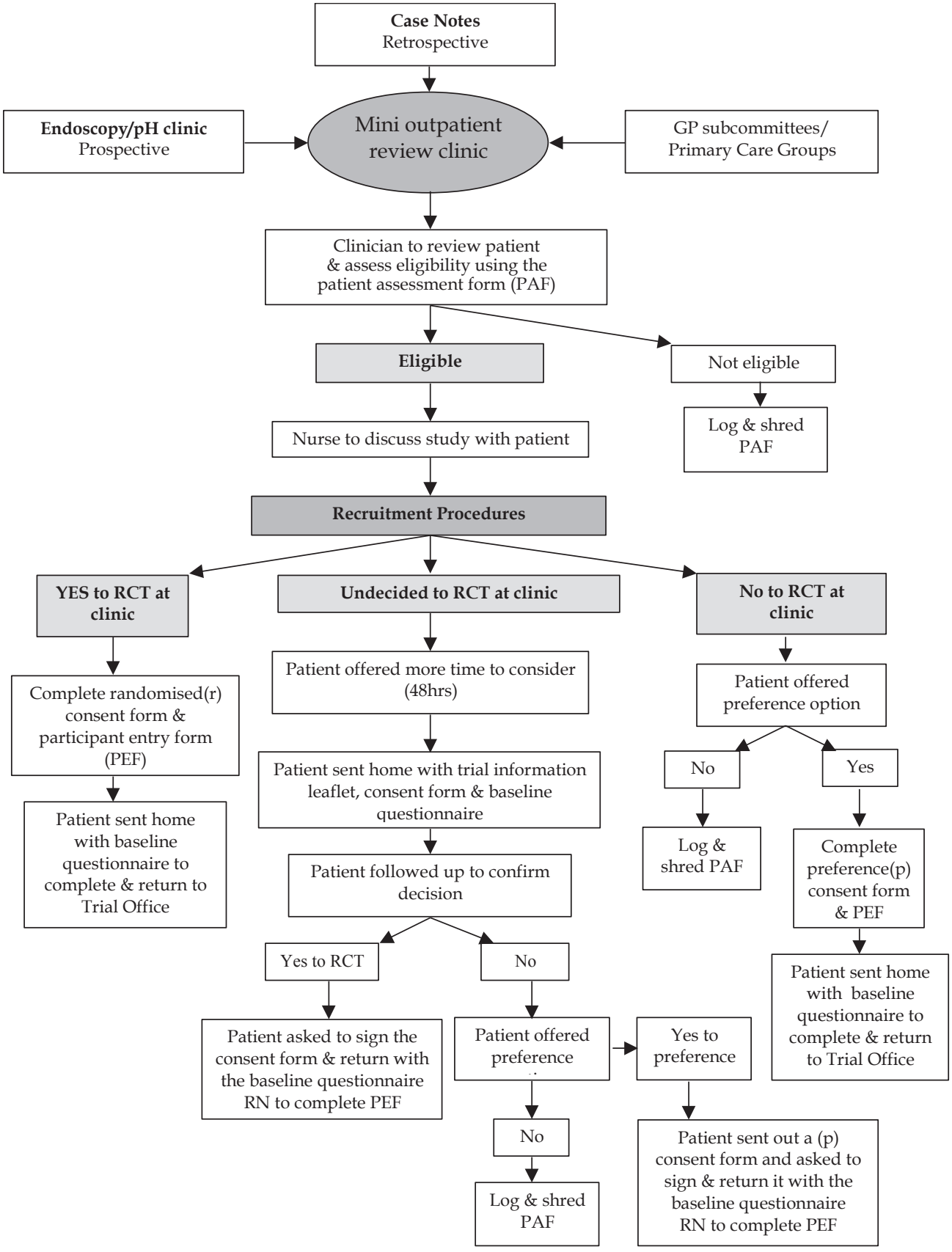

Figure 2. Flowchart describing patient recruitment

Consent to participate

The randomised trial:

Some potential participants will make a decision about participation at this appointment. Those who wish to participate in the randomised trial will be asked to sign a consent form (Appendix XI). On this, they will confirm that they have been given the information they require and that the study has been explained to them. They will also confirm that they understand that they will be sent questionnaires from the Trial Office at participant-specific time intervals after joining the study. (This will be at a time equivalent to around three months and 12 months after surgery.) They will also be told that it is anticipated that further follow-up will be performed periodically thereafter for some years.

The preference study:

A person who does not want to take part in the randomised trial because of a strong preference for one type of treatment management will be asked to take part in the preference arm of the study. Those who wish to participate in the preference study will be given a preference information leaflet and asked to sign a consent form (Appendix XII). In addition to the details collected on the randomised consent form, they will confirm their preferred treatment allocation.

Any person who is uncertain will be given at least 48 hours to consider participation. A research nurse will then phone them to find out their decision and make arrangements as appropriate for them to sign a randomised trial or a preference study consent form.

One copy of the consent form will be given to the participant, another will be filed in the patient's hospital case notes, and the third will be posted to the Trial Office.

Information to be collected at trial entry

Once a participant has agreed to join the trial, the research nurse will record basic identifying and descriptive information on a standard form (Appendix XIII). This information will be sent to the Trial Office.

The participant will take home a baseline questionnaire to complete, and will be asked to return it in a pre-paid envelope to the Trial Office.

Study registration (and treatment allocation when randomised)

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

The treatment allocation for participants consenting to the randomised arm of the trial will be computer-generated in the Trial Office. The allocation will be stratified by centre, with balance in respect of other key prognostic variables – age (18-50 y or 51-65 y), sex (M or F), and BMI (≤28 or >29 kg/m^2) - by a process of minimisation.

A letter will be sent from the Trial Office to each participant (Appendix XIV), their GP (Appendix XV) and the local research nurse, confirming the treatment allocation and whether they are taking part in the randomised- or preference-arm of the trial. A letter will also be sent to the respective collaborating surgeon or gastroenterologist with respect to the treatment the participant is allocated.

Clinical management

Clinical management will be left to the discretion of the clinician responsible for care. A summary of the different clinical management pathways is illustrated in Figure 3.

Participants who are allocated to the surgical arm, will be invited to a consultation with the collaborating surgeon. (Participants who have not already had manometry/pH studies will be booked to undergo these tests prior to this consultation.) During this consultation, the surgeon will confirm that there is no contra-indication to surgery and discuss the operation in more detail with the participant, before arranging a date for the operation. The intra-operative details will be recorded by the surgeon on specially designed study forms (Appendix XVI).

All other in-hospital data collection will be the responsibility of the local study nurse.

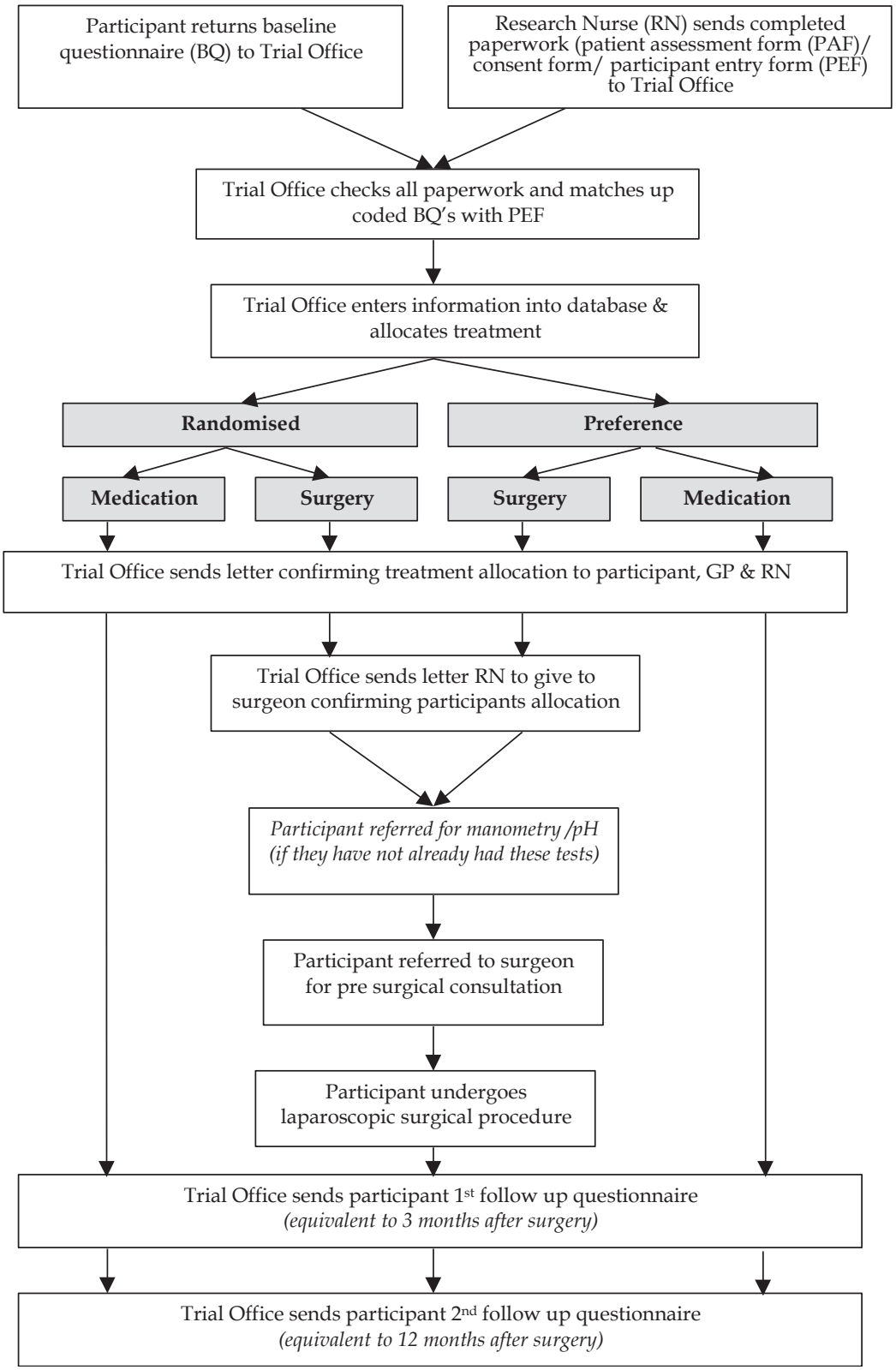

Figure 3. Flowchart showing clinical management post recruitment

Follow-up in the trial

Follow-up by postal questionnaire will be performed twice, at participant-specific time intervals after joining the study. (This will be at a time equivalent to around three and 12 months after surgery). When necessary, clarification of clinical management will be sought through the research nurses (while they are in post) and then subsequently through the recruiting doctor or general practitioner. While it is anticipated that further follow-up will be performed periodically thereafter for some years (dependent on funding being available at that time) these subsequent assessments are not part of this protocol.

Data collection after trial entry

All data will be sent to the Trial Office in Aberdeen for processing. Staff in Aberdeen will work closely with the research nurses to secure as complete and accurate data as possible. A random 10% sample of data will be double-entered to check accuracy. Extensive range and consistency checks will further enhance the quality of the data.

Organisation

Local organisation

The trial is designed to limit the extra work for collaborating clinicians to tasks that only they can do. Research nurses will facilitate the trial locally, and the central organisation will take responsibility for data management and participant follow-up.

Clinical collaborators (gastroenterologist and/or surgeon) will:

1. establish the trial locally (e.g. identifying a 'partnering' clinician or surgeon if not already agreed; facilitating local research ethics committee approval; identifying and appointing a local research nurse; and ensuring that all clinical staff involved in the care of patients with GORD are informed about the trial)
2. take responsibility for clinical aspects of the trial locally (e.g. if any particular concerns emerge)
3. notify the Trial Office of any unexpected clinical events that might be related to trial participation
4. provide support and supervision for all aspects of the work of the local research nurse
5. represent the centre at REFLUX trial collaborators' meetings

Research nurses will:

1. keep local staff informed about the trial and its progress
2. keep regular contact with the local gastroenterologist(s) and surgeon
3. maintain regular contact with the Trial Office
4. identify potential participants and log whether or not they are recruited to the trial (including the preference groups) - with reasons for non-participation
5. arrange for the initial letter of invitation and information leaflet to be sent to potential participants prior to an out-patient assessment.
6. assist the participating clinicians (e.g. at assessment clinics) to give additional information and seek consent to study entry
7. ensure that the baseline data describing participants are collected and sent back to the Trial Office
8. facilitate later follow-up by, for example, helping with local tracing
9. provide support for participants in other ways if there are difficulties
10. represent the centre at trial nurse meetings and collaborators' meetings

5. TRIAL CO-ORDINATION

Trial Offices

The main Trial Office is within the Health Services Research Unit in Aberdeen and gives day-to-day support to the clinical centres. This Office is responsible for all central co-ordination of the trial, including centre and research nurse support, study entry and randomisation, postal follow-up, data processing and statistical analysis.

The economic evaluation and the outcome development work is based in the Centre for Health Economics and the Department of Health Sciences and Clinical Evaluation, respectively, both within the University of York.

The Steering Group

The trial is co-ordinated by a Steering Group (listed in Appendix XVII). The Steering Group, in consultation with the Collaborative Group (see below), will take responsibility for any major decisions, such as the need to close recruitment early to one or more parts of the study or to change the protocol for any reason.

The Collaborative Group

The Collaborative Group is made up of the surgeons, gastroenterologists and research nurses contributing to the trial, members of the Steering Group, and representatives from the Trial Offices.

The Data Monitoring Committee

A data monitoring committee will be established. It will be independent of the trial organisers. During the period of recruitment to the trial, interim analyses will be supplied, in strict confidence, to the data monitoring committee, together with any other analyses that the committee may request. This may include analyses of data from other comparable trials. In the light of these interim analyses, the data monitoring committee will advise the Steering Group if, in its view, the trial has provided both (a) proof beyond reasonable doubt[1] that for all or some types of patients one intervention is clearly indicated in terms of clinical- and cost-effectiveness, and (b) evidence that might reasonably be expected to influence materially the care of people with GORD by clinicians who know the results of this and comparable trials. The Steering Group can then decide to consult the Collaborative Group about whether or not to modify intake into the trial or to report results early. Unless this happens, however, the Steering Group, the Collaborative Group and Trial Offices (except those who supply the confidential analyses) will remain ignorant of the interim results considered by the committee.

The frequency of interim analyses will depend on the judgement of the chairman of the committee, in consultation with the Steering Group.

6. FINANCE

The trial is supported by a grant from the Health Technology Assessment Programme of the NHS Executive Research and Development Programme.

Note:

[1] Appropriate criteria for proof beyond reasonable doubt cannot be specified precisely. A difference of at least three standard deviations in the interim analysis of a major endpoint may be needed to justify halting, or modifying, such a study prematurely. If this criteria were to be adopted, it would have the practical advantage that the exact number of interim analyses would be of little importance, and so no fixed schedule is proposed (Peto R et al *Br J Cancer* 1976; 34: 584-612).

7. A STUDY OF FACTORS IMPACTING ON PATIENTS DECISION TO PARTICIPATE IN THE REFLUX TRIAL (APPENDIX XVIII)

During the recruitment phase of the trial, it is anticipated that a CSO research fellow will undertake supplementary site visits to explore the patients' perspective in relation to trial recruitment. A small number of centres will be purposively selected using qualitative methods (non-participation observation and in-depth interviews). It is proposed that the selected centres will reflect varying recruitment rates.

It is expected that, subject to clinician and patient consent, the research fellow would sit-in and observe reflux clinics where patients are approached to join the study. The researcher would aim to supplement the observational work by interviewing some of the patients (again, subject to consent) about their experience of trial recruitment and factors impacting on their decision to join the trial or not.

It is hoped this small but very useful complementary study nested in the REFLUX trial, will help identify factors impacting on patient recruitment and enable us to look at ways of addressing these issues to facilitate improved future trial recruitment.

8. PUBLICATION

The success of the trial depends entirely on the whole-hearted collaboration of a large number of people. For this reason, chief credit for the trial will be given, not to the committees or central organisers, but to all those who have whole-heartedly collaborated in the trial. The trial's publication policy is described in detail in Appendix XIX. The results of the trial will be reported first to the trial collaborators. The main report will be drafted by the Steering Group, and circulated to all the clinical collaborators for comment. The final version will be agreed by the Steering Group before submission for publication, on behalf of the collaboration. To safeguard the integrity of the study, reports of sub-studies will not be submitted for publication without prior discussion with the Steering Group. Once the main report has been published, a lay summary will be sent to participants who have indicated that they would like to receive one.