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Abstract

Comparing open and minimally invasive surgical procedures for oesophagectomy in the treatment of cancer: the ROMIO (Randomised Oesophagectomy: Minimally Invasive or Open) feasibility study and pilot trial

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Background: Localised oesophageal cancer can be curatively treated with surgery (oesophagectomy) but the procedure is complex with a risk of complications, negative effects on quality of life and a recovery period of 6–9 months. Minimal-access surgery may accelerate recovery.

Objectives: The ROMIO (Randomised Oesophagectomy: Minimally Invasive or Open) study aimed to establish the feasibility of, and methodology for, a definitive trial comparing minimally invasive and open surgery for oesophagectomy. Objectives were to quantify the number of eligible patients in a pilot trial; develop surgical manuals as the basis for quality assurance; standardise pathological processing; establish a method to blind patients to their allocation in the first week post surgery; identify measures of postsurgical outcome of importance to patients and clinicians; and establish the main cost differences between the surgical approaches.

Design: Pilot parallel three-arm randomised controlled trial nested within feasibility work.

Setting: Two UK NHS departments of upper gastrointestinal surgery.

Participants: Patients aged ≥ 18 years with histopathological evidence of oesophageal or oesophagogastric junctional adenocarcinoma, squamous cell cancer or high-grade dysplasia, referred for oesophagectomy or oesophagectomy following neoadjuvant chemo(radio)therapy.

Interventions: Oesophagectomy, with patients randomised to open surgery, a hybrid open chest and minimally invasive abdomen or totally minimally invasive access.

Main outcome measure: The primary outcome measure for the pilot trial was the number of patients recruited per month, with the main trial considered feasible if at least 2.5 patients per month were recruited.

Results: During 21 months of recruitment, 263 patients were assessed for eligibility; of these, 135 (51%) were found to be eligible and 104 (77%) agreed to participate, an average of five patients per month. In total, 41 patients were allocated to open surgery, 43 to the hybrid procedure and 20 to totally minimally invasive surgery. Recruitment is continuing, allowing a seamless transition into the definitive trial. Consequently, the database is unlocked at the time of writing and data presented here are for patients recruited by 31 August 2014. Random allocation achieved a good balance between the arms of the study, which, as a high proportion of patients underwent their allocated surgery (69/79, 87%), ensured a fair comparison between the interventions. Dressing patients with large bandages, covering all possible incisions, was successful in keeping patients blind while pain was assessed during the first week post surgery. Postsurgical length of stay and risk of adverse events were within the typical range for this group of patients, with one death occurring within 30 days among 76 patients. There were good completion rates for the assessment of pain at 6 days post surgery (88%) and of the patient-reported outcomes at 6 weeks post randomisation (74%).

Conclusions: Rapid recruitment to the pilot trial and the successful refinement of methodology indicated the feasibility of a definitive trial comparing different approaches to oesophagectomy. Although we have shown a full trial of open compared with minimally invasive oesophagectomy to be feasible, this is necessarily based on our findings from the two clinical centres that we could include in this small preliminary study.

Trial registration: Current Controlled Trials ISRCTN59036820.

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List of abbreviations

CI	confidence interval
CRF	Clinical Report Form
EORTC	European Organization for Research and Treatment of Cancer
EQ-5D-5L	European Quality of Life-5 Dimensions five-level version
HRG	Healthcare Resource Group
HRQoL	health-related quality of life
HTA	Health Technology Assessment
IDEAL	Innovation, Development, Exploration, Assessment, Long-term study
LAO	laparoscopically assisted oesophagectomy
MFI-20	Multidimensional Fatigue Inventory
MIO	minimally invasive oesophagectomy
MIRO	oesphagectoMIe pour cancer paR voie conventionnelle ou coeliO-assistée
NIHR	National Institute for Health Research
ProtecT	Prostate testing for cancer and Treatment
PSS	Personal Social Services
QALY	quality-adjusted life-year
QLQ-C30	Quality of Life Questionnaire Core 30
QLQ-OES18	Quality of Life Questionnaire Oesophageal Cancer Module
RCT	randomised controlled trial
ROMIO	Randomised Oesophagectomy: Minimally Invasive or Open
TIME	Traditional Invasive versus Minimally invasive Esophagectomy
TNM	tumour, node, metastasis

Plain English summary

The survival of some patients with oesophageal (gullet) cancer can be improved by surgery (oesophagectomy). Surgery traditionally requires large incisions to be made in the abdomen, the chest and sometimes the neck (open surgery). Complications are common and recovery takes ≥ 6 months. Minimally invasive 'keyhole' surgery may achieve the same survival benefit, with quicker recovery. However, to confirm this, a randomised controlled trial (RCT) needs to be carried out to make a fair comparison between the surgical approaches. The present study conducted preparatory work in a small RCT in two departments of surgery.

This trial indicated the feasibility of a full-scale evaluation, with 104 patients agreeing to take part over 21 months. The random allocation of a surgical approach to each patient resulted in similar groups of patients undergoing the different approaches, which, with most patients undergoing their allocated surgery (87%), ensured a fair comparison between the approaches. By bandaging all possible incision points for the first week post surgery, it proved possible to keep patients from knowing which surgical approach they had undergone, improving the assessment of postsurgical pain. Participants are reporting, with high completion rates, on outcomes such as physical function and fatigue over a 3-year period. Patients and clinicians are being consulted on the most important measures of outcome following oesophagectomy. The steps in performing an oesophagectomy have been documented, including the important differences between the approaches, allowing quality control of surgery. Finally, the important costs and methods of measurement have been determined, allowing a cost-effectiveness analysis in the full-scale evaluation.

Scientific summary

Background

Localised oesophageal cancer can be curatively treated with surgery (oesophagectomy). The national audit of patients in England and Wales (2011–20) undergoing oesophagectomy collected details of 1220 operations. Oesophagectomy had a 3% risk of in-hospital mortality, a 9% risk of reoperation and a 16% risk of respiratory complications. Health-related quality of life is significantly worsened after oesophagectomy, with patients reporting major impacts in terms of physical and social function, fatigue, breathlessness and pain for at least 3 months. Recovery takes about 6–9 months after open surgery.

There is therefore a need to improve outcomes of patients undergoing oesophagectomy. Minimal-access surgical techniques may cause less tissue damage and allow a more rapid recovery. Whether or not this is a cost-effective approach, however, is unknown, as high-quality comparative evidence is limited.

Two previous trials had methodological flaws that preclude firm conclusions being drawn from their results. In particular, the sample sizes were small and, therefore, the studies made only a modest contribution to the evidence of equivalent survival benefits with the different approaches to oesophagectomy. The primary end points reflected surgical interest and did not incorporate meaningful benefits for minimal-access surgery from the patients' perspective. Both trials were at risk of biased outcome assessment as assessors were not blinded and one trial used sealed envelopes for randomisation, bringing the concealment of allocation into question.

A UK trial is needed to provide definitive evidence on the relative cost-effectiveness of minimally invasive and open surgery for oesophagectomy. However, there are many challenges to conducting high-quality randomised trials of surgery. The particular hurdles that may affect a full trial of open oesophagectomy and minimally invasive oesophagectomy (MIO) are (1) strong preferences held by surgeons about the two procedures, which may mean that it is difficult to recruit centres to the main trial, and (2) preferences of patients that do not permit randomisation. The feasibility of the main trial would also be in doubt if (3) the number of eligible patients was lower than a mean of 2.5 patients per month per centre. These and further methodological issues were addressed in the feasibility study reported here.

Objectives

The ROMIO (Randomised Oesophagectomy: Minimally Invasive or Open) feasibility study aimed to establish the methodology and infrastructure for a definitive trial comparing the cost-effectiveness of minimally invasive and open surgical techniques for oesophagectomy in the treatment of cancer. 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 can be tackled before the main trial.
- To establish the proportion of potentially eligible patients who can be approached about the trial, who are confirmed as eligible, who are successfully recruited and randomised and who are able and willing to undergo research assessments. This addresses the feasibility of the main trial by indicating the achievable sample size and the number of centres required.

- To document in detail, using IDEAL (Innovation, Development, Exploration, Assessment, Long-term study) recommendations, the technical developments of the totally minimally invasive approach for oesophagectomy, to inform the design and choice of interventions in the main trial. This work developed manuals for the different surgical procedures, and methods of monitoring adherence to them, which will then be available for the main trial. It also informed 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 cutting up of specimens, specimen fixing and pathology to optimise the quality of lymph node counts and ascertainment of positive resection margins.
- To consider the appropriate statistical model for estimating treatment effectiveness while allowing for 'clustering' in the data because of between-surgeon variation.
- To develop and evaluate feasible, acceptable and effective methods of keeping patients blind to their treatment for the first week after surgery.
- To establish outcome measures for the main trial that are recognised as a comprehensive, valid and reliable assessment of oesophagectomy outcome by patients and the clinical community.

Methods

The ROMIO feasibility study was based around a pilot parallel three-arm randomised controlled trial (RCT) nested within feasibility work. This was conducted in two centres, University Hospitals Bristol NHS Foundation Trust and Plymouth Hospitals NHS Trust, which each have a team of upper gastrointestinal cancer surgeons.

Patients were eligible for the pilot trial if they were aged $\geq$ 18 years with confirmed histopathological evidence of oesophageal or oesophagogastric junctional adenocarcinoma, squamous cell cancer or high-grade dysplasia that was referred for oesophagectomy or oesophagectomy following neoadjuvant chemo(radio)therapy. The technology was oesophagectomy, with patients randomised to open surgery, a hybrid open chest and minimally invasive abdomen [laparoscopically assisted oesophagectomy (LAO)] or totally MIO.

The primary outcome measure for the pilot trial was the number of patients recruited per month, with the main trial being considered feasible if at least 2.5 patients per month were recruited. The primary outcome measure for the main trial was to be confirmed during the feasibility study based on expert input from the Trial Steering Committee and the consensus meetings held to inform the core outcome set. At the outset of the feasibility study the initial candidate for the primary outcome of the main trial was a patient report of fatigue.

Participants completed baseline measurements prior to random allocation. On the second day post surgery, patients completed assessments of pain and blinding, followed by completion of the full assessment 6 days, 6 weeks and 3 and 6 months after surgery. During the first year of the feasibility study, permission was obtained to continue follow-up for 3 years post randomisation. Patient-reported outcomes were subsequently administered at 9, 12, 18, 24 and 36 months.

Allocation of patients to surgical procedure was at random, the allocation being conducted separately for the two centres and further stratified by whether or not patients had undergone neoadjuvant treatment. Patients were randomly allocated to one of the three procedures at Bristol and to the open procedure or the two-phase laparoscopically assisted procedure at Plymouth. Allocation was concealed through centralised randomisation.

Recruitment to the pilot RCT was planned for a 12-month period, with 72 potentially eligible patients being expected during that time. This would allow a true 50% recruitment rate to be estimated with a 95% confidence interval of approximately 38% to 62%.

Summary statistics that inform plans for the main trial are presented including the number of potentially eligible patients per month per centre, the percentage of these patients confirmed as eligible, the percentage of patients agreeing to be randomly allocated to a study procedure in the pilot trial and the percentage of randomised patients completing outcome measurements.

Key aspects of the associated methodological work included the qualitative recruitment intervention, the documentation of the different surgical procedures and the production of materials to allow quality assurance of surgery and pathology, determination of outcome measures that are important to patients undergoing oesophagectomy and their clinicians, identification of the key cost differences between the surgical approaches and methods to capture these and establishing a method to keep patients blind to their treatment allocation while pain levels were assessed in the first week post surgery.

Results

In the first 21 months of recruitment (until the end of December 2014) 263 patients have been assessed for eligibility, of whom 135 (51%) were found to be eligible and 104 (77%) were randomised across the two centres. Of the recruited patients, 46 were from Plymouth ($n = 22$ open surgery, $n = 24$ LAO) and 58 were from Bristol ($n = 19$ open surgery, $n = 19$ LAO, $n = 20$ MIO). To allow continuation into the definitive trial, recruitment was continued beyond the planned 12-month period and was ongoing at the time of writing. In this report we focus on those patients randomised on or before 31 August 2014 for whom 6-week follow-up data were expected to be available for analysis.

The majority of participants were male and the mean age at randomisation was approximately 66 years for each treatment group (standard deviation approximately 7 years). A lower proportion of patients had undergone neoadjuvant treatment before surgery in Plymouth than in Bristol, although the proportion in each treatment arm was well balanced within each centre. Considering disease stage at diagnosis, most participants had a tumour that was growing through the wall of the oesophagus but involving one to two lymph nodes at most (stages 2a and 2b) or a cancer that had just started to spread to the tissues surrounding the oesophagus (stage 3a). There was no convincing evidence of imbalance between the randomised intervention arms in terms of disease staging.

The large majority of patients underwent their allocated surgical approach (69/79, 87%). The three patients for whom the allocation to open surgery could not be followed were found to be inoperable. Of the patients allocated to LAO, one converted to open surgery to stop a bleed, one requested MIO having spoken to a patient who had undergone this procedure previously and one underwent a gastrectomy for more extensive disease. Four patients allocated to MIO underwent LAO, two because of the position of the tumour and two because a surgeon was not available to undertake the MIO procedure.

The median length of postsurgical stay across the two centres was 10 days, with stays typically lasting between 8 and 16 days (interquartile range). Among the first 76 patients recruited there was one death occurring within 30 days of surgery, with a further death occurring on the 31st postsurgical day. Four anastomotic leaks occurred, all of which resulted in a return to theatre. A further nine patients returned to theatre one or more times. Eight patients returned to the intensive care unit, six because of respiratory problems and two because of renal failure. Eight patients were readmitted within 30 days of surgery.

Completion of the pain scale at day 2 post surgery was low (39/73, 53%), the reasons for non-completion being illness or insufficient recovery (9/73, 12%), lack of cover to administer the scale at the weekend (16/73, 22%) and administrative error (9/73, 12%). Completion of the pain scale was considerably better at day 6 (64/73, 88%). The primary outcome measure for the planned definitive trial is likely to be a patient-reported outcome at 6 weeks post randomisation; the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30) was available for 74% (54/73) of participants at that time point.

Dressing patients with large bandages, covering all possible incisions, was successful in keeping patients blind while pain was assessed during the first week post surgery. On both day 2 and day 6, the majority of responders believed that they had undergone the LAO procedure, irrespective of their allocation.

Hierarchical task analysis has allowed the documentation of the steps of oesophagectomy and the differences between the open approach and the minimally invasive approach. Assessment tools have been produced for quality assurance of surgery, recorded on video or with photographs. This will be supplemented with an 'op note' allowing the recording of each step of the operation. The study pathologists at the two centres and the study's independent advisor have reached consensus on a standard approach to pathological processing and recording and have planned quality assurance procedures for the proposed main trial.

In conducting the qualitative recruitment intervention, the patient eligibility and recruitment pathway at each centre has been mapped. In-depth interviews with nine clinical investigators and staff undertaking recruitment have been conducted and analysed to explore views about the evidence on which the trial is based, perceptions of levels of equipoise in relation to the trial arms, how the arms are or can be delivered in their clinical centre and methods for identifying eligible patients. Audio recordings of > 100 consultations have also been conducted and analysed to scrutinise recruiters' ability to summarise the details of the trial design and protocol and provide information about the trial and to identify examples of actual recruitment successes and challenges. This has informed feedback and training meetings with recruiters. Furthermore, the patient information provided at recruitment has been updated and a 'recruitment tips' guidance document has been developed.

In developing a core outcome set to evaluate the clinical effectiveness of oesophageal cancer surgery, a literature review identified 901 measures, which were synthesised into 67 outcome domains and operationalised into 68 questions. Delphi methodology was used to reduce the initial list of outcome domains to a final core set according to prespecified criteria, by surveying key stakeholders (consultant surgeons, clinical nurse specialists and patients). Analyses of responses led to 41 and 19 outcomes being retained as important after the first and second surveys, respectively. The retained outcomes from the second survey were presented at a face-to-face patient consensus meeting at which patients were asked to anonymously rate their importance. The final core outcome set consists of 10 outcomes.

One area in which cost differences will exist between the approaches to oesophagectomy is in relation to the actual operation. Piloting of a Clinical Report Form was ongoing at the time of writing, which aimed to capture use of equipment and consumables in terms of brand and quantity and use of operation staff in terms of role and time. This level of detail of the operation itself is unlikely to be available from patients' medical records. Readmissions to the treating hospital will be captured in a review of medical records and it seems reasonable to rely on Healthcare Resource Group codes to indicate the cost of these. Secondary care visits and inpatient stays at other hospitals will not be captured in this way and neither will community-based NHS resource use. These aspects require the patients to provide information and a patient diary with a nurse-led telephone interview has been piloted. Early experience suggests that patients would prefer a narrower NHS and Personal Social Services perspective to reduce the burden of this aspect of the study and that patients vary in whether they prefer to provide their resource use diary to the study team or take part in the telephone interview while referring to the diary.

Conclusions

This feasibility study has demonstrated that different approaches to oesophagectomy can be compared in an unbiased fashion in a RCT and we are now planning the definitive trial.

At the time of writing we are proposing to focus on a comparison between LAO and open oesophagectomy as MIO continues to be subject to refinement. We plan to recruit 406 patients, allowing a clinically important benefit for postsurgical recovery of physical function to be detected with 90% power, and making a major contribution to an individual patient meta-analysis of survival. A seven-centre study is planned; the new centres have varying experience of recruiting to surgical trials and so the qualitative recruitment intervention will be continued. Currently, the plan is for two centres to randomly allocate patients to three interventions, the third being MIO, allowing further unbiased data to be collected on that approach.

Trial registration

This trial is registered as ISRCTN59036820.

Funding

Funding for this study was provided by the Health Technology Assessment programme of the National Institute for Health Research.

Chapter 1 Introduction

Funding history

The ROMIO (Randomised Oesophagectomy: Minimally Invasive or Open) feasibility study and pilot trial was funded by the National Institute for Health Research (NIHR) Health Technology Assessment (HTA) programme (reference number 10/50/65). The ROMIO pilot study was a researcher-led proposal. The funding contract was agreed in October 2012 and the study opened in January 2013. The study was due to close in December 2014 but a contract variation was agreed in November 2014 for a close in December 2015, allowing continuation into a main trial should an application for funding of that subsequent study be successful.

Structure of this report

In this chapter the importance of a rigorous comparison between open oesophagectomy and minimally invasive oesophagectomy (MIO) is made and the need for a preceding feasibility study and pilot trial justified. In *Chapter 2* the pilot randomised controlled trial (RCT) procedure and associated methodological work are described, with the results of this work being presented in *Chapter 3*. The implications of our findings are discussed in *Chapter 4* and the conclusions drawn with regard to the planned full trial are presented in *Chapter 5*.

Background

Oesophageal cancer was the 13th most common cancer in the UK in 2011, with 8332 people diagnosed that year.[1] Two-thirds of these cancers are adenocarcinoma and one-third are squamous cell cancer and about one-quarter of cases are diagnosed while the disease is localised to the oesophagus. Localised oesophageal cancer and high-grade dysplasia (a pre-malignant condition) can be curatively treated with surgery (oesophagectomy). Surgery is frequently combined with neoadjuvant treatment.

The most recent (2011–12) national audit of patients in England and Wales undergoing oesophagectomy collected details of 1220 operations.[2] Oesophagectomy had a 3% risk of in-hospital mortality, a 9% risk of reoperation and a 16% risk of respiratory complications. Complications of any type occurred in 30% of patients. Health-related quality of life (HRQoL) is significantly worsened after oesophagectomy, with patients reporting major reductions in physical and social function and more problems with fatigue, breathlessness and pain for at least 3 months. Recovery takes about 6–9 months after open surgery although patients dying within a year of surgery do not recover preoperative HRQoL. Persistent long-term deficits in HRQoL occur.

There is therefore a need to improve outcomes for patients undergoing oesophagectomy. The past decade has seen improvements in patient selection, neoadjuvant treatment and perioperative care. Minimal-access surgical techniques have been introduced into UK clinical practice, with the theoretical advantages of causing less tissue damage and increasing the speed of recovery. Whether or not this is an effective and cost-effective approach, however, is unknown as high-quality comparative evidence is limited.

There is a growing use of minimal-access surgical techniques for all types of cancer. Whether or not 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[3] in the 1990s, providing evidence of better recovery and equivalent survival. These trials led to changes in practice and surgical training.

Surgery for upper gastrointestinal cancer, however, is much more complex than colorectal cancer surgery and is associated with high rates of mortality and morbidity. Minimal-access surgery may make the procedure even more technically demanding, potentially resulting in greater surgical risks. Although there has been an increase in the UK and worldwide in the uptake of minimal-access techniques for the treatment of 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 created then a standard of surgery for patients can be provided and health-care policy formulated to support this approach.

National audit data[2] show that, of the 1220 oesophagectomies performed between 2011 and 2012 that include details of the procedure, 40% ($n = 492$) used minimal-access surgical techniques. The majority ($n = 314$) were laparoscopically assisted (minimal-access approach for the abdomen and standard open right chest incision) and 140 were oesophagectomies performed by totally minimally invasive techniques.

The 2011/12 national audit did not suggest any marked differences in complications or length of hospital stay following open surgery, laparoscopically assisted surgery or minimally invasive surgery.[2] However, it is likely that patients were specifically selected for these approaches and that the patients had small tumours and little comorbidity. Hence, there is a high chance of bias in observational data such as these, with the patients' prognosis being a factor in determining the method of surgery undertaken. Only a RCT can reliably control for such 'confounding by indication'.

Literature review

At the time of planning this feasibility study we undertook a systematic literature review in the MEDLINE database and Cochrane Central Register of Controlled Trials.[4] Papers were eligible for inclusion in the review if they reported the short-term clinical outcomes of surgery (with or without neoadjuvant treatment) as observed in both randomised and non-randomised studies of patients with oesophageal cancer (squamous cell and adenocarcinoma). Papers reporting outcomes of surgery for high-grade dysplasia only, outcomes of oesophagectomy combined with other procedures such as gastrectomy, based on < 50 oesophagectomies, and retrospective study designs were excluded. MEDLINE and the Cochrane Controlled Trials Register were searched for abstracts with keywords for cancer (neoplasms or cancer or neoplasm$), oesophagus (esophag$or oesophagi$) and surgery (surg$or operation or operable or resect$). The search was limited to human studies published in English between January 2004 and March 2009. Reports available only in abstract form were excluded. Titles and abstracts were screened for eligibility by two reviewers and the full texts of studies meeting the inclusion criteria were analysed by three reviewers. The reference lists of retrieved articles were used to identify additional potentially relevant studies. Data extracted from the included studies were subject to a narrative synthesis.

We 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 two-phase surgery using minimal-access techniques for the abdomen or chest.[4] Three other systematic reviews were identified but none included a randomised trial.[5–7] In a series of 222 patients undergoing totally minimally invasive surgery,[8] the short-term clinical outcomes (morbidity and technical data) were similar to those published in series of open surgery. Few of the above studies reported short-term oncological end points (e.g. lymph node count), although UK national audit data show similar lymph node counts with minimally invasive surgery to those achieved by open procedures, with 68% of open and 78% of minimally invasive procedures yielding > 15 nodes.[2] One cohort study compared the outcomes of open oesophagectomy ($n = 114$), a combined approach ($n = 309$) and totally minimally invasive surgery ($n = 23$) and found no differences in 3- or 5-year survival.[9] There was a lack of published data on cost-effectiveness and only two studies measured HRQoL.[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.[11]

All of these studies have methodological weaknesses because of their small sample sizes and observational designs, with limited details regarding patient selection and outcome assessment. 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 RCT comparing the effectiveness and cost-effectiveness of minimal-access and open surgery is needed to inform current NHS practice, health policy and individual surgeon and patient clinical decision-making. Open oesophagectomy costs about £6000 but the inclusion of reoperations, readmission to intensive care and prolonged stays may significantly increase this cost. Minimally invasive surgery requires additional operative equipment but may reduce hospital stay. An economic analysis, embedded within a pragmatic RCT, is required to establish the relative cost-effectiveness of the different procedures when adopted into routine clinical practice.

Other trials evaluating minimal-access surgery for oesophageal cancer

The French MIRO trial

The oesphagectoMIe pour cancer paR voie conventionnelle ou coeliO-assistée (MIRO) trial of patients with oesophageal cancer, excluding patients with type II and III tumours involving the gastro-oesophageal junction, compared open two-phase surgery (abdomen and right chest) with two-phase laparoscopically assisted oesophagectomy (LAO; minimal access for the abdomen and open right chest incision) [see http://clinicaltrials.gov/show/NCT00937456 (accessed 21 January 2016)]. The primary end point was 30-day morbidity (a composite of all complications from grade II to grade IV on the Clavien-Dindo system[12]) 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. The MIRO trial recruited 207 patients from 12 centres. The results, to date reported only at the American Society of Clinical Oncology Gastrointestinal Cancers Symposium 2015,[13] found that 67 (64.4%) patients in the open surgery group had major morbidity compared with 37 (35.9%) in the minimal-access group [odds ratio 0.31, 95% confidence interval (CI) 0.18 to 0.55; $p = 0.0001$]. There are, however, a number of methodological weaknesses. Although the randomisation sequence was computer generated, allocation concealment was unclear, using sealed envelopes. The outcome assessors were not blinded to the intervention type and methods to quality assure surgical procedures are not described.[14]

The Dutch TIME trial

The Traditional Invasive versus Minimally invasive Esophagectomy (TIME) trial included patients with oesophageal cancer, excluding patients with type II and III tumours involving the gastro-oesophageal junction.[15] It compared open two- or three-phase oesophagectomy with totally MIO (both abdomen and chest access performed with minimal-access approaches in the prone position). Pulmonary complications, strictly defined and graded, were the primary measure of outcome. 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 120 patients from seven surgical centres in four countries (the Netherlands, Spain, India and Italy). In total, 115 patients were recruited, with 16 out of 56 (29%) patients undergoing open surgery having a pulmonary infection in the first 2 weeks compared with five out of 59 (8%) in the minimally invasive surgery group (relative risk 0.30, 95% confidence interval 0.12 to 0.76; $p = 0.005$). The trial includes a comprehensive assessment of HRQoL with the Short Form questionnaire-36 items (SF-36)[16] and the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Oesophageal Cancer Module (QLQ-OES18),[17] but there are no cost analyses and no monitoring of surgical procedures.

Aim and rationale

The overall aim of the ROMIO trial was to compare, in patients with cancer of the oesophagus, the clinical effectiveness and cost-effectiveness of minimally invasive and open surgical procedures in terms of recovery, HRQoL, cost and survival.

Rationale for a UK trial

Although the two previously conducted trials (MIRO[13] and TIME[15]) provide some evidence to inform practice, both have methodological flaws that preclude firm conclusions being drawn from their results and neither will be applicable to the NHS and UK surgeons. In particular, the sample sizes are small and only a modest contribution is made to the evidence of equivalent survival benefits with the different surgical approaches. The primary end points reflect surgical interest and do not incorporate meaningful benefit for minimal-access surgery from the patients' perspective. Both trials are at risk of biased outcome assessment without blinding of assessors and the French trial used sealed envelopes for randomisation with the concealment of allocation consequently being questionable.[14] In addition, the interventions in the Dutch trial[15] (totally minimally invasive surgery) are still being developed in the UK and, as this is an evolving procedure, few UK surgeons and anaesthetists are comfortable with oesophagectomy in the prone position.

Rationale for a feasibility study and pilot trial

There are many challenges to conducting high-quality randomised trials of non-pharmaceutical interventions; the particular hurdles that may affect a full trial of open oesophagectomy and MIO are (1) strong preferences held by surgeons about the two procedures, which may mean that it is difficult to recruit centres to the main trial, and (2) preferences of patients that will not permit randomisation. Addressing the first issue, we planned to secure provisional agreement from clinical centres to take part in the main trial. The recruitment of patients to the study was addressed by the qualitative research integrated within this feasibility study. The feasibility of the main trial would also be in doubt if (3) the number of eligible patients was lower than a mean of 2.5 patients per month per centre. Further potential challenges to the quality of the main trial are (4) an inability to specify the surgical procedures being evaluated and to demonstrate that the specified procedures are being adhered to; (5) bias in outcome measures because of patients and assessors not being blinded to treatment allocation; (6) the lack of a widely accepted battery of outcome measures on which to compare different surgical procedures; and (7) poor standards of pathology with consequently a weak measure of oncological success. These were all addressed by the feasibility study and an unexpected failure to find a practical solution to any of them would compromise the main trial.

Feasibility study objectives

The ROMIO feasibility study established the methodology and infrastructure for the main trial. The core of this preliminary work was an assessment of the feasibility of comparing surgical procedures for oesophagectomy in a pilot two-centre RCT. Specific objectives were:

- To pilot the randomisation process and investigate reasons for any difficulties that affect recruitment so that these can be tackled before the main trial.
- To establish the proportion of potentially eligible patients who can be approached about the trial, who are confirmed as eligible, who are successfully recruited and randomised and who are able and willing to undergo research assessments. This addressed the feasibility of the main trial by indicating the achievable sample size and the number of centres required.
- To document in detail, using IDEAL (Innovation, Development, Exploration, Assessment, Long-term study) recommendations,[18] the technical developments of the totally minimally invasive approach for oesophagectomy, to inform the design and choice of interventions in the main trial. This work developed manuals for the different surgical procedures, and methods of monitoring adherence to

them, which were then available for the main trial. It also informed 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 cutting up of specimens, specimen fixing and pathology, therefore optimising the quality of lymph node counts and ascertainment of positive resection margins, both of which are likely to be important short-term outcome measures for the main trial.
- To consider the appropriate statistical model for estimating treatment effectiveness while allowing for 'clustering' in the data because of 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 that 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.

Chapter 2 Methods

This feasibility study was built around a pilot two-centre pragmatic RCT comparing minimally invasive and open surgical procedures in the treatment of oesophageal cancer. Both the pilot RCT and the integrated feasibility work are described in this chapter.

Patients

The initial plan was to have a 12-month period during which consecutive referrals of patients with oesophageal cancer for oesophagectomy at the Bristol and Plymouth centres were invited to take part in the pilot RCT. Inclusion criteria were oesophageal adenocarcinoma, lower-third squamous cell cancer or high-grade dysplasia; selected for surgery by an upper gastrointestinal multidisciplinary cancer team; and age ≥ 18 years. Patients with stage-4 disease, or evidence of a previous complex thoracotomy or laparotomy, were excluded from participation. Previous neoadjuvant chemotherapy did not exclude participants from the trial. All trial participants were asked to provide written informed consent. We anticipated six potentially eligible patients being identified each month, giving a total of 72 patients invited to participate in the pilot trial.

Open and minimally invasive approaches to oesophagectomy

Open surgery

The oesophagectomy was carried out in two or three phases according to the surgeons' judgement with regard to the patient and the tumour.

- *Abdominal phase*. After initial inspection of the abdomen to exclude inoperability, complete gastric mobilisation was performed with the surgeons' usual practice based on the right gastroepiploic and right gastric arteries. Pyloroplasty, pyloromyotomy or no drainage were at the surgeons' discretion. Lymphadenectomies along the common hepatic artery and left gastric and splenic arteries either en bloc or separately were performed and removal of sufficient crural fibres and a cuff of diaphragm was performed if required for tumour clearance. The pericardial fat pad and strips of pleura were removed. Transection of the lesser curve was undertaken during the abdominal phase or left to the thoracic phase of the operation. Placement of a feeding jejunostomy or nasojejunal tube was optional at the surgeons' discretion as was placement of intra-abdominal and intra-thoracic drains. Methods to close the abdomen were at the surgeons' discretion.
- *Thoracic phase*. After initial inspection of the chest to exclude inoperability, the mediastinal pleura overlying the oesophagus was excised in continuity with the oesophagus. The posterior limit of the dissection was normally the anterolateral wall of the aorta, so that the thoracic duct was mobilised en bloc or separately to the oesophagus and peri-oesophageal tissues. The thoracic duct was ligated and divided at the level of the diaphragm. The oesophagus was mobilised to the level of at least the aortic arch. Para-oesophageal and diaphragmatic nodes were removed in continuity or separately with the oesophagus (at the surgeons' discretion). Lymph nodes at the tracheal bifurcation and along the right and left main bronchi to the pulmonary hilus were removed en bloc or separately at the surgeons' discretion. The anastomotic technique and use of chest drainage was at the surgeons' discretion. Methods to close the chest were at the surgeons' discretion.
- *Cervical phase*. A left neck incision was made if a three-phase operation was undertaken. The oesophagus was mobilised preserving the recurrent laryngeal nerve and the anastomosis was performed using the surgeons' preferred methods. Use of a drain was optional.

Laparoscopically assisted oesophagectomy

The oesophagectomy was performed as described in the previous section and access to the abdominal cavity was achieved using between four and six small incisions, which were placed any way in the abdominal wall at the surgeons' discretion. Placement of a feeding jejunostomy was at the surgeons' discretion and was performed laparoscopically or by extending a port site to an 8-cm abdominal incision. The thoracic part of the operation was performed as described in the previous section with a standard open incision. A cervical incision and a neck anastomosis was normally undertaken if required for tumour clearance.

Totally minimally invasive oesophagectomy

This consisted of performing the steps of the abdominal and chest phases of the operation as described in *Open surgery* but using laparoscopic and thoracoscopic techniques for access to each body cavity for each phase, respectively. A two- or three-phase minimally invasive operation was permissable. In the two-phase procedure the anastomosis was performed in the chest if necessary creating a 15-cm incision in addition to the minimal-access ports. In the three-phase operation the anastomosis was performed with a left cervical incision.

Design of the pilot randomised trial

Setting

Two centres, University Hospitals Bristol NHS Foundation Trust and Plymouth Hospitals NHS Trust, recruited patients and carried out procedures within the pilot trial. Both centres have teams of upper gastrointestinal cancer surgeons (six in Bristol and five in Plymouth). These two centres also undertook the associated feasibility work. Methodological support for the pilot trial was predominantly based in Bristol, with the development of quality assurance protocols for surgical procedures and pathology being based at Imperial College London.

Allocation to treatment arm

Allocation of patients to surgical procedure was at random, the allocation being conducted separately for the two centres and further stratified by whether or not patients had undergone neoadjuvant treatment. Patients were randomly allocated to one of the three procedures at Bristol and to one of the open or two-phase laparoscopically assisted procedures at Plymouth. Randomisation within blocks of varying size prevented large imbalances in the number of patients in each treatment arm. Allocation was concealed through centralised randomisation, with patients being logged into the study before their allocation was revealed to the surgical team.

Sample size

At the two lead centres, recruitment to the pilot RCT was planned for a 12-month period, with 72 potentially eligible patients being expected during that time. This would allow a true 50% recruitment rate to be estimated with a 95% CI of approximately 38% to 62% (CI calculation based on the binomial distribution – the Clopper–Pearson approach[19]). If 11 patients were randomly allocated to each surgical procedure, this would allow a true difference of 1.25 standard deviations between two procedures on a continuous measure of early outcome to be detected with 80% power at the 5% significance level. Hence, the pilot RCT was planned to provide an acceptably precise estimate of the recruitment rate to inform plans for the main trial and perhaps to provide evidence suggestive of an intervention having promise for a beneficial impact on short-term outcomes.

Statistical methods

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

Planned follow-up

Participating patients completed baseline measurements prior to random allocation. On the second day post surgery, patients completed assessments of pain and blinding; this was followed by completion of the full assessment 6 days, 6 weeks and 3 and 6 months after surgery. During the first year of the feasibility study, permission was obtained to continue follow-up for 3 years post randomisation. Patient-reported outcomes were subsequently administered at 9, 12, 18, 24 and 36 months post randomisation (*Table 1*).

Primary outcome measure

The primary outcome measure for the main trial was to be determined during the feasibility study based on expert input from the Trial Steering Committee and the consensus meetings held to inform the core outcome set described in *Development of a core outcome set to assess outcome for oesophageal cancer surgery*. At the outset of the feasibility study, the primary outcome for the main trial was planned to be a patient report of fatigue using the Multidimensional Fatigue Inventory (MFI-20).[22] This validated questionnaire has been used in trials of minimal-access surgery for nephrectomy and it is the primary outcome of an open trial of minimal-access compared with open surgery within an enhanced recovery programme [the Enhanced Recovery Open versus Laparoscopic (EnROL) trial]. Consideration was given to using a dual primary end point including a self-reported measure of fatigue and an assessment of morbidity.

TABLE 1 Assessments completed at each time point during follow-up

Assessment	Pre surgery	2 days	6 days	3 weeks	6 weeks	3 months	6+ months
Sociodemographic details	✗						
Routine clinical measurements	✗	✗					
Pain	✗	✗	✗				
Lung function	✗	✗	✗				
Bang Blinding Index[20]			✗				
Resource use diaries					✗		✗
EORTC QLQ-C30[21] and QLQ-OES18 and MFI-20	✗		✗	✗	✗	✗	✗
EQ-5D-5L	✗		✗	✗	✗	✗	✗

EQ-5D-5L, European Quality of Life-5 Dimensions five-level version; MFI, Multidimensional Fatigue Inventory, QLQ-C30, Quality of Life Questionnaire Core 30.

Secondary outcome measures

The secondary outcome measures for the main trial were to be determined during the feasibility study. During the pilot trial we measured surgical morbidity using the Accordian [see www.accordionclassification.wustl.edu/ (accessed 21 January 2016)] and Clavien–Dindo[23] classifications, which include assessment of in-hospital mortality and need for reoperation. Survival time was recorded for any individual dying during the follow-up period, as was the time until the onset of palliative care/diagnosis of recurrent disease. Procedural outcome measures included the lymph node count, duration of operation and blood loss. Generic and disease-specific measures of patient-reported health were taken, including the EORTC Quality of Life Questionnaire Core 30 (QLQ-C30)[21] and QLQ-OES18[17] plus the European Quality of Life-5 Dimensions five-level version (EQ-5D-5L).[24] Length of hospital stay, defined as time from day of operation to discharge home, was noted for each trial participant. Further measures of resource use were considered in the health economics feasibility work.

Further measures

Presurgical pathological staging used evidence from a multidisciplinary team review of imaging (computerised tomography, positron emission tomography, endoscopic ultrasound and laparoscopy) and was recorded according to the tumour, node, metastasis (TNM) system (*Table 2*). Instances in which the primary tumour (T×), nodes (N×) or metastases (M×) could not be assessed, in which there was no evidence of a primary tumour (T0) and in which carcinoma in situ (Tis) was diagnosed were also recorded using the indicated additional codes. The TNM categories were combined into numerical stages for tabulation, these being stage 1A (cancer in the lining of the oesophagus only), stage 1B (cancer beginning to spread to the muscle wall), stage 2A (cancer has grown through the wall of the oesophagus), stage 2B (cancer has spread to one to two lymph nodes) and stages 3A, 3B or 3C (cancer is beginning to spread beyond the oesophagus into surrounding tissues, lymph nodes and organs).

TABLE 2 The TNM system applied to oesophageal tumours

TMN code	TMN category
T1	Tumour invades the lamina propria or submucosa
T2	Tumour invades the muscularis propria
T3	Tumour invades the adventitia
T4a	Tumour invades the pleura, pericardium or diaphragm
T4b	Tumour invades other adjacent structures, such as the aorta, vertebral body or trachea
N0	No regional lymph node metastasis
N1	Metastasis in one to two regional lymph nodes
N2	Metastasis in three to six regional lymph nodes
N3	Metastasis in seven or more regional lymph nodes
M0	No distant metastasis
M1	Distant metastasis

Source: American Joint Committee on Cancer.[25]

Integrated qualitative research to optimise recruitment

A major focus of the feasibility study was to evaluate the acceptability of the ROMIO trial to patients and clinicians and to investigate the reasons underlying recruitment difficulties to ensure high levels of recruitment and informed consent.[26,27] To this end, an integrated qualitative study, based on previous work by Donovan and colleagues[28–31] in the NIHR HTA programme-funded ProtecT (Prostate testing for cancer and Treatment) study, was undertaken. There were two aspects to this work: understanding recruitment issues and development of a recruitment strategy.

Understanding recruitment issues

The first aspect was addressed through in-depth interviews, undertaken by an experienced qualitative researcher, with a maximum variation sample of between 10 and 15 patients eligible for the trial (selected to include the range of age, disease severity, socioeconomic status and centre). These interviews explored patient perspectives of oesophageal cancer and its treatment, views about surgery and study information and the acceptability of randomisation between procedures, including potential barriers to randomisation. In-depth interviews with clinical investigators and staff undertaking recruitment to the trial explored their ability to summarise the details of the trial design and protocol, their views about the evidence on which it is based, their perceptions of levels of uncertainty/equipoise in relation to the trial arms, their views about how the arms are or can be delivered in their clinical centre, methods for identifying eligible patients and examples of actual recruitment successes and difficulties. Numbers of interviews were guided by the concept of data saturation: the need to continue sampling until findings become repetitious. Interview data were analysed thematically and using case study approaches, looking for shared or disparate views among investigators, clinicians, recruiters and potential participants and within or between centres.[32,33]

Digital audio recorders were provided to the recruitment staff so that they could audio record appointments at which they provided information for patients and attempted to recruit them to the ROMIO trial. These recordings were analysed thematically and also using a version of conversation analysis pioneered in previous studies[33–35] to identify aspects of information provision that were unclear, disrupted and hinder recruitment and that could thus be targeted for improvement.

The qualitative researcher worked with the two study nurses to map the patient eligibility and recruitment pathways that are established, including when patients receive information about the trial and which members of the clinical team they meet and when. Logs of eligible and recruited patients were assembled using simple flow charts and counts to display numbers and percentages of patients at each stage of the eligibility and recruitment process and allow comparison with the original protocol. Previous research[29–31] has shown that logistical and other local issues sometimes prevent full implementation of the protocol and can consequently lead to less efficient recruitment pathways.

Development of a recruitment strategy

The second aspect was the development of a recruitment strategy. The findings from these qualitative investigations and their potential impact on recruitment were summarised and presented to the ROMIO investigators. When necessary the recruitment process was modified in light of the specific qualitative research findings, the changes including a mix of bespoke and generic measures. Actions specific to the ROMIO trial were grounded in the findings of the integrated qualitative research and could include, for example, changes to the descriptions of surgical procedures in study information. Training of recruitment staff is an example of a generic approach that has been found to be useful in previous trials,[29,32] with topics including how to elicit and address patient preferences and how to manage personal (clinical) preferences.

Once the recruitment plan was agreed it was implemented during the latter part of the feasibility study recruitment period. Recruiters were strongly encouraged to continue recording their appointments with potential participants so that these could be analysed iteratively to check that the new process was being implemented and to identify any emergent difficulties. Individual feedback to recruiters was provided

confidentially by the qualitative researcher and anonymised findings from the recordings were used in a recruitment training programme for the main trial. Logs of eligible patients and randomisation rates continued to be measured.

Blinding to treatment allocation

Methods to achieve blinding of patients and outcome assessors were piloted during the feasibility work, to inform whether or not this could be achieved by methods acceptable for the main trial. Attempts were made to blind patients during the first week post surgery when they were completing pain assessments on day 2 and day 6. On day 6 participants also complete questionnaires assessing generic and disease-specific aspects of HRQoL before being unblinded. Blinding was piloted using large adhesive dressings that were provided to participating sites by the trial office for the dressing of patients' surgical wounds. The dressing was positioned similarly on all trial patients regardless of the type of surgery (covering the positions of abdominal, thoracic and cervical incisions). The first dressing was applied by the surgical team in the operating theatre. The dressing was not changed unless required (because of soiling or lack of adherence) until day 3. It was then changed by the research nurses, who were not routinely involved with the patients' care. During the dressing changes patients were asked to turn their head away to prevent them observing the wounds. The nurses washed and cleaned the sites of all actual and potential incisions on the abdomen. Dressings were supplied as part of the set-up process, with additional dressings supplied as required. On days 2 and 6 the success of blinding was assessed. Patients were asked to complete the Bang Blinding Index,[20] which assesses the success of blinding by asking patients to guess which arm of the trial they were allocated to. Dressings were removed after 1 week (after the second questionnaire assessment).

Quality assurance and monitoring fidelity to operative protocols

With regard to quality assurance and monitoring fidelity to operative protocols, the aims of the feasibility work were to develop (1) a manual for mandatory and optional operative steps of oesophagectomy to be followed in the definitive trial; (2) an operation note to record the execution of the oesophagectomy by the surgeon; (3) a reliable video assessment tool to evaluate the technical performance of oesophagectomy prior to a surgeon's entry into the trial; and (4) a photographic evaluation tool for oesophagectomy to assess adherence to the trial protocol. Full ethical approval of this aspect of the research was obtained (Research Ethics Committee reference 11/NW/0895) and confirmed locally as appropriate. *Table 3* defines the technical terms used in the following sections to maintain the clarity and conciseness of the methods described.

Semistructured interviews and structured observations

Semistructured interviews and structured observations,[36] performed with peer-identified expert surgeons at specialist centres for oesophagectomy in the UK, the USA and Japan, provided experience of variations in clinical practice worldwide. Interviews were digitally audio recorded (with the participants' verbal consent) before being transcribed, checked for accuracy and qualitatively analysed using thematic analysis.[37]
By means of contingency, shorthand written records were also kept at the time of interview in case of digital data loss. Structured observations were written in a research diary kept by the researcher. A second researcher was present for some of the procedures in the UK and all of those in Japan. A debrief was held at the end of each observed operation, which permitted comparison of notes between researchers. A second researcher was not present in the USA, although digital video recordings were obtained, with the appropriate approvals in place, for analysis in the UK.

TABLE 3 Definitions of technical terms used in the quality assurance section

Term	Definition
Quality assurance	A method of ensuring that specifications and requirements are met while preventing mistakes
Semistructured interview	A social science research method that permits further exploration of interviewee responses, in addition to a predefined framework of questions
Structured observation	Observations that focus on a predetermined task
Action research	The process of actively participating in a situation while simultaneously performing research
Thematic analysis	A qualitative research method used to identify themes within data
Hierarchical task analysis	A method used to describe a task in great detail, within a hierarchical structure
Delphi consensus process	A process whereby group consensus is achieved through communication of expert opinion
Face validity	The extent to which real life is resembled
Content validity	The extent to which the domain being measured is actually measured
Construct validity	The extent to which a test measures what it purports to measure and/or discriminates between different levels of ability
Inter-rater reliability	The extent to which two or more observers agree

Hierarchical task analysis for oesophagectomy

Findings from the published literature and online digital media were combined with thematic analysis of the semistructured interviews and structured observations to create a hierarchical task analysis for two-field oesophagectomy.[38]

Several iterations of the hierarchical task analysis were written and revised. The accuracy of each hierarchical task analysis was tested against a real-time or recorded oesophagectomy until no additional changes were identified. A final version of the hierarchical task analysis was then constructed and tested against a series of subsequent operations, for which the researcher was present as an observer.

Delphi consensus process for the oesophagectomy hierarchical task analysis

Ten peer-identified expert surgeons, each with significant personal experience of performing oesophagectomy, were electronically invited to participate in a Delphi consensus process.[39] This method was selected to ensure the underlying face and content validity of the final assessment tool as well as surgeon acceptance of the defined procedure. Expert surgeons who had been involved during the development of the hierarchical task analysis were excluded. The 10 invited surgeons were Mr Barham (ROMIO), Mr Berrisford (ROMIO) and Mr Hardwick from the UK; Professor Van Lanschot, Professor Hoelscher, Professor Pera and Professor Zaninotto from Europe; Dr Donald Low from North America; and Professor Simon Law from Hong Kong.

In the first Delphi round, each surgeon was provided with the final hierarchical task analysis and a questionnaire on which they were requested to rate the necessity of each step identified in the analysis as mandatory, optional or prohibited, rather than using the traditional Likert-scale rating system. This was in line with ROMIO trial requirements. Additional free space was available for comments and suggestions on each step of the hierarchical task analysis as well as in general. Completed questionnaires were returned to Professor Hanna electronically and analysed by the clinical research fellow. An arbitrary consensus agreement of 75% was sought for each step.

This process was repeated in the second Delphi round, during which the nine respondents from the first Delphi round were electronically sent the percentage agreement and anonymised comments for each step of the hierarchical task analysis (rather than the traditional mean and standard deviation). The original analysis was resent, along with a fresh Delphi questionnaire. If respondents' answers remained outside of the majority agreement, they were asked to provide reasons for this in the comments section. For steps in which consensus agreement could not be reached by the end of the second Delphi round, the researcher consulted Professor Hanna at Imperial College London. It was decided that a majority opinion could be upheld if it reflected the findings of the evidence-based hierarchical task analysis.

Development of an operation manual for oesophagectomy

A full operation manual was constructed for circulation to surgeons entering the ROMIO trial, based on the Delphi consensus approved hierarchical task analysis and its original evidence base (i.e. the published literature, semistructured interviews and structured observations). The operative steps for both open oesophagectomy and MIO were identical. As such, each step of the operation, both mandatory and optional, was described in detail and diagrams illustrated the required en-bloc lymphadenectomy.

Development of an operation note for oesophagectomy

An operation note was constructed by way of an iterative process. It was designed to satisfy both the clinical requirement of providing a legal record of the operation performed and the research requirement of quality assurance. Its structure was based on the standard operation note currently in use at St Mary's Hospital, London, and combined its generic content (namely patient identifiers, operating surgeon and assistants, procedure performed, operation date, incision, findings, procedure, closure, and postoperative instructions) with the evidence-based operation manual specific to the ROMIO trial.

The body of the operation note included a tick-box version of the operation manual, permitting surgeons to rapidly provide a detailed outline of the procedure performed. White-space boxes were incorporated for patient identifiers; operative findings; specific details of a task, for example the anastomosis; deviations from the trial protocol; errors and their recovery; and postoperative instructions. Two upper gastrointestinal cancer surgeons at St Mary's Hospital, London, piloted the operation note over the course of 3 months and provided informal verbal constructive feedback to the primary researcher. Surgeons at the two centres involved in the ROMIO feasibility study also piloted the operation note.

Development and examination of the reliability of a video assessment tool for oesophagectomy

Results obtained from the semistructured interviews and structured observations performed previously confirmed the importance of the technical performance (i.e. process) and oncological quality (i.e. immediate outcome) of the operation, in accordance with the Systems Engineering Initiative for Patient Safety (SEIPS) model using a structure–process–outcome approach.[40] Various techniques were considered that would permit independent remote blind evaluation of (1) the process (safety and efficiency) and (2) the quality of the end product. It was decided that only a video assessment tool could address all of these aspects.

Elements relevant to the safety and efficiency of the operative process, as well as the oncological quality of the end product, were identified from thematic analysis of the semistructured interviews and structured observations such that clear definitions for each of the terms used were composed. An existing validated consultant-level surgical assessment tool[41] was deconstructed and its underlying principles adapted during the structural development of this video assessment tool.

Several different video assessment tools were written and piloted at St Mary's Hospital, London, over the course of 3 months. Each iteration placed a different emphasis on rating the element being assessed, with the intention of balancing the technical safety with which each task was performed with the surgeons' efficiency and the oncological quality of their dissection. Eight videos, randomly selected from the two centres involved in the study, were rated by two independent blind assessors (senior consultant surgeon with 20 years' experience in upper gastrointestinal surgery and a post Certificate of Completion of Specialist Training clinical fellow at consultant grade) to determine inter-rater reliability, which was calculated using Cohen's kappa.

Development of a photographic assessment tool for oesophagectomy

While in Japan, researchers from Imperial College London had witnessed how photographs taken intraoperatively could be used for quality assurance purposes. Therefore, the outcome component of the final video assessment tool was isolated for use as a photographic assessment tool, focusing on the completeness of the lymphadenectomy and exposure of the relevant anatomical landmarks.

Processing of the pathological specimens

This aspect of the feasibility work aimed to reach agreement on a uniform approach to the processing of pathological specimens, through collaboration between histopathologists at the two centres and the independent study pathology lead. This included the approach to the dissection of lymph nodes from the main specimen and lymphadenectomy specimens, standardised techniques for the sampling of lymph nodes to achieve the maximum yield from all cases and microscopic and macroscopic assessment of the surgical resection margin. Quality control was based on regular exchange of material for cross-evaluation.

Development of a core outcome set to assess outcome for oesophageal cancer surgery

The ROMIO feasibility study incorporated work to develop a core outcome set, defining adverse surgical events and benefits, using similar methodology as used by the Outcome Measures in Rheumatology (OMERACT) group.[42] The basic aim of core outcome set work is to ensure that trials in an area report at least a common set of core outcomes, allowing for evidence synthesis and cross-study comparisons as well as reducing reporting bias.

Systematic literature reviews identified all of the current reported clinical outcomes of oesophageal cancer surgery (and their definitions). Qualitative interviews with clinical nurse specialists, dieticians, patients and primary care representatives identified additional potential outcomes of importance that were not identified from literature searches. Delphi methodology with surgeons and patients reduced the potential list to a shorter list of outcomes to be discussed at the consensus meetings. In the Delphi survey, stakeholders were asked to rate the importance of each potential outcome in the core outcome set and two rounds were undertaken to reduce the list according to prespecified criteria. Each Delphi round was analysed to identify key or redundant items in the list. Consensus meetings were convened to allow further anonymised rating of the importance of retained items. This work linked with the Medical Research Council methodology hub research network-funded project Core Outcome Measures in Effectiveness Trials (COMET)[43] led by Professors Paula Williamson, Jane Blazeby, Doug Altman and Mike Clarke.

Economic evaluation

The objective of the economic evaluation work was to explore the best way of capturing resource use and costs in relation to the interventions and follow-up in secondary care. Questionnaires and resource use logs were also developed to collect use of community-based NHS services and social services and direct and indirect costs incurred by patient and carers. Unit costs from hospital finance and routine sources were then to be applied to the resource use data.

The original intention had been to establish the face validity of the resource use questionnaires for patients through qualitative interviewing using 'thinking aloud' techniques. However, following development of the 3-month follow-up questionnaire, clinician opinion indicated that patients would frequently be too ill to complete the questionnaire. As decision was made to redevelop the questionnaires into a telephone interview format, which could be administered by research nurses at 3 and 6 months post surgery.

The resource use data were separated into different categories (e.g. theatre, outpatient visits, general practitioner visits) and the average costs for all of the different categories were compared by arm. This enabled the main cost drivers of the interventions to be established and the identification of potential areas where cost differences exist between the arms in addition to identifying areas where obtaining accurate estimates of cost is problematic. This would enable a more focused collection of resource use data in the main trial, which will result in a more accurate estimate of cost-effectiveness.

There are two different types of costing methodology that can be used within an economic evaluation: the use of Healthcare Resource Groups (HRGs) and microcosting. HRGs are groups of different events (based on procedures and/or diagnoses) that are deemed to use similar amounts of resources. Costs can then be applied to the HRGs using national reference costs. Microcosting is a methodology in which resource use at a more granular level is captured (e.g. number of consultant contacts, medication use, time in theatre). Given that the different types of oesophagectomy are incorporated within the same HRG, a microcosting approach is needed in terms of the initial inpatient stay for the oesophagectomy, whereas it is possible to use HRGs for subsequent inpatient stays. Within the feasibility trial it was explored how best to microcost the initial inpatient stay and how best to obtain the information needed to use HRGs for the follow-up period.

Chapter 3 Results

Results of the pilot randomised controlled trial

Recruitment

When planning the feasibility study we stated that:

> *We anticipate a smooth progression to the main trial if a randomisation rate of at least 50% of eligible patients can be achieved in the pilot trial, . . . , and if at least a mean of 2.5 eligible patients per month can be identified in each pilot trial centre.*

The feasibility work has shown that it is possible to recruit to a trial in which patients are randomly allocated to the different approaches to oesophagectomy. *Figure 1* shows the accumulation of participants in the ROMIO randomised trial until the end of December 2014. In the 21 months of recruitment 263 patients have been assessed for eligibility, of whom 135 (51%) were found to be eligible and 104 (77%) were randomised across the two centres. These figures exceeded our targets for eligible patients (2.5 patients × two centres × 21 months = 105 eligible patients) and randomised patients (105 eligible patients × 50% = 52.5 patients randomised) by the end of December 2014. Of the 104 randomised patients, 46 were at Plymouth (open surgery, $n = 22$; LAO, $n = 24$) and 58 were at Bristol (open surgery, $n = 19$; LAO, $n = 20$; MIO, $n = 19$).

In the light of the excellent rate of recruitment to the ROMIO pilot trial, we continued beyond the planned closure date of 31 March 2014 and successfully applied for a contract variation to allow recruitment until the start of the main trial (planned start of the main trial is mid-2016). As recruitment is ongoing the database is still live and so, for the purposes of the remainder of this report, we focus on those patients randomised on or before 31 August 2014. By this date there were 48 participants at Bristol

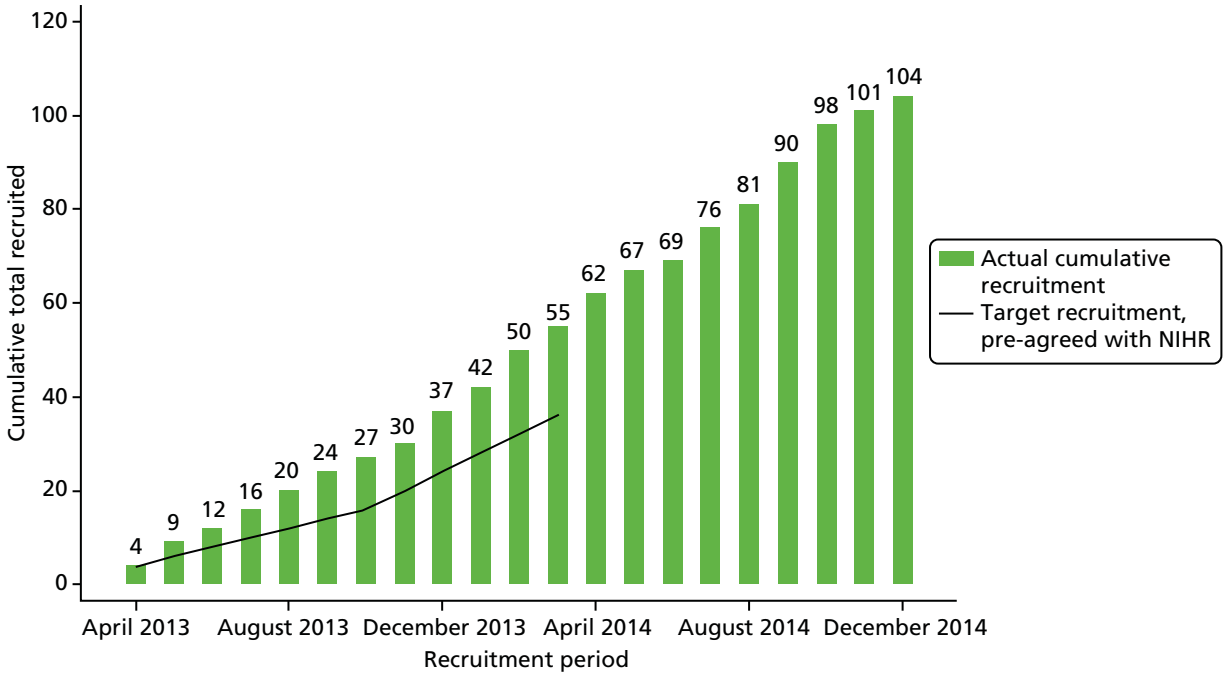

FIGURE 1 Actual and target recruitment up to December 2014. Recruitment to the study is continuing.

and 33 participants at Plymouth. Furthermore, as we now plan to include the pilot trial data in the main trial analysis we no longer plan an unblinded analysis during the feasibility stage and so the only post-randomisation variables that we present by study arm are actual surgery undergone, the assessment of blinding during the first week post surgery and follow-up completion rates.

Balance across treatment arms

Table 4 presents summary statistics for the baseline measures of several important variables by centre and trial arm. Approximately equal numbers of patients were allocated to each of the study arms available within each centre. As expected, by far the majority of participants were male and the mean age at randomisation was approximately 66 years for each treatment group, with a standard deviation of approximately 7 years. A lower proportion of patients had undergone neoadjuvant treatment before surgery in Plymouth than in Bristol, although the proportion in each treatment arm was well balanced within each centre.

The majority of participants had a history of smoking, with perhaps a slightly lower prevalence in Plymouth. At both centres smoking was well balanced across the study arms. About one-third of men had consumed alcohol on ≥ 3 days per week over the 12 months preceding diagnosis at both centres, with this variable being well balanced between the treatment arms.

For the feasibility study, baseline spirometry measurements were taken at Plymouth only (the Bristol group has recently bought a bedside spirometer for use in the study and intend to carry out these measurements in the planned definitive trial). The mean forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC) were markedly lower than expected for men of this average age[44] and both measures were balanced across the two treatment arms at Plymouth.

Table 5 presents the TNM categories and numerical disease staging by intervention arm for each centre. Most participants had a tumour that was growing through the wall of the oesophagus but involving one to two lymph nodes at most (stages 2a and 2b) or a cancer that had just started to spread to the tissues surrounding the oesophagus (stage 3a). There was no convincing evidence of an imbalance between the randomised intervention arms in terms of disease staging. Summarising the three numerical stages, it is apparent that the vast majority of patients had a stage-2 or stage-3 tumour.

TABLE 4 Baseline variable summary statistics presented by allocated arm within each centre

	Bristol			Plymouth	
Variable	Open surgery ($n = 16$)	LAO ($n = 17$)	MIO ($n = 15$)	Open surgery ($n = 17$)	LAO ($n = 16$)
Male, *n* (%)	16 (100)	14 (82)	14 (93)	16 (94)	14 (88)
Age, mean (SD)	68 (7.7)	66 (6.9)	66 (5.5)	65 (11)	67 (9.3)
Ever smoked, *n* (%)	12/16 (75)	14/17 (82)	13/15 (87)	10/16 (63)	8/12 (67)
Consumes alcohol 3+ days a week, *n* (%)	5/16 (31)	6/16 (38)	3/14 (21)	3/16 (19)	6/13 (46)
Neoadjuvant treatment, *n* (%)	14 (88)	14 (82)	14 (93)	12 (71)	11 (69)
FEV_1, mean (SD)				2.7 (0.9)	2.4 (1.1)
FVC, mean (SD)				3.7 (0.9)	3.4 (1.1)

FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; SD, standard deviation.

TABLE 5 Baseline pathological staging by allocated arm within each centre[a]

	Bristol			Plymouth	
TNM category (numerical stage)	Open surgery ($n = 16$)	LAO ($n = 17$)	MIO ($n = 15$[b])	Open surgery ($n = 17$)	LAO ($n = 16$[b])
Not assessed	1	1	1	3	0
Carcinoma in situ	0	1	0	0	0
T1N0 (1a)	1	1	0	0	1
T2N0 (1b)	0	0	3	1	2
T3N0 (2a)	5	4	2	6	7
T1N1, T2N1 (2b)	2	1	1	2	0
T1N2, T2N2, T3N1, T4aN0 (3a)	5	7	7	4	6
T3N2 (3b)	0	1	0	1	0
T1N3, T2N3, T3N3, T4aN1, T4aN2 (3c)	2	1	1	0	0
Summary					
Stage 1	1	1	3	1	3
Stage 2	7	5	3	8	7
Stage 3	7	9	8	5	6

a See *Table 2* for an explanation of the TNM system with respect to the oesophagus.
b Because of non-specific recording of the diagnostic stage, the final pathological stage is included here for two patients.

Adherence to allocated treatment

Tables 6 and *7* present the surgical approach actually undertaken for patients in each arm of the study for the Bristol and Plymouth centres, respectively. For patients recruited up to 31 August 2014 at the Bristol centre, the allocated surgical approach was followed for 79% (38/48) of patients.

The three patients for whom the allocation to open surgery could not be followed were found to be inoperable. Of the patients allocated to LAO, one was converted to open surgery to stop a bleed, one requested MIO having spoken to a patient who had undergone this procedure previously and one underwent a gastrectomy for more extensive disease. Four patients allocated to MIO underwent LAO, two because of the position of the tumour and two because a surgeon was not available to undertake the MIO procedure.

For patients recruited up to 31 August 2014 at the Plymouth centre, the allocated approach to surgery was followed in every case (see *Table 7*). Note that one man at the Plymouth Centre withdrew from the study the day after being allocated to LAO, owing to being very deaf and becoming confused concerning the trial procedures.

TABLE 6 Surgical approach undergone by allocated approach for the Bristol centre

	Allocated		
Undergone	Open surgery ($n = 16$)	LAO ($n = 17$)	MIO ($n = 15$)
Open surgery	13	1	0
LAO	0	14	4
MIO	0	1	11
Other	3	1	0

TABLE 7 Surgical approach undergone by allocated approach for the Plymouth centre

	Allocated	
Undergone	Open surgery ($n = 17$)	LAO ($n = 15$)
Open surgery	17	0
LAO	0	15
Other	0	0

Postsurgical measures

Table 8 presents summary statistics for a number of postsurgical measures for 80 patients recruited on or before 31 August 2014. The median length of postsurgical stay across the two centres was 10 days, with stays typically lasting between 8 and 16 days. Two deaths occurred within 30 days of surgery, with a further death occurring on the 31st postsurgical day. Three patients experienced anastomotic leaks, all of which resulted in a return to theatre. A further nine patients returned to theatre one or more times. Eight patients returned to the intensive care unit, six because of respiratory problems and two because of renal failure. Nine patients were readmitted within 30 days of surgery.

Completeness of follow-up

Table 9 enumerates the numbers of patients who should have been invited to complete the visual analogue scale of pain at days 2 and 6 post surgery, the numbers actually completing the scale and the reasons for non-completion.

Completion of the pain scale at day 2 was low (40/80, 50%), the reasons for non-completion being illness or insufficient recovery (9/80, 11%), lack of cover to administer the scale at the weekend (16/80, 20%) and administrative errors (9/80, 11%), which included erroneously skipping the pain scale if the patient was unblinded. Completion of the pain scale was considerably better at day 6 (65/80, 81%).

TABLE 8 Postsurgical measures

Measure	% (events/number at risk)
Risk of death within 30 days of surgery	2.5 (2/80)
Risk of anastomotic leakage	3.8 (3/80)
Risk of return to theatre	15.0 (12/80)
Risk of return to ITU	10.0 (8/80)
Risk of readmission within 30 days	11.4 (9/79)[a]

a Two patients not included in this measure, one withdrawal and one died during initial admission.

TABLE 9 Completion of pain scales at days 2 and 6 post surgery

Measure	Day 2	Day 6
Patients participating and with data entry finalised, *n*	80	80
Patients completing the pain scale, *n*	39	64
Reasons for non-completion, *n*		
Patient too ill/insufficiently recovered to complete pain scale	9	4
Assessment at weekend and cover not arranged	16	0
Administrative error	9	5

Table 10 indicates the completion of the QLQ-C30 at baseline, 6 days post surgery and 6 weeks and 6 months post randomisation.

The physical function subscale of the QLQ-C30 assessed at 6 weeks will be the primary outcome measure for the planned definitive trial. This assessment was available for 75% (60/80) of participants. Nine of these participants were missing a baseline assessment of this measure, likely because of the short interval between assessment appointment and surgery at one centre. Those participants not having an assessment of the QLQ-C30 were equally split between those who did provide later assessments and those who provided no subsequent information. The nine patients in the latter group included two patients who had been found to be inoperable during surgery.

TABLE 10 Completion of the QLQ-C30 at baseline, 6 days post surgery and 6 weeks and 6 months post randomisation

Measure	Patients, *n*
Patients participating	80
All four assessments complete	28
Baseline and 6-week assessments required for primary analysis complete but at least one other assessment missing	23
Baseline assessment missing	9
6-week assessment missing but subsequent assessments available	10
6-week assessment missing, no subsequent assessments available	10

Quality assurance and monitoring fidelity to operative protocols

Semistructured interviews and structured observations

In total, eight separate semistructured interviews were performed with six surgeons from the UK and two from the USA (*Table 11*). Themes arising from the qualitative analysis of these interviews are documented in *Table 12*. In addition, > 50 operations, performed by 16 surgeons from the UK ($n = 9$), the USA ($n = 6$) and Japan ($n = 1$), were observed in seven different hospitals. Structured observation notes were combined with findings from the 'operative procedure' theme identified from the semistructured interviews and incorporated into the hierarchical task analysis.

Hierarchical task analysis

The result of the hierarchical task analysis is presented in *Appendix 1*.

Operation manual and essential tasks

Appendix 2 presents the operation manual detailing mandatory (essential) and optional tasks. Given the length of the full manual, a separate summary document describing 10 essential steps for each of the abdominal and thoracic phases of the operation was also produced and is presented in *Appendix 3*.

TABLE 11 Surgeon demographics from the semistructured interviews

Characteristics of surgeons interviewed ($n = 8$)	Median (range)
Age in years, median (range)	46 (41–62)
Number of years as a consultant, median (range)	10 (4–21)
Number of years performing oesophagectomies, median (range)	14 (7–21)
Number of oesophagectomy cases performed per year, median (range)	20 (5–50)

TABLE 12 Synopsis of the thematic analysis of the semistructured interviews

Theme	About the theme	Selected quotations
Surgical expertise	Identified key attributes of surgical expertise	S3: 'The provision of safe and effective care' S5: 'The knowledge, experience, and competence of an individual surgeon'
Expert surgeon	Identified how an expert surgeon can be defined	S1: 'Peer recognition and above average patient outcomes' S1: 'Not all consultants are expert surgeons' S2: 'All consultants are experts to some extent' S5: 'Expertise is a scale and its measures are multidimensional'
Operative procedure	Identified key operative steps, focusing on the associated anatomy, process and end product	Hierarchical Task Analysis, see *Appendix 1*
Operative considerations	Identified key perioperative factors	S3: 'The MDT decision making process. No one person is more important than another in this process'
Areas for improvement	Identified key areas that could be improved nationally	S1: 'The surgery. Doing the operation well' S2: 'Post-operative care requires standardisation' S6: 'Guidance on the optimal procedure'

MDT, multidisciplinary team.

Operation note

The operation note is presented in *Appendix 4*. This note allows recording of performance of or variation from steps in the manual, errors incurred and recovery mechanisms. This will allow root cause analysis of adverse events.

Video and photographic assessment tools

To allow a standardised assessment of video and photographic recording of surgical procedures, assessment tools were produced and are presented in *Appendices 5* and *6*, respectively.

Implementation in the feasibility study

The manuals, notes and assessment tools for quality assurance were approved by the ROMIO Trial Steering Committee on 15 November 2013. The approved documents were piloted during the ROMIO feasibility phase. An online encrypted file transfer process was set up by the team at Imperial College London. The Imperial College London Clinical Governance Officer arranged local access to the server and a nominee from each site, for example a nurse specialist, was identified to upload the files. The system was tested in both centres and all surgeons submitted video records from their surgery. Twenty-five operative videos were transferred using the online system. Blind independent assessors evaluated the operative performance using the video assessment tool, indicating that an objective video-based assessment system is feasible and can be applied in the main trial. Sets of intraoperative photographs of the operative field were obtained by the surgeons and transferred using the same online system. Surgeons used the operation notes to record the steps of the procedures.

Processing of the pathological specimens

In two face-to-face meetings between the lead pathologists at each of the two feasibility study centres and Professor Goldin, the study's independent histopathologist, consensus was reached on the following approach to the processing and reporting of 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.[45] The pathology data for the trial will be collected using a standardised form and will represent data points included within the Royal College of Pathologists data set. Data points that will serve as surgical quality assurance 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 (pathologically determined tumour) stage, pN (pathologically determined node) stage and pM (pathologically determined metastasis) stage. For pathology quality assurance purposes, the slides of 10% of all cases from each centre will be reviewed by the lead pathologist.

Blinding to treatment allocation

During the pilot trial, patients were asked at 2 and 6 days post surgery to state which surgical technique they had undergone. *Table 13* gives the responses by allocation for the two assessments for patients randomised up until 31 August 2014 at the Bristol centre (total $n = 47$). Those patients who did not undergo their allocated procedure are excluded from this table ($n = 9$), whereas those patients who became unblinded are included as knowing their allocation. For the day-2 assessment, 12 measurements are missing because of administrative errors (largely problems organising weekend cover in the first few weeks of the study, $n = 9$) and because of patients not being sufficiently recovered from surgery to complete the inventory ($n = 3$). The day 6 assessment is a little more complete. These data indicate that blinding was successful during the first week post surgery, with the majority of patients who stated a surgical approach believing that they had undergone LAO at day 2 and LAO or MIO at day 6, irrespective of the approach that they had actually undergone.

Table 14 provides the patient beliefs about treatment received by allocated treatment arm for the Plymouth centre (total randomised by 31 August 2014 $n = 28$). As for the Bristol centre, the majority of patients believed that they had undergone the LAO procedure at both day 2 and day 6, irrespective of the arm to which they had been allocated.

TABLE 13 Patient beliefs about the surgical approach undergone by actual allocation at day 2 and day 6 at the Bristol centre

	Day 2 ($n = 26$)			Day 6 ($n = 35$)		
	Allocated			Allocated		
Response	Open surgery	LAO	MIO	Open surgery	LAO	MIO
Open surgery	2	0	1	2	0	1
LAO	3	4	5	7	7	5
MIO	3	0	0	2	3	3
Don't know	2	3	3	0	3	2

TABLE 14 Patient beliefs about the surgical approach undergone by actual allocation at day 2 and day 6 at the Plymouth centre

	Day 2 ($n = 23$)		Day 6 ($n = 24$)	
	Allocated		Allocated	
Response	Open surgery	LAO	Open surgery	LAO
Open surgery	1	2	5	1
LAO	9	6	7	7
Do not know	1	4	1	3

Between-centre variability and learning effects

During meetings of co-applicants for the proposed definitive ROMIO trial, it was agreed to follow the same approaches to between-centre variability in, and learning effects on, clinical outcome. The analysis accommodates any between-centre variation by distinguishing the surgical centres through the inclusion of dummy variables as covariates in the analysis model. Learning effects will be controlled for by only allowing surgeons with a defined level of experience to recruit to the definitive ROMIO trial and by monitoring fidelity to the treatment manual through assessment of video and photographic evidence during the trial. Subsequently, during the statistical analysis we will look for evidence of improvement in the results of each procedure over time, by the inclusion of time as a covariate. Evidence of a residual effect of learning will prompt a sensitivity analysis omitting each surgeon's initial operations for the trial.

As we intend to add the feasibility data to those obtained in the planned definitive ROMIO trial, we have not conducted the unblinded by arm analysis on the existing data, necessary to pilot this statistical plan.

Integrated qualitative research to optimise recruitment

A major focus of the ROMIO feasibility study has been to evaluate the acceptability of the ROMIO trial to patients and clinicians and to investigate the reasons underlying any recruitment challenges expected or experienced to optimise recruitment and informed consent. To this end, an integrated qualitative study, based on previous work by Donovan and colleagues[28–31] in the NIHR HTA programme-funded ProtecT study, has been undertaken. The patient eligibility and recruitment pathway at each centre has been mapped through the recruitment process, including when patients receive information about the trial and which members of the clinical team they meet and when, to identify any unique local issues potentially

affecting trial recruitment. Logs of eligible and recruited patients were made using simple flow charts and counts to display numbers and percentages of patients at each stage of the eligibility and recruitment process and allow comparison with the original protocol at each centre. In-depth interviews with nine clinical investigators and staff undertaking recruitment (six surgeons, three nurses) have been conducted and analysed to explore their views about the evidence on which the trial is based, their perceptions of levels of uncertainty/equipoise in relation to the trial arms, their views about how the arms are or can be delivered in their clinical centre and their views about methods for identifying eligible patients. Audio recordings of a little over 100 consultations have also been conducted and analysed to scrutinise the ability of recruiters to summarise the details of the trial design, protocol and provide information about the trial, and to identify examples of actual recruitment successes and challenges. This has informed feedback and training meetings with recruiters in Plymouth (November 2013) and Bristol (February and April 2014), an update of the patient information provided at recruitment and the development of a 'recruitment tips' guidance document for recruiters. The findings from this recruitment investigation in the ROMIO feasibility study will be used to inform the provision of training and guidance for recruiters in the definitive ROMIO trial.

Development of a core outcome set to assess outcome for oesophageal cancer surgery

We developed a core outcome set to evaluate the clinical effectiveness of oesophageal cancer surgery. Literature reviews identified 901 measures, which were synthesised into 67 outcome domains (representing both clinical and patient-reported outcomes) and operationalised into 68 questions. These items were formatted into a questionnaire. Delphi methodology was used to reduce the initial list of outcome domains to a final core set according to prespecified criteria by surveying key stakeholders (consultant surgeons, clinical nurse specialists and patients), asking them to prioritise the items.

Round 1 of the survey commenced in December 2014. First-round questionnaires were returned from 186 out of 221 (84%) participants, including 115 out of 126 (91%) patients and 71 out of 95 (75%) professionals. Second-round response rates were also high for both patients (94/108, 87%) and professionals (65/81, 80%). Analyses of responses led to 41 and 19 outcomes being retained as important after the first and second surveys, respectively. The retained outcomes from the second survey were presented at a face-to-face patient consensus meeting at which patients were asked to anonymously rate their importance. The final core outcome set includes 10 outcomes (*Box 1*).

BOX 1 Core outcome set for oesophageal cancer surgery

1. Overall survival.
2. In-hospital mortality.
3. Inoperability.
4. The need for another operation at any time and for any cause.
5. Chest infection or respiratory complications including reventilation.
6. Conduit necrosis and the need for formation of an oesophagostomy.
7. Severe problems related to nutrition requiring an intervention, such as feeding by intravenous drip or through the stomach.
8. Overall quality of life.
9. The ability to eat and drink more easily, including swallowing.
10. Problems with acid indigestion or heartburn, including at night.

Economic evaluation

Initial inpatient stay incorporating the oesophagectomy

Initial meetings with finance personnel at one of the sites and subsequent approaches to finance departments within all of the sites established how resource use was costed within the different hospitals. This will enable resource use information to be collected in the correct way in terms of measurement (e.g. different types of medical staff contacts can be measured using the number of visits to the patient or the actual time spent visiting the patient), which will then ensure that costs from the finance departments can be applied.

Follow-up inpatient stays and outpatient visits

The follow-up Clinical Report Form (CRF) was designed to enable HRGs to be created. The level of detail needed for this to be carried out correctly can be time-consuming. Different approaches to obtaining the HRGs for any subsequent inpatient stays have been explored.

Coders within the hospitals were initially approached as they allocate codes to diagnoses, procedures, complications and comorbidities. These codes are then submitted into a HRG 'grouper', a software package available for each financial year from the Health and Social Care Information Centre (www.hscic.gov.uk), which produces the HRG code for an individual's inpatient stay. Time constraints may, however, limit their ability to obtain HRG codes for each individual within the trial.

Clinical commissioning groups were approached as they use individual patient HRGs to reimburse hospitals. However, the groups obtain patient HRGs only in a pseudo-anonymised format.

Finally, the use of individual patient records as the source to obtain data on resource use was explored. Finance and costing departments for Bristol, Plymouth and Bath were contacted. Bristol and Plymouth have so far confirmed that individual patient records are available for ROMIO patients. If individual patient records are available for all other sites in the main ROMIO trial then this would be the preferred option. However, although information on operating times would be available through the individual patient records, it is unlikely that differences in equipment use for the main surgical intervention would be accurately captured as needed. This emphasises the need to use microcosting techniques to cost the initial operation, even if individual patient records are used for the remaining aspects of the initial inpatient stay.

Resource use logs (diaries)

These were designed to be used by the patient as an 'aide memoire' to prospectively record health and social service contacts and other expenses incurred, with the format of the logs mirroring that of the questionnaires. Resource use logs have the potential to reduce missing data[46] and therefore lead to more accurate estimates of costs. To allow piloting of the resource use diaries and the telephone-administered questionnaires, a substantial amendment to the ethical approval was sought and this was granted in April 2014. Patients were given the 0–3 months resource use diary by a research nurse at hospital discharge following their oesophagectomy. If they were too unwell to record events a relative or friend could record this information for them. At 3 months following their discharge, a nurse telephoned those patients given the resource use diary to ask them questions about their resource use during that period of time. To not overburden the patients, nurses were encouraged to call back or speak with a relative who could answer the questions on a patient's behalf if the patient did not feel able to answer the questions at that time.

To assess the feasibility of the 6-month telephone administration of the resource use questionnaire the following process was established. Participants who had been discharged prior to ethical approval being granted but who had not yet reached 3 months post discharge were posted the 4–6 months resource use diary at 3 months post discharge and asked to complete it for the following 3 months. At 6 months following their discharge from hospital a research nurse telephoned those patients who had received a 4–6 months resource use diary and asked questions about their resource use.

Initial findings on this process

The organisation of the study, especially for patients who undergo surgery in one site and are followed up in another site (as in the case of Bath patients), means that, if resource use diaries are to be used in the main trial, site-specific resource use diaries and resource use questionnaires will have to be created. Some patients did not want to complete the questionnaire over the telephone; one patient wanted only to read out what he had written in the resource use diary rather than be asked questions. Another patient wanted to return the resource use diary rather than complete the telephone questionnaire. These findings have implications for how resource use is obtained for the main trial, as these two actions resulted in missing data.

To reduce the burden on patients, one suggestion is to use a much narrower NHS perspective or NHS and Personal Social Services (PSS) perspective for the main trial and include an exploration of other resource use within the qualitative component of the trial.

A shortened resource use instrument will still be required as not all secondary care visits and inpatient stays take place within the main treating hospitals where the initial surgery took place, and therefore medical records cannot provide this information. In some instances, when a substantial group of patients is followed up at another site, for example as in Bath in the feasibility study, it makes sense for the correct approvals to be gained so that access to medical records can be granted. In addition, community-based NHS resource use still needs to be obtained.

One solution would be to use the patient diary as the main patient source of information, using telephone interviews for those patients who do not return the diaries. Alternatively, given that patients did seem to be able to complete the resource use diaries, a shortened resource use questionnaire may be acceptable.

Establishing cost differences between the arms

One potential area in which cost differences will exist between the arms of the trial is in relation to the actual operation. A CRF was created that outlined potential equipment and consumables that could be used in all of the operations in terms of brand and quantity and the operation staff potentially involved in terms of their role and time present during the operation. Currently, this CRF is being piloted in Plymouth on the two different types of oesophagectomy. Once the main differences in theatre resource have been identified in this pilot, theatre records will be obtained from Bristol to ascertain whether or not the main differences in resource use can be captured easily within the Bristol centre.

Chapter 4 Discussion

Summary of findings

This feasibility study has demonstrated that different approaches to oesophagectomy can be compared in an unbiased fashion in a RCT. Recruitment to the pilot trial was soon ahead of target at the two centres, Bristol and Plymouth, with the qualitative recruitment intervention overcoming the widely recognised difficulties of presenting to patients the idea of equipoise between surgical techniques and the need for random allocation. The high proportion of eligible patients consenting to join the trial (76.5%; all figures for patients recruited until 31 August 2014) was likely to be one factor behind the profile of participants being typical of the profile of patients seen in clinical practice. The large majority of patients underwent oesophagectomy according to their allocated approach (79% at Bristol, 100% at Plymouth; patients recruited until 31 August 2014). Four out of 10 patients not following their allocated approach at Bristol were found to be inoperable during surgery. Blinding participants to their allocation during the first week post surgery using a large bandage that covered all possible incision sites was found to be successful on the whole, with a similar majority of patients believing that they had undergone the LAO or MIO procedures across all intervention arms at a centre.

Follow-up completion rates were good considering that this is a severely ill population of patients with a poor medium-term prognosis even when suitable for surgery. Surgical complications were common, as they are in clinical practice, and progress was made in agreeing a format for effectively presenting these data. The resource use data collection method was piloted and the appropriate focus of the cost-effectiveness analysis was discussed within the study team. Consensus was reached that the main cost and benefit differences will occur at surgery and in terms of recovery during the subsequent 6 weeks. Differences in costs are likely to arise from the different resources required for the different surgical approaches and from the subsequent time spent in hospital, including the duration of intensive care, and the care required for any complications. The resources used during each surgical approach need to be determined for each centre using microcosting methods applied to several example operations of each type. HRG codes are not sensitive to the differences between the different approaches to oesophagectomy, but they are sufficiently accurate to provide the costs of any subsequent care. The choice of a telephone interview or a patient-completed diary appears to encourage patients to provide data on the NHS and social services care that they receive. Clinical benefits will be measured using quality-adjusted life-year (QALYs), based on the EQ-5D-5L.[24]

The remainder of this chapter considers in more detail the findings of the feasibility study that have particularly influenced the planned approach to the definitive ROMIO trial.

Approaches to oesophagectomy

Minimally invasive oesophagectomy continued to be the subject of ongoing refinements during the feasibility study and the procedure is not yet sufficiently stable for evaluation in a pragmatic Phase III trial. Also, fewer centres are currently using this approach to oesophagectomy. In view of this, in the definitive ROMIO trial we plan to continue to collect robust prospective data on the safety and outcomes of MIO by including it as a third randomised arm in those main trial centres where it is in routine use. This third group of the trial forms a nested IDEAL Phase IIb study,[18] which may inform a future pragmatic trial beyond the definitive ROMIO study with the aim of a full evaluation of MIO. The definitive ROMIO trial at all centres will focus on a comparison between LAO and open oesophagectomy.

Recruitment and sample size

Qualitative recruitment intervention

Recruitment was successful in no small part because, as our qualitative investigation has demonstrated, surgeons were able to present the equipoise that exists between the different approaches in consultations. The qualitative recruitment intervention has identified the key ways to balance the presentation of interventions and to explain to patients the need for a trial.[47,48] We will continue the qualitative recruitment intervention in the proposed definitive trial to ensure that the five centres joining the main trial will meet with the same success so that the definitive ROMIO trial as a whole recruits on time and to target.

Sample size for the planned definitive trial

In this section we illustrate the thinking behind the sample size calculation, as included in the current proposal for a definitive ROMIO trial. 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, with the baseline assessment of physical function 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 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 subscale is 0.4 standard deviations.[49] Allowing for 5% of patients allocated to LAO actually undergoing open surgery and 10% of patients in each arm 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 arm (364 patients in total) will allow a true treatment effect (LAO vs. open oesophagectomy) 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. Allowing for up to 10% of missing primary outcome data, for example because of patients being unwell, 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 open oesophagectomy.

This sample size will also give adequate statistical power to detect a clinically important reduction in postsurgical length of stay. The mean length of stay in the pilot trial (all arms combined) was 13 days (standard deviation 8 days). Allowing for the skewed distribution,[50] 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-day 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.

We are discussing carrying out an individual patient data meta-analysis of survival data from the pilot ($n \approx 150$) and main ($n = 406$) ROMIO trials, the TIME trial[15] ($n = 115$) and the MIRO trial[14] ($n = 200$), giving a combined data set of > 800 patients. A data set of this size will rule out an absolute difference in mortality exceeding 6% (e.g. 7.5% with open surgery and 13.5% with minimally invasive surgery at 1 year) with 85% power and a 95% one-sided CI if true survival is equivalent.

Our experience with the pilot trial indicates that it is reasonable to expect an average of 22 patients to be recruited per centre per year. Seven centres recruiting for 2.5 years will enrol $2.5 \times 7 \times 22 = 385$ patients. The two established centres will continue recruiting up to the definitive trial period and hence will also recruit during the 6 months preceding the main recruitment phase ($0.5 \times 2 \times 22 = 22$ patients), hence meeting the sample size target of 406 patients.

Outcome measures and follow-up

During the conduct of the ROMIO feasibility study the trial management group, which includes oesophageal cancer surgeons, methodologists and patient representatives, discussed outcome measures and follow-up in detail and reviewed the end points of the two previous trials in oesophagectomy.[14,15]

We discussed the end points with members of the Gastro-Oesophageal Support and Help (GOSH) Group in Bristol, and all said that the most important end point of oesophageal cancer surgery is long-term survival. Patients did not want to undergo an operation that may risk long-term survival even if there was a short-term benefit with the minimally invasive approach. However, the patients stated that if minimally invasive surgery led to a similar survival rate as that achieved by standard open surgery then a measure of recovery after hospital discharge was most important to them. The patients defined recovery as a post-discharge experience of being able to perform household activities and get out and about.

The primary end point of the Dutch TIME trial ($n = 115$) was pulmonary infection within the first 2 weeks after surgery and during the whole stay in hospital.[15] The primary end point in the French MIRO trial[14] ($n = 200$) was 30-day major postoperative complications. These two trials are too small to establish equivalent survival between the two surgical approaches. This, and the theoretical benefits of less tissue trauma with minimally invasive surgery, are likely to be behind the choice of a measure of surgical complications as the primary end point in both trials. The two end points of importance to patients, survival and recovery of physical function, remain unaddressed in a randomised comparison of open oesophagectomy and MIO.

Although observational data must be interpreted with caution, because of the high risk of bias in such studies, there is no suggestion in the available evidence of a survival advantage of one technique over the other. We have also reviewed the evidence for minimally invasive versus open surgery for colorectal cancer, which has accumulated in several randomised trials reported during the past 15 years. These trials show that minimally invasive surgery has similar overall mortality, total recurrence and overall 5-year survival rates to those for standard open surgery.[51] It is important to patients that the same equivalence in survival is demonstrated for minimally invasive compared with open surgery for oesophageal cancer, but this would require a very large trial by surgical standards. We propose instead to collaborate with the TIME and MIRO teams in an individual patient meta-analysis, with the resulting sample size of about 800 allowing large differences to be ruled out if indeed survival is equivalent.

As long as the accumulating evidence indicates equivalent survival for minimally invasive and open oesophagectomy, then the patient view, and experience with colorectal cancer surgery suggests that evidence of faster recovery with minimally invasive techniques would be practice changing. A meta-analysis of the short-term outcomes of laparoscopic resection for colorectal cancer showed a reduction in wound infection and less pain but other morbidities were similar in both groups[52] and, in a Cochrane review based on evidence mainly from non-randomised studies, laparoscopic excision appears to have clinically measurable short-term advantages in patients with primary resectable rectal cancer.[53] Minimally invasive techniques are now the surgical standard for colorectal cancer.[53]

We have therefore selected the primary end point to be the assessment of a validated patient report of physical function 6 weeks after randomisation. This primary end point is therefore patient centred and is sensitive to recovery from surgery and from complications of surgery. We are assessing the primary outcome at 6 weeks post randomisation as this time point (typically 2–3 weeks after discharge) is likely to be the most sensitive to differences in recovery between LAO and open surgery, although of course information from later assessments will be important in interpreting the clinical importance of any difference in the primary outcome. Secondary outcomes will include a broader range of patient-reported outcomes, including blinded assessments of pain during the first week post surgery and validated generic and disease-specific measures. Measures of prognosis, such as positive lymph node count, and of surgical quality, such as lymph node yield, will be determined using measures developed in the feasibility study. This will provide surrogate information and we will follow up patients for at least 2 years to assess survival.

Quality assurance and monitoring fidelity to operative protocols

Tools and processes developed in the feasibility study will ensure surgical quality in the proposed definitive ROMIO trial. The operation manual that was developed during the feasibility study details the essential and optional steps of the operations. The manual will guide surgical performance and the evaluation of surgical quality.

i. *Surgeons' entry into the trial*. Surgeons with a minimum procedural volume of 30 cases will be invited. Before participation in the trial, independent assessors who are blinded to the identity of the operating surgeons will evaluate two unedited video records using an objective video-based assessment tool.
ii. *Monitoring adherence to the trial surgical manual*. This will be ensured by the assessment of the photographs of the operative field, which reflect the quality of the lymphadenectomy as an end product of the procedure, using the photograph assessment tool. Two video recordings will also be assessed annually for every participating surgeon.
iii. *Analysis of adverse events and trends in surgical performance and outcomes*. A modified Healthcare Failure Mode and Effects Analysis and frameworks for assessing adverse events[54] that have been established at the Safety Unit at Imperial College London will be used. Operation notes have been designed to report on deviation from protocols, intraoperative errors/adverse events and recovery mechanisms.

Video and photograph assessment tools have been developed in the feasibility study. If a surgeon's performance does not meet safety and efficiency criteria, he or she will need to carry out more operations before recruiting patients into the trial, whereas those surgeons who do not meet the lymphadenectomy criteria will be required to standardise their technique to that specified in the operation manual. This approach will avoid the limitations of using procedural volume as the only criterion for entry into the trial.

Learning effects

Although there are statistical approaches to capturing learning effects, there is currently no satisfactory way to adjust an estimated difference in outcome between interventions to reflect what would have been achieved had all operators been fully competent throughout. Hence, for the definitive ROMIO trial we propose to ensure that only skilled operators (see previous section) recruit patients to the trial. Although even skilled operators are likely to refine their technique as they acquire further experience, the effect of this on the outcome is unlikely to be large. In any case, in terms of implications for routine clinical practice, the effect of a surgical intervention performed by competent operators is arguably more relevant than that achieved by a handful of the most highly skilled surgeons.

Economic evaluation

The in-theatre costs for LAO are likely to be higher than those for open surgery for the treatment of oesophageal cancer but, if quicker recovery results, postsurgical 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[55] and the findings of the feasibility study indicate that NHS and PSS costs are likely to be the main cost drivers and principal source of difference between the approaches to surgery. The economic evaluation will therefore adopt this perspective. We will conduct the primary evaluation at 6 weeks post randomisation, at which point it is anticipated that the major differences in costs between the groups will be detected. We will also carry out an evaluation at 24 months to identify the long-term cost-effectiveness of LAO compared with open surgery in the treatment of oesophageal cancer.

NHS costs include those associated with (1) the operation, (2) the postoperative inpatient stay and (3) the period after discharge until follow-up. PSS costs will relate to social care during the follow-up period. In-theatre costs will be estimated using a microcosting approach. We will collect data from each centre on staff requirements and equipment used for five patients undergoing each type of operation to estimate a typical unit cost per centre per type of operation. In-hospital resource use during the postoperative stay will be driven by length of stay and all-cause complications such as bleeding and return to theatre. We will collect data on these events using the piloted trial CRF developed in the feasibility study and events will be costed using information from hospital finance departments. Resource use during the period between discharge and 6 weeks will include that related to readmissions, outpatient care, primary and community care, medications and use of social services. Information on the use of these services will be collected using a procedure being refined in the feasibility study: patients will be asked to keep a diary of contacts with health and social services and will then take part in a telephone interview with a hospital research nurse. Piloting has identified that some patients preferred to submit the diary rather than take part in the interview and allowing this option is currently being explored. These data will be costed using nationally published sources.[56–58]

Collection of detailed NHS resource by telephone will continue until 6 months and, thereafter, for the long-term follow-up at 24 months, will focus on secondary care, principally hospital admissions and palliative care. The main outcome measure for the economic evaluation will be QALYs, estimated using the EQ-5D-5L,[24] which will be administered at baseline and 6 days post surgery, with subsequent assessments being carried out by post or online. We will estimate the mean costs and QALYs per patient in each group and the differences between the trial arms will be used to estimate an incremental cost per QALY gain. Uncertainty will be addressed in sensitivity analyses and by using bootstrapping to estimate the net monetary benefit and by plotting cost-effectiveness acceptability curves. Longer-term costs and benefits will be discounted in line with recommendations prevailing at the time.[59]

On the more practical side, the importance of close communication between the health economists and the researchers responsible for collecting resource use data was evident during the course of the feasibility study. Resource use data are less familiar to clinical research staff and guidance in their collection improves their quality and completeness. For the proposed definitive trial, this will begin with the health economists playing a part in site initiation visits.

Chapter 5 Conclusions

In this section the conclusions arising from the feasibility study and pertaining to the design and conduct of the main trial are summarised. The planned definitive trial will focus on a comparison between LAO and open oesophagectomy, as MIO continues to be subject to refinement. At present the plan is to recruit a total of 406 patients to the definitive ROMIO trial, randomising 50% to each of the two approaches to oesophagectomy. This will allow a clinically important benefit for postsurgical recovery of physical function to be detected with 90% power and will also make a major contribution to an individual patient meta-analysis, which will also include data from the TIME[15] and MIRO[14] studies, to allow evaluation of any effect on survival. This is a large trial by surgical standards and will require a multicentre approach. Provisional agreement has been reached with an additional five centres to participate in the definitive ROMIO trial. These centres have varying degrees of experience with regard to recruiting to surgical trials and consequently we plan to continue with the qualitative recruitment intervention at the new sites and also with any new recruiters at the established pilot trial sites. Currently the plan is for two of the seven sites to randomly allocate patients to one of three interventions, the third being MIO, so allowing further unbiased effectiveness data to be collected in an embedded early-phase RCT of this approach to oesophagectomy.

As presented in the appendices to this report, we have produced a surgical manual and note for use in the definitive ROMIO trial, which will contribute to the standardisation of the interventions across trial centres and provides a standard against which to assess the quality of surgery. We have built up experience of recording procedures using video and photography and have a better understanding of the resources needed to achieve this for the main study. In the definitive ROMIO trial the assessment tools will be applied to submitted videos and photographs, both to ensure that surgeons have completed their initial learning of the procedures being evaluated before recruiting to the trial and to increase acceptance of the trial results by the surgical community through showing that a high standard of surgery has been maintained.

Trial conduct will be closely monitored at each centre to ensure that the high uptake of the allocated interventions continues and that the success of blinding to allocation during the first postsurgical week continues. The primary outcome measure is now planned to be the physical function scale of the QLQ-C30, which members of our group, based on experience of other surgical trials, believe will be more sensitive to recovery than our original proposal of fatigue measured by the MFI-20. We have found participants to be willing to complete several measures of HRQoL at each assessment during a 3-year follow-up period and we will continue to do this in the definitive trial. Clinical data will be collected around the time of surgery using refinements of our CRFs, notably the operation note and the CRF for histopathology.

Members of the study group are building up experience of collecting and presenting data on treatment complications from the several surgical studies that they are involved with, with these methods not yet being well adapted from pharmacological to surgical trials. This also applies to the methods of collection of resource use data to allow a cost-effectiveness analysis for a surgical trial. The cost-effectiveness analysis will now focus on NHS and PSS costs during the first 6 weeks, when both the major cost differences between the two surgical approaches and the benefits of LAO for postsurgical recovery are likely to be realised. In addition, there will be an analysis of cost-effectiveness over the full 2-year follow-up. The methodology for these two aspects may develop during the conduct of the definitive ROMIO trial and we will look to adopt improved practice where possible.

Further to these refinements to study methodology for the definitive trial, the ROMIO feasibility study has also equipped the study team with practical experience of resourcing and running a complex surgical RCT to a consistently high standard.

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The ROMIO Trial Steering Committee membership consists of Professor Craig Ramsay (Chair, University of Aberdeen), Mr William Allum (Royal Marsden NHS Foundation Trust, London), Dr Heike Grabsch (University of Leeds), Mr Richard Hardwick (Addenbrooke's Hospital NHS Foundation Trust, Cambridge), Dr Anthony Ingold (Oesophageal Patients Association representative) and Professor Sally Stenning (Medical Research Council Clinical Trials Unit, London).

Contributions of authors

Dr Chris Metcalfe (Reader, Medical Statistics) was the chief investigator and a study management group member, developed the protocol and carried out pilot trial monitoring, statistical analysis and report writing.

Dr Kerry Avery (Research Fellow, Health Services Research) was the study manager and a study management group member, developed the protocol, developed the qualitative recruitment intervention and carried out pilot trial monitoring and report writing.

Mr Richard Berrisford (Consultant, Surgery) was a study management group member and the principal investigator for the Plymouth centre, provided surgical expertise and developed the protocol.

Mr Paul Barham (Consultant, Surgery) was a study management group member, provided surgical expertise and developed the protocol.

Dr Sian M Noble (Senior Lecturer, Health Economics) was the study lead for the health economics analysis, identified key resource use and developed methods of measurement.

Miss Aida Moure Fernandez (Research Assistant, Health Economics) carried out the piloting of the resource use measures.

Professor George Hanna (Professor, Surgical Sciences) was the study lead for quality assurance, carried out the hierarchical task analysis of oesophagectomy, documented the key steps in oesophagectomy and developed the operation note and the video and photograph assessments.

Professor Robert Goldin (Professor, Liver and Gastrointestinal Pathology) provided pathology expertise and worked with the pathologists at Bristol and Plymouth to agree methods of processing and reporting.

Mrs Jackie Elliott (Patient and Public Involvement Representative) was a study management group member and provided a link with the Bristol patient group, advising on patient information and outcome measurement.

Mr Timothy Wheatley (Consultant, Surgery) provided surgical expertise and developed the protocol.

Mr Grant Sanders (Consultant, Surgery) provided surgical expertise and developed the protocol.

Mr Andrew Hollowood (Consultant, Surgery) provided surgical expertise and developed the protocol.

Dr Stephen Falk (Consultant, Clinical Oncology) provided oncology expertise and developed the protocol.

Mr Dan Titcomb (Consultant, Surgery) provided surgical expertise and developed the protocol.

Mr Christopher Streets (Consultant, Surgery) provided surgical expertise and developed the protocol.

Professor Jenny L Donovan (Professor, Social Medicine) was the study lead for the qualitative recruitment intervention.

Professor Jane M Blazeby (Professor, Surgery) was the clinical lead for the trial and the principal investigator for the Bristol centre and a study management group member and developed the protocol.

Publications

Avery KN, Barham CP, Berrisford R, Blazeby JM, Blencowe NS, Donovan J, *et al.* Understanding surgical interventions in RCTs: the need for better methodology. *Lancet* 2013;**381**:27–8.

Avery KNL, Metcalfe C, Berrisford RG, Barham CP, Donovan JL, Elliott J, *et al.* The feasibility of a randomized controlled trial of esophagectomy for esophageal cancer – the ROMIO (Randomized Oesophagectomy: Minimally Invasive or Open) study: protocol for a randomized controlled trial. *Trials* 2014;**15**:200–9.

Data sharing statement

We shall make data available to the scientific community with as few restrictions as feasible, while retaining exclusive use until the publication of major outputs. The data will be made available via application to Dr Chris Metcalfe, the corresponding author. Data on the feasibility of the trial (i.e. measures taken during the feasibility study, prior to random allocation of surgical technique) will be available 6 months after publication of the main feasibility study publication in a peer-reviewed journal. Data on the comparative effectiveness of the oesophagectomy techniques will be available 6 months after publication of the primary results paper from the main trial.

References

1. Cancer Research UK. *Oesophageal Cancer Incidence Statistics*. URL: www.cancerresearchuk.org/cancer-info/cancerstats/types/oesophagus/incidence/ (accessed 23 October 2015).
2. Groene O, Cromwell DA, Hardwick RH, Riley SA, Crosby T, Greenaway K. *National Oesophago-Gastric Cancer Audit 2012*. London, England: Royal College of Surgeons; 2012.
3. Morneau M, Boulanger J, Charlebois P, Latulippe J-F, Lougnarath R, Thibault C, *et al.* Laparoscopic versus open surgery for the treatment of colorectal cancer: a literature review and recommendations from the Comité de l'évolution des pratiques en oncologie. *Can J Surg* 2013;**56**:297–310.
4. Blencowe NS, Strong S, McNair AG, Brookes ST, Crosby T, Griffin SM, *et al.* Reporting of short-term clinical outcomes after oesophagectomy: a systematic review. *Ann Surg* 2012;**255**:658–66. http://dx.doi.org/10.1097/SLA.0b013e3182480a6a
5. Gemmill EH, McCulloch P. Systematic review of minimally invasive resection for gastro-oesophageal cancer. *Br J Surg* 2007;**94**:1461–7. http://dx.doi.org/10.1002/bjs.6015
6. Decker G, Coosemans W, De Leyn P, Decaluwé H, Nafteux P, Van Raemdonck D, *et al.* Minimally invasive esophagectomy for cancer. *Eur J Cardiothorac Surg* 2009;**35**:13–20. http://dx.doi.org/10.1016/j.ejcts.2008.09.024
7. Verhage RJ, Hazebroek EJ, Boone J, Van HR. Minimally invasive surgery compared to open procedures in esophagectomy for cancer: a systematic review of the literature. *Minerva Chir* 2009;**64**:135–46.
8. Luketich JD, Alvelo-Rivera M, Buenaventura PO, Christie NA, McCaughan JS, Litle VR, *et al.* Minimally invasive esophagectomy: outcomes in 222 patients. *Ann Surg* 2003;**238**:486–95. http://dx.doi.org/10.1097/01.sla.0000089858.40725.68
9. Smithers BM, Gotley DC, Martin I, Thomas JM. Comparison of the outcomes between open and minimally invasive esophagectomy. *Ann Surg* 2007;**245**:232–40. http://dx.doi.org/10.1097/01.sla.0000225093.58071.c6
10. Boshier P, Anderson O, Hanna GB. Transthoracic versus transhiatal esophagectomy for the treatment of esophagogastric cancer: a meta-analysis. *Ann Surg* 2011;**254**:894–906. http://dx.doi.org/10.1097/SLA.0b013e3182263781
11. Parameswaran R, Blazeby JM, Hughes R, Mitchell K, Berrisford RG, Wajed SA. Health-related quality of life after minimally invasive oesophagectomy. *Br J Surg* 2010;**97**:525–31. http://dx.doi.org/10.1002/bjs.6908
12. Clavien PA, Barkun J, de Oliveira ML, Vauthey JN, Dindo D, Schulick RD, *et al.* The Clavien-Dindo Classification of Surgical Complications. Five-year experience. *Ann Surg* 2009;**250**:187–96.
13. Mariette C, Meunier B, Pezet D, Dalban C, Collet D, Thomas PA, *et al.* Hybrid minimally invasive versus open oesophagectomy for patients with oesophageal cancer: a multicenter, open-label, randomized Phase III controlled trial, the MIRO trial. *J Clin Oncol* 2015;**33**(Suppl. 3):abstract 5.
14. Briez N, Piessen G, Bonnetain F, Brigand C, Carrere N, Collet D, *et al.* Open versus laparoscopically-assisted oesophagectomy for cancer: a multicentre randomised controlled phase III trial – the MIRO trial. *BMC Cancer* 2011;**11**:310.
15. Biere SS, van Berge Henegouwen MI, Maas KW, Bonavina L, Rosman C, Garcia JR, *et al.* Minimally invasive versus open oesophagectomy for patients with oesophageal cancer: a multi-centre, open-label, randomised controlled trial. *Lancet* 2012;**379**:1887–92. http://dx.doi.org/10.1016/S0140-6736(12)60516-9

16. Ware JE, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care* 1992;**30**:473–83.

17. Blazeby JM, Conroy T, Hammerlid E, Fayers P, Sezer O, Koller M, *et al.* Clinical and psychometric validation of an EORTC questionnaire module, the EORTC QLQ-OES18, to assess quality of life in patients with oesophageal cancer. *Eur J Cancer* 2003;**39**:1384–94. http://dx.doi.org/10.1016/S0959-8049(03)00270-3

18. McCulloch P, Altman DG, Campbell WB, Flum DR, Glasziou P, Marshall JC, *et al.* No surgical innovation without evaluation: the IDEAL recommendations. *Lancet* 2009;**374**:1105–12. http://dx.doi.org/10.1016/S0140-6736(09)61116-8

19. Clopper CJ, Pearson SE. The use of confidence of fiducial limits illustrated in the case of the binomial. *Biometrika* 1934;**26**:404–13.

20. Bang H, Ni L, Davis CE. Assessment of blinding in clinical trials. *Control Clin Trials* 2004;**25**:143–56. http://dx.doi.org/10.1016/j.cct.2003.10.016

21. Aaronson N, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez N, *et al.* The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst* 1993;**85**:365–76. http://dx.doi.org/10.1093/jnci/85.5.365

22. Smets EM, Garssen B, Cull A, de Haes JC. Application of the Multidimensional Fatigue Inventory (MFI-20) in cancer patients receiving radiotherapy. *Br J Cancer* 1996;**73**:241–5. http://dx.doi.org/10.1038/bjc.1996.42

23. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg* 2004;**240**:205–13. http://dx.doi.org/10.1097/01.sla.0000133083.54934.ae

24. The EuroQol Group. *EQ-5D-5L* URL: www.euroqol.org (accessed 23 October 2015).

25. American Joint Committee on Cancer. Esophagus and Esophagogastric Junction. In Edge SB, Byrd D, Compton C, Fritz AG, Greene FL, Trotti A, editors. *AJCC Cancer Staging Manual*. 7th edn. New York, NY: Springer; 2010. pp. 103–11.

26. Cook JA. The challenges faced in the design, conduct and analysis of surgical randomised controlled trials. *Trials* 2009;**10**:1–30. http://dx.doi.org/10.1186/1745-6215-10-9

27. Avery KNL, Metcalfe C, Berrisford RG, Barham CP, Donovan JL, Elliott J, *et al.* The feasibility of a randomized controlled trial of esophagectomy for esophageal cancer – the ROMIO (Randomised Oesophagectomy: Minimally Invasive or Open) study: protocol for a randomized controlled trial. *Trials* 2014;**15**:200–9. http://dx.doi.org/10.1186/1745-6215-15-200

28. de Salis I, Tomlin Z, Toerien M, Donovan J. Qualitative research to improve RCT recruitment: issues arising in establishing research collaborations. *Contemp Clin Trials* 2008;**29**:663–70. http://dx.doi.org/10.1016/j.cct.2008.03.003

29. Paramasivan S, Huddart R, Hall E, Lewis R, Birtle A, Donovan JL. Key issues in recruitment to randomised controlled trials with very different interventions: a qualitative investigation of recruitment to the SPARE trial (CRUK/07/011). *Trials* 2011;**12**:78. http://dx.doi.org/10.1186/1745-6215-12-78

30. Hamilton DW, de Salis I, Donovan JL, Birchall M. The recruitment of patients to trials in head and neck cancer: a qualitative study of the EaStER trial of treatments for early laryngeal cancer. *Eur Arch Otorhinolaryngol* 2013;**270**:2333–7. http://dx.doi.org/10.1007/s00405-013-2349-8

31. Howard L, de Salis I, Tomlin Z, Thornicroft G, Donovan J. Why is recruitment to trials difficult? An investigation into recruitment difficulties in an RCT of supported employment in patients with severe mental illness. *Contemp Clin Trials* 2009;**30**:40–6. http://dx.doi.org/10.1016/j.cct.2008.07.007

32. Donovan JL, Lane JA, Peters TJ, Brindle L, Salter E, Gillatt D, *et al.* Development of a complex intervention improved randomisation and informed consent in a randomized controlled trial. *J Clin Epidemiol* 2009;**62**:29–36. http://dx.doi.org/10.1016/j.jclinepi.2008.02.010

33. Donovan JL, Sanders C. Key Issues in the Analysis of Qualitative Data in Health Services Research. In Bowling A, Ebrahim S, editors. *Handbook of Health Research Methods*. Maidenhead: Open University Press; 2005. pp. 515–32.

34. Donovan JL, Mills N, Smith M, Brindle L, Jacoby A, Peters TJ, *et al.* Improving the design and conduct of randomised trials: the role of qualitative research methods in the ProtecT study. *BMJ* 2002;**325**:766–70. http://dx.doi.org/10.1136/bmj.325.7367.766

35. Miles MB, Huberman AM. *Qualitative Data Analysis*. 2nd edn. London: Sage Publications; 1994.

36. Marshall CL, Rossman G. *Designing Qualitative Research*. London: Sage Publications; 1995.

37. Flick U. *An Introduction to Qualitative Research*. London: Sage Publications; 2009.

38. Sarker S, Chang A, Albrani T, Vincent C. Contructing hierarchical task analysis in surgery. *Surg Endosc* 2008;**22**:107–11. http://dx.doi.org/10.1007/s00464-007-9380-z

39. Palter V, Macrae HM, Grantcharov T. Development of an objective evaluation tool to assess technical skills in laparoscopic colorectal surgery: a Delphi methodology. *Am J Surg* 2011;**201**:251–9. http://dx.doi.org/10.1016/j.amjsurg.2010.01.031

40. Carayon P, Schoofs Hundt A, Karsh B-T, Gurses A, Alvarado C, Smith M, *et al.* Work system design for patient safety: the SEIPS model. *Qual Saf Health Care* 2006;**15**(Suppl. 1):i50–8. http://dx.doi.org/10.1136/qshc.2005.015842

41. Miskovic D, Ni M, Wyles S, Kennedy R, Francis N, Parvaiz A, *et al.* Is competency assessment at the specialist level achievable? A study for the national training programme in laparoscopic colorectal surgery in England. *Ann Surg* 2013;**257**:476–82. http://dx.doi.org/10.1097/SLA.0b013e318275b72a

42. Tugwell P, Boers M, Brooks P, Simon L, Strand V, Idzerda L. OMERACT: an international initiative to improve outcome measurement in rheumatology. *Trials* 2007;**8**:38. http://dx.doi.org/10.1186/1745-6215-8-38

43. North West Hub for Trials Methodology Research. *COMET*. URL: www.liv.ac.uk/translational-medicine/departmentsandgroups/nwhtmr/theme-2/ (accessed 23 October 2015).

44. Entwistle IR. *Exacta Medica*. London: Churchill Livingstone; 2003.

45. Mapstone NP. *Dataset for the Histopathological Reporting of Oesophageal Carcinoma* (*2nd edition*). London, England: Royal College of Pathologists; 2007.

46. Marques E, Johnson EC, Gooberman-Hill R, Blom AW, Noble S. Using resource use logs to reduce the amount of missing data in economic evaluations alongside trials. *Value Health* 2013;**16**:195–201. http://dx.doi.org/10.1016/j.jval.2012.09.008

47. Donovan JL, de Salis I, Toerien M, Paramasivan S, Hamdy FC, Blazeby JM. The intellectual challenges and emotional consequences of equipoise contributed to the fragility of recruitment in six randomized controlled trials. *J Clin Epidemiol* 2014;**67**:912–20. http://dx.doi.org/10.1016/j.jclinepi.2014.03.010

48. Donovan JL, Paramasivan S, De Salis I, Toerien M. Clear obstacles and hidden challenges: understanding recruiter perspectives in six pragmatic randomised controlled trials. *Trials* 2014;**15**:1–12. http://dx.doi.org/10.1186/1745-6215-15-5

49. Cocks K, King MT, Velikova G, Martyn St-James M, Fayers PM, Brown JM. Evidence-based guidelines for determination of sample size and interpretation of the European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30. *J Clin Oncol* 2010;**48**:1713–21. http://dx.doi.org/10.1200/JCO.2010.28.0107

50. Wolfe R, Carlin JB. Sample-size calculation for a log-transformed outcome measure. *Control Clin Trials* 1999;**20**:547–54. http://dx.doi.org/10.1016/S0197-2456(99)00032-X

51. Kuhry E, Schwenk WF, Gaupset R, Romild U, Bonjer HJ. Long-term results of laparoscopic colorectal cancer resection. *Cochrane Database Syst Rev* 2008;**16**:CD003432. http://dx.doi.org/10.1002/14651858.cd003432.pub2

52. Abraham NS, Young JM, Solomon MJ. Meta-analysis of short-term outcomes after laparoscopic resection for colorectal cancer. *Br J Surg* 2004;**91**:1111–24. http://dx.doi.org/10.1002/bjs.4640

53. Vennix S, Pelzers L, Bouvy N, Beets GL, Pierie JP, Wiggers T, *et al.* Laparoscipic versus open total mesorectal excision for rectal cancer. *Cochrane Database Syst Rev* 2014;**15**:CD005200. http://dx.doi.org/10.1002/14651858.CD005200.pub3

54. Shebl N, Franklin B, Barber N, Burnett S, Parand A. Failure mode and effects analysis: views of hospital staff in the UK. *J Health Serv Res Policy* 2012;**17**:37–43.

55. Kennedy K, Francis E, Wharton R, Blazeby JM, Quirke P, West NP, *et al.* A multicentre randomised controlled trial of conventional versus laparoscopic surgery for colorectal cancer within an enhanced recovery programme (EnROL). *J Clin Oncol* 2014;**32**:1804–11. http://dx.doi.org/10.1200/JCO.2013.54.3694

56. Department of Health. *NHS Reference Costs*. 23 January 2014. URL: www.gov.uk/government/collections/nhs-reference-costs (accessed 23 October 2015).

57. Curtis L. *Unit Costs of Health and Social Care*. Canterbury: PSSRU, University of Kent; 2014. URL: www.pssru.ac.uk/project-pages/unit-costs (accessed 23 October 2015).

58. Joint Formulary Committee. *British National Formulary*. 68 ed. London: BMJ Group and Pharmaceutical Press; 2014.

59. National Institute for Health and Care Excellence (NICE). *Guide to the Methods of Technology Appraisal*. London: NICE; 2004.

Appendix 1 Oesophagectomy hierarchical task analysis

Abdominal phase

Task 1: Abdominal access

1.1 Opening the abdomen

1.1.1 Obtain safe access to the abdominal cavity.

1.1.2 Confirm the absence of metastatic disease and the appropriateness of the planned procedure.

Task 2: Diaphragmatic hiatus

2.1 Diaphragmatic hiatus

2.1.1 Mobilise the oesophagus from the diaphragmatic hiatus to the gastro-oesophageal junction, resecting a cuff of diaphragm and right and left paracardial lymph (LN) tissue (LN stations 1 and 2).

2.1.2 Dissect along the pericardial adventitia to remove the pericardial fat.

2.1.3 Resect the right pleura to expose the right lung.

2.1.4 Resect the left pleura to expose the left lung.

2.1.5 Dissect along the pre-aortic fascia.

Task 3: Gastric mobilisation

3.1 Gastric mobilisation

3.1.1 Identify the right gastroepiploic artery, which will provide the blood supply to the gastric tube.

3.1.2 Divide the greater omentum, ensuring that the gastroepiploic artery is preserved.

3.1.3 Enter the lesser sac and continue the dissection along the greater curvature of the stomach towards the spleen, dividing the short gastric and left gastroepiploic vessels and resecting the associated LN tissue (LN stations 4sa and 4sb).

Task 4: Coeliac axis

4.1 Portal vein and coeliac axis

4.1.1 Retract the stomach and dissect LN tissue along the superior border of the pancreas, to expose the portal vein.

4.1.2 Sling the common hepatic artery.

4.1.3 Dissect LN tissue along the proper hepatic artery, common hepatic artery, coeliac artery, left gastric artery and proximal splenic artery (LN stations 7, 8a, 9, 11p and 12a).

4.1.4 Ligate and divide the left gastric vein at the portal vein.

4.1.5 Ligate and divide the left gastric artery at its origin from the coeliac artery.

4.1.6 Dissect LN tissue from the left side of the coeliac artery to the left crus at the oesophageal hiatus and left side of Gerota's fascia.

4.2 Splenic artery

4.2.1 Continue the dissection along the anterior surface of the proximal splenic artery towards the splenic hilum.

4.2.2 Ligate the posterior gastric vessels at their origin from the splenic artery.

4.2.3 Dissect the remaining LN tissue along the distal splenic artery, clearing to the splenic vein inferiorly and the abdominal wall posteriorly, until the splenic hilum is reached (LN station 11d).

4.2.4 Clear the splenic hilum of LN tissue (LN station 10).

Note: This dissection should marry up with that performed in Task 3.

Task 5: Gastric tube

5.1 Gastric tube

5.1.1 Perform a lymphadenectomy along the lesser curvature of the stomach until the expected lower resection margin is reached (LN stations 3a and 3b).

5.1.2 Create the gastric tube.

5.1.3 Pyloroplasty, pyloromyotomy, other (e.g. botulinum toxin, Botox®, Allergan) or no action may be performed.

Task 6: Insertion of surgical adjuncts

6.1 Feeding jejunostomy

6.1.1 A feeding jejunostomy may be placed.

6.1.2 If the abdominal phase of the operation has been performed minimally invasively, a port site may be extended to an 8-cm incision to facilitate the placement of a feeding jejunostomy.

6.2 Abdominal drains

6.2.1 Abdominal drain(s) may be placed.

Task 7: Abdominal closure

7.1 Abdominal closure

7.1.1 Perform abdominal lavage.

7.1.2 Confirm haemostasis.

7.1.3 Close the abdomen.

7.1.4 Dress the wound.

Abdominal lymph node stations

Japanese Gastric Cancer Association. Japanese classification of gastric carcinoma: 3rd English Edition. *Gastric Cancer* 2011;**14**:101–12.

See table 5 in the above paper.

Thoracic phase

Task 1: Thoracic access

1.1 Thoracic access

1.1.1 Obtain safe access to the patient's right chest.

Task 2: Thoracic lymphadenectomy

2.1 Thoracic lymphadenectomy

2.1.1 Mobilise the lower lobe of the right lung.

2.1.2 Ligate and divide the azygos vein at the azygos arch.

2.1.3 Dissect along the pericardium until the left lung is reached including the pleura of the left lung in the radial excision margin.

2.1.4 Perform a subcarinal lymphadenectomy (LN station 107).

2.1.5 Clear both bronchi of LN tissue until the hilum of each lung is reached (LN station 109).

2.1.6 Dissect along the right pulmonary veins, continuing posteriorly until the left pulmonary veins are reached.

2.1.7 Dissect the mediastinal pleura at the anterolateral border of the thoracic aorta.

2.1.8 Dissect along the pre-aortic fascia from the proximal resection margin towards the diaphragm (LN station 112).

2.1.9 Dissect LN tissue along the aorto-pulmonary window, clearing the arch of the aorta, pulmonary artery and recurrent laryngeal nerve as it hooks around the arch of the aorta.

2.1.10 Identify and ligate the thoracic duct at the proximal resection margin and at the level of the diaphragm such that it is resected with the specimen.

Task 3: Specimen excision

3.1 Specimen excision

3.1.1 Ensure that the thoracic part of the specimen is circumferentially free, from the previously completed diaphragmatic mobilisation (performed during the abdominal phase) to at least the level of the aortic arch (LN stations 108, 110 and 111).

3.1.2 Deliver the stomach into the right chest cavity, ensuring that the gastric tube can reach the site of anastomosis without tension or torsion.

3.1.3 Excise the specimen with a suitable distal resection margin.

3.1.4 Send the specimen to pathology as per protocol.

Task 4: Anastomosis

4.1 Oesophago-gastrostomy

4.1.1 Perform an oesophago-gastrostomy.

4.1.2 If performing a two-phase minimally invasive procedure, an incision of up to 5 cm may be made in addition to the existing ports.

4.1.3 If performing a three-phase minimally invasive procedure, a left cervical incision is permitted for the anastomosis to be made.

Task 5: Insertion of surgical adjuncts

5.1 Nasogastric/nasojejunal tube

5.1.1 A nasogastric or nasojejunal tube may be placed.

5.2 Thoracic drains

5.2.1 Thoracic drains should be placed prior to the closure of the thoracic incision.

Task 6: Thoracic closure

6.1 Thoracic closure

6.1.1 Perform lavage.

6.1.2 Confirm haemostasis.

6.1.3 Close the chest.

6.1.4 Dress the wound.

Thoracic lymph node stations

Japan Esophageal Society. Japanese classification of esophageal cancer, tenth edition: part 1. *Esophagus* 2009;**6**:1–25.

See page 12 in the above paper.

Appendix 2 Oesophagectomy manual (all tasks)

Operative steps are mandatory unless otherwise stated (O = optional) and may be performed in any order.

Abdominal phase

Task 1: Abdominal access

1.1 Abdominal access

1.1.1 Obtain safe access to the abdominal cavity.

1.1.2 Confirm the absence of metastatic disease and the appropriateness of the planned procedure.

Task 2: Diaphragmatic hiatus

2.1 Diaphragmatic hiatus

2.1.1 Mobilise the oesophagus from the diaphragmatic hiatus to the gastro-oesophageal junction, resecting right and left paracardial lymph node (LN) tissue (LN stations 1 and 2).

2.1.2 A cuff of diaphragm should be resected in advanced disease to achieve a clear circumferential margin if advanced disease.

2.1.3 Dissect along the pericardial adventitia to remove the pericardial fat.

2.1.4 Resect the right pleura to expose the right lung in advanced disease.

2.1.5 Resect the left pleura to expose the left lung in advanced disease.

2.1.6 Dissect along the pre-aortic fascia.

Task 3: Gastric mobilisation

3.1 Gastric mobilisation

3.1.1 Identify the right gastroepiploic artery, which will provide the blood supply to the gastric tube.

3.1.2 Divide the greater omentum to enter the lesser sac, ensuring that the gastroepiploic vessels are preserved.

3.1.3 Continue the dissection along the greater curvature of the stomach towards the spleen, dividing the short gastric and left gastroepiploic vessels.

3.1.4 Resect the associated LN tissue (O) (LN stations 4sa and 4sb).

Task 4: Coeliac axis

4.1 Portal vein and coeliac axis

4.1.1 Retract the stomach and dissect along the superior border of the pancreas to expose the portal vein (O).

4.1.2 Sling the common hepatic artery (O).

4.1.3 Dissect LN tissue along the proper hepatic artery (O) (LN station 12a).

4.1.4 Dissect LN tissue along the common hepatic artery, coeliac artery, left gastric artery and proximal splenic artery (LN stations 7, 8a, 9 and 11p).

4.1.5 Ligate and divide the left gastric vein close to the portal vein.

4.1.6 Ligate and divide the left gastric artery at its origin from the coeliac artery.

4.1.7 Dissect LN tissue from the left side of the coeliac artery to the left crus at the oesophageal hiatus and left side of Gerota's fascia.

4.2 *Splenic artery*

4.2.1 Continue the dissection along the anterior surface of the proximal splenic artery towards the splenic hilum.

4.2.2 Ligate the posterior gastric vessels at their origin from the splenic artery.

4.2.3 Dissect the remaining LN tissue along the distal splenic artery, clearing to the splenic vein inferiorly and the abdominal wall posteriorly, until the splenic hilum is reached (O) (LN station 11d).

4.2.4 Clear the splenic hilum of LN tissue (O) (LN station 10).

Task 5: Gastric tube

5.1 Gastric tube

5.1.1 The lesser curvature of the stomach is cleared of LN tissue at the appropriate level until the expected distal resection margin is reached (LN stations 3a and 3b).

5.1.2 Create the gastric tube. This may be performed in the chest.

5.1.3 Oversew the staple line (O).

5.1.4 Pyloroplasty, pyloromyotomy or other may be performed (O).

Task 6: Insertion of surgical adjuncts

6.1 Feeding jejunostomy

6.1.1 A feeding jejunostomy may be placed (O).

6.1.2 If the abdominal phase of the operation has been performed minimally invasively, a port site may be extended to facilitate the placement of a feeding jejunostomy (O).

6.2 Abdominal drains

6.2.1 Abdominal drain(s) may be placed (O).

Task 7: Abdominal closure

7.1 Abdominal closure

7.1.1 Perform abdominal lavage (O).

7.1.2 Confirm haemostasis.

7.1.3 Close the abdomen.

7.1.4 Nursing staff dress the wound as per ROMIO trial guidelines.

Abdominal lymph node stations

Japanese Gastric Cancer Association. Japanese classification of gastric carcinoma: 3rd English Edition. *Gastric Cancer* 2011;**14**:101–12.

See table 5 in the above paper.

Note: The abdominal lymphadenectomy is identical to that for a D2 gastrectomy *except* LN stations 4d (right gastroepiploic artery), 5 (suprapyloric LN) and 6 (infrapyloric LN) are not included.

Thoracic phase

Task 1: Thoracic access

1.1 Thoracic access

1.1.1 Obtain safe access to the patient's right chest.

1.1.2 Confirm the absence of metastatic disease in the chest.

Task 2: Thoracic lymphadenectomy

2.1 Thoracic lymphadenectomy

2.1.1 Divide the inferior pulmonary ligament.

2.1.2 Ligate and divide the azygos arch.

2.1.3 Dissect along the pericardium until the left lung is reached, including resection of the left pleura in advanced disease to achieve a clear circumferential margin.

2.1.4 Perform a subcarinal lymphadenectomy (LN station 107).

2.1.5 Clear both bronchi of LN tissue until the hilum of each lung is reached (LN station 109).

2.1.6 Dissect along the right pulmonary veins, continuing posteriorly until the left pulmonary veins are reached (O).

2.1.7 Dissect the mediastinal pleura at the anterolateral border of the thoracic aorta.

2.1.8 Dissect along the pre-aortic fascia, from the proximal resection margin towards the diaphragm (LN station 112).

2.1.9 Dissect LN tissue along the aorto-pulmonary window, clearing the arch of the aorta, pulmonary artery and recurrent laryngeal nerve as it hooks around the arch of the aorta (O).

2.1.10 Identify and ligate the thoracic duct at the proximal resection margin and above the level of the diaphragm such that it is resected with the specimen.

Task 3: Specimen excision

3.1 Specimen excision

3.1.1 Ensure that the thoracic part of the specimen is circumferentially free, from the previously completed diaphragmatic mobilisation (performed during the abdominal phase) to at least the level of the aortic arch (LN stations 108, 110 and 111).

3.1.2 Deliver the stomach into the right chest cavity ensuring that the gastric tube can reach the site of anastomosis without tension or torsion.

3.1.3 Excise the specimen with suitable proximal and distal resection margins.

3.1.4 Send the specimen to pathology as per the ROMIO trial protocol.

Task 4: Anastomosis

4.1 Oesophago-gastrostomy

4.1.1 Perform an oesophago-gastrostomy using your preferred method.

4.1.2 If performing a two-phase minimally invasive procedure, a further incision may be made in addition to the existing port sites (O).

4.1.3 If performing a three-phase procedure, a left cervical incision is permitted for the anastomosis to be made (O).

Task 5: Insertion of surgical adjuncts

5.1 Nasogastric/nasojejunal tube

5.1.1 A nasogastric or nasojejunal tube may be placed (O).

5.2 Thoracic drains

5.2.1 Thoracic drain(s) should be placed prior to the closure of the thoracic incision.

Task 6: Thoracic closure

6.1 Thoracic closure

6.1.1 Perform lavage (O).

6.1.2 Confirm haemostasis.

6.1.3 Reinflate the lung under direct vision.

6.1.4 Close the chest.

6.1.5 Nursing staff dress the wound as per ROMIO trial guidelines.

Thoracic lymph node stations

Japan Esophageal Society. Japanese classification of esophageal cancer, tenth edition: part 1. *Esophagus* 2009;**6**:1–25.

See page 12 in the above paper.

Appendix 3 Oesophagectomy manual (essential tasks)

Abdominal phase

Abdominal access

1. Confirm the absence of metastatic disease.

Diaphragmatic hiatus

2. Mobilise the gastro-oesophageal junction, resecting right and left paracardial lymphatic (LN) tissue (LN stations 1 and 2).
3. Resect a cuff of diaphragm and pleura to achieve a clear circumferential margin in advanced disease.
4. Dissect along the pre-aortic fascia.

Gastric mobilisation

5. Mobilise the stomach based on the right gastroepiploic vessels.

Coeliac axis

6. Dissect LN tissue along the common hepatic artery, coeliac artery, left gastric artery and proximal splenic artery (LN stations 7, 8a, 9 and 11p).
7. Ligate and divide the left gastric vein close to the portal vein and the left gastric artery at the coeliac artery.
8. Dissect LN tissue from the left side of the coeliac artery to the left crus at the oesophageal hiatus and the left side of Gerota's fascia.
9. Continue the dissection along the anterior surface of the proximal splenic artery towards the splenic hilum and ligate the posterior gastric vessels at their origin from the splenic artery.

Gastric tube

10. Create the gastric tube, removing tissue along the lesser curvature of the stomach (LN stations 3a and 3b). This step may be carried out in the chest.

Thoracic phase

Thoracic access

1. Exclude metastatic disease in the chest.

Thoracic lymphadenectomy

2. Divide the inferior pulmonary ligament and ligate and divide the azygos arch.
3. Dissect along the pericardium until the left pulmonary vein is reached, including the left pleura in advanced disease.
4. Perform a subcarinal lymphadenectomy (LN station 107) and clear both bronchi of LN tissue (LN station 109).
5. Dissect the mediastinal pleura at the anterolateral border of the thoracic aorta and dissect along the pre-aortic fascia from the proximal resection margin towards the diaphragm (LN station 112).
6. Identify and ligate the thoracic duct at the proximal resection margin and above the diaphragm.

Specimen excision

7. Ensure that the thoracic part of the specimen is circumferentially free, from the previously completed diaphragmatic mobilisation (performed during the abdominal phase) to at least the level of the aortic arch (LN stations 108, 110 and 111).
8. Deliver the stomach into the right chest cavity ensuring that the gastric tube can reach the site of anastomosis without tension or torsion.
9. Excise the specimen with suitable proximal and distal resection margins and send it to pathology as per the ROMIO trial protocol.

Anastomosis

10. Perform an oesophago-gastrostomy using the preferred technique.

Appendix 4 Operation note

This operative case record has specifically been designed for recording the performance of:

Transthoracic oesophagectomy with infra-carinal lymphadenectomy

The primary operating surgeon should complete all sections. Any deviation from the agreed approach to perform the procedure should be explained in the relevant section.

ROMIO ID

Patient name: ……

ABDOMINAL PHASE

Instructions for use:

Please tick the appropriate box to indicate if each task was performed (Column Y), or not (Column N).

Please explain any deviations from this protocol in the allocated box at the end of each section.

However, this is not necessary for optional tasks **(o)**, which can be omitted if not applicable.

Please note that the order in which these tasks may be performed is flexible.

OPERATIVE FINDINGS

Please state operative findings

Abdominal access	**Y**	**N**
Safe access to the abdominal cavity was obtained.	☐	☐
The absence of metastatic disease, and the appropriateness of the planned procedure, was confirmed.	☐	☐
Diaphragmatic hiatus	**Y**	**N**
The oesophagus was mobilised from the diaphragmatic hiatus to the gastroesophageal junction.	☐	☐
The right and left paracardial lymphatic (LN) tissue was resected. (LN stations 1 & 2)	☐	☐
The dissection continued along the pericardial adventitia, removing the pericardial fat.	☐	☐
The dissection continued along the pre-aortic fascia.	☐	☐
A cuff of diaphragm and both the right and left lung pleura were included in the circumferential resection margin **(o)**.	☐	☐

Gastric mobilisation	**Y**	**N**
The right gastroepiploic vessels were identified.	☐	☐
The greater omentum was divided to enter the lesser sac, ensuring that the gastroepiploic vessels were preserved.	☐	☐
LN tissue along the greater curvature was resected **(o)**. (LN stations 4sa & 4sb)	☐	☐

Coeliac axis and portal vein	**Y**	**N**
The stomach was retracted and dissection started along the superior border of the pancreas to expose the portal vein **(o)**.	☐	☐
A sling was placed around the common hepatic artery **(o)**.	☐	☐
LN tissue along the proper hepatic artery was dissected **(o)**. (LN station 12a)	☐	☐
LN tissue along the common hepatic artery was dissected. (LN station 8a)	☐	☐
LN tissue along the coeliac artery was dissected. (LN station 9)	☐	☐
The left gastric vein was ligated and divided close to the portal vein.	☐	☐
The left gastric artery was ligated and divided at its origin from the coeliac artery, resecting LN tissue along left gastric artery. (LN station 7)	☐	☐
LN tissue along the proximal splenic artery was dissected. (LN station 11p)	☐	☐

LN tissue was dissected from the left side of the coeliac artery, to the left crus at the oesophageal hiatus and left side of Gerota's fascia.	☐	☐

Splenic artery and hilum	**Y**	**N**
The dissection was continued along the anterior surface of the proximal splenic artery towards the splenic hilum.	☐	☐
The posterior gastric vessels were ligated at their origin from the splenic artery.	☐	☐
Any remaining LN tissue along the distal splenic artery was resected, clearing to the splenic vein inferiorly and the abdominal wall posteriorly, until the splenic hilum was reached **(o)**. (LN station 11d)	☐	☐
The splenic hilum was cleared of LN tissue **(o)**. (LN station 10)	☐	☐

Gastric tube	**Y**	**N**
The lesser curvature of the stomach was cleared of LN tissue at the appropriate level, until the expected distal resection margin was reached. (LN stations 3a & 3b)	☐	☐
The gastric tube was formed (This may be done in the thoracic phase).	☐	☐
The gastric tube's staple line was oversewn **(o)**.	☐	☐
A pyloric procedure, to avoid delayed gastric emptying, was performed **(o)**.	☐	☐

Type of pyloric procedure: ……..

Site of formation of stomach tube: ……..

Feeding jejunostomy	**Y**	**N**
A feeding jejunostomy was placed **(o)**.	☐	☐
If the abdominal phase of the operation was performed minimally invasively, was a port site incision extended in order to facilitate the placement of a feeding jejunostomy?	☐	☐

Abdominal drains	**Y**	**N**
Abdominal drain(s) were placed **(o)**.	☐	☐

Please expand about site of placement: ..……

Abdominal closure	**Y**	**N**
Abdominal lavage was performed **(o)**.	☐	☐
Haemostasis was confirmed.	☐	☐
The abdomen was closed.	☐	☐
The wound was dressed as per trial guidelines.	☐	☐

DEVIATIONS FROM THE PROTOCOL

Please explain any deviations from the protocol for the abdominal phase of the operation here, numbered in the order in which they appear in the text:

ERRORS AND THEIR RECOVERY

Please describe any errors that occurred, and how they were recovered.

Example errors include damage to surrounding structures and bleeding from major vessels.

THORACIC PHASE

Thoracic access	**Y**	**N**
Safe access to the patient's right chest was obtained.	☐	☐
The absence of metastatic disease was confirmed.	☐	☐

Thoracic lymphadenectomy	**Y**	**N**
The inferior pulmonary ligament was divided.	☐	☐
The azygos arch was ligated and divided.	☐	☐
Dissection was performed along the pericardium.	☐	☐
The left pleura was included in the radial excision margin **(o)**.	☐	☐
A sub-carinal lymphadenectomy was performed. (LN station 107)	☐	☐
Both bronchi were cleared of LN tissue until the hilum of each lung was reached. (LN station 109)	☐	☐
The dissection continued along the right pulmonary veins, progressing posteriorly until the left pulmonary veins were reached **(o)**.	☐	☐
The mediastinal pleura was dissected at the anterolateral border of the thoracic aorta.	☐	☐
The pre-aortic fascia was dissected from the proximal resection margin towards the diaphragm. (LN station 112)	☐	☐
LN tissue along the aorto-pulmonary window was dissected, clearing the arch of the aorta, pulmonary artery, and recurrent laryngeal nerve as it hooks around the arch of the aorta **(o)**.	☐	☐
The thoracic duct was identified and ligated at the proximal resection margin and above the level of the diaphragm, such that it was resected with the specimen.	☐	☐

Specimen excision	**Y**	**N**
The thoracic part of the specimen was circumferentially free, from the previously completed diaphragmatic mobilisation (performed during the abdominal phase) to at least the level of the carina. (LN stations 107, 108, 109, 110, 111 & 112)	☐	☐

The stomach was delivered into the right chest cavity, ensuring that the gastric tube could reach the site of anastomosis without tension or torsion.	☐	☐
The specimen was excised with suitable resection margins.	☐	☐
The specimen was sent to pathology as per the trial protocol.	☐	☐

Anastomosis	**Y**	**N**
An oesophago-gastrostomy was performed.	☐	☐
If a 2-phase minimally invasive procedure was performed, a further incision was made in addition to the existing ports **(o)**.	☐	☐
If a 3-phase procedure was performed, a left cervical incision was required for the anastomosis.	☐	☐

Details of anastomosis …….

Nasogastric and nasojejunal tubes	**Y**	**N**
A nasogastric and/ or nasojejunal tube was placed.	☐	☐

Thoracic drains	**Y**	**N**
Thoracic drain(s) were placed prior to the closure of the thoracic incision.	☐	☐

Please expand on location: ……..

Thoracic closure	**Y**	**N**
Lavage was performed **(o)**.	☐	☐
Haemostasis was confirmed.	☐	☐
The lung was re-inflated under direct vision.	☐	☐
The chest was closed.	☐	☐
The wound was dressed as per the trial protocol.	☐	☐

DEVIATIONS FROM THE PROTOCOL

Please explain any deviations from the protocol for the thoracic phase of the operation here, numbered in the order in which they appear in the text:

ERRORS AND THEIR RECOVERY

Please describe any errors that occurred, and how they were recovered.

Example errors include damage to surrounding structures and bleeding from major vessels.

POSTOPERATIVE INSTRUCTIONS

Please describe instructions for postoperative care

Surgeon name

Surgeon signature

Appendix 5 Video assessment tool

Please tick the appropriate descriptions of the safety, efficiency, and quality of the end product for each task, according to the key below.

i) TECHNICAL SAFETY

Safe	No adverse events or near misses occurred.
Near miss	Potential harms were narrowly avoided.
Unsafe	Adverse event(s) that resulted in reversible harm occurred.
Dangerous	Adverse event(s) that resulted in permanent harm occurred.

ii) OPERATIVE EFFICIENCY

Optimal	Purposeful and progressive movements throughout.
Adequate	Some unnecessary movements, but generally progressive.
Inefficient	Repeated, unproductive, movements.
Poor	Wrong movements that compromised patient safety.

iii) QUALITY OF THE END PRODUCT

Complete	Anatomical structure is clearly demonstrated following complete dissection of all associated lymphatic (LN) tissue.
Incomplete	Incomplete LN clearance of the anatomical structure (quantify if possible please)

TASK 1: DIAPHRAGMATIC HIATUS

i) Safety	**Safe**	**Near miss**	**Unsafe**	**Dangerous**	**Comments**
	☐	☐	☐	☐	.....
ii) Efficiency	**Optimal**	**Adequate**	**Inefficient**	**Poor**	**Comments**
	☐	☐	☐	☐	.....

iii) Quality of end product	**Complete**	**Incomplete**	**Not performed**	**Comments**
Right crus	☐	☐	☐	.....
Left crus	☐	☐	☐	.....
Aorta	☐	☐	☐	.....
Pericardium	☐	☐	☐	.....
Right lung	☐	☐	☐	.....
Left lung	☐	☐	☐	.....

TASK 2: ABDOMINAL LYMPHADENECTOMY

i) Safety	**Safe**	**Near miss**	**Unsafe**	**Dangerous**	**Comments**
	☐	☐	☐	☐	.....
ii) Efficiency	**Optimal**	**Adequate**	**Inefficient**	**Poor**	**Comments**
	☐	☐	☐	☐	.....

iii) Quality of end product	**Complete**	**Incomplete**	**Not performed**	**Quantify if incomplete**
Portal vein	☐	☐	☐	.....
Proper hepatic artery	☐	☐	☐	.....
Common hepatic artery	☐	☐	☐	.....
Coeliac artery	☐	☐	☐	.....
Left gastric artery (stump)	☐	☐	☐	.....
Left gastric vein (stump)	☐	☐	☐	.....
Proximal splenic artery	☐	☐	☐	.....
Distal splenic artery	☐	☐	☐	.....
Splenic vein	☐	☐	☐	.....
Splenic hilum (if appropriate)	☐	☐	☐	.....

TASK 3: THORACIC LYMPHADENECTOMY

i) Safety	**Safe**	**Near miss**	**Unsafe**	**Dangerous**	**Comments**
	☐	☐	☐	☐	.....
ii) Efficiency	**Optimal**	**Adequate**	**Inefficient**	**Poor**	**Comments**
	☐	☐	☐	☐	.....

iii) Quality of end product	Complete	Incomplete	Not performed	Quantify if incomplete
Carina	☐	☐	☐	.....
Right main bronchus	☐	☐	☐	.....
Left main bronchus	☐	☐	☐	.....
Right pulmonary veins	☐	☐	☐	.....
Left pulmonary veins	☐	☐	☐	.....
Pericardium	☐	☐	☐	.....
Aorta	☐	☐	☐	.....

TASK 4: RECONSTRUCTION

i) Safety	Safe	Near miss	Unsafe	Dangerous	Comments
	☐	☐	☐	☐	.....
ii) Efficiency	**Optimal**	**Adequate**	**Inefficient**	**Poor**	**Comments**
	☐	☐	☐	☐	.....
iii) Quality of end product		**Yes**	**No**	**Borderline**	**Comments**
Viable colour of gastric tube		☐	☐	☐	.....
Lesser curve cleared of LN tissue		☐	☐	☐	.....
Tension free anastomosis		☐	☐	☐	.....
Appropriate approximation of sutures		☐	☐	☐	.....

ANY OTHER COMMENTS:

Appendix 6 Photograph assessment tool

Instructions: *Please tick the appropriate description for the quality of the end product for each task.*

Complete: Anatomical structure is clearly demonstrated following complete dissection of all associated lymphatic (LN) tissue.
Incomplete: Incomplete LN clearance of the anatomical structure (Quantify if incomplete).

Task 1

Diaphragmatic hiatus	Complete	Incomplete	Not performed	Quantify if incomplete
Right crus	☐	☐	☐	……
Left crus	☐	☐	☐	……
Aorta	☐	☐	☐	……
Pericardium	☐	☐	☐	……
Right lung	☐	☐	☐	……
Left lung	☐	☐	☐	……

Task 2

Abdominal lymphadenectomy	Complete	Incomplete	Not performed	Quantify if incomplete
Portal vein	☐	☐	☐	……
Proper hepatic artery	☐	☐	☐	……
Common hepatic artery	☐	☐	☐	……
Coeliac artery	☐	☐	☐	……
Left gastric artery (stump)	☐	☐	☐	……
Left gastric vein (stump)	☐	☐	☐	……
Proximal splenic artery	☐	☐	☐	……
Distal splenic artery	☐	☐	☐	……
Splenic vein	☐	☐	☐	……
Splenic hilum (if appropriate)	☐	☐	☐	……

Task 3

Thoracic lymphadenectomy	Complete	Incomplete	Not performed	Quantify if incomplete
Carina	☐	☐	☐	……
Right main bronchus	☐	☐	☐	……
Left main bronchus	☐	☐	☐	……
Right pulmonary veins	☐	☐	☐	……
Left pulmonary veins	☐	☐	☐	……
Pericardium	☐	☐	☐	……
Aorta	☐	☐	☐	……

Task 4

Reconstruction	Yes	No	Borderline	Quantify if incomplete
Viable colour of gastric tube	☐	☐	☐	……
Lesser curve cleared of LN tissue	☐	☐	☐	……
Tension free anastomosis	☐	☐	☐	……
Appropriate approximation of sutures	☐	☐	☐	……

EME
HS&DR
HTA
PGfAR
PHR

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