Randomised Oesophagectomy: Minimally Invasive or Open

The ROMIO Study

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Sponsor

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Glossary / abbreviations

APACHE II	Acute Physiology And Chronic Health Evaluation II
ARDS	Acute respiratory distress syndrome
BRTC	Bristol Randomised Trials Collaboration
CI	Chief Investigator
ConDUCT-II	Collaboration and innovation in Difficult and Complex randomised controlled Trials In Invasive procedures
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
CTEU	Clinical Trials and Evaluation Unit Bristol
DMSC	Data Monitoring and Safety Committee
EQ-5D-5L	EuroQol health status questionnaire
EORTC	European Organisation for Research and Treatment of Cancer
HRG	Health Resource Group
HRQL	Health Related Quality of Life
HTA	Health Technology Assessment
ICH-GCP	International conference for harmonisation of good clinical practice
ICNARC	Intensive Care National Audit Research Centre
IDEAL	Idea, Development, Evaluation, Audit and Long term follow up
ISD	Information Services Division
ITT	Intention to treat
LAO	Laparoscopically-Assisted Oesophagectomy
MRC	Medical Research Council
MDT	Multi-Disciplinary Team
MIO	Minimally Invasive Oesophagectomy
MIRO	Open versus laparoscopically-assisted oesophagectomy for cancer: a multicentre randomised controlled phase III trial - the MIRO trial
MRSA	Meticillin-resistant staphylococcus aureus
NCRAS	National Cancer Registry Analysis Services
OCHRA	Observational Clinical Human Reliability Assessment
ODR	Office for Data Release
OO	Open Oesophagectomy
QLQ-C30	Quality of life Questionnaire - Core
QLQ-OES18	Quality of life Questionnaire- Oesophageal
PCF	Participant consent form
PSS	Personal social services
PI	Principal Investigator
PIL	Participant Information Leaflet
PHE	Public Health England
QA	Quality assurance
QALY	Quality adjusted life years
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
ROMIO	Randomised Oesophagectomy: Minimally Invasive or Open
RTDS	Radiotherapy Dataset
SACT	Systemic Anti-Cancer Therapy
SSA	Site Specific Assessment
SCF	Staff consent form

SOFA	Sepsis-related Organ Failure Assessment
SOP	Standard Operating Procedure
TIME	Traditional invasive vs. minimally invasive oesophagectomy: a multi-centre randomised trial (TIME-trial)
TMG	Trial management group
TSC	Trial steering committee
UK	United Kingdom

1. Trial summary

Oesophageal (gullet) cancer is relatively common in the UK. If detected early, it may be cured with surgery (oesophagectomy). Traditionally this was performed with large incisions in the abdomen, the chest, and sometimes the neck, to remove the cancer and replace the gullet with the stomach. The operation is complex, 30% of patients experience complications, and about 3% of patients die soon afterwards (England & Wales audit 2011-12 [1, 2]). The benefit of surgery is survival, about 40 to 50% of patients living for 3 years. However, surgery is followed by a reduction in health related quality of life; it is important to establish refinements to the surgery which lessen this impact and quicken recovery. Minimally invasive 'keyhole' surgery for oesophageal cancer may achieve the same survival benefit, but with better recovery than open surgery. However, this impression is largely based on observational studies, and the apparent faster recovery may be due to the selection of fitter patients for the minimally invasive procedure. There are just two randomised controlled trials (RCTs) with modest sample sizes (115 & 200 patients) and methodological shortcomings. We have refined the methodology for a trial in a preparatory study, and this main trial will be a methodologically robust RCT which is large enough to detect clinically important improvements in recovery with minimally invasive surgery. We propose to conduct the RCT at 7 UK centres, involving surgeons who can provide evidence of their skill using minimally invasive techniques. Patients with localised oesophageal cancer referred for surgery by their multi-disciplinary cancer care team, will be invited into the study. The only major factors preventing participation are previous surgery or cancer where these will make the oesophagectomy more difficult, and pregnancy. Following informed consent, patients will be randomly allocated to open oesophagectomy or "laparoscopically-assisted" oesophagectomy (LAO), with the abdominal surgery conducted using minimally invasive methods in the latter case. The primary measure of outcome will be a validated measure of physical function. We will recruit 406 patients in total, allowing clinically important differences in postsurgical recovery to be detected. Other outcome measures will include survival, days in hospital, complications, pathological specimen quality, and health-related quality of life. We will also collect resource use data, to allow a comparison of the cost-effectiveness of the two approaches. All participants will be followed for at least two years post-surgery. A substudy at two centres will also randomly allocate patients to a fully minimally invasive oesophagectomy, giving unbiased early information on this novel approach - please see Appendix 1.

2. Background

2.1 Existing research evidence

Oesophageal cancer was the 13th most common cancer in the UK in 2011, with 8332 people diagnosed that year. Two thirds are adenocarcinoma, one third squamous cell cancer, and about one quarter of cases are diagnosed whilst the disease is localised to the oesophagus. ref Surgery alone or in combination with chemotherapy or chemoradiation treatment is the mainstay of cure for localised oesophageal adenocarcinoma, but oesophageal squamous cell cancer may also be radically treated with definitive chemoradiotherapy or radiotherapy alone[3]. 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. There is a growing use of minimal access surgical techniques for all types of cancer. Whether these provide patient benefit in the short term and maintain long term survival is important to establish so that a high standard of surgical care can be provided. In some cancer sites there is good evidence that minimal access techniques are beneficial. For example minimal access surgery for colorectal cancer was evaluated in several large scale trials in the 1990s, providing evidence

of better recovery and equivalent survival. These trials led to changes in practice and surgical training.

Surgery for upper gastro intestinal cancer, however, is much more complex than colorectal cancer surgery and is associated with high mortality and morbidity. Minimal access surgery may make the procedure even more technically demanding potentially resulting in greater surgical risks. Whilst there is an increase in the UK and worldwide in the uptake of minimal access techniques for oesophageal cancer, there are also centres and surgeons who continue with standard open surgery. It is necessary to ensure that these approaches are effective and cost effective. If high quality evidence can be collected then a standard of surgery for patients can be established and health care policy made to support this approach.

2.1.1 Surgery for oesophageal cancer

Oesophagectomy is a major procedure involving surgery within two or three operative fields (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 50% of patients and 10% experience serious morbidity requiring re-operation or re-ventilation. Surgery is associated with 2-4% 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[4, 5]. Over time there is some recovery of HRQL, but persistent long term deficits occur[4]. 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[2].

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 involved open surgery with standard abdominal and right chest incisions. The remainder were left sided surgery (thoraco-abdominal, 13%), surgery involving incisions in the neck, abdomen and right chest (7.4%) or undertaken using a transhiatal approach (4.5%)[3]. Well-designed prospective comparative studies and randomised trials of these different 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 [6, 7]. 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 laparoscopically assisted approaches are increasing, although procedures performed totally using minimally invasive techniques were still uncommon (<15%). In the 2007-2009 [3] 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. The subsequent National Audit did not suggest any marked differences in complications or length of hospital stay following open surgery, laparoscopically assisted or minimally invasive methods. [8] However, it is likely that these results are subject to confounding by indication, where the patient's prognosis is a factor in determining the method of surgery undertaken. This can cause severe bias in estimates of the relative effectiveness of the surgical methods being compared in an observational study.

Hence a randomised trial is needed, and 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 surgery, using minimal access techniques for the abdomen or chest [9]. Three other systematic reviews were identified but none included a randomised trial [10-12]. 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 [13]. 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 [3]. One cohort study compared outcomes of open oesophagectomy (OO, n=114), 'a combined approach' (n=309) and 'totally minimally invasive surgery'(n=23) and found no differences in 3 or 5-year survival [14]. There was a lack of published data of cost effectiveness and only two studies measured HRQL[6, 10]. One used validated generic and disease specific tools for a year after minimal access surgery and showed an early recovery of most aspects of health, but the study was small and without a comparison group [15].

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 National Health Service (NHS) practice, health policy and individual surgeon and patient clinical decision-making. OO costs about £10K, 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

<u>The French 'MIRO' trial</u>

This is a trial involving patients with oesophageal cancer, excluding patients with types II and III tumours involving the gastro-oesophageal junction. It compared OO (abdomen and right chest) with LAO (minimal access for the abdomen and open right chest incision) (http://clinicaltrials.gov/show/NCT00937456) [16]. The primary end point was 30 day morbidity and the trial was powered to test the hypothesis that minimal access surgery leads to a reduced rate of complications (45% vs. 25%) at 30 days. Complications were measured as a composite outcome. MIRO completed recruitment of 207 patients in July 2015. There were 104 patients to the OO group and 103 to the LAO group. In an early (not peer-reviewed) report, sixty-seven (64.4%) patients in the OO group had major postoperative morbidity compared with 37 (35.9%) in the minimally invasive group (OR 0·31, 95% CI 0·18-0·55; p=0·0001). Thirty-one (30.1%) patients in the OO group had major pulmonary complications compared with 18 (17.7%) in LAO

group p=0·037), whereas 30-day mortality was 5 (4.9%) vs. 5 (4.9%), respectively. The authors concluded that the findings provide evidence for the short-term benefits of minimally invasive surgery for patients with resectable oesophageal cancer. [17] However, there were weaknesses in the study design: randomisation used sealed envelopes, outcome assessors were not blinded to the intervention type and methods to quality assure surgical procedures were not described in the protocol.

The Dutch 'TIME' trial

This trial included patients with oesophageal cancer, excluding patients with type II and III tumours involving the gastro-oesophageal junction [18]. It compared OO with totally minimally invasive oesophagectomy (MIO) (both abdomen and chest performed with minimal access approaches in the prone position). The trial was 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. The criteria for surgeon involvement in this trial were evidence of prior completion of 10 minimally invasive procedures and production of one video showing surgical competence. This trial recruited 115 patients from seven surgical centres in four countries (Netherlands, Spain, India and Italy).

The published results showed that totally MIO was associated with fewer pulmonary complications at two weeks post-surgery compared to the standard open procedure and provides evidence for efficacy of minimally invasive surgery. [19] In addition, MIO resulted in a better mid-term 1-year quality of life for the physical component summary of the SF-36 questionnaire, EORTC C30 global health domain and OES 18 pain domain compared to OO. There were no differences in survival and late complications at 1 year between the groups. [20] This trial therefore shows that minimal access surgery is safe in the short-term, but a large scale pragmatic trial designed to test patient benefit and cost-effectiveness is required to change UK practice. The trial included a comprehensive assessment of HRQL.

2.1.5 Benefits of the proposed ROMIO main trial

Although the above two trials have provided 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 (MIRO) 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 (TIME) 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 trial will be relevant to the UK, will test a clinically relevant hypothesis, include at least 7 surgical centres, undertake surgical quality assurance procedures and include patient reported outcomes. It will 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; and this is why this main trial was preceded by a feasibility study. The challenges that were identified prior to the feasibility study included patient factors such as a need to be

reassured of genuine equipoise between the different procedures, which we believe has been successfully addressed and demonstrated by the better than expected recruitment rates to the feasibility study. We have also addressed the need for a battery of outcome measures which are recognised as comprehensive, valid and reliable.

2.1.7 Feasibility study objectives

The core of this preliminary work was an assessment of the feasibility of comparing surgical procedures for oesophagectomy in a pilot two-centre randomised trial. Specific objectives were:

- To pilot the randomisation process and investigate reasons for any difficulties that affect recruitment so that these could 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 was to establish the feasibility of the main trial, by indicating the achievable sample size and the number of centres required.
- To document in detail, using Idea, Development, Evaluation, Audit and Long term follow up (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 was to 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 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

This work has been successfully completed [21] [22] and will be described in a forthcoming Health Technology Assessment (HTA) monograph.

3. Aims and objectives

3.1 Research aim of the main trial

To compare, in patients with cancer of the oesophagus and 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.

4. Plan of Investigation

4.1 Participants

4.1.1 Setting

At least seven centres will recruit patients and carry out procedures for this RCT. All centres have teams of upper gastro intestinal cancer surgeons and centres undertake at least 50 oesophago gastric resections of which 30 operations for oesophageal cancer per year.

Methodological support for the RCT, along with the development of quality assurance protocols for surgical procedures and pathology, will predominantly be based in Bristol. The Royal College of Surgeons Bristol Surgical Trials Centre, the Medical Research Centre (MRC) ConDuCT-II Hub for Trials Methodology Research, the Bristol Randomised Trial Collaborative (BRTC) and the Clinical Trials and Evaluation Unit Bristol (CTEU Bristol) are involved in supporting and delivering the ROMIO trial.

4.1.2 Participating surgeons

All participating centres will have surgeons able to undertake open and minimal access (laparoscopic abdominal mobilisation) surgery, and will work within a specialist multi-disciplinary team. Audit data for the last 5 years will be used to confirm that the units are regularly performing minimal access surgery. Surgeons participating in the trial will have completed at least 20 oesophagectomies either open or laparoscopic (20 of each if able to perform both operations). Only consultants, or trainees under direct supervision, will perform the procedures. A video assessment tool will be used to evaluate each surgeon's technical performance of oesophagectomy prior to entry into the trial (see 5.2).

4.1.3 Recruitment and informed consent

All patients being considered for surgery will be screened for trial eligibility using the multi-disciplinary team meetings as a source of data. Patients recommended for surgery (as a primary procedure or following completion of neoadjuvant treatment) will be registered into the screening log. Only patients with definitive cancer will be recruited to the study.

Where possible, information about the trial will be posted to patients in advance of their pre-operative clinic appointment. However, there may be a short amount of time between the multi-disciplinary team (MDT) meeting and clinic attendance so patients do not always receive the trial information before attending clinic. Where patients have not received information about the trial, the research nurse will give them the information leaflets and talk them through audio-recording participant information leaflet (PIL_Audio) when they arrive at the clinic. The patient will be given as much time as possible to consider whether they are happy to have the appointment audio-recorded and analysed, but the time available may be short. If the patient wishes to participate in the audio-recording part of the study, written consent will be taken from the patient before the clinic appointment using the appropriate participant consent form (PCF_Audio). Staff will also be asked to consent to this recording (Staff Consent Form audio SCF_audio). It will only be necessary to consent staff once to participate in the whole study.

If there is time, the research nurse may also discuss the main trial with the patient before their clinic appointment. The surgeon and the research nurse will discuss the trial in detail at the

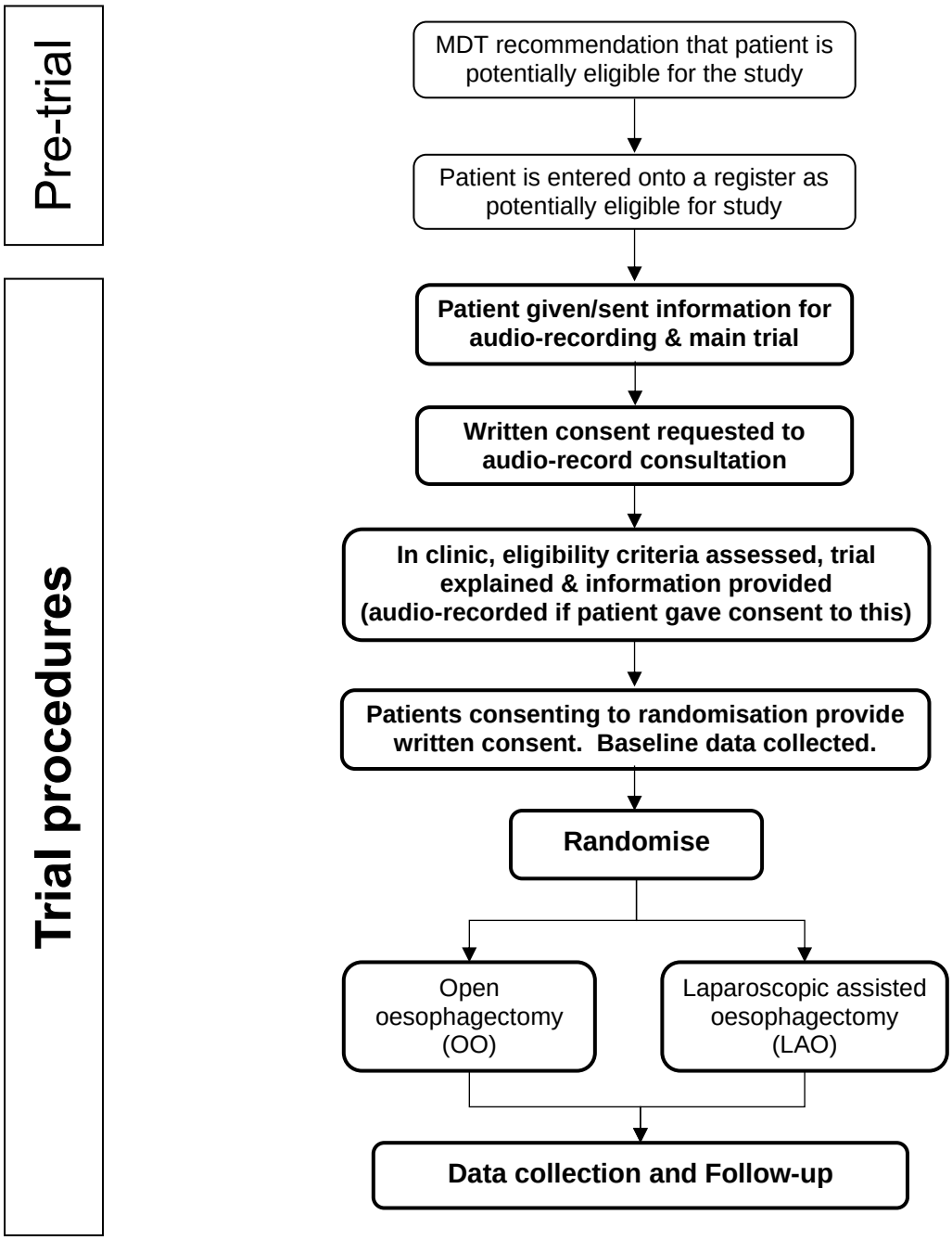
clinic appointment with the patient. The patient will be given the opportunity to ask questions and written informed consent will be taken if they are eligible and would like to participate. Where eligible patients did not receive the trial information before the clinic appointment and would like more time to consider participating in the trial, they will be given the option of posting the consent form and baseline questionnaire back to the centre. The research nurse will telephone the patient after the clinic appointment to check if the patient wishes to participate and, once consent is received, to obtain some baseline information from the patient. If they prefer they may visit the centre and have a face-to-face appointment with a member of the research team to give written consent before their surgery. Where attending hospital is preferred, the research team will arrange an appointment with the patient.

Occasionally patients require further tests as part of their standard care. In these cases it may be that the trial is discussed and written consent taken at a later hospital appointment.

Patients can consent to audio recordings without consenting to participating in the main trial. Patients can consent to the main trial without consenting to audio recordings.

Centres will randomise to a two group trial to compare OO with LAO (Figure 1). See appendix 1 for the description of a sub-study running at 2 centres.

Figure 1. Design flow diagram for participants in the ROMIO trial



4.2 Inclusion criteria

Participants may enter study if ALL of the following apply:

1. 18 years of age or above;
2. Referred for primary oesophagectomy by the MDT or oesophagectomy following re-staging after neoadjuvant chemotherapy or neoadjuvant chemoradiotherapy (N.B, in this any type of neoadjuvant treatment may be used);
3. Confirmed MDT evidence of at least adenocarcinoma or at least squamous cell cancer of the oesophagus or oesophago-gastric junction;
4. Fit for pre-operative anaesthesia and surgery, assessed by the MDT;
5. Able to provide written informed consent;
6. Measurement (endoscopic or otherwise) that the tumour starts more than 5cm below crico-pharyngeus;
7. Measurement (endoscopic or otherwise) that the tumour involves less than 4 cm of the gastric wall;
8. The final pre-treatment tumour stage is between T1N0M0 and T4aN1M0, i.e. including all stages (T1N0M0, T1N1M0, T1N2M0, T2N0M0, T2N1M0, T2N2M0, T3N0M0, T3N1M0, T3N2M0, T4aN0M0 and T4aN1M0) in which T4a is a resectable tumour invading pleura, pericardium, or diaphragm.

4.2.1 Exclusion criteria

Participants may not enter study if ANY of the following apply

1. Patients with high grade dysplasia (squamous cell or adenocarcinoma);
2. Patients with T4b, or any stage with M1;
3. Type 3 tumours of the oesophago-gastric junction that are scheduled for total gastrectomy;
4. Patients with squamous cell cancer of the oesophagus who the MDT recommends or who individually elect to undergo definitive chemoradiotherapy;
5. Evidence of previous complex thoracotomies or laparotomies that preclude a minimal access approach;
6. Evidence of previous/concomitant malignancy that would interfere with this treatment protocol;
7. Pregnancy;
8. Patients participating in other trials that would interfere with the implementation of this protocol at a particular site.

4.3 Trial interventions

During the feasibility study, the key components of oesophagectomy to be standardised were established. The surgery is deliberately allowed to be flexible within the boundaries of the mandated components because of the pragmatic nature of the study. The mandatory steps will be monitored in the trial using data collection forms and digital photography in each site (see

5.3). Where surgeons do not undertake mandated components of the surgery and when they perform prohibited ones it will form non- protocol compliance. We will regularly review all non-compliance to the protocol by sites and individual surgeons. Confidential and team meetings will be organised to provide feedback. All such protocol non-compliance will be reviewed by the Trial Steering Committee (TSC) and Data Monitoring and Safety Committee (DMSC).

4.3.1 All types of oesophagectomy

The operation consists of a two-field lymphadenectomy (abdomen and thorax). It is expected that operations will be 2-phase (abdomen and chest) although 3 phase procedures (abdomen, chest, neck) are also permitted in both intervention groups.

Abdominal phase: Complete gastric mobilisation will be performed based on the right gastroepiploic and right gastric arteries. Drainage procedures (e.g. pyloroplasty, pyloromyotomy, botox injection) can be performed at the surgeon's discretion. Lymphadenectomies along the common hepatic, left gastric, splenic and coeliac arteries, either en bloc or separately will be performed. Removal of crural fibres, with or without a cuff of diaphragm, should be performed if required for tumour clearance. The hiatal dissection should remove the pericardial fat pad and incise the right pleura and (where indicated) left pleura to allow en bloc resection of the distal thoracic oesophagus from the chest phase. Transection of the lesser curve may be undertaken during this phase of the operation or left until the thoracic phase. Placement of a feeding jejunostomy or naso-jejunal tube is at the surgeon's discretion, as is the use of intra-abdominal and intra-thoracic drains. Procedures to minimise diaphragmatic herniation (e.g. omentopexy, narrowing of the hiatus) can be performed at each surgeon's discretion.

Chest phase: The chest is opened through a right thoracotomy and the mediastinal pleura overlying the oesophagus will be 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 will be tied on the aorta low in the chest cavity. The oesophagus will be mobilised to the level of at least the aortic arch. Paraoesophageal nodes should be 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 is at the surgeon's discretion.

4.3.2 Open oesophagectomy (OO)

The following approaches are permitted: 2-phase (right thoracotomy, laparotomy), 3-phase (right thoracotomy, laparotomy, cervical incision). Transhiatal and left thoracoabdominal approaches are not permitted. The location and length of incisions are at each surgeon's discretion. Methods to close the incisions are also at the surgeon's discretion.

4.3.3 "Laparoscopically assisted" oesophagectomy (LAO)

Access to the abdominal cavity will be achieved with 5mm and/or 12mm incisions (as many as needed, according to surgeon preference) and surgery performed laparoscopically. Laparoscopic transhiatal approaches are prohibited. Methods to create the pneumoperitoneum are at the surgeon's discretion. If a feeding jejunostomy is placed, this may be performed

laparoscopically or by creating an additional abdominal incision (maximum length of 8cm). The thoracic part of the operation will be performed as described above (4.3.1 and 4.3.2). Methods to close the incisions are at the surgeon's discretion.

4.3.4 Concomitant interventions

Concomitant interventions (co-interventions) are defined as those that naturally accompany the surgical intervention itself, and can be divided into pre-operative, peri-operative and post-operative components. Details of co-interventions are important in fulfilling the Consolidated Standards of Reporting Trials (CONSORT) criteria for reporting evaluations of complex interventions. Co-interventions associated with oesophagectomy will be considered as part of the process evaluation during the main trial and are likely to include the anaesthetic and other peri-operative procedures, immediate post-operative care (including intensive care management), patient rehabilitation, and input from allied health professionals such as physiotherapy and dietetics (which may or may not be encompassed into a formal enhanced recovery programme). The process evaluation will be used to develop a co-intervention manual which will define standard protocols for peri-operative care and acceptable and prohibited (unacceptable) protocol deviations, to minimise the risk of performance bias.

All surgical interventions will be carried out under general anaesthesia. Patients will receive antibiotic and deep vein thrombosis prophylaxis according to local hospital policies.

4.3.5 Cross overs

In this study we will consider that a patient has 'crossed over' if they do not receive their allocated treatment and they receive one of the other treatment allocations in the trial. We will monitor rates of cross over for all centres and groups. We will record reasons for cross over as follows, i) before surgery due to a) patient preference, b) surgeon preference, or ii) during surgery due to a) technical reason due to adverse event, b) technical reason due to the tumour. We will also request expanded text of these details in the case report forms (CRFs).

4.3.6 Not proceeding to surgery after randomisation

In this study we will record the rates of 'not proceeding to surgery' in each group following randomisation. We will record the reasons for this as follows i) before surgery due to, a) new evidence of disease progression, b) new co-morbidities, c) patient preferences, d) surgeon preferences, and, ii) during surgery due to a) metastatic disease in the abdomen, b) locally advanced disease in the abdomen, c) metastatic disease in the chest, d) locally advanced disease in the chest, e) unexpected co-morbidities precluding resection. We will also request expanded text of these details in the CRFs.

4.3.7 Re-operation

In this study we will record all operations that occur in randomised patients within 2 years. These will be classified as follows, i) re-operation performed within the initial hospital admission when oesophagectomy was performed (in-hospital reoperation), ii) re-operation within 3 months i.e. before the primary end point of the trial), iii) re-operation between 3 and 24 months. We will record the type of operations undertaken and classify these as a) related to the oesophagectomy, b) unrelated.

4.4 Primary and secondary outcomes

4.4.1 Primary outcome

The primary outcome will be the mean of the three assessments of physical function (a subscale of the EORTC QLQ-C30) assessed at three and six weeks post-surgery and three months after randomisation.

4.4.2 Secondary outcome measures

Secondary outcomes will assess the efficacy of the two approaches (morbidity and safety) and establish oncological markers of quality assurance of surgery which are surrogate markers of long term survival (detailed histopathology and quality assurance of the radicality of surgery). Secondary outcomes will include:

1. All cause short and long term complications
2. Impact of the post-operative complications will be categorised using the Clavien-Dindo System at discharge[7].
3. Spirometry measures of forced expiratory volume 1 and forced vital capacity
4. Success of blinding during the first six days post-surgery, using the Bang Blinding Index [23] procedure
5. Generic and disease specific HRQL measures EORTC QLQ-C30 [13, 24] and QLQ-OES18 [14, 25], multidimensional fatigue inventory (MFI-20) [15, 26], EuroQOLEQ-5D-5L [27, 28]
6. Quality assurance of surgery with histopathological and surgical measures
    a. Histopathological measures (with the pathologist assessing these blind to treatment allocation)
        i. length of the oesophagus
        ii. total count of malignant ‘positive’ nodes
        iii. total count of all nodes
        iv. rates of positive circumferential resection margins
        v. rates of positive proximal and distal resection margins
        vi. pT stage (proportions of patients with each pT stage)
    b. Surgical measures assessed by a surgeon blind to patient allocation
        i. quality of abdominal lymphadenectomy
        ii. quality of mediastinal lymphadenectomy
7. Overall and disease-free survival to 2-years
8. Length of hospital stay, defined as length of primary hospital stage plus readmission within 30 days (and length of primary hospital stay plus length of hospital stay if discharged to community hospital).
9. Further measures of resource use including: staff time and resources used in theatre in the interventions; subsequent inpatient stays, outpatient visits, general practitioner visits and other community based resource use.

These include the items recently identified in the core outcome set developed during the feasibility work.

4.5 Sample size calculation & statistical analysis

4.5.1 Sample size

The theoretical advantage of LAO compared to OO for patients is improved short term recovery with the long term survival benefit of surgery maintained. Consequently the primary endpoint for the proposed definitive ROMIO trial is the mean patient reported physical function (the QLQ C30 Physical Function sub-scale) at 3 and 6 weeks post-surgery and 3 months post-randomisation, with patients being followed-up for at least 24 months in order gain estimates of survival. For simplicity, and to indicate the minimum statistical power that will be achieved for the comparison of recovery, we consider just the 6 week assessment of physical function. The planned analysis, based on the mean of 3, 6 week and 3 month assessments of patient-reported physical function (primary outcome), and the baseline assessment as a covariate, is likely to have greater power than indicated here. We are assuming that having adjusted analyses for centre, there will no further need to accommodate clustering of outcomes by surgeon. In fact, as a team of surgeons is involved in each case (in decision-making and in-hospital care, and often in theatre), it would be difficult to do this in practice. A recent review of patient reported outcomes has indicated that the minimum clinically important difference on the QLQ-C30 Physical Function Scale is 0.4 standard deviations [24, 29]. Allowing for 5% of patients allocated to LAO actually undergoing OO and 10% of patients in each group being found during surgery to have more extensive disease, can be achieved by reducing the effect size to be detected to 0.34 standard deviations. In this situation 182 patients in each group (364 patients in total) will allow a true treatment effect (LAO versus OO) of 0.4 standard deviations to be detected with 90% power at the 5% significance level, when up to 15% of patients are not able to follow their allocated procedure. Further allowing for up to 10% missing primary outcome data, e.g. due to the patient being too sick, increases the target sample size to 364/0.9 = 406 patients in total. Hence our sample size target for the definitive ROMIO trial is 203 patients allocated to LAO and 203 patients allocated to OO. This sample size will also give adequate statistical power to detect a clinically important reduction in post-surgical length of stay. The mean length of stay in the pilot trial (all groups combined) is 13 days with standard deviation 8 days. Allowing for the skewed distribution [25, 30], 182 patients per group will allow a ratio of means of 0.84 to be detected with 80% power at the 5% significance level. This ratio of means corresponds to a 2.25 days reduction, from 14 to 11.75 days. Meta-analysis with data from the feasibility study will allow us to detect smaller differences in the average length of stay. Our experience with the pilot trial indicates that it is reasonable to expect an average of 22 patients recruited per centre per year. Seven centres recruiting for 2.5 years will enrol 2.5 X 7 X 22 = 385 patients. The two established centres will continue recruiting in to the definitive trial period, and hence will also recruit during the six months preceding the main recruitment phase = 0.5 X 2 X 22 = 22, hence meeting the sample size target of 406 patients in total.

203 patients in each of the LAO and OO groups will allow a minimum clinically important difference of 0.4 standard deviations on the primary outcome to be detected with more than 90% power at the 5% significance level, allowing for 15% of patients not following their allocated procedure, & 10% failure to complete the primary outcome.

We agreed with the NIHR on the 24th January 2019 to extend recruitment up to the end September 2019 to allow a minimum of 300 patients to be recruited to the main study. The remaining (approx. 120) patients will come from the feasibility study cohort. This is treating the

feasibility study as an internal pilot, this being possible as it had the same design as the main trial, and it continued to recruit whilst preparations were made for the main trial.

4.5.2 Statistical methods

The data will be analysed according to the intention to treat (ITT) principle and reported according to the CONSORT guidelines. Randomised patients will be included in the analysis if possible, in their randomly allocated intervention arm. Patients missing all three assessments contributing to the primary outcome measure will not be included in the primary analysis, but the potential impact of this missing data on the study conclusions will be investigated in sensitivity analyses. Where a patient has completed one or two assessments contributing to the primary outcome measure, the missing assessments will be imputed according to reasonable assumptions about the missing values. Analyses will be adjusted for treatment centre and for the design factor included in the minimisation, i.e. whether or not the patient underwent neoadjuvant chemo(radio)therapy. A detailed analysis plan will be prepared prior to locking the database.

The relative effectiveness of the two approaches will be quantified as a difference in mean response on the physical function scale of the QLQ-C30 (LAO mean – OO mean), using patients' available measures from the three-week and six-week post-surgery, and the three-month post-randomisation assessments. The difference in mean response will be presented with its 95% confidence interval, and p-value. The relative effectiveness will be estimated in a mixed effects linear regression model with patient response at three-week and six-week post-surgery, and three-month post-randomisation as the outcome variables (i.e. between one and three outcome measurements per patient). A normally distributed random effect will accommodate the correlation between each patient's responses. A normal distribution is assumed for the residual errors. The coefficient for the treatment allocation covariate is the intention to treat estimate of treatment effectiveness, comparing LAO to OO. The estimates from the feasibility and full trial patients will both be presented, with a third pooled estimate computed as a mean of the feasibility and full trial estimates, weighted by the inverse of the variance of the estimate (equivalent to a fixed-effects meta-analysis).

Using the full analysis set, the primary analysis plan will be adapted to the analysis of each of the other scales from patient reported outcomes. In addition, the approach will be adapted to a comparison of post-surgical length of stay, the skewed distribution of this measure being accommodated by presenting ratios of geometric means, 95% confidence interval and p-value. Frequencies of all-cause complications will be presented by study group. For each patient the most severe impact of 30-day complications will be categorised using the Clavien-Dindo system, patients in the LAO and OO groups being compared using ordered logistic regression. We will use proportional hazards regression to estimate the treatment difference in overall and disease-free survival. A Kaplan-Meier plot will present survival over time in the OO and LAO groups.

The primary outcome requires that the average time from randomisation to surgery is the same for the intervention arms being compared. We will monitor this in each centre as the study is ongoing, and take corrective action if differences between trial arms occur. In addition, we will conduct a sensitivity analysis, additionally adjusted for each patient's time from randomisation to surgery.

4.5.3 Subgroup analyses

A sub-group analysis will investigate whether the relative effects of OO and LAO differ according to whether a patient underwent neoadjuvant chemotherapy beforehand.

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.

Participating patients will complete baseline measurements prior to random allocation. On the day 3 and 6 post-surgery patients will complete assessments of pain and blinding. At randomisation and at each study assessment time point (6 days, 3 weeks and 6 weeks post-surgery and 3 months, 6 months, 9 months, 12 months, 18 months, 24 months and 36 months* after randomisation), participants will be assessed by the doctor for current health status (performance status World Health Organisation 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 will be measured before randomisation in the hospital to allow calculation of body mass index. 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[1].

*NB 36 month follow-up will only be completed if it falls within the planned length of the study.

Patients recruited to the feasibility study who have not completed the follow-up period when the feasibility study closes will be followed up as part of the main trial. Patients from the feasibility study will not be re-consented for being followed up under the main study (the follow-up questionnaires and timepoints are the same and the study is still being managed by the University of Bristol).

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 1**. 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 stamped addressed envelope which will be provided. Follow up questionnaires will be posted by sites. If questionnaires are not returned within 2 weeks, follow up calls 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). To ensure that time points are followed the database will issue reminders for upcoming and overdue follow time-points until follow-up data has been collected or a reason given why follow-up data will not be completed.

4.6.3 Study within a trial evaluating retention

We will conduct a study within a trial (SWAT) to evaluate the impact of including a “withdrawal slip” that patients can complete to indicate that they wish to miss a timepoint or withdraw from further follow-up. The withdrawal slip will emphasise the importance of the questionnaire data to the research as patient feedback has indicated that patients do not always realise the value of their responses to questionnaires. The withdrawal slip has been developed in response to, and in discussion with, the ROMIO PPI group.

[1] Where day 3 or 6 falls on a Saturday/Sunday, the measurement should be taken on the closest week day (e.g. day 3 falls on a Saturday, the lung function should be assessed on the Friday).

SWAT population
All patients randomised to the ROMIO study will be randomised in the SWAT. Patients will not be consented separately to be randomised in the SWAT as there is no additional burden or risk to the patient by including them in the SWAT. Patients will be randomised by the study statistician and randomisation will be stratified by centre and surgical approach (OO, LAO or TMIO).

SWAT intervention
Both groups will continue to receive the reminder calls as per the study protocol. Where follow-up reminder calls are made and a second "reminder" copy of the postal questionnaire is sent, patients will be randomised to either:

- receive withdrawal slips with any "reminder" postal questionnaire(s) sent, or
- only receive the "reminder" postal questionnaire(s).

If the patient is randomised to receive the withdrawal slip with the "reminder" postal questionnaire, this will apply to any timepoint that a second "reminder" postal questionnaire is sent.

SWAT sample size
There is no formal sample size calculation for this SWAT as numbers are limited to the number of patients participating in the ROMIO study. SWATs often do not have sample size calculations as they are intended to be analysed through meta-analysis[31]. This SWAT will be submitted to the SWAT repository held by the Northern Ireland Network to enable other studies to adopt it.

SWAT outcomes
The primary outcome of the SWAT will be the number of questionnaires that are returned in each group. Secondary outcomes will be the number of participants who missed one or more timepoints and the number of participants withdrawing from the study.

The continuation of the SWAT will be reviewed every 6 months by the SEG.

Table 1. Patient data collection at the pre-surgery and the post-surgery/post-randomisation assessment points

	Pre-surgery**	**3 days****	**6 days****	**3 weeks****	**6 weeks****	**3 months**	**6 months**	**9 months**	**12 months**	**18 months**	**24 months**	**36 months#**
Socio-demographic details	X											
Height	X											
Weight	X					X	X					
Routine clinical measures	X	X	X	X	X	X	X					
Resource use schedule			X		X	X	X	X	X	X	X	
MFI-20	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									
Lung function tests	X	X	X									
In-depth interviews*	X				X	X	X					
Bang Blinding Index		X	X									
Chemotherapy	X			X	X	X	X	X	X			

*undertaken in a purposeful sample of participants # NB 36 month follow-up will only be completed if it falls within the planned length of the study.

**measured relative to date of surgery, all other time-points are measured from the day of randomisation

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: before the day of surgery

Post-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

3 weeks: completed no earlier than day 10 and no later than day 34

6 weeks: completed no earlier than day 35 and no later than day 66

Post-randomisation:

3 months: completed no earlier than day 67 and no later than day 111

6 months: completed no earlier than 5 months and no later than 7 months

9 months: completed no earlier than 8 months and no later than 10 months

12 months: completed no earlier than 11 months and no later than 14 months

18 months: completed no earlier than15 months and no later than 20 months

24 months: completed no earlier than 21 months and no later than 30 months.

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 10 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 group

Allocation of patients to surgical procedure to the two or three groups will be random, will be conducted separately for each centre, and further stratified by whether the patient has undergone neoadjuvant treatment or not. Randomisation within blocks of varying size will prevent large imbalances in the number of patients in each treatment group, whilst maintaining allocation concealment.

5.1.2 Timing of randomisation

Randomisation will be carried out after trial eligibility has been confirmed and consent given. Every effort should be made for surgery to be carried out within (or as close as possible to) two weeks of randomisation. Adherence to this will be monitored. Patients will be informed about their randomisation group on or after day six post-surgery following the assessments.

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

A video assessment tool will be used to evaluate technical performance of oesophagectomy prior to a surgeon's entry into the trial. Patients will be asked to give written informed consent to recording of the procedure and transfer of the data to Bristol (either using local consent forms, as appropriate, or PIL_video and PCF_video). Surgeons intending to carry out LAO in ROMIO will submit two anonymised unedited videos of the laparoscopic approach. Surgeons intending to carry out MIO in ROMIO will submit two anonymised unedited videos of the thoracoscopic approach in addition to the laparoscopic approach (the laparoscopic and thoracoscopic approaches may be in the same operation). The surgical methods will be analysed by the research team. The methods for this were developed during the feasibility phase [22, 32]. Digital video recordings of the operations will be performed using standard techniques [32]. 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. Recordings will be transferred by secure means to the NHS network in UHBristol for analysis by the ROMIO study team. The video recordings will be pseudonymised with a unique identifier. For long-term storage, the anonymised videos will be transferred to the University server. It will not be possible to identify the patient from the data stored on the University server.

5.3 Adherence to the surgical protocol

We intend to use a photographic evaluation tool to assess adherence to the mandatory core steps of each procedure. Procedural steps will also be documented in the case report forms. Individual meetings between Barham, Blazeby and the local PIs will review the local surgical practice and provide feedback as required.

The following photographs should be taken during each trial operation, to demonstrate the lymphadenectomy, hiatal dissection and nature of incisions used:

- Coeliac trunk, stumps of left gastric artery and vein, hiatal dissection
- Carina, bronchi, right and left pulmonary veins, completed conduit vascularity
- Abdominal and chest incisions (to be taken at the end of the procedure)

5.4 Process evaluation

The process evaluation will establish the key co-interventions associated with oesophagectomy, and will comprise the following parts:

1. Care pathways, patient information leaflets and other documents will be obtained from all participating centres, to comprehensively identify co-interventions and elicit potential differences in the ways that they are delivered.

2. Non-participant observation: Non-participant observation of a purposively selected sample (n=10-20) of operations will be performed by one or two researchers. Observations will focus on the co-interventions occurring before, during and after the operation, whilst patients are in hospital. Observation data will supplement the written information provided by each centre, and identify whether there were differences between how co-interventions were expected to be delivered, and actually delivered.

3. Interviews with surgeons, anaesthetists and other health professionals: A purposefully selected sample of surgeons and other team members (n=20-30) will be interviewed during the peri-operative period (either before or just after the operations) 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:

a) What they think are the most important elements of the co-interventions that influence outcomes

b) Views of the impact of variations in the ways that co-interventions are delivered

c) Hospital, team or equipment factors that influence the delivery of oesophagectomy (and co-interventions) and in what ways this may differ if they are training others to do the procedure

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

Interview 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.

5.5 Processing of the pathological specimens:

All trial pathology specimens will be prepared and macroscopically and microscopically assessed in a uniform manner as per the current Royal College of Pathologists Dataset for Oesophageal Carcinomas. The pathology data for the trial will be collected using a standardised form and represent data points included within the Royal College of Pathologists Dataset. Data points that will serve as surgical quality assurance (QA) indicators include the length of the oesophagus and the number of harvested lymph nodes. Data points that will serve as surrogate markers for patient survival include pT stage, pN stage and pR stage. For pathology QA purposes, the slides of 10% of all cases from each centre will be reviewed by the Lead Pathologist. Pathologists will be blinded to the randomised allocation for each sample.

5.6 Blinding study participants

In this trial it will not be possible to blind surgeons, but we have shown in the feasibility study that it is possible to blind patients, and those assessing outcomes, to the type of surgery, at least during the initial post-surgery period.

In first week post-surgery patients will be blinded using large adhesive dressings. 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). It will then be changed according to local practice. If dressings are changed the 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. On days three and six patients will be asked to complete the Bang Blinding Index which assesses the success of blinding by asking them to guess which group of the trial they were allocated to [23]. Dressings will then be removed as per local practice.

5.7 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 [33-36], ROMIO will include an integrated qualitative study which has two key parts:

5.7.1 Phase 1: Understanding and improving 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

Consent will be sought to audio-record in-depth, semi-structured interviews with a sample of members of the ROMIO Trial Management Group (TMG), PIs and active recruiters. Participants will be asked to provide written informed consent using PCF_audio.

An interview topic guide 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. Interviews will be conducted either face-to-face, or on the telephone, according to the preference of the respondent. Additionally, respondents who are active recruiters will be asked whether they are willing to audio-record their appointments with patients, with a view to discussing any discomfort or perceived difficulty with doing so.

(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 PILaudio, 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 (PCF_audio for patients and SCF_audio for staff). At the end of the appointment, the audio recording will be anonymised and sent to the School of Social and Community Medicine via the secure study portal. The qualitative researcher will listen to appointments, document relevant details and provide an account for the qualitative research lead. 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. These interviews will be guided by an interview Topic Guide. Interviewees will include those who have agreed to randomisation, and those who have rejected it but are willing to discuss their views (providing consent to audio-recording on PCF_audio).

5.7.2 Analyses of qualitative data

In-depth interviews and recruitment appointments will be audio-recorded. The in-depth 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 [34]. When analysing the in-depth interview data, 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 where communication appears problematic [34]. Audio recordings will be transcribed as required, and then any recommendations 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 group 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.

5.7.3 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 during the early stages of the trial 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 information, discussions about equipoise or evidence, issues with patient pathways, and logistical issues in particular centres. These may be addressed by a new or amended PIL, 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.

5.8 Economic evaluation

The in-theatre costs for LAO and the totally minimally invasive surgery are likely to be higher than those for open surgery in the treatment of oesophageal cancer but, if quicker recovery results, post-surgical costs may be reduced, and a better clinical outcome secured. Therefore, the balance of costs and benefits between surgical approaches will be established using techniques piloted in the feasibility study. Previous research [37, 38] and the findings of the feasibility study indicate that NHS and personal social services (PSS) costs are likely to be the main cost drivers and principal source of difference between the two groups in this trial. The economic evaluation will therefore adopt these perspectives. We will analyse the data at 3 and 24 months post randomisation. These timepoints have been selected to determine the short- and long-term cost-effectiveness of LAO compared with open surgery in the treatment of oesophageal cancer.

NHS costs include those associated with (i) the index operation (anaesthesia, surgery and recovery), (ii) the initial and subsequent intensive care stays, (iii) the post-operative ward in-patient stay, (iv) any complications or reinterventions, including reoperation, and (v) the period after discharge until completion of follow-up. PSS costs will relate to social care during the follow up period. A published model[39] of the economic costs of open versus minimally invasive oesophagectomy (MIO) showed that ICU stay and total length of stay are the primary cost drivers for the difference in cost-effectiveness between the two oesophagectomy techniques.

Theatre costs for the index operation will be estimated using a micro-costing approach. Staff time will be estimated from reported theatre time; including anaesthetic time, duration of the procedure, and time spent in recovery. Additionally, we will observe and collect data on theatre staffing requirements and equipment for both open and laparoscopic operations in at least one

centre. We will elicit heterogeneity across centres from a surgical resource survey of principal investigators. This should allow us to estimate a typical unit cost per centre for each type of operation. The cost of reinterventions, including reoperation under general anaesthetic will be estimated using the unit costs for staff time & theatre resources derived during the micro-costing exercise.

Intensive care length of stay and level of organ support will be collected in the case report forms. We may access Intensive Care National Audit Research Centre (ICNARC) and Information Services Division (ISD) Scotland data for individual patient level data on ICU resource use. In-hospital resource use during the post-operative stay will be driven by length of stay, which in turn is likely to be driven by the occurrence of complications. National reference cost excess bed day (unit) costs will be applied to each non-ICU day prior to hospital discharge.

Resource use following initial discharge will include readmissions, outpatient care, primary & community care, additional treatments for progression or recurrence of disease, and use of social services. Information on the use of these health services will be collected using a procedure refined in the feasibility study: patients will be asked to keep a diary of contact with health and social services, which they will refer to in reporting the use of these services to the hospital research nurse over the telephone. These data will be costed using nationally published sources [40] [41] [42]. Collection of detailed NHS resource use will continue until 6 months. Thereafter, for the long term follow up at 24 months, will focus on secondary care - principally hospital admissions. We may access ISD and National Cancer Registry Analysis Services (NCRAS) to obtain patient-level information on chemotherapy and radiotherapy treatment – specifically information from the Systemic Anti-Cancer Therapy (SACT) dataset and the Radiotherapy Dataset (RTDS). We may also link this data with information about hospital attendances and admissions data from the ISD, Hospital Episode Statistics (HES) dataset, including but not limited to length of stay data and Health Resource Group (HRG) codes, and mortality data from the Office of National Statistics (ONS).

The main outcome measure for the economic evaluation will be quality adjusted life years (QALYs) estimated using the EuroQol EQ-5D-5L [27, 43] which will be administered at baseline and then at 6 days post-surgery, and subsequent assessment points via post or online (see table 1 pg. 22). We will estimate the mean cost and QALY per patient in each group and the differences between the study groups will be used to estimate the net monetary benefit and, if applicable, an incremental cost per QALY gain and a cost-effectiveness acceptability curve. Uncertainty will be addressed in sensitivity analyses and bootstrapping will be used, as necessary, to refine the estimated standard errors. Longer term costs and benefits will be discounted in line with recommendations prevailing at the time [44].

5.9 Definition of the end of the study

The end of the study is defined as the point where all pathology slides have been returned to the originating hospital, all queries have been resolved in the study database, the database has been locked, the data analysis has been completed and the main study paper has been accepted for publication.

5.10 Data procedures

5.10.1 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. 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 each 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) Data relating to the participant's surgery and hospital stay will be documented in the CRFs.

(g) Photographs as described in section 5.3.

(h) Audio-recording of consultations and interviews as outlined in section 5.7.

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

5.10.2 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.

Photographs will be collected of the surgical procedure with explicit patient consent. Consent will also be collected to use anonymised photographs of the surgical procedure to report and present on quality assurance of the study (both for dissemination and training purposes).

We plan to access national datasets for research secondary usage such as the NCRAS, HES, ONS data and ISD Scotland. NCRAS routinely collects information on all cancer patients in England and is controlled by Public Health England (PHE). We plan to access information collected about chemotherapy and radiotherapy treatments received by patients to treat recurrence or progression of disease after surgery, through the SACT dataset, Scottish Cancer Registry and the RTDS. We may also access mortality data held by the ONS and HES data held by NHS Digital and by ISD. HES and ISD will allow us to obtain details of admissions including length of stay and HRG code data, outpatient and A&E attendances during the trial follow up. Both HES and ONS data may be accessed alongside the SACT and RTDS data through the PHE Office for Data Release (ODR). To retrieve this information, patient identifiers (e.g. NHS or CHI number, postcode and date of birth) will be shared with the appropriate data controller with explicit patient consent.

In addition, for patients who have consented to the study, we may access individual patient data collected and held by the ICNARC. By accessing this dataset we will be able to obtain data about how much critical care was required for patients post-operatively. We will also be able to

capture details of their critical care episodes (e.g. the reason for admission to critical care, length of stay, the types and duration of critical care treatment received and any readmissions to critical care). Through accessing the ICNARC dataset we will also obtain standardised scoring information (e.g. Sepsis-related Organ Failure Assessment (SOFA) scores and Acute Physiology And Chronic Health Evaluation (APACHE)II scores), which will help us to determine whether there was any difference in post-operative recovery between the two groups. We also intend to collect equivalent data for Scottish patients from ISD. These data will be linked to data from the other sources described above.

5.11 Discontinuation / withdrawal of participants and payment of expenses

5.11.1 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 group 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 not be used.

5.11.2 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%.

5.11.3 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- 6 weeks for the duration of the study. The TMG will be chaired by the CI and will include all members of the named research team (see *Chief Investigators & Research Team Contact Details above)*.

The TMG will be supported by CTEU Bristol and the BRTC, both are UK Clinical Research Collaboration registered Clinical Trials Units. CTEU Bristol will prepare all the trial documentation and data collection forms, develop and maintain the study database include functionality for randomisation, monitor recruitment and manage the trial on a day to day basis. The BRTC will specify the randomisation scheme, check data quality as the trial progresses, 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 CTEU Bristol. 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 (CTEU Bristol) will carry out central monitoring and audit of compliance of centres with The International Conference for Harmonisation of Good Clinical Practice (ICH-GCP) and data collection procedures. As monitoring will be carried out centrally CTEU Bristol will not normally check CRFs against the data entered and source data, unless there are good reasons to visit the site to complete a monitoring visit.

6.4 Trial Steering Committee and Data Monitoring and Safety Committee

The TSC is made up of representatives of ROMIO TMG, and independent members to be appointed by the funders.

The DMSC consists of medical statisticians and medical experts in this field.

6.5 Patient and public involvement

The patient and public involvement group will meet regularly to review / provide feedback on aspects of the study (e.g. participant documents, increasing retention).

7. Safety reporting

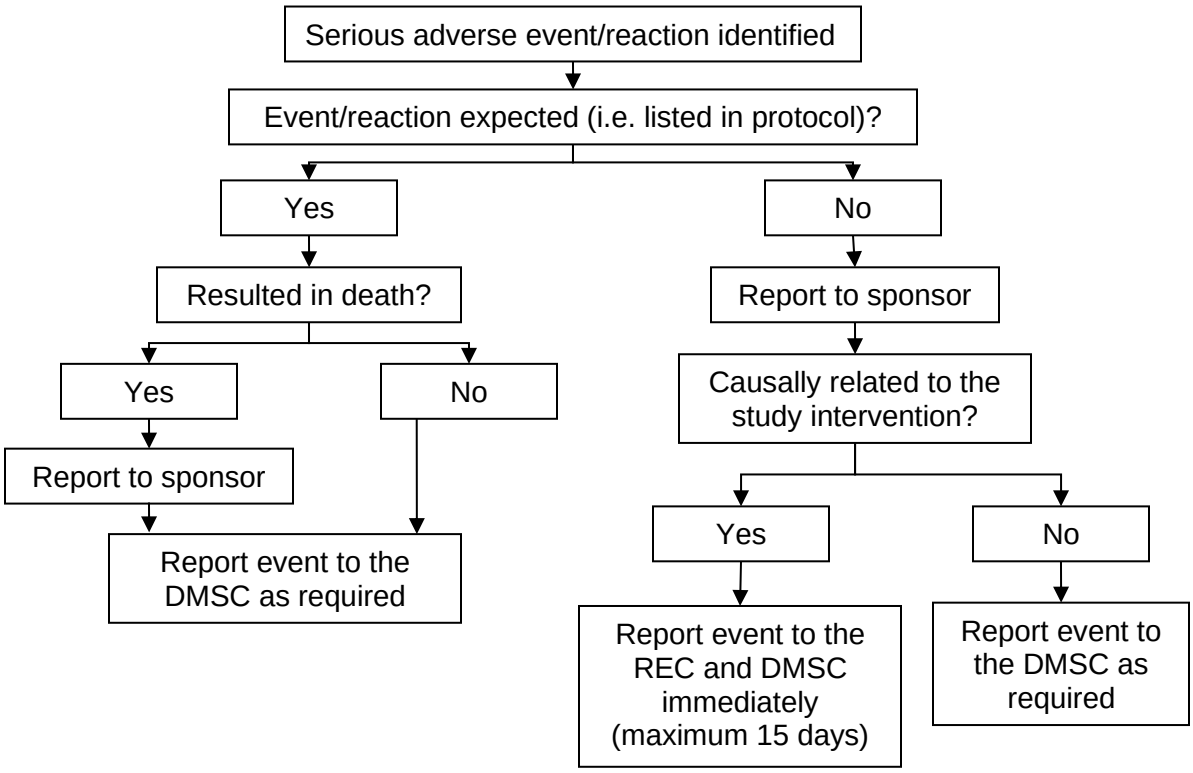
Adverse events will be recorded in accordance with University Hospitals Bristol's Safety Reporting Standard Operating Procedure (SOP) and the following protocol (see Figure 2).

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 CRF. 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 unexpected serious adverse events, the subject will be actively followed up, and the investigator (or delegated person) will provide follow-up every five working days after the initial report 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 a serious 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

Bleeding requiring removal of spleen

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

Intra-operative damage to organs or structures in chest, abdomen or neck, including requirement for removal or repair of structure/organ(s) (e.g. splenectomy).

7.1.2 General complications post operatively

We have used the following complications, which were agreed through an international consensus [45] convened to standardise data collection for complications associated with oesophagectomy.

i) Pulmonary:

pneumonia[2]

pleural effusion requiring additional drainage procedure

pneumothorax requiring treatment

atelectasis mucous plugging requiring bronchoscopy

respiratory failure requiring re-intubation

acute respiratory distress syndrome (ARDS)[3]

acute aspiration

tracheobronchial injury

chest tube maintenance for air leak for >10 d postoperatively

ii) Cardiac:

cardiac arrest requiring cardiopulmonary resuscitation

myocardial infarction (confirmed by intensivists / cardiology team)

disrhythmia atrial requiring treatment

disrhythmia ventricular requiring treatment

congestive heart failure requiring treatment

pericarditis requiring treatment

[2] **Pneumonia** defined as: New lung infiltrates plus clinical evidence that the infiltrate is of an infectious origin, which includes the new onset of fever, purulent sputum, leukocytosis or a decline in oxygenation.

[3] **ARDS** defined (using the Berlin Definition) as
Timing: Within 1 week of a known clinical insult or new or worsening respiratory symptoms.
Chest imaging: Bilateral opacities—not fully explained by effusions, lobar/lung collapse, or nodules.
Origin of oedema: Respiratory failure not fully explained by cardiac failure or fluid overload. Need objective assessment (eg, echocardiography) to exclude hydrostatic oedema if no risk factor present.
Oxygenation:

Mild—200 mm < Hg PaO_2/FIO_2 ≤ 300 mm Hg with PEEP or CPAP ≥ 5 cm H_2O
Moderate—100 mm Hg < PaO_2/FIO_2 ≤ 200 mm Hg with PEEP ≥ 5 cm H_2O
Severe— PaO_2/FIO_2 ≤ 100 mm Hg with PEEP ≥ 5 cm H_2O

iii) Gastrointestinal:

Oesophagoenteric leak from anastomosis, staple line, or localised conduit necrosis[4]

Conduit necrosis / failure[5]

Ileus (defined as small bowel dysfunction preventing or delaying enteral feeding)

Small bowel obstruction

Feeding J-tube complication

Pyloromyotomy / pyloroplasty complication

Clostridium difficile infection

GI bleeding requiring intervention or transfusion

Delayed conduit emptying requiring intervention or delaying discharge or requiring maintenance of NG drainage >7days post-operatively

Pancreatitis

Liver dysfunction

Anastomotic stricture (requiring endoscopic intervention)

iv) Urological:

Acute renal insufficiency (defined as doubling of creatinine)

Acute renal failure requiring dialysis

Urinary tract infection

Urinary retention requiring reinsertion of urinary catheter, delaying discharge, or discharge with urinary catheter

v) Thromboembolic:

Deep venous thrombosis

Pulmonary embolus

Stroke (CVA)

Peripheral thrombophlebitis

[4] **Oesophagoenteric leak** defined as: Full thickness GI defect involving oesophagus, anastomosis, staple line or conduit irrespective of presentation or method of identification.

Type I: Local defect requiring no change in in therapy or treated medically or with dietary modification.
Type II: Localised defect requiring interventional but not surgical therapy, e.g., interventional radiology drain, stent or bedside opening, and packing of incision.
Type III: Localised defect requiring surgical therapy.

[5] **Conduit necrosis / failure** defined as:
Type I: Conduit necrosis focal. Identified endoscopically. Treatment – additional monitoring or non-surgical therapy.
Type II: Conduit necrosis focal. Identified endoscopically and not associated with free anastomotic or conduit leak. Treatment – surgical therapy not involving oesophageal diversion.
Type III: Conduit necrosis extensive. Treatment – treated with conduit resection with diversion.

vi) Neurological / psychiatric:

Recurrent nerve injury[6]

Other neurological injury

Acute delirium

Delirium tremens

vii) Infection:

Wound infection requiring opening wound or antibiotics

Central IV line infection requiring removal or antibiotics

Intrathoracic / intra-abdominal abscess

Generalised sepsis[7]

Other infections requiring antibiotics

viii) Wound / diaphragm:

Thoracic wound dehiscence

Acute abdominal wall dehiscence / hernia

Acute diaphragmatic hernia

[6] **Recurrent nerve injury** defined as**:** vocal cord dysfunction post-resection. Confirmation and assessment should be by direct examination.

Type I: Transient injury requiring no therapy. Dietary modification allowed.
Type II: Injury requiring elective surgical procedure, for example, thyroplasty or medialization procedure .
Type III: Injury requiring acute surgical intervention (due to aspiration or respiratory issues), for example, thyroplasty or medialization procedure
Severity Level A: Unilateral.
Severity Level B: Bilateral.
For example, a unilateral vocal cord injury requiring elective medialization procedure. Final Type IIA

[7] **Generalised sepsis** defined as: SIRS (systemic inflammatory response syndrome) plus a documented infective source, where SIRS is the presence of two or more of the following:

Temperature >38.3°C or <36°C
Heart rate >90 beats/min
Respiratory rate >20 breaths/min
WBC >12,000 cell/mm^3 or <4,000 cell/mm^3
Acutely altered mental status
Hyperglycaemia (plasma glucose of >7.7mM/L) in the absence of diabetes

ix) Other:

Chyle leak [8]

Re-operation for reasons other than bleeding, anastomotic leak, or conduit necrosis

Multiple organ dysfunction syndrome[9]

7.1.3 Other complications

i) The need to return to intensive care:

mechanical ventilation

organ support

invasive monitoring

tracheostomy

ii) Inoperability at planned surgery

iii) Cancer progression

iv) 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 to participate in the randomised study until the end of the follow-up period. Any SAEs directly related to the chemotherapy will not be reported.

[8] **Chyle leak** defined as:
Type I: Treatment – enteric dietary modifications
Type II: Treatment – total parenteral nutrition
Type III: Treatment – interventional or surgical therapy (not including elective insertion of additional surgical or interventional chest drains).
Severity level (A) <1 L output / day or (B) >1 L output / day
For example, a chyle leak initially producing 1200mL/day and successfully treated by stopping enteric feeds and initiating TPN would be classified as Type IIB.

[9] **Multiple organ dysfunction syndrome** defined as: Presence of altered organ function in an acutely ill patient such that homeostasis cannot be maintained without intervention.

8. Ethical considerations

8.1 Review by an NHS Research Ethics Committee

The research will be performed subject to a favourable opinion from an NHS Research Ethics Committee (REC), including any provisions of Site Specific Assessment (SSA), and local NHS Permission. 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 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

There should be no additional risk to participants when taking part in this study. All three interventions are standard of care and there are no new or experimental surgical interventions. However, at present there is a lack of well-designed empirical evidence to suggest that one surgical technique is superior to the other; this forms the rationale for this study and will be the main benefit to society. In particular the totally minimally invasive surgery is also performed across and the country and worldwide and methods for doing the surgery are adapting as surgeons gain more experience. Such evidence will inform NHS policy and patient and clinician decision-making.

The main participant benefit is the hypothesised improvement in post-operative physical function in the minimal access group. Surgeons recognise that any benefits of minimal access techniques are likely to be in earlier post-surgical recovery. The complications that may theoretically be reduced by minimal access surgery relate to the wound (fewer infections with minimal access surgery) and to respiratory infection (fewer problems with minimal access surgery). Recovery of physical function will follow resolution of these complications

However, this potential benefit may be mitigated by the possibility that open surgery may be required for those allocated to this group in the event of operative complications and the long term effects of minimal access surgery are unknown.

Potential risks and adverse events for the surgical interventions are identified in section 7.1.

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 taking part in the quality assurance study for surgeon participation in the trial will be required to give consent on a separate form. 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 study manual.

9. Research governance

This study will be conducted in accordance with:

- ICH GCP guidelines
- UK Policy Framework for Health & Social care Research

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 Research & Development 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, CTEU Bristol 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 is an NHS-sponsored research study. For NHS sponsored research HSG(96)48 reference no. 2 refers. If there is negligent harm during the clinical trial when the NHS body owes a duty of care to the person harmed, NHS Indemnity covers NHS staff, medical academic staff with honorary contracts, and those conducting the trial. NHS Indemnity does not offer no-fault compensation and is unable to agree in advance to pay compensation for non-negligent harm. Ex-gratia payments may be considered in the case of a claim.

9.6 Clinical Trial Authorisation

Oesophagectomy is not classed as investigational medicinal products and therefore a Clinical Trial Authorisation from the Medicines and Healthcare products Regulatory Agency 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 be entered into a purpose-designed server database hosted on the NHS network. 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 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 network in an encrypted form. The participants will be identified using their name and unique study identifier on the secure database.

Data will be entered promptly and data validation and cleaning will be carried out throughout the trial. The trial manual will cover database use, data validation and data cleaning. The manual will be available and regularly maintained. Where electronic patient medical notes are used, local Trust policies will be followed.

10.2.2 Data storage

All study documentation will be retained in a secure location during the conduct of the study and for 5 years after the end of the study, when all patient identifiable paper records will be destroyed by confidential means. 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, with a 'do not destroy' label. The 'do not destroy' label will request that medical records will be kept for at least 5 years after the end of the study. In compliance with the MRC Policy on Data Preservation, with patient consent, 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 with patient consent, 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 research. 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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Department of Health Disclaimer:

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12. Appendix 1

Sub-study – An exploratory comparison of OO, LAO, and MIO – a nested IDEAL Phase 2b RCT and comprehensive cohort embedded within the main ROMIO RCT.

The sub-study is an IDEAL phase 2b study because the MIO is a relatively novel intervention. It is only currently undertaken in about 10% of UK centres [1]. The procedure is also evolving. In the ROMIO feasibility study two major developments were documented, i) it changed from a 3-phase procedure to 2-phase, and, ii) the method for the anastomosis changed from hand sewn to a combined stapled and hand sewn approach. In addition to the evolving technical nature of the procedure, it was demonstrated in the feasibility work that surgeons are not learning the operation widely. It was therefore considered that this intervention is insufficiently developed to evaluate within a pragmatic study. However, to allow prospective documentation of the outcomes of the procedure within the context of a randomised setting an embedded study will take place. The purposes of this sub-study are:

1. To document if additional inclusion/exclusion criteria are needed for patients selected for MIO by use of the screening logs and understanding the intra-operative reasons for cross over during or shortly before the operation

2. To document prospectively the complications of this procedure

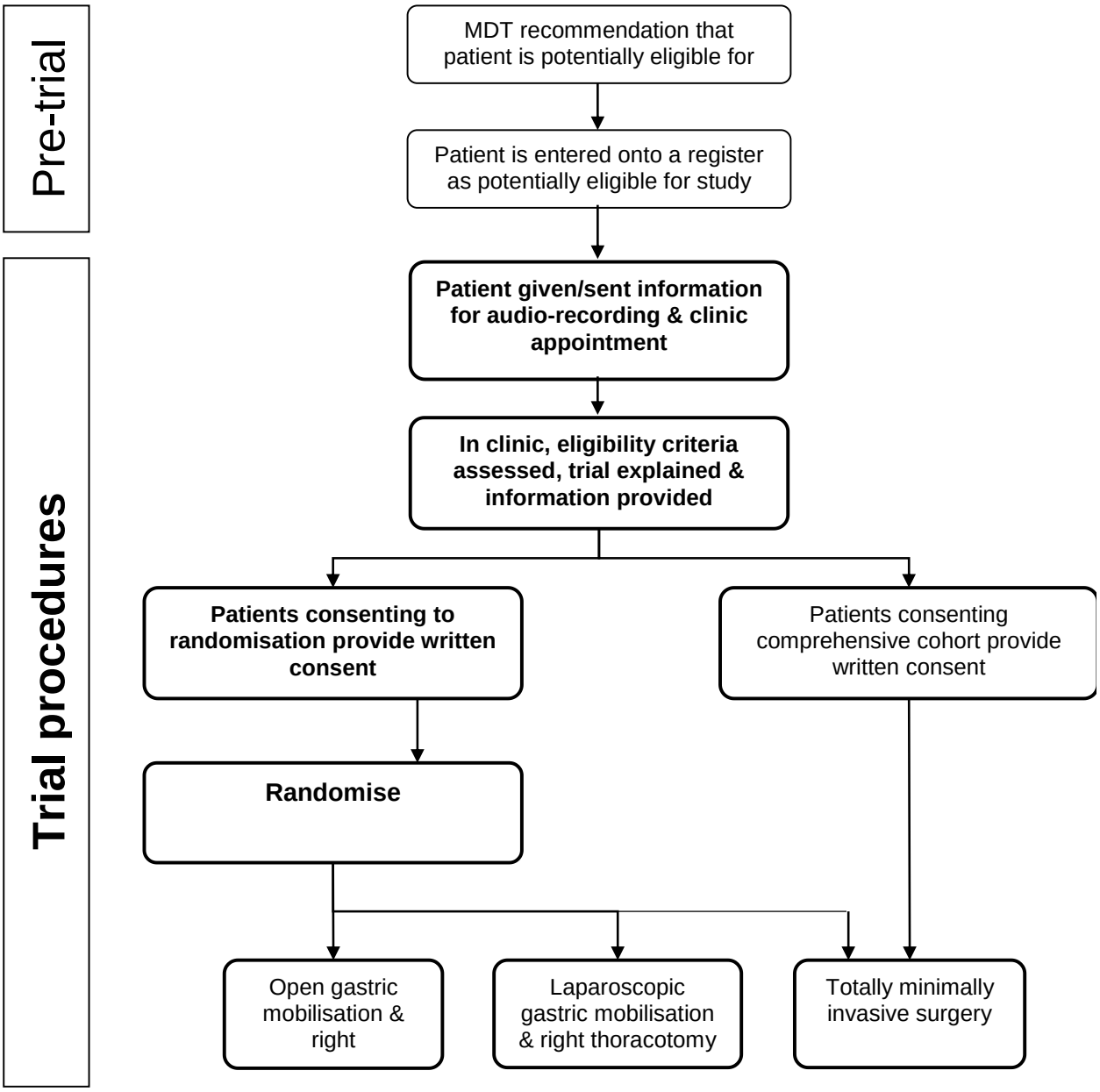
3. To use the data to undertake analyses of safety and adverse events compared to the two other groups

4. To prospectively document technical changes in the procedure during the course of the study and to document the rationale for these changes

5. To ensure that patients participating in the sub-study give fully informed consent about this more novel intervention and to explore this within the qualitative recruitment intervention information study

In two centres, which have extensive experience of MIO, the trial will run as a three group RCT comparing OO, LAO and MIO. Data collection will also take place for all non-trial patients who undergo MIO and who consent to their data to be used to create a comprehensive cohort. The patients randomised to MIO will be in addition to the 406 required for the main study; we anticipate that approximately 40 will be randomised to MIO resulting in a total sample size of around 446.

The purpose of this sub-study is to evaluate MIO with the informed consent of patients and the comprehensive data collection that being part of an RCT will ensure. Including MIO as one of the randomised groups also ensures that evaluation of MIO will take place in a variety of patients, i.e. patients will not be ‘cherry picked’ to undergo MIO which may inflate possible benefits.



Oesophagectomy will be performed as previously described in section 4.3.1. For the abdominal phase, laparoscopic techniques will be used as described in section 4.3.3. Access to the thoracic cavity will be achieved with several 12 or 5mm incisions (as many as needed) and surgery performed thoracoscopically. As with OO and LAO, both two and three phase procedures are permitted and transhiatal surgery is prohibited.

Evolution of the technical aspects of this procedure will be documented as part of the IDEAL phase 2b part of the study.

All other aspects of this study are as described in the main protocol above.

Amendments to protocol

Amendment number (i.e. REC amendment number)	Previous version & date	New version & date	Brief summary of change	Date of ethical approval (or NA if non-substantial)
1	2.0 28/04/2016	3.0 20/10/2016	Some minor errors have been corrected. Exclusion criteria 2 - wording amended for clarification. Review of trial interventions to ensure they are detailed clearly and correctly. Clarification about collecting videos. Update of expected adverse events section to reflect consensus paper (Low et al, 2015) on standardising reporting of complications of oesophagectomy and clarify not collecting events related to chemotherapy.	09/11/2016
2	3.0 20/10/2016	4.0 26/05/2017	Added definition of the end of the study and information about the PPI group	22/06/2017
4	4.0 26/05/2017	5.0 23/03/2018	Health economic analysis section updated. Included information about plans to link with external registries (ICNARC, PHE, ISD) for more detailed data about patient care in hospitals for both economic analysis and as a measure of post-op patient recovery. Added that we intend to share anonymised photos for training and reporting purposes. Some other minor clarifications, including adding reference to CHI number.	02/05/2018
5	5.0 23/03/2018	6.0 02/05/2018	We have added that anonymised videos will be stored on the University server long-term	15/05/2018
6	6.0 02/05/2018	7.0 25/10/2018	We have amended the definition for pneumonia to be in accordance with the consensus paper (Low et al, 2015)	20/11/2018
7	7.0 25/10/2018	8.0 04/04/2019	Post-operative complications will be assessed using Clavien Dindo at discharge, rather than 30 days. Economic analyses will be performed at 3 and 24 months post-randomisation. We have corrected a typo on p23, pain scores are assessed at 6 days, not 6 weeks.	12/06/2019
8	8.0 04/04/2019	9.0 29/08/2019	The statistical analysis section has been updated to reflect the proposed analyses in the statistical analysis plan. A study within a trial has been introduced for patient follow-up.	15/10/2019

			Other minor changes have been made for accuracy.	