

Oesophageal squamous cell cancer: induction chemotherapy and oesophagectomy versus induction chemotherapy and chemoradiotherapy - a feasibility study

A feasibility trial of chemoradiation or surgery for oesophageal cancer

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Summary

Lay summary

Cancer of the gullet (oesophagus) is a serious disease that is difficult to treat. There are two types of oesophageal cancer and for the squamous cell type there are two treatments that are widely used to try and cure the disease. One involves chemotherapy (drug treatment that kills cancer cells) and then surgery (to excise the cancer within the oesophagus). The other treatment involves chemotherapy and then chemotherapy and radiotherapy together (radiotherapy burns and kills cancer cells). At present there is a lack of high quality evidence that compares the two treatments and selecting a treatment depends upon doctors' or patients' preferences and not on evidence about which treatment produces the best outcomes. The aim of this study is to determine the feasibility of a randomised trial of chemotherapy and oesophagectomy versus chemotherapy and chemoradiotherapy for patients with oesophageal squamous cell cancer. If the full multi-centre trial is feasible it will provide high quality evidence to use in clinical practice and inform treatment choice.

The feasibility study will also establish methods for recruiting participants from multi-disciplinary cancer team meetings into randomised trials. It will use qualitative research to work with doctors and nurses to improve communication with patients regarding the two types of treatments and to improve trial recruitment. Additionally surveys with health professionals and patients will be undertaken to identify the core information to be communicated about each treatment.

Scientific summary

The optimal treatment for localised oesophageal squamous cell cancer is controversial. Surgery alone or in combination with neoadjuvant treatment can achieve cure but is highly invasive, associated with significant risks and high rates of disease recurrence. Definitive chemoradiotherapy may lead to long-term survival although there may be local treatment failure. There are no adequate randomised controlled trials comparing the effectiveness and cost-effectiveness of surgical and non-surgical treatments. Previous attempts have failed because of difficulties in identifying patients and poor acceptance of randomisation. Treatment decision making, therefore, is not evidence-based and depends on clinician or patient preference. The overall aim of this study is to determine whether a full multi-centre randomised trial of the two standard treatments is feasible. This will be achieved by undertaking a randomised pilot trial of induction chemotherapy and oesophagectomy versus induction chemotherapy and definitive chemoradiotherapy with intergrated qualitative research to establish recruitment rates, to understand barriers to recruitment and to pilot procedures and trial outcome measures.

In addition, research will be undertaken to establish methods to identify patients eligible for randomisation using records from multi-disciplinary team meetings. This will determine and maximize recruitment and allow estimation of potential numbers for a full trial. Methods will also be used to reach consensus between health professionals and participants regarding clinically important treatment effects. These treatment effects will then be tested in the full trial. The final part of the feasibility study is to develop an intervention (information checklist) for surgeons, oncologists and nurses to use during consultations to describe the two standard treatments. This will be informed by information obtained from systematic reviews, the consensus methods, qualitative analysis of audio-recordings of consultations and semi-structured interviews with participants, in which their understanding of information provided will be elicited.

Background

Introduction

Oesophageal squamous cell cancer is a serious health problem. In the UK there are 2,500 incident cases per year and only 30% of these patients may be offered potentially curative treatment. Potentially curative treatment may include oesophagectomy or definitive chemoradiotherapy (CRT), but both approaches are associated with risks of death, major complications and a detrimental impact on health-related quality of life. Reports of survival after surgical based treatments vary, with possible one year survival between 30% and 60% and five year survival between 15% and 35%¹. In-hospital mortality rates after surgery have reduced to between 2% and 5% but complications are common^{2;3}. Several longitudinal studies have shown that surgery has a major negative effect on all aspects of health related quality of life with residual deficits in long term survivors^{4;5}. In the presence of such poor (and variable) survival rates and the significant risk of treatment-related death, morbidity and reduced health related quality of life, attention has turned to the outcomes of non-surgical management of oesophageal squamous cell cancer.

The non-surgical management of oesophageal squamous cell cancer has included radiotherapy, alone or in combination with chemotherapy. A systematic review comparing these modalities in patients unsuitable for surgery concluded that CRT was superior to radiotherapy alone⁶. Despite the seemingly poor prognostic features of the patients in the trials, definitive CRT was associated with long-term survival and disease control, reaching 52% and 27% survival at one-year and five years respectively⁶. Recently, a cohort study from the UK demonstrated a five year survival of 32% with CRT⁷. Toxicity and side effects also occur with CRT but there is some non-randomised evidence that health related quality of life with CRT may be less severe than surgery⁸. This evidence suggests that a trial of CRT compared to treatment including surgery is an imperative next development in this evolving area of importance and uncertainty.

There have been three attempts to undertake randomised controlled trials of surgical versus non-surgical treatments for oesophageal cancer, but each have suffered problems⁹⁻¹¹. Two trials were equivalence studies powered to determine whether the two treatments could be considered equivalent in terms of survival at two-years^{9;10}. Equivalence was defined as a difference of less than 10% and 15% respectively. It is questionable for a cancer with such a low survival rate, that such differences would not be deemed clinically important. The third study was powered to detect superiority of one treatment over another but failed to report what magnitude of difference was considered superior¹¹. None were able to rule out much larger beneficial and detrimental effects of treatment including surgery compared to CRT, all producing wide confidence intervals. In addition, none provided a robust assessment of health related quality of life.

Rationale for a feasibility study

There is a need for a well designed trial to compare the effectiveness and cost-effectiveness of the current standard treatments for oesophageal squamous cell cancer. This trial was proposed to the National Cancer Research Institute (NCRI) Upper Gastrointestinal Clinical Study Group in November 2006. The group supported the need for such a trial, but felt that recruitment would be difficult because eligible patients may not arise incidentally in sufficient numbers to provide adequate power for a trial and because in the absence of randomised evidence in this area, clinicians and patients often have strong preferences for particular treatments making randomisation difficult. Indeed these problems were experienced by the US Intergroup and the MRC clinical trials unit who have

both made previously unsuccessful attempts to mount a trial of a surgical versus non-surgical therapy in this area¹². It was therefore proposed that a detailed feasibility study be undertaken to address issues raised by the NCRI group and resolve the design problems surrounding this complex trial.

Expected benefits to the NHS

The study will show whether a full randomised controlled trial (RCT) is feasible. A full trial would provide high quality evidence to help doctors and patients make better decisions. If a full trial is not feasible the proposed study will still have an important impact for cancer services in the UK. It will clarify a method for recruiting participants into randomised controlled trials using multi-disciplinary team records. This may have a major influence on recruitment into clinical trials in oncology. The study will also refine methods for developing information checklists that can be used to communicate clearly the benefits or risks of treatment for gastrointestinal cancer.

Aims and objectives

The overall aim of the research is to determine the feasibility of an RCT comparing two standard treatments, induction chemotherapy and definitive oesophagectomy versus induction chemotherapy and definitive chemoradiotherapy for oesophageal squamous cell cancer.

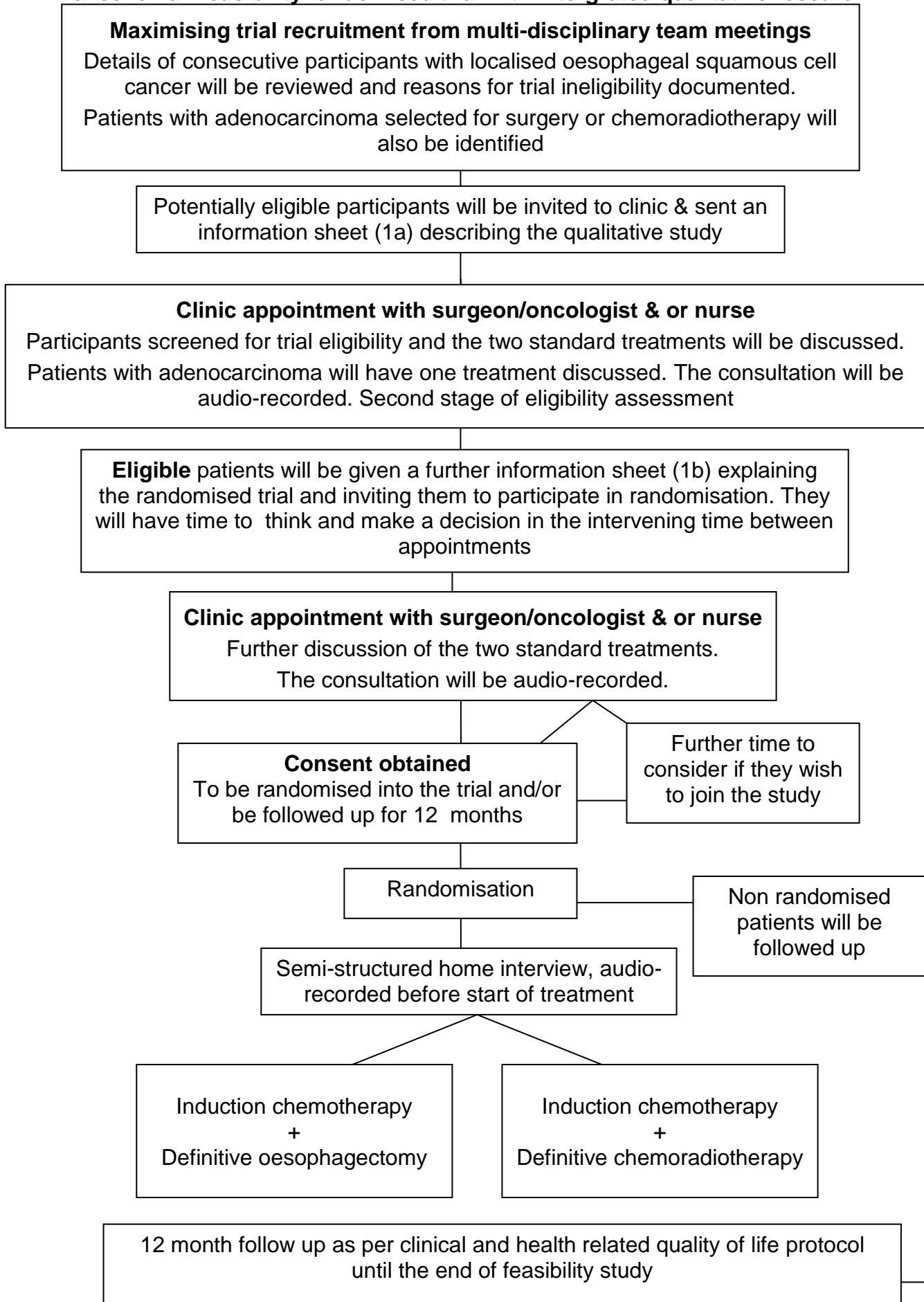
The study will address previous difficulties in mounting a trial by achievement of the following objectives:

1. to determine the number of patients eligible to enter a trial by identifying 'cases' using multi-disciplinary team records from the three feasibility centres
2. to undertake a pilot study for the main trial in three feasibility centres to establish recruitment rates, to use qualitative research to explore barriers to recruitment and to pilot cost and outcome measures and procedures for the trial
3. to ascertain consensus from professionals and patients of clinically important treatment effects to be tested in a trial and communicated to patients
4. to develop an information checklist to improve the communication between clinicians and patients about the two diverse treatments, this, in turn, will improve recruitment into a full trial

Summary of trial design

This is an open randomised controlled pilot trial designed to determine the feasibility of a full multi-centre trial comparing induction chemotherapy and oesophagectomy versus induction chemotherapy and definitive chemoradiotherapy for localised oesophageal squamous cell cancer. Associated research, to underpin the pilot RCT, will produce methods to recruit participants from multi-disciplinary team meetings, develop an information checklist with key clinical and health related quality of life outcomes associated with both treatments for use in consultations and establish clinically important treatment effects to be tested in a full multi-centre trial. Figure 1 shows the design, selection and recruitment process for the RCT.

Figure 1.
Trial schema - feasibility randomised trial with intergrated qualitative research



Selection of participants

Multi-disciplinary team meetings

Multi-disciplinary team meeting records from the participating centres will be collated by the local research nurse and/or an multi-disciplinary team core member in each centre and anonymised (to maintain patient confidentiality). Potentially eligible trial participants, and patients with adenocarcinoma that are selected for surgery or definitive chemoradiotherapy will be sent an appointment to meet the clinical team. This invitation will include information about the qualitative research (Patient information sheet 1a). The number of multi-disciplinary team decisions regarding patients with oesophageal squamous cell cancer and those potentially eligible for the trial will be recorded.

Initial trial eligibility criteria:

- Histological evidence of squamous cell cancer
- No evidence of metastases
- Fit for radical treatment

Meeting with consultant and nurse (clinical nurse specialist / research nurse)

During this meeting potentially eligible trial participants will be informed about the nature of the two standard treatments (N.B participants will be aware of the diagnosis of cancer for between one and four weeks before this appointment). Patients with adenocarcinoma will be informed about their recommended treatment (surgery or chemoradiotherapy) The information will be given verbally from the specialist upper gastro-intestinal consultant surgeon or specialist gastro-intestinal consultant oncologist and a clinical nurse specialist, trained research nurse or information radiographer. This information appointment will be audio-recorded and patient consent for the audio-recording requested (Consent form No. 1)

A member of the research team will explain the randomisation process and give the patient the information sheet explaining the randomisation process (patient information sheet 1b) to potentially eligible trial patients

Screening for entry into the trial

During this consultation the participant will be screened for study eligibility. Reasons for ineligibility will be recorded and care will continue as usual.

Inclusion criteria

This study will include participants:

1. Aged 18 years of age or older on the date of first clinic appointment.
2. With histologically confirmed oesophageal squamous cell cancer.
3. With tumours staged as T2N0/1M0, T3N0/1M0, T4N0/1M0, where the T4 tumour involves the diaphragmatic crura or mediastinal pleura only (TNM classification)¹³.
4. With a total primary tumour and nodes less than 10cm length.
5. Considered sufficiently fit for both treatments in the trial by a surgeon and an oncologist, both of whom are members of the core multi-disciplinary team*.
6. Willing to use contraception, if applicable.
7. Able to give informed written consent to participate in the randomised trial.

*If the participant is of uncertain fitness for both treatments, then respiratory and cardiac function tests should be performed according to local practice within 4 weeks of

randomisation. Suggested levels: FEV1 >1.5 litres; cardiac ejection fraction >50% of normal echocardiography.

Exclusion criteria

Participants will be excluded from entry into the trial if they have:

1. Concomitant or past malignancies within five years prior to randomisation, except basal or squamous cell carcinoma of the skin or in situ carcinoma of the cervix.
2. Prior treatment for oesophageal cancer (not including photodynamic therapy or laser therapy for high grade dysplasia or carcinoma in situ).
3. Type I or II tumours of the oesophago-gastric junction with more than 2cm gastric wall involvement (measured on EUS).
4. Previous treatment that compromises the ability to deliver definitive mediastinal chemoradiotherapy or to undergo oesophagectomy.

Any queries about whether a patient is eligible to enter the trial should be addressed to the local principle investigator before study entry. Concerns will then be discussed with the Chief Investigator.

Second appointment with consultant and nurse

Following this meeting, a second appointment with an oncologist or surgeon, clinical nurse specialist, research nurse or information radiographer will be arranged and any further staging investigations or tests of fitness can be completed. If the first appointment happens to be with an oncologist (which may occur for pragmatic reasons), the second appointment will be with a surgeon to ensure that the participant has the opportunity to be given detailed information and ask surgical, chemotherapeutic and radiotherapy questions (and vice versa).

At this second hospital appointment, the issues surrounding treatment for localised oesophageal squamous cell cancer will be discussed again. The advantages and disadvantages of both treatments will be explained using the checklist and the purposes of randomisation will be further described. This appointment will be audio-recorded where written consent is obtained (Consent form 1.0).

Consent to participate in randomised study

The decision to participate in the trial will be voluntary and participants will be competent to understand what is involved. It will be made clear to all participants they will be free to decline without prejudicing future care. Participants consenting to randomization will complete another consent form (Consent form No. 2). After the second appointment, participants will be given a further 60-hour period to reflect on their potential involvement in the study. During this time the participant is provided with the contact details of the research nurse, specialist nurse, information radiographer or core multi-disciplinary team member to ask further questions about the study. If they then agree to participate they will be sent another appointment for completion of the consent forms.

Written consent for audio-recordings of all consultations will be gained at each separate consultation. Both investigators and participants will retain copies of each signed consent form.

Randomisation

If the participant agrees to take part in the trial the research nurse will use the Bristol Randomised Trials Collaboration automated randomisation web based system to register the patient and allocate a unique participant number and treatment will be allocated. Treatment allocation will be determined using computer-generated random numbers, and will be stratified by participating centre. The unique participant number will be the primary way in which the participant will be identified and will be used in all correspondence.

Alternative to randomisation

If randomisation is unacceptable to the participant, a participant-led treatment decision will be reached. These participants will be asked to provide consent to be followed up (in the same way as the trial participants) for the duration of the feasibility study (Consent form no. 3).

For each study participant a letter will be sent to the participant's GP and referring clinical team (if appropriate) indicating participation in the study and treatment allocation (GP letter no. 1 or 2).

Withdrawal from allocated trial treatments

Participants should be given every encouragement to receive per protocol treatment unless clinical issues occur or participant choose to withdraw from the trial treatment. The reasons for this should be recorded wherever possible.

Clinical issues that may influence per protocol treatment implementation

- i. tumour progression during treatment.
- ii. unacceptable toxicity or intercurrent illness preventing treatment.
- iii. any change in the participant's condition which, in the clinician's opinion, justifies the discontinuation of treatment.

Withdrawal from the trial follow up

Although a trial treatment may be withdrawn for the above reasons, participants should continue to be followed up in the trial. Participants who explicitly withdraw consent to have any data recorded or any follow up must be respected and this will be recorded. Participants can change their minds about withdrawal at any time and re-consent to participate in the trial. Follow up data can only be recorded from the point when consent was reinstated.

ASSESSMENTS BEFORE RANDOMISATION

Tumour staging

Each of the tumour staging investigations outlined below should be aimed at being performed within 4 weeks prior to randomisation. However if this is not possible, the last staging investigation, which may include CT, EUS, PET/CT and laparoscopy, should normally be performed within 4 weeks prior to randomisation. If the last staging investigation is > 4 weeks, please contact the Chief investigator.

1. physical examination of neck and abdomen.
2. spiral/multislice computerised tomography (CT) scan of thorax and abdomen (neck and pelvis optional).

3. endoscopic ultrasound (EUS) of oesophagus and stomach.
4. bronchoscopy if the tumour is close to or invading either bronchii or trachea.
5. positron emission (PET)/CT, bone scans and laparoscopy are optional and should be performed according to local practice.

The final pre-treatment TNM stage will be based upon information collated from all tests. These are recommendations and should not replace local guidelines.

Assessment of fitness

These following investigations should be undertaken within four weeks prior to randomisation.

1. Clinical assessment of cardiovascular history function
2. Clinical assessment of respiratory history & function
3. Smoking and alcohol history
4. Detailed drug history
5. Body mass index
6. WHO Performance status
7. Full blood count
8. Serum renal, liver and bone profile (including serum magnesium).
9. Glomerular filtration rate
10. Electrocardiogram
11. Pregnancy test in females of child bearing age

If concerns are raised further investigations may be performed according to local guidelines.

CLINICAL DATA COLLECTION

Before randomisation at clinic appointments

All potential participants who are discussed at the multi-disciplinary team meetings, will be logged on a database at the department of Social Medicine, University of Bristol. Data regarding whether these individuals were then approached to participate in the study, randomised and agreed to be followed up, will also be recorded in a screening and enrolment log by the local research nurses. **For each patient anonymised clinical data will be collected regarding the reasons for trial ineligibility, the treatment recommendation of the MDT and the final treatment recieved** .When consent to participate in the randomised trial/follow up is received the names and addresses of participants will be entered on the project database along with the date on which consent was given. Eligible men or women who decline participation in the study will have no further information recorded, however. Details of the reasons for non-participation in the study will be recorded at all stages of this process.

After study entry

The following information will be recorded after agreement to participate in the study:

1. Which part of the study they participant has consented to take part in (and randomisation and/or follow up)
2. Date of completion of the consent form (s)
3. Full clinical details of staging investigations and co-morbidity
4. Full details of dates of clinic appointments
5. Health related quality of life and health economics assessments

This information will be entered onto the study database at the earliest opportunity. It is possible that there will be several appointments and data collection must occur after each appointment. If the participant is excluded for any reason e.g. for health grounds, then this must be fully documented.

During treatment

The research nurse in each centre will keep prospective records of the following details during treatment:

1. date of start and finish of treatment and dates and reasons for treatment delays;
2. full clinical details of hospital admissions or problems during treatment, including toxicity, surgical morbidity and in-hospital mortality;
3. date of treatment finally received and reasons for changes;
4. full histopathological results from surgery.
5. Health related quality of life and health economics assessments

At end of induction chemotherapy

After completion of induction chemotherapy in both study arms the following assessments will be undertaken:

1. a clinical examination and history, if new concerns regarding fitness to continue with definitive treatment arise, tests of cardiac and/or respiratory function may be undertaken according to local policy;
2. spiral/multislice computerised tomography (CT) scan of thorax and abdomen (neck and pelvis optional);
3. optional re-discussion of participant and review of CT co-morbidity tests at multi-disciplinary team meeting.

During follow up

After completion of both treatments participants will be followed up according to local policies. In addition participants will be followed up by phone calls from the research nurse at 16 and 24 weeks post randomisation and after 12 months throughout the duration of the feasibility study. Where patients have passed the 12 month follow up stage, data already collected will be retained. Phone calls will record details of:

1. Hospital admissions, requirement for interventions/investigations

ASSESSMENT OF HEALTH RELATED QUALITY OF LIFE

The purpose for measuring health related quality of life in the feasibility study is to trial best methods for data collection, establish whether the instruments are suitable in this setting and to use the results to inform the sample size calculation of the full trial.

Generic domains of health related quality of life will be assessed with the EORTC core questionnaire - the EORTC QLQ-C30¹⁴. Disease and treatment specific symptoms and side effects will be assessed with the oesophago-gastric cancer specific module - the EORTC QLQ-OG25¹⁵. The EQ-5D will be used to value quality of life and combine it with survival to calculate quality adjusted life years (QALYs) for the economic analysis (see below).

Baseline questionnaires will be completed by participants in clinic after written consent has been obtained and prior to randomisation (Consent form No.4). Follow-up questionnaires will be administered by post following a phone call reminder to the participant made

centrally from the research associate based in Bristol. Participants will be asked to fill out the questionnaires themselves as completely and accurately as possible and return within a stamp-addressed envelope, which will be provided by the research nurse. If this is not possible research staff may administer them and this will be recorded. Reasons for questionnaire non-completion will be documented.

Timing of health related quality of life assessment

- Baseline questionnaire.
- During week 7 post randomisation (end of induction chemotherapy)
- During week 16 post randomisation (after completion of treatment).
- Post randomisation 24 weeks and 12 months.

HEALTH ECONOMIC DATA COLLECTION

Details of resources used during induction chemotherapy will be recorded by the research nurse from the medical record using a standardised data collection form. This will include drug regimen used and number of cycles. In the surgical group theatre time and duration of time on intensive care or surgical wards and any readmissions will be recorded. In the definitive chemoradiotherapy group documentation of the drug regimen, number of cycles, number of fractions of outpatient or inpatient therapy and hospital admissions will occur.

In a brief addendum to the health related quality of life postal questionnaire at each follow up timepoint, we will ask patients about any cancer/ gastro-intestinal related use of health services in the interim. This will include medications taken, GP surgery/home visits, nurse visits, outpatient appointments, accident and emergency visits, inpatient admissions and utilisation of nursing home or hospice care.

The pilot study will help refine the resource use data collection forms for a subsequent definitive trial. Unit costs of care will be identified from national sources (e.g. NHS reference costs) and local hospital finance departments. The costs will be combined with resource use to estimate the comparative costs of surgery and chemoradiotherapy. The pilot data will enable us to calculate the expected value of sample information from a definitive trial.

TREATMENT PROTOCOLS

Following entry into the study, participants will receive one of the two standard treatments that will commence within one week of randomisation.

Chemotherapy and surgery protocol

Induction chemotherapy before surgery

Standard induction chemotherapy will consist of two cycles of 21 days i.e. a total of 42 days therapy. There are two schedules that may be used according to local practice.

i) Cisplatin $80\text{mg}/\text{m}^2$ to be given by intravenous infusion on day 1, with pre and post hydration (a recommended hydration schedule is given on page 23, table 4).

5-Fluorouracil $1\text{g}/\text{m}^2/\text{day}$ to be given by continuous intravenous infusion for 4 days starting on day 1 (i.e. total cycle dose = $4\text{g}/\text{m}^2$).

ii) Cisplatin 80mg/m² to be given by intravenous infusion on day 1, with pre and post hydration (a recommended hydration schedule is given on page 23, table 4).

Capecitabine 625mg/m² to be given orally twice daily within 30 mins of food, starting in the evening of day 1 and finishing on the morning of day 43.

Pre-meds and anti-emetics may be administered according to local practice.

Surgical protocol

Centres recruiting to this study will be expected to deliver surgical management that conforms to the standards set out in the NICE Improving Outcomes Guidance¹⁶. Surgery should be performed within four to six weeks after completion of induction chemotherapy.

The operation may consist of a two or three-phase oesophagectomy and it may be performed with an open, laparoscopic, open or combined approach. The phase of operation carried out first is dependant upon the planned operation and its approach. The stomach is the preferred organ for reconstruction, where this is unavailable, colonic or small bowel transposition should be performed.

Abdominal phase

The intra-abdominal contents should be carefully inspected, paying particular attention to the omentum and peritoneal surfaces in the supracolic compartment for metastases and the para-aortic region in patients with otherwise resectable nodal disease. Lesions suspicious of metastatic disease should be biopsied and sent for frozen section. Gastric mobilisation can proceed but the operation should be terminated if there is unequivocal evidence on frozen section that there is disease outside the proposed surgical field.

Complete gastric mobilisation based on the right gastroepiploic and right gastric arteries should be achieved. The left gastric vein should be divided as low as possible, where it disappears behind the hepatic artery at the upper border of the pancreas. The left gastric artery should be divided at its origin.

Lymphadenectomies along the hepatic artery and splenic artery will be performed, either en bloc or separately at the surgeon's discretion. The hepatic artery dissection should remove all nodal tissue overlying the hepatic artery proper and the common hepatic artery. (This ensures removal of all group 8 nodes). Lymphadenectomy on the splenic artery extends from the origin of this vessel as far lateral as the point of ligation of the uppermost posterior short gastric vessel. The abdominal phase should result in a dissection that has removed lymph nodes from stations 1, 2, 3, 7, 8 and 11.

The exact extent of the dissection at the diaphragm will be influenced by the results of pre-operative staging, as well as intra-operative assessment. For tumours at the level of the diaphragm, it may be necessary to remove crural fibres and a cuff of diaphragm. Mobilisation of the left lateral segments of the liver, division of the inferior phrenic vein well to the right and to the left of the oesophagus, may be used to facilitate extension into the mediastinum. Both pleural cavities may be opened, although this can be deferred until the thoracic phase. Removal of the pericardial fat pad anteriorly and strips of parietal pleura should usually be achieved at this stage, to again minimise the risk of a positive radial margin, although these steps can be undertaken during the thoracic phase of the operation.

Preparation of the transection site on the lesser curve, without compromise to the extent of lymphadenectomy, can be undertaken during the abdominal or thoracic phase of the operation.

Thoracic phase

This may be either via the right or left thorax. The intra-thoracic contents should be carefully inspected, paying particular attention to the pleural surfaces. Lesions suspicious of metastatic disease should be biopsied and sent for frozen section. Oesophageal mobilisation can proceed but the operation should be terminated if there is unequivocal evidence on frozen section that there is disease outside the proposed surgical field.

The oesophagus is fully mobilised with mediastinal pleura overlying the oesophagus excised in continuity. If necessary during a right thoractomy, the azygos vein is divided where it crosses the oesophagus. The posterior limit of the dissection should be the antero-lateral wall of the aorta, so that the thoracic duct is mobilised with the oesophagus and peri-oesophageal tissues. The thoracic duct is ligated and divided at the level of the diaphragm and at the upper level of transection. The mediastinal pleura overlying the left side of the oesophagus should also be excised to the level of the tumour.

Para-oesophageal and diaphragmatic nodes (groups 108, 110, 111) are removed in continuity with the oesophagus. Lymph nodes at the tracheal bifurcation and along the right and left main bronchi to the pulmonary hilus, can be removed en bloc or separately (nodal groups 107, 109). The extent of lymphadenectomy for the upper thoracic para-oesophageal nodes (group 105), will be determined by the site of oesophageal transection. This must be above the aortic arch and preferably within 5 cm of the thoracic inlet. Enlarged nodes in the para-tracheal group (group 106), should be removed for sampling purposes. Complete dissection of the left sided recurrent laryngeal nerve nodal chain is not mandatory.

The stomach is delivered into the chest and formed into an oesophageal conduit using a stapled or hand sewn technique. An anastomosis between the conduit and oesophagus is formed according using a stapled or hand sewn technique. A nasogastric tube is placed via the nasopharynx into the conduit.

Cervical phase

The cervical incision is at the discretion of the surgeon (left neck, vertical or skin crease). The oesophagus is identified, preserving and minimising traction on the left recurrent laryngeal nerve. The oesophagus is divided maintaining the maximum proximal length to enable the anastomosis to be at the level of the skin (two stay sutures may be placed in the proximal oesophagus).

The divided distal oesophagus is sutured closed with an attached NG tube. Using the abdominal incision the oesophagus (and attached NG tube) are delivered into the abdominal cavity and the tumour and oesophagus are removed by division of the proximal stomach (ensuring an adequate distal resection margin). Leaving the NG tube passing from the neck incision via the thorax into the abdominal wound.

The free NG tube, is then fixed to the neo-oesophagus/conduit and this is delivered into the neck using gentle traction. An anastomosis between the conduit/neooesophagus and proximal oesophagus in the neck is performed using staples or sutures at the discretion of the surgeon. An NG tube (nasopharyngeal to the conduit) is placed under direct vision.

Optional procedures

The placement of a feeding jejunostomy, intra-abdominal, intra-thoracic drains and cervical drains are optional. Pyloroplasty, pyloromyotomy or no drainage may also be performed at the surgeon's preference. The techniques for closure of the laparotomy, thoracotomy or port sites is at the surgeon's discretion.

Lymph node numbers referred to are those used in the Japanese Classification for oesophageal cancer .

Chemoradiotherapy protocol

Induction chemotherapy before definitive chemoradiotherapy

Standard induction chemotherapy before chemoradiotherapy will consist of two cycles of 21 days i.e. a total of 42 days therapy. There are two schedules that may be used according to local practice.

i) Cisplatin $80\text{mg}/\text{m}^2$ to be given by intravenous infusion on day 1, with pre and post hydration (a recommended hydration schedule is given on page23, table 4).

5-Fluorouracil $1\text{g}/\text{m}^2/\text{day}$ to be given by continuous intravenous infusion for 4 days starting on day 1 (i.e. total cycle dose = $4\text{g}/\text{m}^2$).

ii) Cisplatin $80\text{mg}/\text{m}^2$ to be given by intravenous infusion on day 1, with pre and post hydration (a recommended hydration schedule is given on page 23, table 4).

Capecitabine $625\text{mg}/\text{m}^2$ to be given orally twice daily within 30 mins of food, starting in the evening of day 1 and finishing on the morning of day 43.

Pre-meds and anti-emetics may be administered according to local practice

Definitive chemoradiotherapy protocol

Definitive chemoradiotherapy should start as soon as induction chemotherapy has finished (i.e. day 43). The chemotherapy component is identical to the induction chemotherapy and will continue for a further 2 cycles (i.e. from day 43 to day 84). The radiotherapy protocol also starts on day 43.

Patients should be planned and treated in the supine position with their arms above their heads. The planning CT scan should be performed within two weeks of starting the induction chemotherapy and within six weeks of the staging spiral CT scan. The planning CT scan should be performed according to local practice but should be at 3-5mm slices incorporating the whole thorax to below the level of kidneys. It is helpful to use intravenous contrast to help distinguish the gross tumour volume (GTV) from surrounding tissues but in most cases is not helped by oral contrast which may interfere with planning calculations. In most cases the GTV (extent of primary and nodal disease) is defined by the EUS taking into account information from the diagnostic spiral CT scan, barium studies and 18-FDG PET scan if performed. Radiotherapy will be delivered in a single phase: 50Gy in 25 fractions.

Gross tumour volume

The target volumes are localised on axial slices of the planning CT scan. The EUS GTV is used to define the longitudinal margins with the aid of an EUS derived reference point (i.e. arch of aorta or tracheal carina which is easily seen on CT axial images e.g. if the carina is

26cm ab oral on EUS and the proximal tumour extent is at 28cm, this would be 4 x 5mm CT slices below the carina as seen on the CT. However, one should encompass 'tumour' seen on the CT plan even if outside the EUS defined disease extent i.e. the GTV should be the most proximal and distal extension of disease as seen on EUS or CT scan). The lateral and anterior-posterior GTV margins are derived from the planning CT scan. The GTV is marked on axial CT images and clinical target volume (CTV) and planning (PTV) increased with appropriate lateral margins. The CTV for the superior and inferior margins should be drawn manually to follow the axis of oesophagus, i.e. not generated automatically in the sup-inf direction by the planning system.

Table 1: Clinical target volume

Superiorly & inferiorly	The EUS defined extent of tumour (primary or nodal) with a 2cm margin along the axis of the oesophagus (see above)
Laterally & anteriorly	1cm margin around the tumour defined by the planning CT scan
Posteriorly	0.5-1cm cm margin around tumour defined by the planning CT scan

Table 2: Planning target volume

Superiorly & inferiorly	CTV + an increase of 1cm by planning system i.e. geometrically superior-inferiorly
Laterally & anteriorly/posteriorly	CTV + 0.5cm increase by planning system
The maximum treatment field length is 17cm, i.e. maximum EUS disease length (primary tumour & lymph nodes 10cm assuming 1cm extension from PTV to field length).	

Lower third tumours

If the tumour involves the gastro-oesophageal junction, i.e. Siewert Type 1, the inferior margins to define the PTV should be 3 cm below the EUS defined GTV. However the inferior volume should be increased as described above to cover the lymph node stations along the lesser curve to include the para-cardial, and left gastric lymph nodes along the lesser curve of the stomach as seen on the CT scan.

All treatment will be delivered in a single 3D (conformal) CT planned phase i.e. treatment cannot start following conventional simulation. Given the target volume described above and the normal tissue dose constraints below, it is up to individual participating centres to decide the field arrangements. It is recommended however that a 3 or 4 field technique is usually satisfactory, with anterior-posterior parallel opposed and two posterior oblique or lateral fields. The treatment should be delivered with a single phase technique.

The plan should be verified in the simulator (or equivalent) prior to starting treatment and at least one portal image taken in the first week of treatment on the linear accelerator and weekly throughout treatment thereafter.

The total dose is 50Gray delivered in 25 fractions, treating each field daily Mon-Fri and prescribed to the ICRU (International Commission on Radiation Units and Measurements) 50 reference point, usually the point of intersection of the central axes. The PTV min should be no less than 93% and the PTV max should be no more than 107% of the dose

prescribed to the ICRU 50 reference point. No point outside the PTV should receive >105%.

Table 3: Normal tissue tolerance

The following normal tissue tolerance doses should be observed and recorded for each patient plan;

Spinal cord	Less than 5% of the spinal cord within the target volume should receive more than 40Gy and none should receive more than 45Gy i.e. D 40<5%, D45<0.
Heart	Less than 30% of the total volume of heart should receive more than 40Gy i.e. V40 < 30%
Lung	Less than 25% of the total lung volume should receive more than 20Gy i.e. V20 < 25%.

Unscheduled breaks in treatment should not lead to prolonged overall treatment time where possible e.g. by delivering two fractions per day (more than six hours apart).

Salvage treatment

Following either induction chemotherapy and definitive oesophagectomy or chemoradiotherapy participants may develop systemic and/or local recurrence. Where there is clinical, CT or PET evidence of systemic disease participants will be offered palliative treatment according to the local policy.

Participants with evidence of localised disease within the oesophagus or at the level of the anastomosis may be offered salvage treatment with surgery or chemoradiotherapy according to local policy following discussion at the multi-disciplinary team meeting.

Medications permitted

Pre-medication with steroids such as dexamethosone, analgesic (e.g. paracetamol), anti-emetic (e.g. granisetron, ondansetron) and H2 blockers (e.g. ranitidine) are recommended prior to trial treatment.

Medications permitted with caution

The following drugs have been shown to potentially have some interaction with cisplatin and may require dose modification:

- Ototoxic drugs like aminoglycoside antibiotics or loop diuretics (e.g. furosemide), may increase ototoxic potential of cisplatin.
- Cisplatin may reduce the serum level of phenytoin so levels should be monitored and the dose adjusted accordingly.
- Cisplatin may reduce renal excretion of bleomycin and methotrexate which may increase toxicity of these agents.
- Anti-gout agents (like allopurinol, colchicine, probenecid or sulfinpyrazone).

The following drugs have been shown to potentially have some interaction with Pyrimidine analogues like Capecitabine or 5FU and may require dose modification:

- Coumarin derivative anticoagulants (like warfarin) require more frequent monitoring due to altered coagulation parameters, and effects may occur up to several months after initiating capecitabine therapy.
- There can also be interactions with cytochrome P-450 (isozymes 1A2, 2C9 and 3A4).

- Allopurinol (reduce the efficacy of 5FU).
- Phenytoin plasma levels may be increased, levels should be regularly monitored.

Non permitted medications

The following drugs have been shown to interact with cisplatin and should be avoided if possible:

- Cumulative nephrotoxicity may be potentiated by aminoglycoside antibiotics e.g. gentamicin. These should not be administered, if possible, simultaneously or 1-2 weeks after treatment with cisplatin.
- Cisplatin can also react with aluminium and all aluminium containing IV sets, needles, catheters and syringes should be avoided.

The following drugs have been shown to have some interaction with pyrimidine analogues like capecitabine or 5FU and should be avoided:

- Sorivudine and analogues (would require a 4-week wash out prior to the trial)
- Aluminium hydroxide or magnesium hydroxide containing antacids.
- Methotrexate is not recommended with any form of chemotherapy.

Clinical considerations

Pregnancy

Patients should be advised that contraception should be used where applicable to avoid the possibility of pregnancy occurring to themselves, or their partners, due to the potentially harmful effects of chemo-radiation. In the very unlikely event that a pregnancy occurs patients should be advised to report this to their treatment centre immediately. The PI is responsible for reporting this information to the Chief investigator and the Trial Office immediately who will then inform the Research and Development Department at UH Bristol (sponsor). The pregnancy should be followed up by the PI, and follow-up reports provided to the Trial Office, who will provide the onward reports to the Research and Development Department at UH Bristol (sponsor) for pharmacovigilance purposes.

Nutritional status

Patients with oesophageal cancer may have a poor nutritional status and centres should be aware that good clinical practice would normally include a basic dietician's review. Patients within the trial would be expected to receive the same nutritional support as those not included, and where there is a clinical need for invasive enteral nutrition, such as insertion of a jejunostomy or a PEG, this is permitted, and data will be collected to confirm the rate of enteral nutritional required.

DPD deficiency

Occasionally (approximately 1-3%) a patient may have a markedly exaggerated toxicity due to reduced 5FU catabolism. If this occurs, await full recovery of toxicities. Further treatment should be carried out at a much reduced capecitabine or 5 FU dose (e.g. 50%). This should be discussed with the Chief Investigator or one of the clinical co-investigators as required.

DRUG SUPPLY, DOSING, SIDE EFFECTS AND MODIFICATIONS

Chemotherapy should only be administered under the direction of oncologists in specialist units under conditions permitting adequate monitoring and surveillance. Supportive equipment should be available to control anaphylactic reactions

Drug Supply

Cisplatin, capecitabine and 5FU (when used in place of capecitabine) shall be available through routine medical supplies. Patients will be asked to bring any remaining tablets to their next visit so that they can be counted for drug accountability and compliance. Patient diaries will also be used to check compliance.

Dosing and precautions

Body Surface Area (BSA) should be calculated according to local policy. If required the formula and calculator are available at <http://www.halls.md/body-surface-area/refs.htm>.

Cisplatin

Cisplatin will be administered as an intravenous infusion with adequate pre- and post hydration and electrolyte correction (see recommended hydration schedule below). On days of concurrent chemo-radiation, cisplatin should be completed before radiotherapy treatment. Patients may undergo their radiotherapy during the post-hydration following cisplatin, which may be interrupted provided it is completed afterwards.

Cisplatin should only be administered under the direction of oncologists in specialist units under conditions permitting adequate monitoring and surveillance. Supportive equipment should be available to control anaphylactic reactions.

Table 4: Recommended fluid hydration for cisplatin

Infusion fluid & additives	Volume	Infusion time
Sodium Chloride 0.9%	1000ml	1 hour
Mannitol 20%	200ml	30 minutes
Ensure urine output >100ml/hour prior to giving Cisplatin. Give a single dose of furosemide 20mg iv if necessary.		
Cisplatin	500ml	1 hour
Sodium Chloride 0.9% + 2g MgSO ₄ + 20mmol KCl	1000ml	2 hours

Capecitabine

Capecitabine treatment is usually administered on an outpatient basis. Oral capecitabine 625mg/m² twice a day (to the nearest achievable dose using 500mg and 150mg tablets). Patients will be asked to take the medication every 12 hours for example 8:00am / 9:00 am and 8:00 pm / 9:00 pm each day, within 30 minutes after eating.

If a patient vomits after taking the capecitabine tablets they should not take another dose. The next dose of capecitabine should be taken at the planned usual time.

Table 5:Dosing

Calculated capecitabine dose at dose level 625 mg/m².

Dose level 625 mg/m ² (twice daily)		Number of tablets administered in the morning		Number of tablets administered in the evening	
Body surface area (m ²)	Dose per administration (mg)	150 mg	500 mg	150 mg	500 mg
≤1.38	800	2	1	2	1

1.39 – 1.52	950	3	1	3	1
1.53 – 1.78	1000	-	2	-	2
1.79 – 1.92	1150	1	2	1	2
1.93 – 2.18	1300	2	2	2	2
≥ 2.19	1450	3	2	3	2

Table 6: Calculated capecitabine dose at dose level 75%.

75% Dose level (twice daily)		Number of tablets administered in the morning		Number of tablets administered in the evening	
Body surface area (m ²)	Dose per administration (mg)	150 mg	500 mg	150 mg	500 mg
≤1.38	650	1	1	1	1
1.39 – 1.52	650	1	1	1	1
1.53 – 1.78	750	5	-	5	-
1.79 – 1.92	800	2	1	2	1
1.93 – 2.18	1000	-	2	-	2
≥ 2.19	1150	1	2	1	2

Table 7: Calculated capecitabine dose at dose level 50%.

50% Dose level (twice daily)		Number of tablets administered in the morning		Number of tablets administered in the evening	
Body surface area (m ²)	Dose per administration (mg)	150 mg	500 mg	150 mg	500 mg
≤1.38	450	3	-	3	-
1.39 – 1.52	500	-	1	-	1
1.53 – 1.78	500	-	1	-	1
1.79 – 1.92	600	4	-	4	-
1.93 – 2.18	650	1	1	1	1
≥ 2.19	650	1	1	1	1

Patients with difficulty swallowing capecitabine tablets may dissolve them in lukewarm water. The capecitabine tablets should be placed in approximately 200 mls of lukewarm water. By stirring for about 15 minutes the tablets should dissolve. There is no stability data for any form of capecitabine suspension, so this should be done immediately prior to use and the solution swallowed immediately, rinsing to ensure all of the contents are ingested. As the solution will have a bitter taste it could be flavoured with a fruit juice or squash but grapefruit juice should not be used. The solution may also be administered through a naso-gastric or other enteral feeding tube.

5-Fluorouracil

5-Fluorouracil will be administered as continuous intravenous infusion over 4-days according to local practice.

Possible side effects of Cisplatin and Capecitabine (or 5FU)

Haematological toxicity: Myelosuppression is uncommonly observed with cisplatin and capecitabine (or 5FU). Neutropaenia and thrombocytopaenia should be monitored according to the recommended protocol and appropriate dose modifications made. Anaemia may occur cumulatively with cisplatin and should be corrected during radiotherapy to maintain the haemoglobin > 12g/dL.

Nephrotoxicity: Renal toxicity has been noted in about one third of patients given a single dose of cisplatin when prior hydration has not been employed. Renal toxicity becomes more prolonged and severe with repeated courses of the drug. Serum renal function should be used to estimate renal function as a baseline prior to and during treatment using the Cockcroft & Gault formula (Appendix II). An EDTA clearance should be performed where indicated in the protocol and an appropriate dose adjustment made to the chemotherapeutic agents.

Gastrointestinal toxicity: Nausea and vomiting is common following cisplatin, usually starting within 1 hour of treatment and lasting up to 24 hours. Anorexia, nausea and occasional vomiting may persist for up to one week. Nausea occurs less commonly with capecitabine (or 5FU).

Diarrhoea occurs with capecitabine (or 5FU) and patients should receive advice regarding discontinuation of therapy and use of loperamide or codeine phosphate. Clinicians should be aware of infective causes of diarrhea (e.g. Clostridium difficile), and patients should be tested in cases of concern. Antibiotic treatment is not recommended routinely but may be required in such circumstances. Stomatitis occurs with capecitabine and patients should receive advice regarding good oral care, and the use of mouthwash (e.g. Corsodyl™).

Hand-foot syndrome (Palmar-plantar erythrodysesthesia/PPE): Occurs with capecitabine (or 5FU) and is reversible, where necessary with dose delay and reduction (see below). Other side effects include dermatitis, pigmentation and nail changes.

Cardiac: An infrequent association with capecitabine (or 5FU) is acute chest pain that appears to be related to coronary artery spasm and occurs more frequently in patients with known ischaemic heart disease. Fluoropyrimidines are also associated with tachyarrhythmias and ECG changes.

Neurotoxicity: Cisplatin neurotoxicity is characterised by peripheral neuropathies and paraesthesia in both upper and lower extremities and while reversible, may take a year or more to recover. Losses of taste and seizures have also been reported. This is quite different to 5FU associated neurotoxicity characterised by a transient reversible cerebellar syndrome.

Ototoxicity: Ototoxicity is cumulative with cisplatin and is not reversible. Unilateral or bilateral tinnitus, which is usually reversible, and/or hearing loss in the high frequency range, may occur. These abnormalities usually appear within 4 days after drug administration. Patients with significant neuro- and ototoxicity are not eligible and where necessary patients should be changed to Carboplatin.

Anaphylaxis: Reactions to cisplatin therapy have been occasionally reported in patients who were previously exposed to cisplatin. Patients who are particularly at risk are those with a prior history or family history of atopy. Serious reactions may be controlled by IV adrenaline, corticosteroids or antihistamines.

Serum electrolyte disturbances: Hypomagnesaemia, hypocalcaemia, hyponatraemia, hypokalaemia and hypophosphataemia have been reported to occur in patients treated with cisplatin and should be monitored according to the protocol.

Other toxicities: Hair loss is not expected with this combination but may rarely occur with most chemotherapeutic agents. Vascular toxicities coincident with the use of cisplatin in combination with other antineoplastic agents have been reported rarely. These events may include myocardial infarction, cerebrovascular accident, thrombotic microangiopathy (haemolytic uraemic syndrome) or cerebral arteritis. There have been reports of optic neuritis, papilloedema and cerebral blindness following treatment with cisplatin.

Dose modifications chemotherapy

Protocol chemotherapy may have to be modified if toxicity arises. Full blood count, serum creatinine, magnesium, calcium and LFTs should be measured prior to each cycle of chemotherapy.

Haematological toxicity

If the neutrophil count is $<1.0 \times 10^9/l$ and/or the platelet count $<100 \times 10^9/l$, the next course of chemotherapy should be delayed for 1 week and blood counts repeated. If blood counts have recovered (i.e. the neutrophil count is $\geq 1.0 \times 10^9/l$ and the platelet count is $\geq 100 \times 10^9/l$), treat with a 25% reduction of both cisplatin and 5FU/capecitabine. If, on repeating the blood count after the week's delay, the blood counts have not recovered, delay the next course by one further week, and give it with a 50% dose reduction of both cisplatin and 5FU/ capecitabine once the blood counts have recovered.

Nephrotoxicity

Cisplatin produces cumulative nephrotoxicity. If a baseline estimate of renal function using the Cockcroft & Gault formula predicts the GFR to be $\geq 60 \text{ mL/min}$ full dose Cisplatin should be used. If the estimate is $<60 \text{ mL/min}$ an EDTA Creatinine clearance should be performed and the appropriate cisplatin dose used (see table 8, below). In the case of a 25% deterioration in estimated renal function (using the Cockcroft & Gault formula) on pre-treatment blood samples an EDTA Creatinine clearance should be performed and pending this an appropriate dose reduction in cisplatin should be made. The EDTA Creatinine clearance result, when available, takes precedent over estimated GFR for subsequent cisplatin dose calculations.

Table 8

GFR (mls/min) baseline and prior to Day 1	Action
$\geq 60 \text{ ml/min}$	Continue full dose
50-59 ml/min	Cisplatin 50% dose
40-49ml/min	Cisplatin 50% dose Capecitabine 75% dose
30-39 ml/min	Stop cisplatin, use carboplatin AUC 5 Capecitabine 50% dose
$< 30 \text{ ml/min}$	Stop cisplatin, use carboplatin AUC 5 Stop capecitabine

Consider dose reduction of 5FU in cases of severe renal impairment (i.e. $\text{GFR} \leq$

10ml/min.

Neurotoxicity / ototoxicity

Patients with CTC grade 2 or greater neurotoxicity or new functional deterioration in hearing, new tinnitus or new significant high frequency hearing loss on audiogram should have cisplatin discontinued. In this situation, carboplatin at a dose of AUC5 may be substituted at the discretion of the investigator.

Capecitabine (or 5-FU) dose non-haematological modifications

Toxicity due to capecitabine administration may be managed by symptomatic treatment and/or modification of the dose (treatment interruption or dose reduction). Once the dose has been reduced, it should not be increased at a later time. Patients taking capecitabine should be informed of the need to interrupt treatment immediately if moderate or worse toxicity occurs. Doses of capecitabine omitted for toxicity are not replaced or restored, instead patients should resume the planned treatment cycle. The following are the recommended dose modifications for toxicity. In addition patients should receive loperamide in case of diarrhoea, pyridoxine for PPE and mouthwashes and anti-emetics according to local policy.

Toxicities should be graded according to CTCAE v3.0. An abridged version is included in Appendix A for use when completing CRFs. In particular, diarrhoea, nausea, vomiting, stomatitis and skin reactions are to be noted.

Please use alternative specific toxicity for Hand-foot syndrome (PPE), the frequency of which in patients receiving capecitabine has led to altered toxicity ratings.

Table 9

Grade of hand-foot syndrome	
1	Numbness, dysaesthesia/paraesthesia, tingling, painless swelling or erythema of the hands and/or feet and/or discomfort which does not disrupt the patient's normal activities.
2	Painful erythema and swelling of the hands and/or feet and/or discomfort affecting the patient's activities of daily living.
3	Moist desquamation, ulceration, blistering and severe pain of the hands and/or feet and/or severe discomfort that causes the patient to be unable to work or perform activities of daily living.

If grade 2 or 3 hand-foot syndrome occurs, administration of capecitabine/5FU should be interrupted until the event resolves or decreases in intensity to grade 1. Following grade 3 hand-foot syndrome, subsequent doses of capecitabine/5FU should be decreased.

Table 10:Capecitabine (or 5FU) dose reduction schedule for non-heamatological toxicities.

Toxicity	During a course of therapy	Dose adjustment for next cycle (% of starting dose)
Grade 1		
	Maintain dose level	Maintain dose level
Grade 2		

1st appearance	Interrupt until resolved to grade 0-1	100%
2nd appearance	Interrupt until resolved to grade 0-1	75%
3rd appearance	Interrupt until resolved to grade 0-1	50%
4th appearance	Discontinue treatment permanently	
Grade 3		
1st appearance	Interrupt until resolved to grade 0-1	75%
2nd appearance	Interrupt until resolved to grade 0-1	50%
3rd appearance	Discontinue treatment permanently	
Grade 4		
1st appearance	Discontinue permanently or If physician deems it to be in the patient's best interest to continue, interrupt until resolved to grade 0-1	50%

Chest pain

If unexplained chest pain occurs on treatment, capecitabine (or 5FU) should be stopped, an ECG performed and cardiac enzymes measured. In the case of angina or myocardial infarction being confirmed this should be managed according to usual local practice. Patients should not recommence capecitabine (or 5FU) therapy and further therapy should be discussed with the Chief Investigator. Such cardiac toxicity should be reported through a SAE form.

ADVERSE EVENTS

Complications and adverse events related to both treatment arms of this protocol (chemotherapy and oesophagectomy (surgery)) or chemotherapy and chemoradiotherapy are the same as those experienced by participants undergoing the treatments outside of this protocol. Adverse events will be recorded and reported in accordance with UH Bristol's Research Related Adverse Event Reporting Policy. They are listed here.

Adverse events related to surgery

Oesophageal surgery is associated with complications. These may occur during the operation itself, whilst recovering from surgery in hospital and there are complications that may occur after discharge and during the months following surgery.

Operative complications

During the operation it may be necessary to perform additional surgery because of damage to organs close to the oesophagus or stomach or because the blood supply to other organs is damaged during the dissection. Splenectomy may be necessary and although this does not usually lead to long-term problems after recovery from surgery it is necessary to remain on long term antibiotics.

Damage to the pancreas may occur during mobilisation of the stomach. This may lead to leakage of pancreatic enzymes and formation of an intrabdominal abscess or a fistula to the skin. Pancreatic collections/fistula may be small and lead to a delay in discharge, occasionally they are large and problematic requiring percutaneous drainage, prolonged courses of antibiotics and rarely re-operation.

Damage to the lung or airway may occur during mobilisation of the oesophagus in the chest. This will require immediate repair and it may lead to air leakage. Occasionally this requires prolonged ventilation and rarely re-operation.

In hospital complications

Failure of an anastomosis or staple line to heal may occur following oesophagectomy. Leakage of the oesophago-gastric anastomosis or feeding jejunostomy may occur. Leakage may also occur from the gastric staple line. Leakage may lead to problems with sepsis requiring intravenous antibiotics, or it may cause an intra-abdominal or intra-thoracic collection and abscess requiring percutaneous or open drainage. An anastomotic leak may also require reoperation or endoscopic stenting to adequately drain or repair the problem. If there is an anastomotic leak after surgery, it may result in multi-system organ failure and admission to an intensive care unit.

Damage to the thoracic duct may occur during mobilisation of the thoracic oesophagus. This may lead to leakage of chyle in the early post-operative time. If the leakage is small this may be treated with a change in nutrition, however, a large leak will require a second operation to repair the duct.

General complications

Following surgery, patients are at risk of general complications that may occur after any abdominal and thoracic procedure. These include chest infection (pneumonia), pulmonary embolic problems (deep vein thrombosis and pulmonary emboli), wound infections, cardiac dysfunction (arrhythmia or ischaemia) or renal failure or urinary problem related to catheterisation.

In-hospital mortality

Following any of the above complication there is a risk of death whilst in hospital. The estimated risk of in-hospital mortality after oesophagectomy is about 1 in 20 in large cancer centres.

Frequency of complications

The overall frequency of any complications occurring after oesophagectomy is between 40 and 60% in all published series. Risks of serious complications are less than 20% and there is a spectrum of all general cardio-respiratory, infective and thrombo-embolic complications. In addition the rate of inoperability is approximately 5%

Reporting adverse events related to chemotherapy

Both the investigators and sponsors will follow specific procedures when reporting adverse events/reactions in clinical trials. These procedures are described in this section of the protocol and they are in line with current ICH GCP. Side effects of the individual chemotherapy drugs are described above.

Definitions

The definitions of the EU Directive 2001/20/EC Article 2 based on ICH GCP apply in this trial protocol. These definitions are given in Table 11, below.

Table 11: Table of definitions

Name (abbreviation)	Definition
Adverse Event (AE)	Any untoward medical occurrence in a patient or clinical trial subject to whom a medicinal product has been administered

	including occurrences which are not necessarily caused by or related to that product.
Adverse Reaction (AR)	Any untoward and unintended response to an investigational medicinal product related to any dose administered.
Unexpected Adverse Reaction (UAR)	An adverse reaction, the nature or severity of which is not consistent with the information about the medicinal product in question set out in the summary of product characteristics (or Investigator brochure) for that product.
Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR) or Suspected Unexpected Serious Adverse Reaction (SUSAR)	Respectively any adverse event, adverse reaction or unexpected adverse reaction that: <ul style="list-style-type: none"> - results in death - is life-threatening* - requires hospitalisation or prolongation of existing hospitalisation** - results in persistent or significant disability or incapacity - consists of a congenital anomaly or birth defect

Clarifications and exceptions

*The term 'life-threatening' in the definition of 'serious' refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

**Hospitalisation is defined as an inpatient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Hospitalisations for a pre-existing condition (including elective procedures that have not worsened) do not constitute an SAE (serious adverse event).

Medical judgement should be exercised in deciding whether an adverse event (AE) or adverse reaction (AR) is serious in other situations. Important AE/ARs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

Trial-specific exceptions

Disease progression or death as a result of disease progression are not considered to be SAEs and should be reported on the relevant form

SAE excluded from expedited notification

The following situations that fulfil the definition of an SAE are excluded from expedited notification on an SAE form. Nausea, vomiting, diarrhoea and neutropenia should be reported on the Chemotherapy Form.

- i. Elective hospitalisation and surgery for treatment of oesophageal cancer or its complications.
- ii. Elective hospitalisation to simplify treatment or procedures.
- iii. Elective hospitalisation for pre-existing conditions that have not been exacerbated by trial treatment
- iv. Nausea and vomiting
- v. Central line complications
- vi. Diarrhoea caused by Capecitabine or 5FU
- vii. Neutropenia

Institution/Investigator responsibilities

All non-serious AEs/ARs, whether expected or not, should be recorded in the toxicity

(symptoms) section of the Chemotherapy forms and AEs/ARs section of the CRF and sent to the Trial Office within one month of the form being due.

SAEs/SARs should be notified to the Trials Office as described below who will notify the Chief Investigator and the Research and Development Department at UH Bristol in accordance with UH Bristol's Research Related Adverse Event Reporting policy.

The severity (i.e. intensity) of all AEs/ARs (serious and non-serious) in this trial should be graded using Common Terminology Criteria for Adverse Events (CTCAE) v3.0 (<http://ctep.cancer.gov/reporting/index.html>), Appendix A. Any questions concerning this process should be directed to the local principal investigator and then to the Chief Investigator of the study in the first instance.

Investigator Assessment

(a) Seriousness

When an AE/AR occurs the investigator responsible for the care of the patient must first assess whether the event is serious using the definitions given in Table 11. If the event is serious and not exempt from expedited reporting, then an SAE form must be completed and faxed to the Trial Office who will notify the Chief Investigator and the Research and Development Department at UH Bristol in accordance with UH Bristol's Research Related Adverse Event Reporting policy.

**Trial office fax for the attention Joanna Nicklin
0117 342 4834**

(b) Causality

The Investigator must assess the causality of all serious events/reactions in relation to the trial therapy using the definitions in Table 11. There are 5 categories: unrelated, unlikely, possible, probable and definitely related. If the causality assessment is unrelated or unlikely to be related the event is classified as a SAE. If the causality is assessed as either possible, probable or definitely related then the event is classified as a SAR.

Table 12. Definitions of causality

Relationship	Description	Event type
Unrelated	There is no evidence of any causal relationship	SAE
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the patient's clinical condition, other concomitant treatment).	SAE
Possible	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant treatments).	SAR
Probable	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.	SAR
Definitely	There is clear evidence to suggest a causal relationship and other possible contributing factors	SAR

can be ruled out.	
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(c) Expectedness

If the event is a SAR the Investigator must assess the expectedness of the event. Please see page 24 in the protocol for the list of expected toxicities associated with the drugs being used in this trial. If a SAR is assessed as being unexpected it becomes a SUSAR.

(d) Notification

Investigators must notify the Trial Office of all SAEs occurring from the time of randomization until 30 days after the last protocol treatment administration. The Trial Office will notify the Chief Investigator and the Research and Development Department at UH Bristol in accordance with UH Bristol's Research Related Adverse Event Reporting policy. SARs and SUSARs must be notified to the Trial Office indefinitely (i.e. no matter when they occur after randomisation) who will notify the Chief Investigator and the Research and Development Department at UH Bristol in accordance with UH Bristol's Research Related Adverse Event Reporting policy

Notification Procedure:

1. The SAE form must be completed by the Investigator (consultant named on the signature list and delegation of responsibilities log who is responsible for the patient's care), with due care being paid to the grading, causality and expectedness of the event as outlined above. In the absence of the responsible investigator the form should be completed and signed by a member of the site trial team. The responsible investigator should subsequently check the SAE form, make changes as appropriate, sign and then re-fax to the Trial Office as soon as possible. The Trial Office will notify the the Chief Investigator and Research and Development Department at UH Bristol in accordance with UH Bristol's Research Related Adverse Event Reporting policy. The initial report shall be followed by detailed, written reports as appropriate.
2. Send the SAE form by fax to the Trial Office within 24 hours who will notify the Chief Investigator and the Research and Development Department at UH Bristol in accordance with UH Bristol's Research Related Adverse Event Reporting policy within 24 hours.

<p style="text-align: center;">Trial office fax for the attention of Joanna Nicklin 0117 342 4834</p>

3. Follow-up: Patients must be followed-up until clinical recovery is complete and laboratory results have returned to normal or baseline, or until the event has stabilised. Follow-up should continue after completion of protocol treatment if necessary. Follow-up information should be noted on a further SAE form by ticking the box marked 'follow-up' and faxing to the Trial Office 0117 928 7305 as information becomes available. Extra, annotated information and/or copies of test results may be provided separately. The patient must be identified by trial number, date of birth and initials only. The patient's name should not be used on any correspondence.

4. The Research and Development Department at UH Bristol will notify the MHRA and Research Ethics Committee of any SAEs/SUSARs requiring expedited reporting in accordance with UH Bristol's Research Related Adverse Event Reporting policy.

Bristol Randomised Trials Collaboration responsibilities

The responsibility of the BRTC is to provide expertise in the design and analysis of the study. The BRTC will also provide the Web-based randomisation service.

Any interim analysis warranted by adverse events will be carried out by the study statistician.

The Chief Investigator (or a medically qualified delegate) may carry out a secondary clinical review of SAE reports received. The causality assessment given by the local Investigator at the hospital cannot be overruled and in the case of disagreement, both opinions will be provided in any subsequent reports.

The Trial Office and Chief Investigator will also keep all investigators informed of any safety issues that arise during the course of the trial.

Adverse events related to radiotherapy

Radiotherapy for oesophageal cancer is associated with complications. These may occur over the month in which it is administered and there are complications that may occur during the months following radiotherapy. Appendix B provides a commonly recognised grading system for recording events related to radiotherapy.

STATISTICAL ANALYSES

1. The primary outcome for the feasibility study is the proportion (and number) of eligible patients randomised. Secondary outcomes will include health related quality of life, survival at one and two years post-randomisation, treatment related toxicity and morbidity.

The proportion of eligible patients randomised will be calculated from data obtained systematically from multi-disciplinary team meetings and screening and enrollment logs. This will be studied within each centre. Data on toxicity will also be recorded and graded according to acute and late NCI Common Toxicity Criteria (version 3). Health related quality of life will be assessed with validated self report questionnaires as described above.

2. Other important endpoints of the feasibility study are the development of an information checklist to use during consultations in the main trial to communicate clinical equipoise surrounding the two treatment arms and ensuring that procedures and outcomes are developed and ready to use in the main trial and acceptability of the proposed multi-centre trial design to staff and participants.

Descriptive statistics will be used to describe the characteristics of the patients randomised to the two groups, and to compare them with those eligible but not randomised. The magnitude of between group differences for survival at one- and two-years post randomisation will be estimated using Cox Proportional Hazards regression models (after distributional checks). Attention will be focused on 95% confidence intervals in order to estimate potential effect sizes to be tested for in a main trial. P values will not be considered in the feasibility study since there will be insufficient power for these to be informative.

Analyses for intergrated qualitative research

The purpose of the qualitative research intergrated into the feasibility study is to understand how information about the trial and two treatments is communicated to patients and to identify optimal ways for doing this to feedback to participating clinicians. It will involve:

1. Audio-recordings of the consultations
2. Semi-structured interviews with patients
3. Semi-structured interviews with healthcare professionals

Audio-recordings of consultations

Consultations will be recorded and transcribed in full. The text will be coded and codes scrutinised for emerging themes. A constant comparison approach will be undertaken until it is certain that no new themes are emerging.

Semi-structured patient interviews

Patients consenting to participate in the qualitative study will undergo audio-recorded semi-structured interviews (at their homes or in the hospital, according to their choice) within a week of the out patient clinic appointment. The interviews will be based on a topic guide which will be refined as the study progresses. The guide will include, patients' understanding and interpretation of the information given during the consultation; acceptance of clinical equipoise; ideas about how information giving could be improved; evaluations of different treatment outcomes in terms of survival and health related quality of life and perspectives on what are important differences in outcomes between treatments.

Transcribed audio-recordings of the interviews will be read and systematically coded and common themes determined. Data relating to each code will be retrieved and the relationships between codes explored.

Information from the audio-recorded consultations and patient interviews will identify best methods for communication of trial details and the equipoise surrounding both treatments. This will be iteratively feedback to participating consultants and research nurses to explore information provision and communication of equipoise. If required clinical meetings with key staff to discuss equipoise will also be arranged.

Semi-structured interviews with healthacre professionals

Semi structured interviews will be undertaken, with consenting healthcare professionals, who are responsible for recruiting to the study. The interviews will be conducted with the aid of a topic guide and will aim to explore understanding of the study and the role of teamwork in recruitment.

Transcribed audio-recordings of the interviews will be read and systematically coded and common themes determined. Data relating to each code will be retrieved and the relationships between codes explored.

Information gained from the analysis of these interviews will be used to further understand the role of teamwork in trial recruitment.

Survey to agree clinical important treatment effects to be tested in the main trial

The objective of this part of the study is to identify what constitutes an important clinical difference in outcome between surgical and definitive chemoradiotherapy treatment and what constitutes equivalence to be tested in the main trial. The main trial will then be powered to detect the minimally important difference with sufficient power. This will directly

inform the sample size calculation for the main trial and ensure an adequately powered study.

Development of core information

The objective of this part of the research is to develop core information that is required by patients to provide them with sufficient knowledge to understand the two trial treatments. The core information will include data about survival, morbidity and health related quality of life and the uncertainty around these outcomes for each of the two treatments. The outcome information will be put together from systematic literature reviews of clinical and patient reported outcomes from trials in oesophageal cancer. This evidence will be synthesised to produce a summary of key outcomes and how commonly they occur with each treatment. Experts will be consulted using Delphi methodology. This will ask selected individuals to rate the importance of each outcome for communication to patients before randomisation and during information provision for informed consent. As is expected that approximately 100 health professionals will complete the survey and then the number of outcomes will be reduced and another round completed. Up to three rounds will reduce the list to core outcomes for information provision for patients. Once the core information is established this will be used by participating clinicians and nurses in consultations.

Health professionals will complete the survey using web based technology and patients will complete a separate survey using a paper questionnaire. Healthcare professionals will be provided with written information about the delphi process (Information sheet 4) and be consented (Consent 6, v2).

Patients will be selected from the databases of participating NHS trusts. Participants attending a national upper gastrointestinal cancer patient support meeting will also be invited to participate in a Delphi study of core information. Participants will have been informed about the research presentation prior to attending the meeting. Information about the study will be given verbally to participants during the meeting. Written information will also be provided (patient information sheet 3, V2). These participants will consent (Consent form 7) participation in the Delphi survey by means of a postal questionnaire.

Following implementation of the core information the qualitative interviews and observations of consultations will continue to established best methods for communicating the relevant details.

ETHICAL AND GOVERNANCE ISSUES

The study performed will be subject to Research Ethics Committee approval, including any provisions of Site Specific Assessment (SSA) and local Research and Development (R & D) approval.

Regulatory status

MHRA approval has been granted

Study medication

Study medication will be stored and dispensed by the trial site's pharmacy department in accordance with Good Clinical Practice and Good Manufacturing Practice.

Indemnity

This is an NHS sponsored research study. For NHS sponsored research HSG (96) 48 reference no. 2 is relevant. If there is negligent harm during the clinical trial when the NHS body owes a duty of care to the person harmed, NHS indemnity covers NHS staff,

medical academic staff with honorary contracts and those conducting the trial. NHS indemnity does not offer no-fault compensation and is unable to agree in advance to pay compensation for non-negligent harm. Ex-gratia payments may be considered in the case of a claim.

Data protection

The University of Bristol department of Social Medicine and the Research and Development Department at UH Bristol will act to preserve patient confidentiality and will not disclose or reproduce any information by which patients could be identified, (except where patients are registered with the Office for National Statistics or traced via the NHS Central Register, which requires separate consent). Data will be collected and retained in accordance with the Data Protection Act 1998.

Storage of records

Participant data will be stored on a server located within the Department of Social Medicine, University of Bristol. Study documents (paper and electronic) will be retained in a secure location during and after the trial has finished. All stored documents will be retained for a period of 15-years following the end of the study. Where trial related information is documented in the medical records – those records will be identified by a 'Do no destroy before dd/mm/yyyy label' where date is 15 years after the last patient's visit.

Publication policy

Data from all centres will be analysed together and published as soon as possible. Individual participants may not publish data concerning their patients that are directly relevant to questions posed by the trial until the Trial Management Group (TMG) has published its report. The TMG will form the basis of the Writing Committee and advise on the nature of publications.

All publications shall include a list of contributors, and if there are named authors, these should include the Chief Investigator, Co-Investigators, Trial Manager, and statistician(s) involved in the trial. If there are no named authors then a writing committee will be identified.

Investigator responsibilities

The principal clinical investigator at each centre will be responsible for the clinical conduct of the study staff. The clinical investigators will maintain a Trial Site File including a list and CVs of appropriately qualified persons to whom they have delegated significant trial-related duties. The investigator will ensure that all such identified persons will be thoroughly familiar with the protocol and study procedures, as well as being aware of the principles of Good Clinical Practice (GCP). A research nurse/research associate shall be appointed by the investigator at each centre and shall have responsibility for the efficient operation of the study to GCP guidelines.

Co-enrolment guidelines

It may be possible for patients to be enrolled in other clinical trials, but this will need to be discussed with the Chief Investigator or Co-Investigator. It is preferable that the Trial Office should be notified in writing, with details of the trial name, sponsor, randomisation arms, study endpoints and a declaration that follow up in this trial will not be impeded before the patients is co-enrolled.

Finance

This study is supported by a NIHR Research for Patient Benefit Grant PB-PG-0807-14131.

Monitoring and audit

The study will be monitored and audited in accordance with University Hospitals Bristol NHS Trust policy. All trial related documents will be made available on request for monitoring and audit by UH Bristol, the relevant Research Ethics Committee and for inspection by the Medicines and Healthcare products Regulatory Authority or other licensing bodies.

Research governance statement

This study will be conducted in accordance with

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

Trial steering committee

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Data monitoring committee

A Data Monitoring Committee (DMC) will be established. The DMC will meet annually and be responsible for reviewing recruitment, interim monitoring of safety and effectiveness, trial conduct and external data. The DMC will provide a recommendation to the Trial Steering Committee concerning study continuation as appropriate.

PARTICIPATING CENTRE SELECTION

The feasibility study will be carried out in three centres within the UK. Pre-requisites for centre participation include:

- i. A weekly meeting of a specialist upper gastro-intestinal multi-disciplinary team
- ii. All members of the multi-disciplinary team consent to participate in qualitative research processes including audio-recording of consultations
- iii. Experience with radical oesophagectomy and 2-phase lymphadenectomy
- iv. Experience with definitive chemoradiotherapy (participating in SCOPE 1¹⁸)
- v. Access to contrast enhanced spiral or multi-slice CT and EUS
- vi. Appropriate pathologists who are experienced in the reporting of oesophageal cancer, with agreement to peer review specimens and to participate in a laboratory based translational project.

The following accreditation documentation must be received by the Trial Office in order for a centre to be opened to recruitment into the trial:

- Completed signed Site Specific Information form for each site
- CV lead oncologist, surgeon and research nurse
- Confirmation of Trust R&D approval.
- Signed Clinical Trial agreement between each Trust R&D and UH Bristol NHS Trust.
- A copy of the most recent version of the Patient Information Sheet and Consent Forms on local headed paper.
- Completed delegation log (signature list and delegation of responsibilities).
- Full contact details for all site personnel.
- Set of lab normal ranges from laboratory being used for analyses.
- Successful pass of quality assurance test for radiotherapy planning and treatment (per SCOPE 1 protocol).
- Evidence of pathology outcomes for undertaking radical oesophagectomy (review of PI of last 10 procedures)

All this documentation must be stored in the Trial Site File at the centre. The Trial Office (and if applicable the Research and Development Department at UH Bristol) will be

notified of any changes to the trial personnel and their responsibilities during the running of the trial and the respective trial master files must contain this up to date information.

Once all the above documents have been received, confirmation of centre approval will be sent to the Principal Investigator. Site initiation will be by attendance at regional set-up meetings and occasionally by teleconference or site visits. Recruitment may then commence.

Quality assurance of surgery, chemotherapy and radiotherapy

Oesophagectomy will be performed as described in the protocol. The quality assurance procedures in place to ensure protocol compliance are a very important aspect of this study and site visits will be performed to observe surgery.

The steering group will ensure that participating surgeons have a high level of expertise in performing the procedure. The results of their last 20 cases using oesophagectomy will be audited prior to involving them in the study. The Data monitoring and safety committee will be provided with anonymised surgeons' data. If any surgeons are outside acceptable limits, the chair of the trial steering committee will be informed and will discuss the implications and necessary action with the principle investigators.

Radiotherapists with a special interest in gastro-intestinal oncology will be responsible for this treatment, and their results will be audited before and throughout the trial. Dr Crosby is on the study TSC, and will critically appraise progress of treatments administered within the trial. All participating centres must have previous experience in Upper gastro intestinal chemoradiotherapy. A CD ROM will be sent to centres wishing to participate in this study which will include a Practical Guide to Oesophageal Planning using the technique described, three example cases and a test case to be planned by each Investigator supervising patients in this trial.

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APPENDIX A

COMMON TOXICITY CRITERIA BASED ON CTCAE VERSION 3.-0

Short Name	1	2	3	4
Allergic reaction	Transient flushing or rash; drug fever >38°C (<100.4°F)	Rash; flushing; urticaria; dyspnea; drug fever ≥30°C (≥100°F)	Symptomatic broncospasm, with or without urticaria; parenteral medication(s) indicated; allergy-related oedema / angioedema; hypotension	Anaphylaxis
Hearing (without monitoring program)	-	Hearing loss not requiring hearing aid or intervention (i.e. not interfering with activities of daily living (ADL))	Hearing loss requiring hearing aid or intervention (i.e. interfering with ADL)	Profound bilateral hearing loss (>90 dB)
Haemoglobin	<LLN-10.0g/dL	<10.0 - 8.0g/dL	<6.5 - 8.0g/dL	<6.5g/dL
Leukocytes (total wbc)	<LLN - 3.0x10 ⁹ /L	3.0x10 ⁹ /L - 2.0x10 ⁹ /L	<2.0x10 ⁹ /L - 1.0x10 ⁹ /L	<1.0x10 ⁹ /L
Neutrophils	< LLN-1.5 x 10 ⁹ /L	< 1.5 – 1.0 x 10 ⁹ /L	<1.0 – 0.5 x 10 ⁹ /L	<0.5 x 10 ⁹ /L
Platelets	< LLN-75.0 x 10 ⁹ /L	< 75.0 – 50.0 x 10 ⁹ /L	<50.0 – 25.0 x 10 ⁹ /L	<25.0 x 10 ⁹ /L
ALT	> ULN - 2.5 x ULN	2.5 - 5 x ULN	5 - 20 x ULN	> 20 x ULN
AST	> ULN - 2.5 x ULN	2.5 - 5 x ULN	5 - 20 x ULN	> 20 x ULN
Bilirubin	> ULN - 1.5 x ULN	1.5 - 3.0 x ULN	3 - 10 x ULN	> 10 x ULN
Cardiac Ischemia/infarction	Asymptomatic arterial narrowing without ischaemia	Asymptomatic and testing suggesting ischaemia; stable angina	Symptomatic and testing consistent with ischemia; unstable angina; intervention indicated	Acute myocardial infarction
Hypertension	Asymptomatic, transient (<24hrs) increase by > 20mmHg (diastolic) or to > 150/100 if previously WLN ^Y ; intervention not indicated	Recurrent or persistent (>24hrs) or symptomatic increase by > 20mmHg (diastolic) or to >150/100 if previously WLN; monotherapy may be indicated	Requiring more than one drug or more intensive therapy than previously	Hypertensive crisis
Left ventricular systolic dysfunction	Asymptomatic, resting ejection fraction (EF) <60-50%; shortening fraction (SF) <30-24%	Asymptomatic, resting EF <50-40% SF <24-15%	Symptomatic congestive heart failure (CHF) responsive to intervention. EF <40—20% SF <15%	Refractory CHF or poorly controlled; EF <20%; intervention such as ventricular assist device, ventricular reduction surgery, or heart transplant indicated

Pulmonary hypertension	Asymptomatic without therapy	Asymptomatic, therapy indicated	Symptomatic hypertension, responsive to therapy	Symptomatic hypertension, poorly controlled
INR (International Normalized Ratio of prothrombin time)	>1 - 1.5 x ULN	>1.5 - 2 x ULN	> 2 x ULN	-
PTT (Partial Thromboplastin Time)	>1 - 1.5 x ULN	>1.5 - 2 x ULN	> 2 x ULN	-
Fatigue	Mild fatigue over baseline	Moderate or causing some difficulty performing some ADL	Severe fatigue interfering with ADL	Disabling
Weight Loss	5 to <10% from baseline; intervention not indicated	10 - <20% from baseline; nutritional support indicated	≥ 20% from baseline; tube feeding or TPN indicated	
Alopecia	Thinning or patchy	Complete	-	-
Injection site reaction / extravasation reaction	Pain, itching, erythema	Pain or swelling, with inflammation or phlebitis	Ulceration or necrosis that is severe, operative intervention indicated	-
Urticaria	Intervention not indicated	Intervention indicated for <24 hours	Intervention indicated for ≥24 hrs	
Wound complication, non-infectious	Incisional separation of ≤25% of wound, no deeper than superficial fascia	Incisional separation of > 25% of wound with local care, asymptomatic hernia	Symptomatic hernia without evidence of strangulation; fascial disruption/dehiscence without evisceration; primary wound closure or revision by operative intervention indicated; hospitalization or hyperbaric O ₂ therapy indicated	Symptomatic hernia with evidence of strangulation; fascial disruption with evisceration; major reconstruction flap, grafting, resection or amputation indicated
Diarrhoea	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4-6 stools per day over baseline; IV fluids indicated <24 hrs; moderate increase in ostomy output compared to baseline; not interfering with ADL	Increase of ≥ 7 stools per day over baseline; incontinence; IV fluids <24 hrs; hospitalisation; severe increase in ostomy output compare to baseline; interfering with ADL	Life-threatening consequences (e.g. hemodynamic collapse)
Dysphagia	Symptomatic, able to eat regular diet	Symptomatic and altered eating/swallowing (e.g. altered dietary habits, oral supplements); IV fluids indicated <24 hrs	Symptomatic and severely altered eating/swallowing (e.g. inadequate oral caloric or fluid intake); IV fluids, tube feedings, or TPN indicated ≥24 hrs	Life-threatening consequences (e.g. obstruction, perforation)
Oesophagitis	Asymptomatic pathologic, radiographic, or endoscopic findings only	Symptomatic; altered eating/swallowing (e.g. altered dietary habits, oral supplements); IV fluids indicated <24 hrs	Symptomatic and severely altered eating/swallowing (e.g. inadequate oral caloric or fluid intake); IV fluids, tube feedings, or TPN indicated ≥ 24 hrs	Life threatening consequences

Mucositis/ Stomatitis (clinical exam)	Erythema of the mucosa	Patchy ulcerations or pseudomembranes	Confluent ulcerations or pseudomembranes; bleeding with minor trauma	Tissue necrosis; Significant spontaneous bleeding; life threatening consequences
Mucositis/ Stomatitis (symptomatic)	Minimal symptoms, normal diet	Symptomatic but can eat and swallow modified diet	Symptomatic and unable to adequately aliment or hydrate orally	Symptoms associated with life-threatening consequences
Nausea	Loss of appetite without alteration in eating habits	Oral intake decreased without significant weight loss, dehydration or malnutrition; IV fluids indicated <24hrs	Inadequate oral caloric or fluid intake; IV fluids, tube feedings or total parenteral nutrition (TPN) indicated ≥24 hrs	Life-threatening consequences
Vomiting	1 episode in 24 hours	2-5 episodes in 24 hours; IV fluids indicated < 24hours	≥ 6 episodes in 24 hours; IV fluids, or TPN indicated ≥ 24hrs	Life- threatening consequences
Perforation GI (oesophagus, Stomach, duodenum, ileum, colon)	Asymptomatic, radiographic finding only	Medical intervention indicated, IV fluids indicated < 24hrs	IV fluids, tube feedings, or TPN indicated ≥ 24hrs; operative intervention indicated	Life-threatening consequences
Haemorrhage, GI	Mild, intervention not indicated	Symptomatic and medical intervention or cauterization indicated (depending on site)	Transfusion, interventional radiological, endoscopic or operative intervention indicated; radiotherapy (haemostasis of bleeding site)	Life- threatening consequences; major urgent intervention indicated
ALT / AST	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN
Bilirubin	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 10.0 x ULN	>10.0 x ULN
Hypocalcemia	<LLN – 2.0 mmol/L	<2.0 – 1.75 mmol/L	<1.75 – 1.5 mmol/L	<1.5 mmol/L
Creatinine	>ULN-1.5 x ULN	>1.5-3.0 x ULN	>3.0-6.0 x ULN	>6.0 x ULN
Glomerular Filtration Rate	<75-50% LLN	<50-25% LLN	<25% LLN, chronic dialysis not indicated	Chronic dialysis or renal transplant indicated
Hypomagnesia	<LLN – 0.5 mmol/L	<0.5 – 0.4 mmol/L	<0.4 – 0.3mmol/L	<0.3 mmol/L
Proteinuria	1+ or 0.15-1.0g.24hrs	2+ to 3+ or 1-3.5g/24hrs	4+ or >3.5g/24hr	Nephrotic syndrome
Hyperuricemia	>ULN – 10mg/dL ≥0.59 mmol/L without physiologic consequences		>ULN – 10mg/dL ≥0.59 mmol/L with physiologic consequences	>10mg/dL ≥0.59 mmol/L
Dizziness	With head movements or nystagmus only; not interfering with function	Interfering with function, but not interfering with ADL	Interfering with ADL	Disabling
Bronchospasm	Asymptomatic	Symptomatic not interfering with function	Symptomatic interfering with function	Life-threatening

Cough	Symptomatic, non-narcotic medication only indicated	Symptomatic and narcotic medication indicated	Symptomatic and significantly interfering with sleep or ADL	
Dyspnea	Dyspnea on exertion but can walk 1 flight of stairs without stopping	Dyspnea on exertion but unable to walk 1 flight of stairs of 1 city block (0.1km) without stopping	Dyspnea with ADL	Dyspnea at rest; intubation/ventilator or indicated
Cytokine release syndrome	Mild reaction; infusion interruption not indicated; intervention not indicated	Requires therapy of infusion interruption but responds promptly to symptomatic treatment (e.g. antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for ≥24 hrs	Prolonged (i.e. not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicate for other clinical sequelae (e.g. renal impairment, pulmonary infiltrates)	Life-threatening; pressor or ventilatory support indicated
Tumour flare	Mild pain not interfering with function	Moderate pain; pain or analgesics interfering with function, but not interfering with ADL	Severe pain; pain of analgesics interfering with function and interfering with ADL	Disabling
Arterial vessel injury	Asymptomatic diagnostic finding, intervention not indicated	Symptomatic (e.g. claudication) not interfering with ADL, repair or revision not indicated	Symptomatic interfering with ADL; repair or revision indicated	Life-threatening; disabling; evidence of end organ damage (e.g. CVA, MI, organ or limb loss)
Thrombosis/ thrombus/embolism	-	Deep vein thrombosis or cardiac thrombosis; intervention (e.g., anticoagulation, lysis, filter, invasive procedure) not indicated	Deep vein thrombosis or cardiac thrombosis; intervention (e.g., anticoagulation, lysis, filter, invasive procedure) not indicated	Embolus event including pulmonary embolism or life threatening thrombus

NB: These are selected categories. For full list see <http://ctep.cancer.gov/reporting/ctc.html>

For all cases where applicable grade 5 is death

APPENDIX B

RTOG acute radiation morbidity scoring criteria

	0	1	2	3	4
Skin	NCOB	Follicular, faint or dull erythema/ epilation/dry desquamation/ decreased sweating	Tender or bright erythema, patchy moist desquamation/ moderate edema	Confluent, moist desquamation other than skin folds, pitting edema	Ulceration, hemorrhage, necrosis
MUCOUS MEMBRANE	NCOB	Injection/ may experience mild pain not requiring analgesic	Patchy mucositis which may produce an inflammatory serosanguinitis discharge/ may experience moderate pain requiring analgesia	Confluent fibrinous mucositis/ may include severe pain requiring narcotic	Ulceration, hemorrhage or necrosis
EYE	NC	Mild conjunctivitis with or without scleral injection/ increased tearing	Moderate conjunctivitis with or without keratitis requiring steroids &/or antibiotics/ dry eye requiring artificial tears/ iritis with photophobia	Severe keratitis with corneal ulceration/ objective decrease in visual acuity or in visual fields/ acute glaucoma/ panophthalmitis	Loss of vision (unilateral or bilateral)
EAR	NCOB	Mild external otitis with erythema, pruritis, secondary to dry desquamation not requiring medication. Audiogram unchanged from baseline	Moderate external otitis requiring topical medication/ serious otitis medius/ hypoacusis on testing only	Severe external otitis with discharge or moist desquamation/ symptomatic hypoacusis/tinnitus, not drug related	Deafness
Salivary Gland	NCOB	Mild mouth dryness/ slightly thickened saliva/ may have slightly altered taste such as metallic taste/ these changes not reflected in alteration in baseline feeding behavior, such as increased use of liquids with meals	Moderate to complete dryness/ thick, sticky saliva/ markedly altered taste	-----	Acute salivary gland necrosis
Pharynx & Oesophagus	NCOB	Mild dysphagia or odynophagia/ may require topical anesthetic or non-narcotic analgesics/ may require soft diet	Moderate dysphagia or odynophagia/ may require narcotic analgesics/ may require puree or liquid diet	Severe dysphagia or odynophagia with dehydration or weight loss(>15% from pre-treatment baseline) requiring N-G feeding tube, I.V. fluids or hyperalimentation	Complete obstruction, ulceration, perforation, fistula

Larynx	NCOB	Mild or intermittent hoarseness/cough not requiring antitussive/erythema of mucosa	Persistent hoarseness but able to vocalize/referred ear pain, sore throat, patchy fibrinous exudate or mild arytenoid edema not requiring narcotic/cough requiring antitussive	Whispered speech, throat pain or referred ear pain requiring narcotic/confluent fibrinous exudate, marked arytenoid edema	Marked dyspnea, stridor or hemoptysis with tracheostomy or intubation necessary
UPPER G.I.	NC	Anorexia with <=5% weight loss from pretreatment baseline/ nausea not requiring antiemetics/ abdominal discomfort not requiring parasympatholytic drugs or analgesics	Anorexia with <=15% weight loss from pretreatment baseline/nausea &/ or vomiting requiring antiemetics/ abdominal pain requiring analgesics	Anorexia with >15% weight loss from pretreatment baseline or requiring N-G tube or parenteral support. Nausea &/or vomiting requiring tube or parenteral support/abdominal pain, severe despite medication/hematemesis or melena/ abdominal distention (flat plate radiograph demonstrates distended bowel loops)	Ileus, subacute or acute obstruction, perforation, GI bleeding requiring transfusion/abdominal pain requiring tube decompression or bowel diversion
LOWER G.I. INCLUDING PELVIS	NC	Increased frequency or change in quality of bowel habits not requiring medication/rectal discomfort not requiring analgesics	Diarrhea requiring parasympatholytic drugs (e.g., Lomotil)/ mucous discharge not necessitating sanitary pads/rectal or abdominal pain requiring analgesics	Diarrhea requiring parenteral support/severe mucous or blood discharge necessitating sanitary pads/abdominal distention (flat plate radiograph demonstrates distended bowel loops)	Acute or subacute obstruction, fistula or perforation; GI bleeding requiring transfusion; abdominal pain or tenesmus requiring tube decompression or bowel diversion
LUNG	NC	Mild symptoms of dry cough or dyspnea on exertion	Persistent cough requiring narcotic, antitussive agents/ dyspnea with minimal effort but not at rest	Severe cough unresponsive to narcotic antitussive agent or dyspnea at rest/ clinical or radiologic evidence of acute pneumonitis/ intermittent oxygen or steroids may be required	Severe respiratory insufficiency/ continuous oxygen or assisted ventilation
GENITOURINARY	NC	Frequency of urination or nocturia twice pretreatment habit/ dysuria, urgency not requiring medication	Frequency of urination or nocturia which is less frequent than every hour. Dysuria, urgency, bladder spasm requiring local anesthetic (e.g., Pyridium)	Frequency with urgency and nocturia hourly or more frequently/ dysuria, pelvis pain or bladder spasm requiring regular, frequent narcotic/gross hematuria with/ without clot passage	Hematuria requiring transfusion/ acute bladder obstruction not secondary to clot passage, ulceration or necrosis

HEART	NCOB	Asymptomatic but objective evidence of EKG changes or pericardial abnormalities without evidence of other heart disease	Symptomatic with EKG changes and radiologic findings of congestive heart failure or pericardial disease/ no specific treatment required	Congestive heart failure, angina pectoris, pericardial disease responding to therapy	Congestive heart failure, angina pectoris, pericardial disease, arrhythmias not responsive to non-surgical measures
CNS	NCOB	Fully functional status (i.e., able to work) with minor neurologic findings, no medication needed	Neurologic findings present sufficient to require home care/ nursing assistance may be required/ medications including steroids/anti-seizure agents may be required	Neurologic findings requiring hospitalization for initial management	Serious neurologic impairment which includes paralysis, coma or seizures >3 per week despite medication/hospitalization required
Haematologic WBC (X1000)	≥4.0	3.0 - <4.0	2.0 - <3.0	1.0 - < 2.0	<1.0
Platelets (X1000)	≥100	75 - <100	50 - <75	25 - <50	<25 or spontaneous bleeding
Neutrophils	≥1.9	1.5 - <1.9	1.0 - <1.5	0.5 - <1.0	<0.5 or sepsis
Haemoglobin (GM%)	>11	11 - 9.5	<9.5 - 7.5	<7.5 - 5.0	-----
Haematocrit (%)	≥32	28 - <32	<38	Packed cell transfusion required	-----

NC/OB: No change / over baseline

GUIDELINES: The acute morbidity criteria are used to score/grade toxicity from radiation therapy. The criteria are relevant from day 1, the commencement of therapy, through day 90. Thereafter, the EORTC/RTOG Criteria of Late Effects are to be utilized.

The evaluator must attempt to discriminate between disease- and treatment-related signs and symptoms.

An accurate baseline evaluation prior to commencement of therapy is necessary.

All toxicities Grade 3, 4 or 5* must be verified by the Principal Investigator.

* ANY TOXICITY WHICH CAUSED DEATH IS GRADED 5.

APPENDIX C

Renal Function

Cockcroft & Gault formula

$$\text{GFR for males} = \frac{1.23 \times [140 - \text{age}] \times \text{weight (kg)}}{\text{Serum creatinine } (\mu\text{mol/l})}$$

$$\text{GFR for females} = \frac{1.05 \times [140 - \text{age}] \times \text{weight (kg)}}{\text{Serum creatinine } (\mu\text{mol/l})}$$

- A patient with a Cockcroft & Gault estimate of GRF ≥ 60 ml/min using the above formula is eligible for the trial.
- Patients with GFR < 60 ml/min should have confirmation by EDTA clearance, other isotopic method or 24hr creatinine clearance and will be eligible if the GFR ≥ 60 .
- After start of treatment, if Cockcroft & Gault estimate falls by 25% from baseline to below 50 ml/min, the EDTA should be performed but an appropriate dose modification made according to protocol pending this result