Randomised Oesophagectomy: Minimally Invasive or Open, a feasibility study

The ROMIO trial.

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Glossary / abbreviations

AE	Adverse event - any undesirable event in a subject receiving treatment according to the protocol, including occurrences which are not necessarily caused by or related to administration of the research procedures.
BRTC	Bristol Randomised Trials Collaboration
BMI	Body Mass Index
CI	Confidence Interval
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
DVT	Deep Vein Thrombosis
EQ-5D	EuroQol health status questionnaire
EORTC	European Organisation for Research and Treatment of Cancer
GP	General practitioner
HRQL	Health Related Quality of Life
HTA	Health Technology Assessment
ICH-GCP	International conference for harmonisation of good clinical practice
IDEAL	Idea, Development, Evaluation, Audit and Long term follow up
MRC	Medical Research Council
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
NIHR	National Institute for Health Research
MDT	Multi-Disciplinary Team
MIO	Minimally Invasive Oesophagectomy
O-CAT	Oesophageal Competency-Assessment Tool
OCHRA	Observational Clinical Human Reliability Assessment
QLQ-C30	Quality of life Questionnaire - Core
QLQ-OES18	Quality of life Questionnaire- Oesophageal
PCT	Primary care trust
PIL	Patient Information Leaflet
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SOP	Standard Operating Procedure
SSAR	Suspected serious adverse reaction
SUSAR	Suspected unexpected serious adverse reaction
TMG	Trial management group
TSC	Trial steering committee

1. Trial summary

Oesophageal cancer is a serious health problem. There are about 8,000 new cases per year in England and Wales and this number is rising [1]. Surgery is the mainstay of cure and about 1,000 oesophagectomies are performed annually. Surgery involves at least a six hour procedure, admission to intensive care and about 14 to 20 days in hospital. Complications of any severity occur in up to 50% of patients, although 10% experience serious morbidity requiring re-operation or re-admission to intensive care. Surgery is also associated with 5% risk of in-hospital death and a major short term detrimental impact on health-related quality of life (HRQL) [2,3]. Recently there has been an interest in minimally invasive surgery which uses small incisions and special instruments to undertake the operation. Observational studies show that minimally invasive surgery may improve short-term outcomes and reduce the short term detrimental impact on HRQL during recovery while maintaining long term survival and a small trial comparing open with minimally invasive surgery from the Netherlands has confirmed the safety of this procedure [4]. There are, however, no well designed large randomized trials supporting its use and a lack of information about clinical and cost effectiveness. Minimally invasive surgery is established in colorectal cancer based on well designed and conducted trials [5,6]. These have influenced the standard of surgical care in the UK and minimally invasive surgery is now the recommended approach and there is investment in specialist centres to safely train consultant surgeons [7,8]. It is therefore considered necessary to undertake a high quality multi-centered trial of minimally invasive surgical techniques versus open oesophagectomy so that an evidence base can be established to inform the standards of care of upper gastro intestinal cancer surgery.

There are several different surgical techniques for open and minimally invasive oesophagectomy. The most commonly performed open procedure involves an incision in the abdomen (to allow the stomach to be mobilised) and an incision in the right chest (thoracotomy) to allow removal of the oesophagus and cancer and positioning of the stomach in the chest to replace the oesophagus. This may be undertaken totally using minimally invasive techniques or partially, when the abdominal part of the operation is performed with minimally invasive techniques and the chest part performed using a standard incision. Currently these minimally invasive techniques are evolving and in the UK about a third of all procedures use these approaches (http://www.augis.org/clinical_audits/clinical_audits_og_cancer.htm).

Trials of surgical procedures have particular challenges:

- Many surgeons are unfamiliar with participating in trials and have little experience of describing clinical equipoise and recruiting potential participants. In addition, much of the supporting infrastructure for conducting trials in the NHS is orientated towards evaluations of pharmaceutical products. Consequently surgical trials often have problems in recruiting sufficient participants in a reasonable amount of time [9].
- Compared to trials of pharmaceutical products, in trials of surgical procedures it is impossible to blind the surgeon to treatment allocation and very difficult to keep patients and treatment staff blind for more than an initial period.
- Trials are also hampered by lack of standardization of surgical procedures, and difficulties in establishing when a surgeon has deviated from the intended procedure in an important way. Surgical teams are likely to adopt different variations of a procedure, to best suit their skill set and local clinical environment. In addition, when a procedure is still evolving, pioneering teams will experiment with, and may adopt refinements to the

procedure. Manualization of surgical procedures is fairly rare, with very few distinguishing between acceptable variations of the same procedure.

- A surgical procedure can only be evaluated in a randomised controlled trial once there are enough surgeons who are competent to perform it, but the evaluation must take place before the procedure is accepted practice ("Buxton's Law" [10]).
- Comparisons of two procedures with the same clinical objective (the current example being a comparison of open and minimally invasive oesophagectomy) will commonly not be expected to result in survival differences. Instead the novel technique will be expected to improve recovery by, for example, reducing blood loss. How exactly "recovery" should be measured is not yet well defined [11,12].

The evidence base for many surgical procedures is therefore often weak and practice varies widely across the country. Recent consensus meetings between methodologists and surgeons have recommended that surgical innovations be evaluated using study designs that allow a developing intervention to be evaluated appropriately until it is stable (IDEAL stage 1, 2a and 2b). Once the intervention is stabilised and there are sufficient surgeons to undertake the procedure, then a phase 3 randomised evaluation is recommended (IDEAL stage 3) [13]. For the evaluation of minimally invasive oesophagectomy, therefore, it is considered that before a multi-centre phase 3 trial can be initiated, it is necessary to undertake feasibility work (IDEAL stages 2a and b) that will establish the optimal trial design and surgical techniques, standardise and maximise recruitment procedures, pilot process measures, develop a core outcome set for oesophageal cancer and establish a competency assessment tool to define the exact surgical techniques to be employed in the full scale study. It will also afford the opportunity to recruit further centres and establish a culture of trial participation so that the main trial can be undertaken efficiently.

ROMIO, therefore, is feasibility work in two hospitals. It will test the feasibility of recruitment, randomisation and develop ways to optimise information for patients to maximise trial recruitment. It will also establish a core set of clinical outcomes to use to evaluate the surgery for oesophageal cancer. It will importantly develop methods to standardise and monitor surgical interventions in the main trial and it will establish the best way of capturing resource use and cost in relation to the interventions and follow up in primary and secondary care. This will inform the design of the full multi-centre trial which will be a separate project. In this feasibility stage we will recruit for up to 30 months and follow-up participants for 36 months.

2. Background

2.1 Existing research evidence

Oesophageal cancer is the ninth most common cancer in the UK, and around 8,000 people are newly diagnosed with the disease each year [1]. Two thirds of cases are adenocarcinoma, and the remainder are squamous cell cancers. Surgery alone or in combination with chemotherapy or chemoradiation treatment is the mainstay of cure for localised oesophageal adenocarinoma but oesophageal squamous cell cancer may also be radically treated with definitive chemoradiotherapy or radiotherapy alone [14]. Treatment aimed at cure is offered to about a quarter of all new patients as most are precluded from radical therapies because of advanced disease, frailty or pre-existing co-morbidities. The recent national audit of patients in England and Wales, including cases from 2008 to 2009, showed that approximately 1200 oesophagectomies were undertaken per year [14].

2.1.1 Surgery for oesophageal cancer

Oesophagectomy is a major procedure involving surgery within two or three body cavities (abdomen, chest, neck). Patients are routinely observed within an intensive or high dependency unit for several post operative days and hospital stay is approximately two weeks. Complications of any severity occur in up to 60% and 10% experience serious morbidity requiring re-operation or re-ventilation. Surgery is associated with 4% risk of 30-day death and a major short term detrimental impact on health-related quality of life (HRQL), with patients reporting reduction in physical, role and social function and marked increases in fatigue, breathlessness and pain scores for at least three months after surgery [2,3]. Over time there is some recovery of HRQL, but persistent long term deficits occur [3]. Survival after surgery may be extended with preoperative chemotherapy or chemoradiotherapy, but overall it is modest with one, two and five year survival rates being approximately 70%, 45% and 35% respectively [1].

2.1.2 Current practice and minimal access surgery for oesophageal cancer

There are several approaches for resection of oesophageal tumours. In the UK national audit 75% of operations were 2-phase procedures, involving open surgery with standard abdominal and right chest incisions. The remainder were left sided surgery (thoraco-abdominal, 13%), 3-phase surgery (a cervical incision in addition to the abdominal and chest surgery, 7.4%) or undertaken using a transhiatal approach (abdominal and cervical incision, 4.5%) [14]. Well designed prospective comparative studies and randomised trials of these many open standard surgical approaches for oesophageal cancer are unusual in the surgical literature and have been summarised in systematic reviews. Data show no differences in survival between different open surgical techniques and suboptimal reporting of process measures and outcomes [15,16]. All report high levels of post operative morbidities.

The past decade has seen growing interest in minimal access surgical techniques for all types of cancer surgery with the advantages of causing less tissue trauma and better recovery. Several national and international centres have adopted these approaches for oesophagectomy with the National Audit showing that of 2,200 oesophagectomies performed between 2007 and 2009, 30% (n=659) used minimal access surgical techniques [14]. These were mostly laparoscopically assisted 2-phase approaches (minimal access approach for the abdomen and standard open right chest incision), and 115 oesophagectomies (5%) performed by totally minimally invasive techniques. In the audit, outcomes of open and minimal access approaches were similar except for more frequent anastomotic leakage with minimal access (10.5%) compared to open surgery (7.4%). This difference did not translate into worse 30 or 90-day mortality or re-operation rates. Hence, minimally invasive surgery is at a point where a randomised trial is still possible because it is not widely adopted, and yet there is sufficient experience in enough centres, for the comparison of minimally invasive and open procedures.

2.1.3 Systematic reviews and the need for an RCT

We have undertaken a systematic literature review in Medline and the Cochrane Trials Database and identified 23 non-randomised studies describing outcomes of minimally invasive procedures for oesophageal cancer. Sixteen papers described outcomes of totally minimally invasive surgery and seven reported outcomes of laparoscopically assisted 2-phase surgery, using minimal access techniques for the abdomen or chest [17]. Three other systematic reviews were identified but none included a randomised trial [18-20]. Looking at the individual studies, in

a series of 222 patients undergoing totally minimally invasive surgery, the short term clinical outcomes (morbidity and technical data) were similar to those published in series of open surgery [21]. Few of the above studies reported short term oncological endpoints (e.g. lymph node count), although UK national audit data shows similar lymph node counts with minimally invasive surgery to that achieved by open procedures, with 68% of open and 78% of minimally invasive procedures yielding greater than 15 nodes [14]. One cohort study compared outcomes of 'open oesophagectomy' (n=114), 'a combined approach' (n=309) and 'totally minimally invasive surgery'(n=23) and found no differences in 3 or 5-year survival [22]. There was a lack of published data of cost effectiveness and only two studies measured health related quality of life (HRQL) [16,19]. One used validated generic and disease specific tools for a year after minimal access surgery and showed a early recovery of most aspects of health, but the study was small and without a comparison group [23].

All these studies have methodological weaknesses because of their observational designs, with limited details regarding patient selection, outcome assessment, and small sample sizes. It is not possible to draw meaningful conclusions from the available non-randomised studies and the evidence base for minimally invasive surgery for oesophageal resection is weak. A well designed and conducted randomized trial comparing the effectiveness and cost-effectiveness of minimal access and open surgery is needed to inform current NHS practice, health policy and individual surgeon and patient clinical decision-making. Open oesophagectomy costs about £6K, but inclusion of re-operations, re-admission to intensive care and prolonged stays may significantly increase this price. Minimally invasive surgery requires additional operative equipment but may reduce hospital stay. An economic analysis, embedded within a pragmatic randomised trial, is required to establish the relative cost-effectiveness of the different procedures when adopted into routine clinical practice.

2.1.4 Other trials evaluating minimal access surgery for oesophageal cancer

The French 'MIRO' trial

This is a trial for patients with oesophageal cancer excluding patients with types II and III tumours involving the gastro-oesophageal junction. It compares open 2-phase surgery (abdomen and right chest) with 2-phase laparoscopically-assisted oesophagectomy (minimal access for the abdomen and open right chest incision) (http://clinicaltrials.gov/show/NCT00937456) [24]. The primary end point is 30 day morbidity and the trial is powered to test the hypothesis that minimal access surgery leads to a reduced rate of complications (45% vs. 25%) at 30 days. Complications are measured as a composite outcome. MIRO aims to recruit 200 patients (trial opened in 2009). Randomisation is using sealed envelopes, outcome assessors are not blinded to the intervention type and methods to quality assure surgical procedures are not described in the protocol.

The Dutch 'TIME' trial

This is a trial for patients with oesophageal cancer excluding patients with type II and III tumours involving the gastro-oesophageal junction [4]. It compares open 2 or 3 phase oesophagectomy with totally minimally invasive oesophagectomy (both abdomen and chest performed with minimal access approaches in the prone position). The trial is powered to test the hypothesis that totally minimally invasive surgery is associated with fewer pulmonary complications at two weeks after surgery than the standard open procedure. Pulmonary complications are strictly

defined and graded. It aims to recruit 120 patients, with assumptions that there will be a difference of 28% in respiratory complications between the two arms of the trial (57% for open surgery and 29% for minimal access surgery). The criteria for surgeon involvement in this trial are evidence of prior completion of 10 minimally invasive procedures and production of one video showing surgical competence. This trial has recruited 120 patients from seven surgical centres in four countries (Netherlands, Spain, India and Italy). The trial includes a comprehensive assessment of HRQL with the SF36 and QLQ-OES18, but there are no cost analyses and no monitoring of surgical procedures.

Personal correspondence with this group reveals that another trial is planned, the 'IVORY' trial, 'Minimally invasive Ivor Lewis Versus Orringer oesophagectomy' for patients with cancers of the gastro-esophageal junction. This trial will compare two types of minimally invasive oesophagectomy with the primary study objective of showing that minimally invasive oesophagectomy with extended en bloc lymphadenectomy (2 fields) provides a more radical surgical resection specimen for cancer of the gastro-oesophageal junction, this being expected to translate into an improved 5-year survival rate compared to the minimally invasive transhiatal procedure.

2.1.5 Benefits of the proposed ROMIO feasibility and main trial

Although the above two trials will provide some evidence to inform practice both have methodological flaws that preclude firm conclusions being drawn from their results and neither will be applicable to the NHS and UK surgeons. In particular the sample size targets are based on the true benefits of minimally invasive techniques being large, and are insufficient to detect more modest but still clinically important differences between minimally invasive methods and the open procedure. The primary endpoints reflect surgical interest and do not incorporate meaningful benefit for minimal access surgery from the patients' perspective. The French trial is at risk of bias without blinding outcome assessors and the use of sealed envelopes for randomisation. In addition the interventions in the Dutch trial (totally minimally invasive surgery) are still being developed in the UK and as this is an evolving procedure, few UK surgeons and anaesthetists are comfortable with oesophagectomy in the prone position.

The proposed ROMIO feasibility study will be relevant to the UK by providing information to design an efficient multicentre study that will test a clinically relevant hypothesis, include at least 10 surgical centres, ensure that surgical interventions are carried out in a standardised way and include patient reported outcomes. The main trial will also include an economic evaluation to provide information relevant to policy making in the NHS.

2.1.6 Challenges with surgical trials

There are many challenges to conducting high-quality randomised trials of non-pharmaceutical interventions; because of this we are proposing to precede the main trial of oesophagectomy procedures with a feasibility study in which the challenges are characterised and addressed. These challenges are considered below and are likely to include patient factors such as a need to be reassured of genuine equipoise between the different procedures, and methodological factors such as the need for a battery of outcome measures which are recognised as comprehensive, valid and reliable. The feasibility study will prevent the early stages of the main

trial from being compromised, and is a recognised stage in evaluating complex interventions [25] and surgery in particular [12,26].

3. Aims and objectives

3.1 Research aim of the main trial

To compare, in patients with cancer of the oesophagus (which may include the oesophago-gastric junction), the clinical and cost-effectiveness of minimally invasive and open surgical procedures in terms of recovery, health related quality of life, cost and survival.

3.2 Feasibility study objectives

The present proposal is for a feasibility study, a necessary precursor during which the methodology and infrastructure for the main trial will be established. The core of this preliminary work will be an assessment of the feasibility of comparing surgical procedures for oesophagectomy in a pilot two-centre randomised trial. Specific objectives are:

- To pilot the randomisation process and investigate reasons for any difficulties that affect recruitment so that these can be tackled before the main trial
- To establish the proportion of potentially eligible patients who can be approached about the trial, who are confirmed as eligible, who are successfully recruited and randomised, and who are able and willing to undergo research assessments. This will establish the feasibility of the main trial, by indicating the achievable sample size and the number of centres required.
- To document in detail, using IDEAL recommendations the technical developments of the totally minimally invasive approach for oesophagectomy, to inform the design and choice of interventions in the main trial. This work will allow the development of manuals for the different surgical procedures, and methods of monitoring adherence to them, which will then be available for the main trial. It will also inform the development of a competency assessment tool for objective evaluation of technical performance to be used to evaluate surgeons' skills before participating in the main trial.
- To develop a manual for the specimen fixing, cutting up, and pathology reporting, so optimising the lymph node counts and ascertainment of positive resection margins, both of which are likely to be important short-term outcome measures for the main trial
- To consider the appropriate statistical model for estimating treatment effectiveness whilst allowing for "clustering" in the data due to between-surgeon variation. This will allow the statistical analysis plan to be written during the early stages of the main trial.
- To develop and evaluate feasible, acceptable and effective methods of keeping patients blind to their treatment for the first week after surgery, so reducing bias in self-reported outcomes during the main trial
- To establish outcome measures for the main trial which are recognised as a comprehensive, valid and reliable assessment of oesophagectomy outcome by patients

and the clinical community, and which include a set of core outcome measures considered to be essential in studies of oesophageal cancer

4. Plan of Investigation

4.1 Participants

This protocol is for the ROMIO feasibility RCT, designed to inform the ROMIO main multi-centre RCT. At the end of the feasibility phase a report describing the results and proposals for the main trial design will be written and discussed with the Trial Steering Committee (TSC) and submitted to the funder, NIHR-HTA. The ROMIO feasibility study corresponds to IDEAL stages 2a and 2b [26].

4.1.1 Setting

Two centres, University Hospitals Bristol NHS Foundation Trust and Plymouth Hospitals NHS Trust, will recruit patients and carry out procedures within the pilot RCT. Both centres have teams of upper gastro intestinal cancer surgeons (6 in Bristol and 5 in Plymouth) and each undertake at least 50 operations for oesophageal cancer per year.

Methodological support for the feasibility RCT will predominantly be based in Bristol and the development of quality assurance protocols for surgical procedures and pathology will be based at Imperial College London.

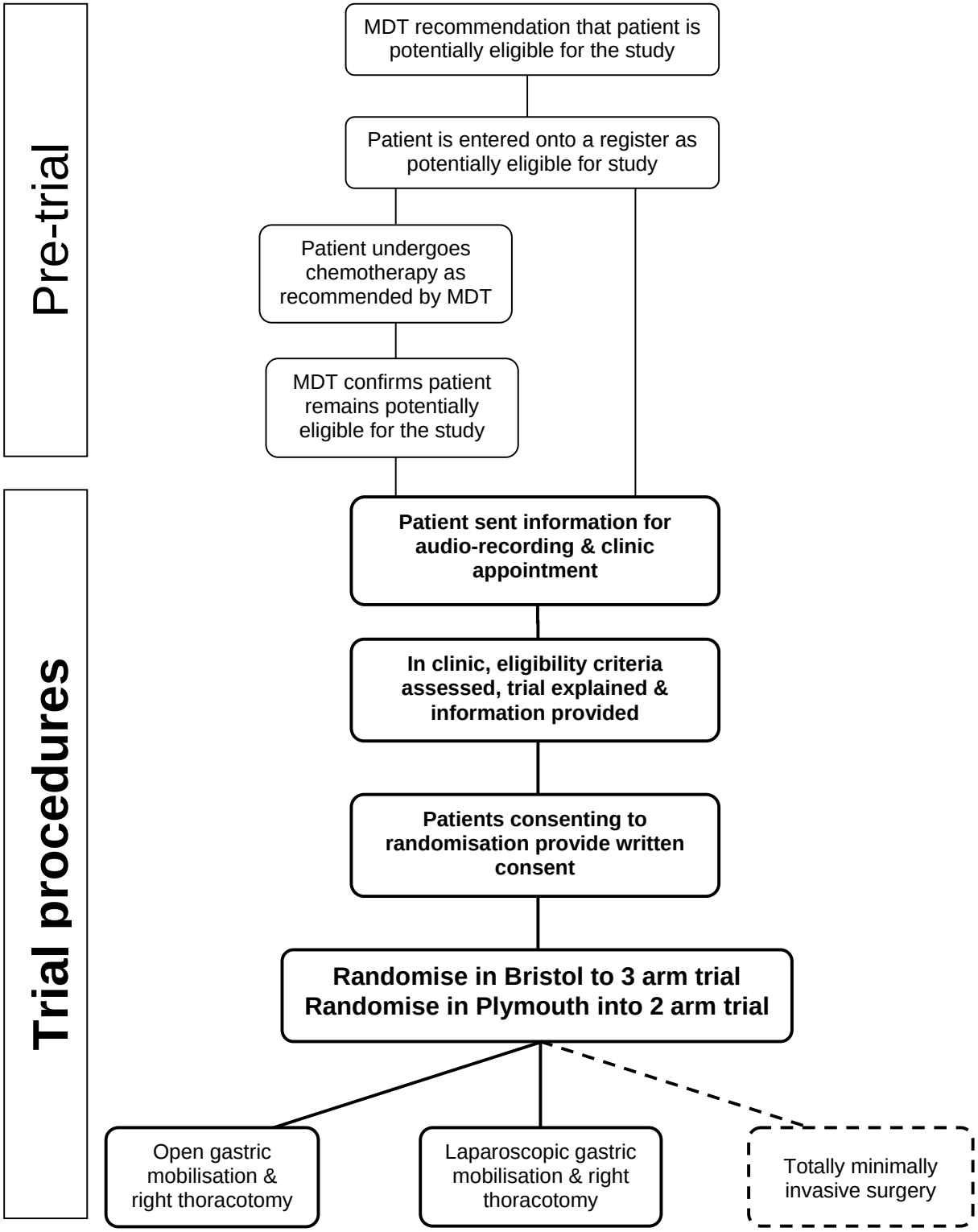
4.1.2 Participating surgeons

All participating surgeons will work within a specialist multi-disciplinary team and individual participating surgeons will have performed more than 50 open oesophagectomies and 50 minimally invasive procedures.

4.1.3 Recruitment and informed consent

For a 12-month period all referrals of patients with oesophageal cancer for primary oesophagectomy or neoadjvuvant chemotherapy before oesophagectomy at the Bristol and Plymouth centres will be considered for eligibility in the feasibility RCT. Patients recommended for neoadjuvant chemotherapy and surgery will be registered into the screening log but full eligibility criteria only confirmed once chemotherapy is completed, restaging undertaken and the MDT confirms that they are eligible to proceed to surgery. At this point eligible patients will be informed about the trial and sent Patient Information Leaflet 1 (PIL1) and an appointment for a 'recruitment consultation.' The leaflet will inform patients that they will be asked at the start for their consent to record the consultation (Participant Consent Form 1 = PCF1), and that the recordings will be examined to ensure that the study is clearly described. Staff will also be asked to consent to this recording (Participant Consent Form 2 = PCF2). At the consultation the patient will be given information about the trial (Patient Information Leaflet 2 = PIL2, separate Bristol and Plymouth versions), allowed the opportunity to ask questions about the trial and treatments, and asked to give written informed consent to the trial (Participant Consent Form 3 = PCF3). Depending on the date of their scheduled surgery, patients may be posted PIL2 after the MDT confirms that they are eligible to proceed to surgery to allow them more time to consider participating in the trial.

Figure 1. Design flow diagram for participants in the ROMIO feasibility study



An optional Patient Information Leaflet (PIL5), which summarises both the information study and the randomised trial, may be given to potential participants prior to their ROMIO study recruitment consultation(s) and prior to when they are given PIL1 and PIL2. This PIL5 is intended to facilitate participants' understanding of the ROMIO study and the recruitment process.

In Plymouth a two-arm trial will compare standard open oesophagectomy with 2-phase laparoscopically assisted oesophagectomy. In Bristol patients meeting the same inclusion/exclusion criteria will be randomised into a three-arm trial which will compare standard open oesophagectomy with 2-phase laparoscopically assisted oesophagectomy and with 3-phase minimally invasive surgery (Figure 1).

4.2 Inclusion criteria

Participants may enter study if ALL of the following apply:

1. Male or female patients
2. Over 18 years of age
3. Referred for primary oesophagectomy by the multi-disciplinary team (MDT) or oesophagectomy following re-staging after neoadjuvant chemotherapy (NB, in this feasibility trial any type of preoperative chemotherapy may be used)
4. Confirmed MDT evidence of oesophageal or oesophago-gastric junctional adenocarcinoma, squamous cell cancer or high grade dysplasia.
5. Fit for pre-operative anaesthesia and surgery, assessed by the MDT
6. Able to provide written informed consent.
7. Endoscopic measurement before chemotherapy that the tumour starts more than 5cm below crico-pharyngeus
8. Endoscopic measurement before chemotherapy that the tumour involves less than 4 cm of the gastric wall
9. The final pre-treatment tumour stage is between high grade dysplasia and T4aN1M0

4.2.1 Exclusion criteria

Participants may not enter study if ANY of the following apply

1. Stage 4 disease
2. Type 3 tumours of the oesophago-gastric junction that are scheduled for total gastrectomy
3. Patients with squamous cell cancer of the oesophagus who the MDT recommends or who individually elect to undergo definitive chemoradiotherapy
4. Evidence of previous complex thoracotomies or laparotomies
5. Evidence of previous/concomitant malignancy that would interfere with this treatment protocol
6. Pregnancy

7. Patients participating in other trials that would interfere with the implementation of this protocol at a particular site.

4.3 Trial interventions

Trial surgical procedures will be carried in a standard fashion under general anaesthesia with all patients receiving antibiotic and DVT prophylaxis according to local hospital policies. The surgical procedures last between 5 and 8 hours. For the purposes of this pragmatic trial each intervention will be allowed to be implemented according the standard local policy. Particular aspects of each intervention that are considered mandatory or prohibited are listed below. During this feasibility study a process evaluation will be undertaken which will lead to the production of an intervention manual and a manual for measuring intervention delivery. The process evaluation will use qualitative methods and literature searches to consider which aspects of the intervention are crucial and need to be strictly adhered to in the main trial. The process evaluation will consider the surgical intervention itself, plus contextual and concomitant interventions as detailed below.

4.3.1 Open oesophagectomy

The operation consists of a two-phase oesophagectomy (abdomen and right chest) with a two-field lymphadenectomy (abdomen and thorax) and it will involve these key steps,

Abdominal phase:

The incision, (midline or subcostal) is at the surgeon's discretion. Complete gastric mobilisation will be performed based on the right gastroepiploic and right gastric arteries. Pyloroplasty, pyloromyotomy or no drainage is at the surgeon's discretion. Lymphadenectomies along the common hepatic artery, left gastric and splenic artery either *en bloc* or separately will be performed and removal of sufficient crural fibres and a cuff of diaphragm performed if required for tumour clearance. The pericardial fat pad and strips of pleura will be removed. Transection of the lesser curve may be undertaken or left to the thoracic phase of the operation. Placement of a feeding jejunostomy or naso-jejunal tube is at the surgeon's discretion as is placement of intra-abdominal and intra-thoracic drains. Methods to close the abdomen are at the surgeon's discretion.

Thoracic phase:

The chest is opened through a right thoracotomy and the mediastinal pleura overlying the oesophagus excised in continuity with the oesophagus. The posterior limit of the dissection should be the antero-lateral wall of the aorta, so that the thoracic duct is mobilised with the oesophagus and peri-oesophageal tissues. The thoracic duct is ligated and divided at the level of the diaphragm. The oesophagus is mobilised to the level of at least the aortic arch. Para-oesophageal and diaphragmatic nodes are removed in continuity with the oesophagus. Lymph nodes at the tracheal bifurcation and along the right and left main bronchi to the pulmonary hilus, can be removed en bloc or separately at the surgeon's discretion. The anastomotic technique and method of chest drainage is at the surgeon's discretion. Methods to close the chest are at the surgeon's discretion.

4.3.2 Laparoscopically assisted oesophagectomy

This operation will consist of identical steps as described above, but access to the abdominal cavity will be achieved with four or five 10 or 5mm incisions and surgery performed

laparoscopically. Placement of a feeding jejunostomy is at the surgeon's discretion and may be performed laparoscopically or by extending a port site to a 8cm abdominal incision. The thoracic part of the operation will be performed as described above.

4.3.3 Totally minimally invasive oesophagectomy

This will consist of performing the steps of the abdominal and chest phases of the operation as described above, but using laparoscopic and thoracoscopic techniques for each phase respectively. It may be a 3 phase minimally invasive operation. And the anastomosis is performed with a left cervical incision.

4.3.4 Concomitant interventions and contextual factors and the enhanced recovery protocol

Concomitant interventions are defined as naturally accompanying or associated elements of the surgical intervention itself, and can be divided into pre-operative, peri-operative and post-operative components. Concomitant interventions to be considered as part of the process evaluation during the feasibility trial include the anaesthetic and other peri-operative procedures, immediate post-operative care (including intensive care management), patient rehabilitation, input from allied health professionals such as physiotherapy and dietetics, which may or may not be encompassed into a formal enhanced recovery programme. Standard protocols for follow-up care after both procedures will be used to minimise the risk of performance bias arising from carers differentially providing co-interventions.

Contextual factors are distinctive features of a trial's setting, participants, clinicians and other staff [27]. Potential contextual factors to be considered as part of the process evaluation during the feasibility trial include non-technical skills and environmental factors. Non-technical skills can be categorised as interpersonal (teamwork, communication and leadership) and cognitive factors (situational awareness and problem solving or decision making ability). Environmental factors include distractions, interruptions, time pressure, mood, stress, tiredness and training as well as equipment and patient issues.

This work will inform development of an enhanced recovery pathway/manual to be used in the main trial to provide the minimum standard of care permitted. Together with the surgical intervention itself, concomitant interventions and contextual factors will be considered during the process evaluation and incorporated into the manual if identified as important.

4.4 Primary and secondary outcomes

4.4.1 Primary outcome

Currently the primary outcome for the main trial is planned to be a patient report of fatigue using the MFI20 [28]. This validated questionnaire has been used in trials of minimal access surgery for nephrectomy and it is the primary outcome of an open trial of minimal access versus open surgery within an enhanced recovery programme (the EnROL trial, www.octo-oxford.org.uk/alltrials/trials/EnROL.html). Consideration will be given to using a dual primary endpoint including a self reported measure of fatigue and an assessment of morbidity. The Dutch TIME trial will have reported by early 2013 and this will inform the decision.

4.4.2 Secondary outcome measures

During the pilot trial we will refine and/or gain experience of the secondary outcome measures which are anticipated for use in the main trial. This will include

1. Surgical morbidity using the Accordian and Clavian-Dindo classifications which include assessment of in-hospital mortality and need for re-operation (http://www.accordionclassification.wustl.edu/) [29].
2. Survival time will be recorded for any individual dying during the six-month follow-up period, as will the time until the onset of palliative care/diagnosis of recurrent disease.
3. Procedural outcome measures
    i. lymph node count and rates of positive resection margins
    ii. duration of operation
    iii. blood loss.
4. Health-related quality of life: Generic and disease specific measures EORTC QLQ-C30 & QLQ-OES18, EQ-5D-5L [30-34]
5. Length of hospital stay, defined as day of operation to discharge home
6. Further measures of resource use including: staff time and other resources used in the interventions; subsequent inpatient stays, outpatient visits, general practitioner visits and other community based resource use.
7. Spirometry – this will be assessed at the bedside using a portable device.

4.4.3 Feasibility measures

A number of measures will be taken to inform the main trial. The screening log will record the details of patients who are or are not screened for trial entry after the MDT has recommended surgery or neoadjuvant treatment and surgery. For patients referred for neoadjuvant treatment only, hospital records will be used to record reasons for ineligibility. For patients referred for primary oesophagectomy or those completing neoadjuvant treatment and who are then recommended for surgery the screening log will also record if eligible participants do not consent for randomisation (and reasons for this choice) as well as recording the treatment they finally received. The screening log will only contain anonymous data. The log will be used to understand barriers to trial recruitment and patient and surgeon preferences and how inclusion criteria are implemented.

This information will be reviewed on a monthly basis to provide feedback to recruiters and it will help in understanding surgeons' and patients' preferences for types of surgery. It will also allow the trial results to be reported in accordance with CONSORT guidelines. Patients declining randomisation within the study will be asked for written consent to access clinical records and a sample will be invited for a follow up interview which will explore the reasons for declining trial participation.

This feasibility study will not be able to provide a usefully precise measure of the variability in outcomes between surgical teams. Instead the sample size calculation for the main trial will be informed by estimates available from a review conducted by the University of Aberdeen Health Services Research Unit [35].

4.5 Sample size calculation & statistical analysis

4.5.1 Sample size

At the two lead centres, recruitment to the feasibility RCT will occur over a 12-month period, with 72 potentially eligible patients being expected during that time (**Table 1**). This will allow a true 50% recruitment rate to be estimated with a 95% confidence interval of approximately 38%

to 62%. If 11 patients are randomly allocated to each surgical procedure, this will allow a true difference of 1.25 standard deviations between two procedures on a continuous measure of early outcome to be detected with 80% power at the 5% significance level. Hence the pilot RCT will provide an acceptably precise estimate of the recruitment rate to inform plans for the main trial, and may provide evidence suggestive of an intervention having promise for a beneficial impact on short term outcomes.

4.5.2 Statistical methods

Summary statistics which will inform plans for the main trial will be presented including the number of potentially eligible patients per month per centre, the percentage of these patients confirmed as eligible, the percentage of patients agreeing to be randomly allocated to a study procedure in the pilot RCT, and the percentage of randomised patients completing outcome measurements. Mean scores on short-term outcome measures will be presented for each study arm, with p-values and 95% confidence intervals presented for treatment comparisons where at least 10 patients have been randomised to each study arm. Additional summary statistics will arise from the feasibility work, e.g. mean scores on the blinding scale achieved by different blinding procedures.

Table 1. Estimated recruitment rates, assuming 60% of patients undergoing oesophageal cancer surgery are eligible for the trial

Centre	Oesophagectomies/yr	n (30% recruited)	n (50% recruited)	n (60% recruited)
Bristol	30/50 eligible	9	15	18
Plymouth	42/70 eligible	13	21	25

The main trial will be analysed on an intention-to-treat basis, i.e. outcomes will be analysed according to the treatment allocation, irrespective of future management and events, and every effort will be made to include all randomised participants. Variation in outcomes between surgeons will be accommodated in the analysis. Follow-up for the outcome measures during the participant's stay in hospital should be complete for all participants.

4.5.3 Subgroup analyses

There are no planned subgroup analyses.

4.6 Planned follow-up

4.6.1 Follow-up schedule

The hospital stay is typically between 8 and 14 days. Patients are routinely followed up clinically every three months in the first year, six monthly in the second year and annually thereafter. In this feasibility study all participants will complete research measurements for at least 36 months, but research follow-up of the study cohort will continue alongside clinical appointments once the feasibility study has closed.

Participating patients will complete baseline measurements prior to random allocation. On the second day post surgery patients will complete assessments of pain and blinding. At randomisation and at each study assessment timepoint (6 days, 21 days, 42 days, 90 days, 185

days/6 months, 9 months, 12 months, 18 months, 24 months and 36 months after surgery), participants will be assessed by the doctor for current health status (performance status WHO assessment, dysphagia scores, and pain scores) and undergo a clinical examination to check for signs of disease recurrence. They will be weighed in kilograms (kg) using calibrated electronic clinic scales. Height in centimetres (cm) will be measured before randomisation in the hospital to allow calculation of BMI. Lung function measurements will be taken during the first week post-surgery, at days three and six as a minimum, using a portable device at the bedside.

4.6.2 Assessment of patient reported outcomes

Pre-surgery questionnaires will be given to patients to complete themselves when they attend for hospital visits as outlined in **Table 2**. A portable device will be used to measure lung function at the bedside. Participants may elect to complete the questionnaires at home and return by post in a stamp-addressed envelope which will be provided. Follow up questionnaires will be posted by the trials unit (to ensure that time points are followed). If these are not returned within 10 days, one follow up call will be made (if appropriate the questionnaire can be read to the participant over the phone, a second set posted for completion, or an appointment arranged to coincide with an outpatient appointment with the clinical team).

Table 2. Data collection at the pre-surgery and the post-surgery assessment points (in days after the day on which the surgical procedure is completed).

	Pre-surgery	**2 days**	**3 days**	**6 days**	**21 days**	**42 days**	**90 days**	**185 days**	**9 months**	**12 months**	**18 months**	**24 months**	**36 months**
Socio-demographic details	X												
Echo-cardiogram	X												
Height	X												
Weight	X			X	X	X	X	X					
Routine clinical measures	X		X	X	X	X	X	X					
Resource use schedule				X		X							
MFI-20	X	X		X	X	X	X	X	X	X	X	X	X
EORTC QLQ-C30	X			X	X	X	X	X	X	X	X	X	X
EORTC QLQ-OES18	X			X	X	X	X	X	X	X	X	X	X
EQ-5D-5L	X			X	X	X	X	X	X	X	X	X	X
Visual analogue pain score*	X	X	X	X									
Lung function tests*	X		X	X									
In-depth interviews**	X					X	X	X					
Bang Blinding Index		X		X									

*these three assessments are a minimum, and up to daily measurements may be taken over the six days following surgery, **undertaken in a purposeful sample of participants

Reasons for the non-completion of questionnaires will be recorded. Missing or erroneous items on questionnaire measures will be handled according to the questionnaire developers' scoring manuals. Late completion of assessments may prove unavoidable in a small number of cases, but for the data to be accepted the assessments must be completed:

pre-surgery: pre-surgery

3 day: completed no earlier than day 2 and no later than day 4

6 day: completed no earlier than day 5 and no later than day 9

21 day: completed no earlier than day 10 and no later than day 34

42 day: completed no earlier than day 35 and no later than day 56

90 day: completed no earlier than day 76 and no later than day 111

185 day: completed no earlier than day 171 and no later than day 206

274 day/9m: completed no earlier than day 246 and no later than day 330

365 day/12m: completed no earlier than day 331 and no later than day 455

548 day/18m: completed no earlier than day 456 and no later than day 638

731 day/24m: completed no earlier than day 639 and no later than day 916

1096 day/36m: completed no earlier than day 917 and no later than day 1186

Wide windows for completion have been allowed, so that all data obtained from the longer-term follow-up can be used. However, efforts will be made to encourage completion within 30 days of each precise assessment point. Variation in the timing of completion will be accommodated by the statistical analyses.

Reasons for withdrawal from the study, loss to follow up or death (and cause of death) will be recorded.

Self-completion HRQL measures will inevitably be susceptible to bias although we believe that expectations about the effects of the different procedures prior to surgery are likely to wane with follow-up.

5. Trial procedures

5.1 Randomisation procedure

5.1.1 Allocation to treatment arm

Allocation of patients to surgical procedure will be random, will be conducted separately for the two centres, and further stratified by whether the patient has undergone neoadjuvant treatment or not. In Bristol, the random allocation will be to any of the three arms and in Plymouth randomisation is restricted to two of the study arms. Randomisation within blocks of varying size will prevent large imbalances in the number of patients in each treatment arm, whilst maintaining allocation concealment.

5.1.2 Timing of randomisation

Randomisation will be carried out after trial eligibility has been confirmed and consent given. It will usually be carried out within 2 weeks, and no longer than 6 weeks before the timing of the operation itself (after the patient has completed neoadjuvant chemotherapy). Patients will be informed about their randomisation arm when dressings are removed on day seven post-surgery.

Randomisation will be performed by an authorised member of the local research team using a secure internet-based randomisation system ensuring allocation concealment and the avoidance of selection bias.

5.2 Quality control of surgery

Only surgeons, or trainees under direct supervision, will perform the procedures. All procedures will be video or digitally recorded and surgeons will submit anonymised unedited DVDs of the procedures which will be analysed by the research team at Imperial College London.

5.2.1 Developing an operative manual:

During the feasibility phase we will develop i) a surgical manual to be used in the main trial and ii) an oesophageal competency-assessment tool (O-CAT) based on the Observational Clinical Human Reliability Assessment (OCHRA) techniques to assess the level of competency for technical surgical performance [36]. The manual will define the framework for the steps of each trial intervention and describe acceptable protocol deviations. The oesophageal competency assessment tool will monitor adherence to procedural steps, protocol deviations, errors and near miss events.

Protocol fidelity will be classified into significant and non significant surgical deviations. Errors will be divided into consequential and non-consequential events. The surgery undertaken to correct errors (recovery mechanism) will be documented and errors classified as inconsequential or consequential. The protocol deviation number and severity will be used as indicators of fidelity to the protocol. The number and severity of errors will be used as indicators for the quality of technical performance.

5.2.2 Development of a manual for concomitant trial interventions:

During the feasibility phase we will develop i) a manual to be used in the main trial to describe concomitant interventions and ii) a manual to monitor adherence to procedural steps within the manual, protocol deviations, errors and near miss events. The manual will define the mandatory concomitant components that are undertaken with oesophagectomy and describe acceptable and prohibited (unacceptable) protocol deviations. Protocol fidelity will be classified into significant and non significant deviations. Errors will be divided into consequential and non-consequential events and the surgery undertaken to correct a consequential error will be documented. The protocol deviation number and severity will be used as indicators of fidelity to the protocol. The number and severity of errors will be used as indicators for the quality of care.

Details of concomitant interventions are important in fulfilling the CONSORT criteria for reporting evaluations of complex interventions. It is anticipated that the concomitant interventions that will be manualised may include type of anaesthesia, pre and post operative rehabilitation, and key

elements of enhanced recovery pathways that may be manualised. This work will be led by N Blencowe (supervised by Blazeby as part of her NIHR Ph.D. fellowship)

5.2.3 Processing of the pathological specimens:

This will be performed in an agreed uniform manner, with collaboration between respective histopathologists in the centres. Dissection of lymph nodes from the main specimen and lymphadenectomy specimens will follow the proforma. Professor Goldin will visit centres to oversee training for this and lead the quality control by regular exchange of material for cross evaluation. Standardised techniques for sampling lymph nodes will be adopted so that the maximum yield will be obtained from all cases. Involvement of the surgical resection margin will be assessed both microscopically and macroscopically.

5.3 Blinding patients

In this trial it will not be possible to blind surgeons, but it may be possible to blind patients, and those assessing outcomes, to the type of surgery, at least during the initial post-surgery period. This will be attempted to avoid reporting bias in the patient's assessment of pain. Methods to achieve blinding of patients and outcome assessors will therefore be piloted during to inform whether this can be achieved and whether these methods are acceptable in the main trial.

In first week post surgery patients will be blinding using large adhesive dressings that will be provided to participating sites by the trial office for the dressing of patient's surgical wounds. Dressings will be positioned similarly on all trial patients regardless of the type of surgery (covering the abdominal, thoracic and cervical incisions). The first dressing should be applied by the surgical team in the operating theatre. The dressing will not be changed unless required (because of soiling or lack of adherence) until day three. It will then be changed by the research nurse who will not be routinely involved with the patient's care. During the dressing changes patients will be asked to turn their head away from the wound sites to prevent them observing the wounds. The nurse will clean the sites of all actual and potential incisions on the abdomen. Dressings will be supplied as part of the set up process, with additional dressings supplied as required. On days two and six patients will be asked to complete the Bang Blinding Index which assesses the success of blinding by asking them to guess which arm of the trial they were allocated to [37]. Dressings will be removed on day seven (after the second questionnaire assessment made by the patient). Patient experience of blinding and experiences of ward staff and nurses involved these processes will be further explored in the qualitative interviews described below

5.4 Integrated qualitative research

The ROMIO trial compares different surgical procedures that are in common use in specialist centres, and therefore the trial is likely to face a number of recruitment challenges. Based on previous work by Donovan and colleagues [38-41], ROMIO will include an integrated qualitative study which has two key parts:

5.4.1 Understanding and improving recruitment

The integrated recruitment study will itself be in two key phases:

Phase I: Understanding recruitment

This phase aims to understand the recruitment process in each of the centres, as it happens, and includes four parts:

(a) Interviews with members of the TMG, PIs and active recruiters

Participants will be asked to provide written informed consent to audio-recording using Participant Consent Form 4 (PCF4). Interview topic guide 1 will be used to ensure similar areas are covered in each interview within each group, based on those used in previous studies, but also encouraging the informants to express their own views about the RCT and any recruitment challenges expected or experienced. Members of the TMG will be asked about the background, development and purpose of the RCT, including their knowledge of the evidence and equipoise; their role in the trial and recruitment, including their expectation of the pathway through eligibility and recruitment. PIs and active recruiters will be asked questions about their knowledge of the evidence and personal views about equipoise; the recruitment pathway, how they feel the protocol fits their clinical setting and any adjustments they think are needed. They will also be asked how they explain the RCT and the randomisation process. They will be asked to audio-record their appointments with patients, with a view to discussing any discomfort or perceived difficulty with this.

(b) Patient pathway mapping

The qualitative researcher will work with other ROMIO staff to delineate the pathway that patients follow through recruitment in terms of who they see, when and what sorts of issues are discussed. This mapping will help to identify the most appropriate appointments to audio-record (see below)

(c) Audio-recordings of recruitment appointments

Patients potentially eligible for the trial will be sent an appointment with the surgeon and receive PIL1, which informs the patient that they will be asked to consent to audio-recording. During this appointment the surgeon will discuss the treatment options with the patient and introduce the ROMIO trial. If the patient agrees this information appointment consultation will be audio-recorded. Both surgeon and patient will provide written consent for the audio-recording (PCF1 for patients and PCF2 for surgeons). At the end of the appointment, the audio recording will be anonymised and sent to the School of Social and Community Medicine via the NHS net. The qualitative researcher will listen to appointments, document relevant details and provide an account for the qualitative study PI (JD). Issues will be fed back to the ROMIO CI/TMG, and these data will form the basis for confidential feedback to individuals and, anonymised, to determine the content of information and training programmes to be initiated in Phase II.

(d) Interviews with study participants

In-depth interviews with a maximum variation sample of between 10 and 15 patients eligible for the trial will explore patient perspectives of surgery, previous experiences with treatments, views about surgery, and the acceptability of randomisation between the procedures. These interviews will by guided by Interview Topic Guide 2. Interviews will include those who have agreed to randomization, and those who have rejected it but are willing to discuss their views (providing consent to audio-recording on Participant Consent Form 5 = PCF5).

Phase II: Plan for improving recruitment

The qualitative researcher will present summaries of anonymised findings to the ROMIO CI and TMG, identifying any aspects of RCT design and conduct that could be hindering recruitment with the supporting evidence. There are likely to be several meetings regularly during the feasibility phase of the study to present these findings and discuss a plan of action to try to improve recruitment, if this proves necessary. The plan will be agreed by the RCT CI/TMG and qualitative PI and researcher. No activities will be undertaken by the researcher without the prior approval of, and collaboration with, the RCT CI and TMG. The plan will be focused on the

issues emerging from the qualitative recruitment study. It is likely that some aspects will be generic, such as difficulties with the application of eligibility criteria or explaining randomisation. The plan is likely to include some or all of: reconsideration of study information, advice about presenting the study, discussions about equipoise or evidence, issues with patient pathways, and logistical issues in particular centres. These may be addressed by a new PIS, changes to the protocol, or training for recruiters in the presentation of RCTs in general or the specific RCT.

Numbers of eligible patients, and the percentages of these that are approached about the RCT, consent to be randomised and immediately accept or reject the allocation will be assessed before the plan of action is implemented, and regularly afterwards to check whether rates are improving. Interviews with recruiters will ask about the acceptability of the qualitative research and any changes that occur.

5.4.2 Process evaluation

The process evaluation will comprise three parts:

1. Non-participant observation:

Non-participant observation of a purposively selected sample (n=10-20) operations will be performed by one or two researchers to supplement and triangulate information obtained from a) video and audio recordings and b) interviews of surgeons and team members (below). Observations will focus on the surgical intervention itself, concomitant interventions occurring in the operating theatre, and also contextual factors (e.g. noise, interruptions, team working and communication). Observations will either be recorded by hand or using the Observer XT 10.5 PDA. Dual observation will increase the study validity and ensure that both clinical and non-clinical interactions will be recorded. Patients will provide written consent for the recording of their surgery on Participant Consent Form 6 (PCF6).

2. Video and audio recording of surgical procedures:

Digital video recordings of the operations will be performed using standard techniques [42]. Data will be collected directly from the laparoscopy 'stack' already in routine use for the procedures. Recording will start from when the surgeon has placed the camera port and will end when the camera is removed after the procedure. For operations that are not laparoscopic a camera will be fixed within the operating theatre to record the procedure and key steps photographed in details. Recordings will be stored in a secure USB hard drive and then transferred (via USB or a secure file transfer software package e.g. Filezilla) to a secure server/external hard drive (to be kept in a locked filing cabinet only accessible by study research staff) held at the Academic Unit of Surgical Research at the University of Bristol and/or the research team at Imperial College London, who are undertaking the video analyses. These will be anonymised with study ID, patient initials and date of birth. Audio recordings will be made using a digital recorder and start at the beginning of the procedure (where the patient is anaesthetised and the equipment prepared and checked), continuing through all of the operation itself, including the end of the procedure, patient recovery and clearing up of the theatre and equipment, when the patient has left the operating theatre.

3. Interviews with surgeons, anaesthetists and nurses:

A purposefully selected sample of surgeons and other team members (n=20-30) will be interviewed after the operation (within 3 days) and also several weeks later, at around the time the patient is due to go home. Interviews will be guided by a topic guide which will be a list of open-ended questions to ensure that all topics are covered in each interview but will be sufficiently flexible to enable topics of importance to the informant to emerge. The topic guide is likely to adapt as interviews and analyses proceed but proposed topics include:

Exploration of knowledge of the trial and trial protocol, the intervention and if/how they plan to modify it for the particular patient/disease state

Views of the impact of variations from the surgical (or anaesthetic) protocol

Reasons for advocating or not advocating surgery and any particular surgical approach

Questions about which parts of the operation and protocol are considered to be difficult and how patient factors influence this

Hospital, team or equipment factors that influence carrying out surgery and in what ways this may differ if they are training others to do the procedure

What advice surgeons give to patients about the surgical intervention in a trial (if any)

What they think are the most important elements of the surgical (or anaesthetic or nursing) intervention that influence outcomes (and how these might change in light of complications)

Self-reported expertise

Staff will provide written consent for the audio-recording of these interviews on PCF4.

5.4.3 Analyses of qualitative data

In-depth interviews and recruitment appointments will be audio-recorded. Interviews will be fully transcribed, and the data will be analysed using the methods of constant comparison to elicit themes that will be written up into descriptive accounts that will be shared with the study team [41]. In the recruitment study, the aspects of most interest will be issues of equipoise among surgeons/recruiters, and the acceptability of the procedures and the information provided to patients. The data from recruitment appointments will be documented through summaries of the content, with thematic analyses of areas of the appointments where information is articulated by recruiters and interpreted by patients. This will be supplemented by targeted conversation analysis focussing on areas of appointments were communication appears problematic [41]. Data will be transcribed as required, and then incorporated into training programmes and materials or used in individual confidential feedback for recruiters. In-depth interviews with a sample of trial participants in each arm will focus on experiences of management following surgery and outcome, and will be analysed thematically.

For the process evaluation, interview, audio and observational data will initially be coded separately, resulting in two separate coding frames. Relevant themes will then be considered together, with the interview data being used to confirm, challenge, or clarify the observation findings. The intention is to take an inductive approach to the data analysis, enabling theories to be derived from the data. Additionally, negative cases will actively be sought; patients, surgeons or other team members with contrasting views or attitudes, as this will help gain deeper understanding of the data.

It will be possible to synchronise video and observation recordings using the Observer XT 10.5 software, as well as audio recordings, as all equipment can be activated simultaneously.

5.5 Development of a core clinical outcome set for oesophageal cancer surgery

A list of all possible outcomes related to oesophagectomy has been generated from four different sources as part of an earlier project and this long list includes clinical and patient reported outcomes. It has been condensed into outcome health domains and within ROMIO, a survey will be developed (based on the domains). Key stakeholders (consultant surgeons, clinical nurse specialists and patients who have undergone oesophagectomy) will be informed about this aspect of the study using PIL4 and Participant Invitation Letter 2.1, 2.2 and 5, which

will be sent to patients and health professionals by a member of the usual care team. Patients will also be asked to complete Patient Consent Form 8 (PCF8). This Delphi survey questionnaire will then be circulated to those stakeholders who agree to take part, with a request to prioritise the outcomes.

Patients to be surveyed include: (i) patients who have previously been diagnosed with oesophageal cancer and/or who have undergone oesophagectomy via existing hospital databases at each centre, the Gastro-Oesophageal Support and Health group (GOSH) and the Oesophageal Patients Association (OPA), (ii) participants invited but who declined to participate in the ROMIO trial who are awaiting oesophagectomy and who have already consented (via Participant Consent Form 7), to be contacted about related research within the ROMIO trial. Details of those patients who have not already agreed to be contacted about future research should not be passed on to a researcher who is not part of the usual care team.

Delphi methodology will be used to reduce the initial list of outcome domains to a shorter list according to pre-specified criteria and each Delphi round will be analysed to identify key or redundant items. There may be up to three rounds and it is expected that a consensus meeting will be convened with stakeholders at the same time as a trial steering committee to discuss the survey results and to perform further anonymous rating of retained items (Participant Invitation Letter 3.1 and 3.2). This work will link with 'COMET' (http://www.liv.ac.uk/nwhtmr/research/theme_2/core_outcomes.htm), funded by the MRC ConDuCT and North West Hubs for trials methodology research. The final core set of outcomes for oesophageal cancer surgery is expected to be less than 10 items. Given the difficulty in keeping participants, clinicians and researchers blind to treatment allocation, a proportion of objective outcome measures will be included in the core set.

5.6 Development of Resource use data collection instruments.

The best way of capturing resource use and cost in relation to the interventions and follow-up in secondary care will be explored, e.g. the use of electronic versus hard copy individual patient medical records.

Data on the use of primary NHS services and social services and direct and indirect costs incurred by patient and carers will be collected at timepoints during the study. This will be facilitated by the creation of resource use logs/diaries to be used as an “aide memoire” for the patients.

A copy of the ‘Resource use 0-3M diary’ will be given to all patients on Day 6 following their surgery (pre-discharge), with a request for the patient (or a friend/relative) to complete the diary during months 0-3 post-discharge with details of their use of NHS services; personal social services and direct and indirect costs related to their surgery. Patients will be informed that they will be contacted by telephone by one of the research nurses at approximately 3 months post-discharge to arrange a time for a telephone conversation during which the nurse will collect the resource use data.

Patients will be posted a copy of the ‘Resource use 4-6M diary’ at approximately 4 months post-surgery, with a request for the patient (or a friend/relative) to complete the diary during months 4-6 post-surgery. The posted diary will be accompanied by a cover letter (‘Participant Invitation Letter 4 - resource use 4-6 months diary’. At approximately 6 months post-discharge, patients will be contacted by telephone by one of the trial team research nurses to arrange a time for a telephone conversation during which the nurse will collect the resource use data.

Unit costs from hospital finance and routine sources will be applied to the resource use data. The resource use data will be separated into different categories (e.g. theatre, outpatient visits, GP visits). The average costs for all the different categories will be compared by arm. This will enable: the main cost drivers of the interventions to be established; identification of potential areas where cost differences exist between the arms; in addition to identifying areas where obtaining accurate estimates of cost is problematic. This will allow a more focused collection of resource use data in the main trial which will result in a more accurate estimate of cost-effectiveness.

5.7 Data procedures

5.7.1 Data management

A unique file identified by the study number will be maintained for participants. All study data recorded on case report forms relating to the participant will be located in these files. A list will be maintained at each centre of staff with authorisation to make alteration to the study records, including the study database (see section 10.2 for information on the database architecture and data handling). The baseline data will be collected at the pre-operative assessment clinic where consenting patients will be seen by an authorised member of the local research team (as specified in the delegation log) who will answer any questions, confirm the patient's eligibility and take written informed consent if the patient decides to participate.

Data collection will include the following elements:

(a) A screening log of all patients referred for oesophageal cancer surgery and those who are approached for the trial (including the date when they are given the PIL).

(b) Patients approached and assessed against the eligibility criteria and, if ineligible, reasons for ineligibility.

(c) Eligible patients approached and not randomised and reasons for this and the final treatment that they received.

(d) Consent and baseline information (e.g. history and planned operation and response to health status questionnaires) collected prior to randomisation in participating patients.

(e) Baseline data, and participant responses to health status questionnaires collected at follow-up as indicated in Table 1.

(f) Audio-recording of consultations and interviews as outlined in section 5.3.

(g) Receipt of allocated procedure, and completion of post-surgery outcome measures.

5.7.2 Source data

The primary data source will be the participant's medical notes. The laboratory reports will be the primary data source for the results of the histopathological analyses. The CRFs will be the source data for the resource use data and the completed patient questionnaires will be the primary data source for these measures. The audio recordings will be the primary data source for the qualitative aspects of the study.

5.8 Discontinuation / withdrawal of participants and payment of expenses

5.8.1 Procedure following patient discontinuation / withdrawal

Each participant has the right to discontinue their part in the study at any time. In addition, the investigator may withdraw the participant from their allocated treatment arm if subsequent to randomisation a clinical reason for not performing the surgical intervention is discovered. Participants withdrawn from their allocated intervention but willing to continue completing follow-up schedules will be encouraged to do so. All discontinuations and withdrawals will be documented. If a participant wishes to discontinue, data collected up until that point will be included in the analyses, unless the participant expresses a wish for their data to be destroyed.

5.8.2 Likely rate of loss to follow-up

After discharge from hospital, the only losses to follow-up will be due to death or participant discontinuation. It is expected that 30% of patients will die within a year of surgery. We expect loss to follow-up after discharge over the year to be less than 5%.

5.8.3 Expenses

Participant travel expenses will not be reimbursed for the follow up visits which would be expected to occur as part of normal surgical follow up. Exceptions can be considered on a case by case basis.

6. Trial management

6.1 Trial Management Group (TMG)

The trial will be managed by a TMG, which will meet face to face or by teleconference every month for the duration of the study. The TMG will be chaired by the Chief Investigator and will include all members of the named research team (see *Chief Investigators & Research Team Contact Details above)*.

The TMG will be supported by the BRTC which is an UK Clinical Research Collaboration registered Clinical Trials Unit. The BRTC will prepare all the trial documentation and data collection forms, specify the randomisation scheme, develop and maintain the study database, check data quality as the trial progresses, monitor recruitment and carry out trial analyses in collaboration with the clinical investigators.

6.2 Day-to-day management

A research nurse in each centre will be responsible for identifying potential trial participants, seeking informed participant consent, randomising participants, liaising with the theatre planning manager, collecting trial data and ensuring the trial protocol is adhered to.

6.3 Monitoring of sites

6.3.1 Initiation visit

Before the study commences training session(s) will be organised by the BRTC. These sessions will ensure that personnel involved fully understand the protocol, CRFs and the practical procedures for the study.

6.3.2 Site monitoring

The trial coordinating centre (BRTC) will carry out regular monitoring and audit of compliance of centres with GCP and data collection procedures described in section 5 above.

6.4 Trial Steering Committee

The Trial Steering Committee (TSC) is made up of the following representatives of ROMIO TMG, and independent members to be appointed by the funders:

Dr Chris Metcalfe (Chief Investigator, methodology, Bristol)

Prof Jane Blazeby (Chief investigator, methodology & clinical, Bristol)

Mr Richard Berrisford (Lead clinician, Plymouth)

Mrs Jackie Elliot (Lay member)

This feasibility study will not have a separate Data Monitoring and Safety Committee. The data collected will provide essential information for the design of the main trial, but will not be sufficient to evaluate the relative effectiveness of the different surgical procedures. Hence there will be no confidential interim analysis of effectiveness for a Data Monitoring and Safety Committee to undertake, and the Trial Steering Committee will provide oversight of the data collection and analysis that is undertaken to establish the feasibility and optimal design of the main trial.

7. Safety reporting

Adverse events will be recorded in accordance with the following protocol (see Figure 2).

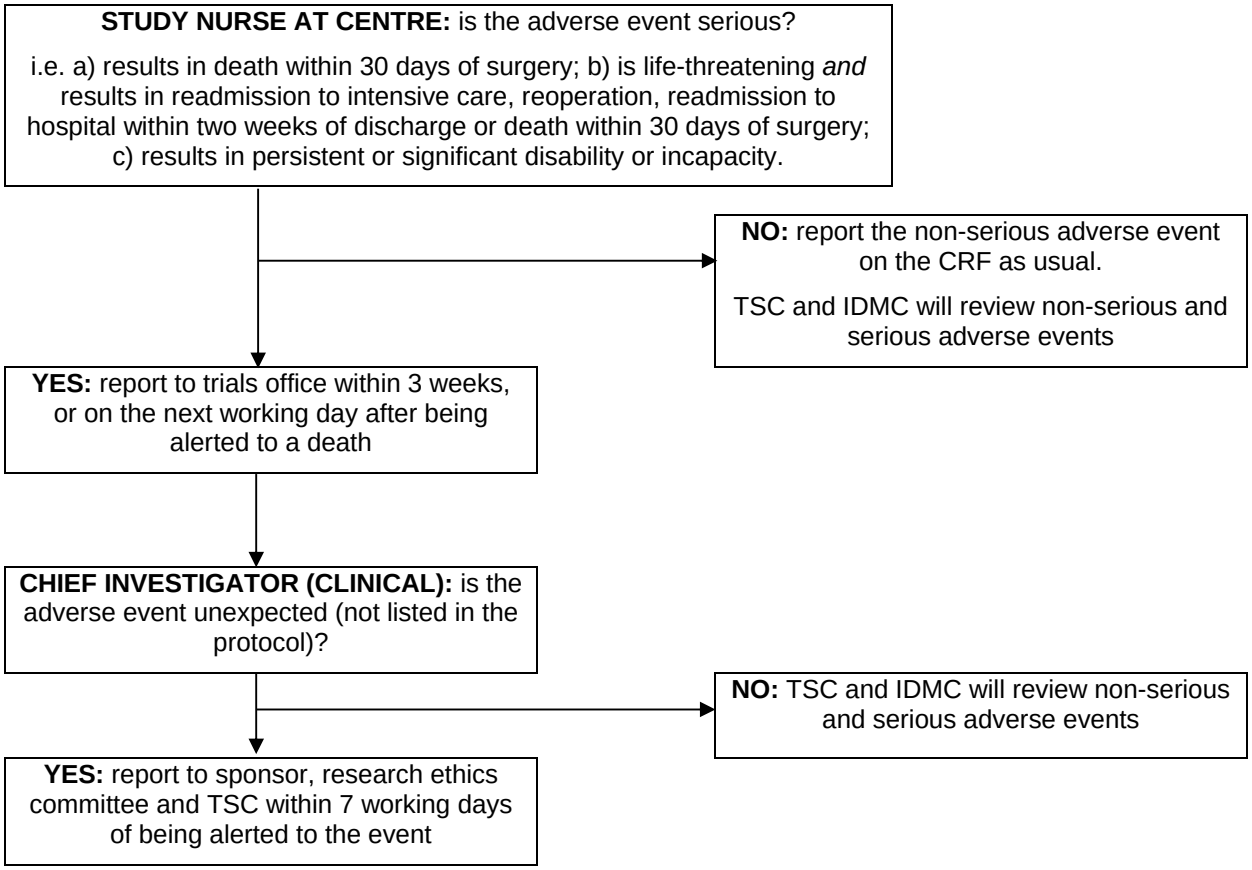
In oesophageal surgery, post-operative complications are not unexpected and are not infrequent, often causing an extension of the patient's hospital admission. The research team will only notify fatal and unexpected non-fatal serious adverse events to the trial sponsor. ‘Expected’ adverse events are listed in section 7.1 below.

All adverse events will be recorded in detail on a case record form. At the conclusion of the study, all adverse events recorded during the study will be subject to statistical analysis, and the analysis and subsequent conclusions will be included in the final study report. Abnormalities in laboratory test results or other investigations will only be recorded if they are considered to be clinically significant.

For all serious adverse events, the subject will be actively followed up, and the investigator (or delegated person) will provide information missing from the initial report within five working days of the initial report. The investigator (or delegated person) will provide follow-up information each time new information is available, using the study follow-up report form until the serious adverse event has resolved or a decision for no further follow-up has been taken.

Figure 2 Serious adverse event reporting flow chart

When an adverse event occurs, this flow diagram is to be followed:



7.1 Expected adverse events

The following adverse events are 'expected':

7.1.1 Intra operative complications

Bleeding requiring blood transfusion

Removal of spleen

Removal of part of the colon

Removal of part of the small bowel

Removal of part of the liver

Removal of part of the lung

Damage to the airway requiring repair

Anaesthetic related problems

Complications related to the epidural such as abscess, or neurological problems

Damage to major vessels with venous or arterial catheters

7.1.2 General complications post operatively

i) Pulmonary:

- pneumonia
- pneumothorax
- empyema
- atelectasis
- aspiration
- pleural effusion
- ventilator-related complications
- adult respiratory distress syndrome
- respiratory failure
- the need for prolonged mechanical or positive pressure airway ventilation

ii) Cardiac:

- myocardial infarction
- arrhythmia
- heart failure
- angina
- pericardial effusion
- pericarditis

iii) Renal:

- urinary tract infection
- renal failure maybe requiring full renal support
- renal dysfunction
- urinary retention
- haematuria

iv) Cerebral:

- delirium
- disorientation
- psychosis
- transient ischaemic attack
- stroke
- depression
- alcohol withdrawal
- epilepsy
- Guillan-Barre syndrome

v) Thrombotic:

- deep vein thrombosis
- pulmonary embolism
- mesenteric thrombosis
- other thromboses (e.g. limb)

vi) Bowel:

- infective diarrhoea or colitis (e.g. *Clostridium difficile*)
- diarrhoea of other causes
- bowel ischaemia
- ileus

vii) Hepatobiliary:

- pancreatitis
- liver failure
- gallstone disease and its sequelae
- hepatitis

viii) Wound:

- infection
- septicaemia
- pyrexia
- dehiscence

adhesions
perforation
bowel obstruction
gastric or intestinal volvulus
internal herniation
leakage of pyloroplasty
formation of cervical oesophagostomy
evisceration
hernia

ix) Bleeding

x) Other miscellaneous general complications

gout
hyper osmolar non ketotic syndrome
decubitus ulcer
other infections (e.g. MRSA)
anaesthetic-related complications

7.1.3 Specific complications

i) Anastomosis and conduit:

anastomotic leak
delayed gastric emptying
gastric outlet obstruction
anastomotic stricture
bile reflux
gastric tube perforation
non-anastomotic leakage
conduit necrosis
necessitation for oesophagostomy formation

ii) Jejunostomy:

obstruction
dislodgement
infection
leakage
the need for prolonged feeding

iii) Intra-operative damage to organs or structures in chest, abdomen or neck, including:

vocal cord paralysis or palsy
chyle leak
requirement for removal or repair of structure/organ(s) (e.g. splenectomy)

iv) Inoperability at planned surgery

7.1.4 Other complications

i) The need for re-intervention of these sorts:

bedside procedure (e.g insertion if chest drain, ascites drain, drainage, abscess or wound)

medical intervention (e.g. antibiotics, TPN, blood transfusion)

invasive procedure without general anaesthesia (surgical or radiological)

invasive procedure, general anaesthesia or single organ failure

invasive procedure, general anaesthesia, single organ failure or multi-organ failure

ii) The need to return to intensive care:

mechanical ventilation

organ support

invasive monitoring

tracheostomy

iii) In-hospital death

iv) Death due to advanced cancer

v) Readmission to hospital following discharge due to complications of surgery, worsening cancer or causes not resulting in a specific diagnosis

7.2 Period for recording serious adverse events

Data on adverse events will be collected for each participant from the point at which they consent until at least 6 months post surgery (the final scheduled assessment in this feasibility study) although data from subsequent three-monthly assessment and will also be considered if occurring during the feasibility study period.

8. Ethical considerations

8.1 Review by an NHS Research Ethics Committee

Ethics review of the protocol for the trial and other trial related essential documents (e.g. Participant Information Leaflets and Consent Forms) will be carried out by a UK Research Ethics Committee (REC). Any subsequent amendments to these documents will be submitted to the REC for approval prior to implementation.

8.2 Risks and anticipated benefits for trial participants and society

All participants will undergo one of the three standard operations currently carried out in routine care of cancer of the oesophagus or high grade dysplasia.

8.3 Information to potential trial participants of possible benefits and known risks

The potential risks and benefits are well known and are similar for the three procedures; they will be discussed with the patients when seeking informed consent.

8.4 Obtaining informed consent from participants

All participants will be required to give separate written informed consent for audio-recording of sessions and for random allocation of treatment. This process, including the information about the trial given to patients in advance of recruitment, is described above in sections 4 and 5. The research nurse/PI/clinical research fellow will be responsible for the consent process, which will be described in detail in a Standard Operating Procedure.

9. Research governance

This study will be conducted in accordance with:

- The Medicine for Human Use (Clinical Trial) Regulations 2004
- The International Conference for Harmonisation of Good Clinical Practice (ICH GCP) guidelines
- The Research Governance Framework for Health and Social Care

9.1 Sponsor approval

Trial documents and any subsequent amendments will be approved by the sponsor prior to submission to the REC.

9.2 NHS approval

Trial documents and any subsequent amendments approved by the REC will be submitted to each participating Trust's R & D department for information and approval.

9.3 Investigators' responsibilities

Investigators will be required to ensure that local research approvals have been obtained and that any contractual agreements required have been signed off by all parties before recruiting any participant. Investigators will be required to ensure compliance to the protocol and study manual and with completion of the CRFs. Investigators will be required to allow access to study documentation or source data on request for monitoring visits and audits performed by the Sponsor or BRTC or any regulatory authorities.

Investigators will be required to read, acknowledge and inform their trial team of any amendments to the trial documents approved by the REC that they receive and ensure that the changes are complied with.

9.4 Monitoring by sponsor

The study will be monitored and audited in accordance with the Sponsor's policy, which is consistent with the Research Governance Framework. All study related documents will be made available on request for monitoring and audit by the sponsor and the relevant REC.

9.5 Indemnity

This study is indemnified by the University of Bristol.

9.6 Clinical Trial Authorisation

Oesophagectomy is not classed as investigational medicinal products and therefore a Clinical Trial Authorisation from the MHRA is not required.

10. Data protection and participant confidentiality

10.1 Data protection

Data will be collected and retained in accordance with the UK Data Protection Act 1998.

10.2 Data handling, storage and sharing

10.2.1 Data handling

Data will also be entered into a purpose-designed server database. Information capable of identifying individuals and the nature of treatment received will be held in the database with passwords restricted to ROMIO study staff. Information capable of identifying participants will not be removed from the BRTC or clinical centres or made available in any form to those outside the study.

Access to the database will be via a secure password-protected web-interface (NHS clinical portal). Study data transferred electronically between the University of Bristol and the NHS will only be transferred via a secure NHSnet network in an encrypted form.

Data will be entered promptly and data validation and cleaning will be carried out throughout the trial. Standard operating procedures (SOPs) for database use, data validation and data cleaning will be available and regularly maintained.

10.2.2 Data storage

All study documentation will be retained in a secure location during the conduct of the study and for 3 years after the end of the study, when all patient identifiable paper records will be destroyed by confidential means. Prior to destruction, paper records will be scanned and stored on the University server with limited password controlled access. Where trial related information is documented in the medical records, these records will be identified by a label bearing the name and duration of the trial in accordance to policy of the sponsor. In compliance with the MRC Policy on Data Preservation, relevant 'meta'-data about the trial and the full dataset, but without any participant identifiers other than the unique participant identifier, will be held indefinitely (University server). A secure electronic 'key' with a unique participant identifier, and key personal identifiers (.e.g. name, date of birth and NHS number) will also be held indefinitely, but in a separate file and in a physically different location (NHS hospital server). These will be retained to allow the possibility of secondary research projects which may arise from the current proposal.

10.2.3 Data sharing

Data will not be made available for sharing until after publication of the main results of the study. Thereafter, anonymised individual patient data will be made available for secondary research, conditional on assurance from the secondary researcher that the proposed use of the data is compliant with the MRC Policy on Data Preservation and Sharing regarding scientific quality, ethical requirements and value for money. A minimum requirement with respect to scientific quality will be a publicly available pre-specified protocol describing the purpose, methods and analysis of the secondary research, e.g. a protocol for a Cochrane systematic review. The second file containing patient identifiers would be made available for record linkage or a similar purpose, subject to confirmation that the secondary research protocol has been approved by a UK REC or other similar, approved ethics review body.

11. Dissemination of findings

The findings will be disseminated by usual academic channels, i.e. presentation at international meetings and peer-reviewed publications. A full report for the HTA will be written on completion of the feasibility study. A lay summary of the results will be provided to local patient organisations.

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Amendments to protocol

Amendment number (i.e. REC and/or MHRA amendment number)	Previous version	Previous date	New version	New date	Brief summary of change	Date of ethical approval (or NA if non-substantial)
1 (Non-substantial amendment)	1.0	25/04/12	1.0	25/04/12	Inclusion of new NHS research sites and investigators (Royal United Hospital Bath, Royal Devon & Exeter, Northern Devon, Royal Cornwall Hospitals NHS Trusts)	N/A (notified 18/12/12)
2	1.0	25/04/12	2.0	03/12/12	Safety reporting, blinding, measures at timepoints.	23/01/13
3 (substantial and non-substantial amendments)	2.0	03/12/12	3.0	24/04/13	Non-substantial amendment – GP letters' signatory. Substantial amendment - Inclusion/exclusion criteria, recruitment process (posting of PIL2), data collection (participation in other trials), description of blinding in protocol.	07/05/13 (both)
4	3.0	24/04/13	4.0	22/10/13	Core outcome set development.	23/10/13

Table continued overleaf

5 (Non-substantial amendment)	4.0	22/10/13	5.0	01/04/14	Extension to recruitment period	N/A (acknowledgement received only)
6	5.0	01/04/14	6.0	02/04/14	(i) Mini PIL, (ii) Development of resource use instruments, (iii) Safety reporting, (iv) Video- and audio-recording of surgery	07/05/14
7	6.0	02/04/14	7.0	06/05/14	(i) Follow-up assessments, (ii) COS health professionals' letter	28/05/14
8	7.0	06/05/14	8.0	16/07/14	(i) Follow-up assessments	Pending
9 (Non-substantial amendment)					(i) Resource use instruments (Bath version)	Pending

13. Appendix – List of current study documentation

	Site	Version	Date
Letters of invitation to participant			
Participant invitation letter 1a-Bris	1,3	2.0	09/07/12
Participant invitation letter 1b-Plym	2	2.0	09/07/12
Participant invitation letter 2.1	1,2	1.0	17/09/13
Participant invitation letter 2.2	1,2	1.0	17/09/13
Participant invitation letter 3.1	1,2	1.0	17/09/13
Participant invitation letter 3.2	1,2	1.0	17/09/13
Participant invitation letter 4	1,2	1.0	02/04/14
Participant invitation letter 5	1,2	2.0	11/08/14
GP letters			
GP letter 1a-Bris	1,3	2.0	09/07/12
GP letter 1b-Plym	2	2.0	09/07/12
Participant information sheets			
PIL1-patient-information study	1,2,3	2.0	09/07/12
PIL2a-patient-trial Bris	1,3	3.0	06/05/14
PIL2b-patient-trial Plym	2	3.0	06/05/14
PIL4-patient-Delphi	1,2,3	1.0	17/09/13
PIL5a-Brief PIL	1,3	1.0	02/04/14
PIL5b-Brief PIL	2	1.0	02/04/14
Participant consent forms			
PCF1-patient-consultations	1,2,3	2.0	09/07/12
PCF2-staff-consultations	1,2,3	2.0	09/07/12
PCF3-patient-trial	1,2,3	2.0	09/07/12
PCF4-staff-interviews	1,2,3	2.0	09/07/12
PCF5-patient-interviews	1,2,3	2.0	09/07/12
PCF6-patient-recording operation	1,2,3	2.0	09/07/12
PCF7-patient-non trial participation	1,2,3	1.0	03/12/12
PCF8-patient-Delphi	1,2,3	1.0	17/09/13
Topic guides			
Interview Topic Guide 1 – TMG, PIs, active recruiters	1,2,3	1.0	18/04/12
Interview Topic Guide 2 - patient	1,2,3	1.0	18/04/12
Validated questionnaires			
MFI20 measure of fatigue	1,2,3	1.0	1995
EORTC QLQ-30 Quality of life measure for patients with cancer	1,2,3	3.0	1996
EORTC QLQ-OES18 Quality of life measure for patients with oesophageal cancer	1,2,3		2003
EQ-5D-5L Generic health related quality of life measure	1,2,3	2.0	2009
Pain score	1,2,3	2.0	24/04/13
Bang Blinding Index-Bris	1,3	1.0	2004

Bang Blinding Index-Plym	2	1.0	2004
Other documents			
Resource use 0-3M diary	1,2	1.0	02/04/14
Resource use 4-6M diary	1,2	1.0	02/04/14
Resource use 0-3M diary (Bath)	3	1.0	29/07/14
Resource use 4-6M diary (Bath)	3	1.0	29/07/14