Project title

Cancer of Oesophagus or Gastricus: New Assessment of Technology of Endosonography (COGNATE).

Funding

National Coordinating Centre for Health Technology Assessment (NCCHTA) [project number 01/01/03].

Planned investigation

Research objectives

What is the problem to be addressed?

The aim of this trial is to evaluate the role that endoscopic ultrasound (EUS) staging plays in the management of patients with gastro-oesophageal cancer (GOC). Specific objectives:

1. To estimate the marginal effect of EUS staging, compared with a standard staging algorithm, on the selection of treatment for patients with GOC viz the proportions of patients treated surgically, with multimodality treatment, or without surgery.
2. To estimate the effect of EUS staging on the outcome of care of patients with GOC. The outcome indicators include:
    a. Primary outcome: Quality-adjusted survival
    b. Secondary outcomes:
        i. Proportion of patients undergoing a complete resection.
        ii. Survival.
        iii. Quality of survival.
        iv. Resource use including treatment and subsequent use of health care.
3. To assess the cost-effectiveness of EUS by comparing improvements in patient outcomes with the marginal cost of EUS.
4. To estimate the proportion of patients with GOC who benefit from EUS and thus to model the need for EUS facilities within a defined population.

How the results of this trial will be used

The results of this multi-centre trial will inform policy whether EUS staging should be routine for patients with GOC and for which patients it is likely to benefit outcome. These data will be useful in modelling the resources required for EUS within a defined population.

The trial will provide robust evidence to underpin the development of guidelines for the effective staging of patients with GOC. We shall circulate such guidelines, initially among participating centres, but thereafter through national groups.

Existing research

Background

The Scottish Audit of Gastric and Oesophageal Cancer (SAGOC) is a prospective audit of gastric and oesophageal cancers. Data are available on 3300 patients with gastric and oesophageal cancers, that is

more than 95% of those diagnosed during 1997–1999. The data from SAGOC provide a population-based description of the current treatment of GOC and also predict the numbers of patients likely to be eligible for trials or treatments.

The change in the demography of upper gastro-intestinal cancers, well documented in Western series, is characterised by an increased incidence of lower oesophageal and proximal gastric cancers but a decreased incidence of distal gastric cancers.[1–3] Figures from Scottish and other UK centres have reflected the trend elsewhere – an increase in oesophageal cancers of 2% a year.[4,5] Unfortunately the survival of these patients is poor (*Table 1*), and treatment is associated with significant morbidity and mortality.[6–10]

The prognosis of patients with GOC depends on pre-morbid status, as many of these cancers occur in elderly and frail patients. Grading systems like that of the American Society of Anaesthesiologists (ASA) can predict survival (*Figure 1*). The World Health Organisation (WHO) performance status of patients can also predict survival. In patients with a good pre-morbid status, prognosis depends on the stage of the tumour; patients with metastatic disease have a poor prognosis.[11,12] For those with localised disease the anatomical extent of the tumour and nodal status are the most important prognostic indicators[7,13] (*Figure 2*).

In patients in whom surgery was performed SAGOC identified the following independent predictors of one-year survival: ASA grading; curative versus palliative intent of surgery; incomplete resections; and complications associated with surgery.

The most commonly used staging techniques were trans-abdominal ultrasonography scan (USS), chest X-ray (CXR), contrast-enhanced computerised tomography (CT) scan, and laparoscopy in selected patients; there was little use of magnetic resonance imaging (MRI) at that time (*Table 2*). Similar results were reported from Wales.[14] When centres use only these conventional staging techniques many patients undergo non-curative resections.[7,9] SAGOC has shown under-staging of oesophageal and gastro-oesophageal junctional cancers in approximately 20% of patients with operable tumours. This results in non-curative resections with macroscopic or microscopic tumour remaining, and does not improve length or quality of survival.[15] This is a particular problem for patients with T3 tumours, i.e. those that have breached the wall of the oesophagus or stomach but are not invading adjacent structures. Alternatives to surgery using chemotherapy and radiotherapy appear to be effective in such patients with advanced localised tumours.[16–19]

Alternative treatments are also now available for patients with cancers limited to the mucosa. Such tumours have a low risk of lymph node metastases and may be treated with mucosal ablative techniques such as endoscopic mucosal resection (EMR). Such treatment has been shown to be effective for mucosal cancers and avoids both immediate and long-term problems associated with surgery.[20,21] As tumours invade the sub-mucosal layer, however, there is increased risk of lymphatic dissemination and EMR is not an adequate treatment.[22] Using standard staging techniques it is difficult to differentiate between mucosal and sub-mucosal tumours and thus select appropriate patients for EMR.

Endoscopic ultrasound and staging of GOC

Initial reviews of CT, MRI and trans-abdominal ultrasonography suggested a tendency to under-stage tumours; furthermore MRI does not appear to improve good quality CT.[23–26] New developments may improve our ability to stage gastric and oesophageal cancers. The introduction of modern CT protocols and spiral images have improved the accuracy of CT staging.[27] Endoscopic ultrasonography (EUS) allows a high frequency ultrasound probe mounted at the end of an endoscope to be placed directly against either an oesophageal or gastric cancer. The high frequency of the ultrasound improves the spatial resolution that can be obtained and may thus improve the accuracy of tumour staging.[28–30] The systematic review preceding COGNATE showed that relative to conventional techniques EUS improves the accuracy of staging local GOC and the nodal status of these tumours[31] (*Table 3*).

TABLE 1 Survival from diagnosis of gastro-oesophageal cancer patients in Scotland (SAGOC data)

Tumour	6 months	12 months	18 months	24 months	30 months
Oesophagus	51.4%	29.0%	19.8%	13.8%	11.1%
OG junction	49.6%	32.7%	23.1%	16.6%	10.7%
Gastricus	50.7%	34.5%	25.7%	20.4%	17.4%

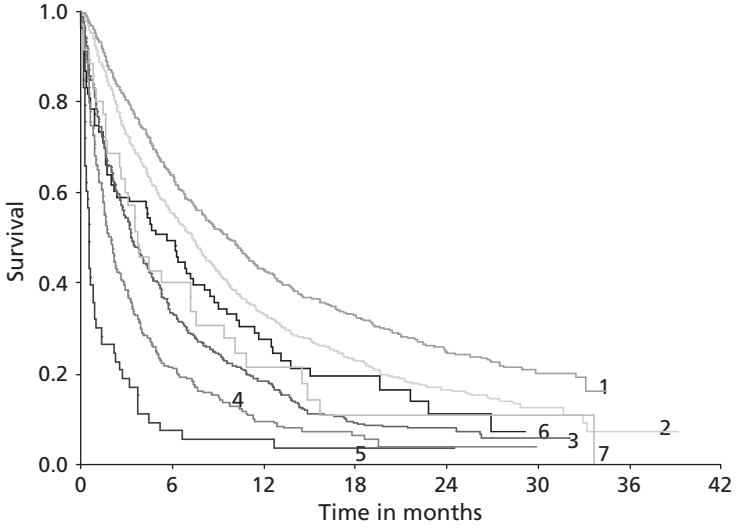

FIGURE 1 Unadjusted survival from localised malignancy (Kaplan–Meier estimates) by ASA grading (SAGOC data).
Key (ASA 1) no physiological disturbance (ASA 2) minor physiological impairment (ASA 3) significant physiological impairment but responsive to treatment with medication (ASA 4) severe physiological impairment not responsive to treatment (ASA 5) patient moribund (6) grade not recorded (7) average survival of SAGOC patients.

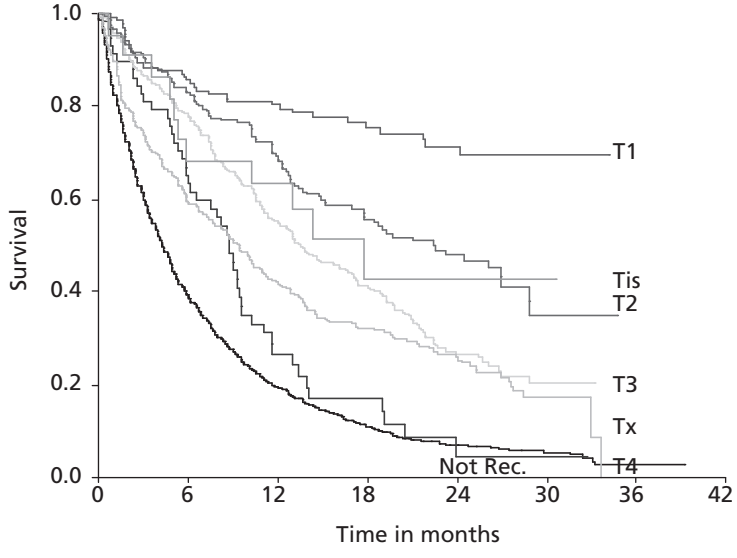

FIGURE 2 Unadjusted survival (Kaplan–Meier estimates) by stage (SAGOC data).
Key (Tx) tumour not evaluable (Tis) carcinoma in-situ (T1) tumour limited to mucosa or sub-mucosa (T2) tumour invades muscularis propria (T3) tumour invades adventitia (T4) tumour involves adjacent structures (Not Rec) Stage not recorded.

TABLE 2 Staging investigations used in population based studies: percentage of patients with given tumour who received specified investigation

	SAGOC			Wales[18]	
	Oesophageal	OG junction	Gastric	Oesophageal	Gastric
CT	71%	73%	60%	70%	59%
CXR	62%	61%	65%	NR	NR
USS	22%	30%	40%	64%	58%
Laparoscopy	16%	26%	23%	5%	16%
Bronchoscopy	7%	2%	1%	–	–
Endoscopic US	4%	4%	2%	–	–
MRI	1%	0.4%	0.5%	–	–

TABLE 3 Reported sensitivity and specificity of endoscopic ultrasonography[31]

Category	Sensitivity range	Specificity range
Oesophageal (T)	71–100%	67–100%
Gastro-oesophageal junction (T)	42–100%	67–100%
Gastric (T)	68–100%	88–100%
Nodes (N)	60–97%	40–100%

The need for a trial

Though EUS has been recommended as essential in staging of oesophageal cancers,[32] it has not been critically assessed. There are problems in EUS staging of non-traversable tumours;[33] the majority of these are T3 or T4 lesions, which need better staging to avoid non-curative resections. EUS was least accurate in carcinomas around the gastro-oesophageal junction[33] – the tumours which are increasing most rapidly in incidence. Furthermore there are few studies comparing the value of EUS with that of modern CT protocols.[33] Therefore, although there is evidence that EUS improves the anatomical staging of GOC, it is not clear how it affects patient management. In particular it is not clear whether there is any benefit from adding EUS to contemporary staging protocols based on helical CT techniques. SAGOC shows that before COGNATE only a minority of patients with GOC underwent EUS (*Table 2*). Hence the decision to use EUS more widely depends crucially on whether evaluation shows that it is of major benefit to patients. Therefore it is essential to estimate the effect of EUS staging on the management of gastric and oesophageal cancers. Furthermore it is important to know the proportion of patients with GOC that are likely to benefit from EUS. To answer these questions rigorously needs a randomised controlled trial which assesses patients by a conventional staging algorithm and then randomises them between EUS or not.

EUS may especially benefit three groups of patients with GOC:

1. Patients with T1 tumours localised to the mucosa, which EUS may identify as likely to benefit from endoscopic treatment, thus avoiding unnecessary surgery.
2. Patients with tumours which EUS may discriminate as either likely to benefit from 'curative' surgery' or to have residual disease after major surgery with attendant risks.
3. Patients with T3 or T4 tumours which EUS may identify as likely to benefit from multi-modal treatment or not.

Research design

Summary

Participating centres will use a defined staging algorithm based on usual practice for patients with GOC. Patients with localised tumours will be randomised to receive EUS or not after stratification by location – gastric, oesophageal or gastro-oesophageal junction. In both groups multi-disciplinary teams will choose between three main treatments:

1. Tumours adjudged mucosal will undergo endoscopic mucosal resection (EMR) with or without argon beam ablation of the surrounding mucosa.
2. Tumours adjudged resectable will undergo surgical resection, with or without neo-adjuvant cisplatin and 5FU.
3. Tumours adjudged not to be resectable will receive chemotherapy, with or without radiotherapy depending on the site.

We shall compare the two groups for treatment received, rate of complete resections, and length and quality of survival.

Trial design

Figures 3 and *4* summarise the trial design. A multi-centre randomised controlled trial will ensure that there is no bias in the selection of patients for EUS or not. Randomisation will take place after the initial staging investigations have been completed and reviewed at a multi-disciplinary meeting. At this stage clinicians will agree a conditional management plan and randomise patients either to receive EUS or to proceed directly to the agreed management plan. They will report patients whom they decide not to randomise to the trial co-ordinating centre in Bangor, with the reasons for their exclusion.

Interventions

We developed the staging algorithm from usual practice, as identified by SAGOC before the trial began:

a. Chest x-ray, pulmonary function tests, haematology and biochemistry, together with assessment of cardiac status. Patients of WHO performance status 3 or 4 or medically unsuitable for either surgery or chemotherapy will be excluded.
b. Patients who are medically fit will undergo a trans-abdominal USS. Those found to have metastatic liver disease will be excluded.
c. Patients without evidence of metastases will undergo a CT scan following an agreed protocol using a spiral scanner, oral water contrast and intravenous contrast. Laparoscopy will be undertaken in patients with any suspicion of peritoneal disease, as this remains the best means of detecting peritoneal deposits of tumour.[11]
d. Only patients with localised tumours will be randomised between EUS or not.

In the resulting non-EUS group the choice of treatment will depend on the results of these standard investigations. In the EUS group that choice will follow the extra investigation. At the end of staging, with or without EUS, multi-disciplinary teams will allocate patients to one of three treatment groups:

1. Patients adjudged to have mucosal tumours will be treated with EMR and the surrounding mucosa ablated.
2. Patients with tumours adjudged to be resectable will be treated with surgery, with or without neo-adjuvant chemotherapy.
3. Patients with advanced localised disease for which a complete resection is not adjudged possible will receive multi-modal treatment, possibly including palliative surgery in patients with gastric cancers.

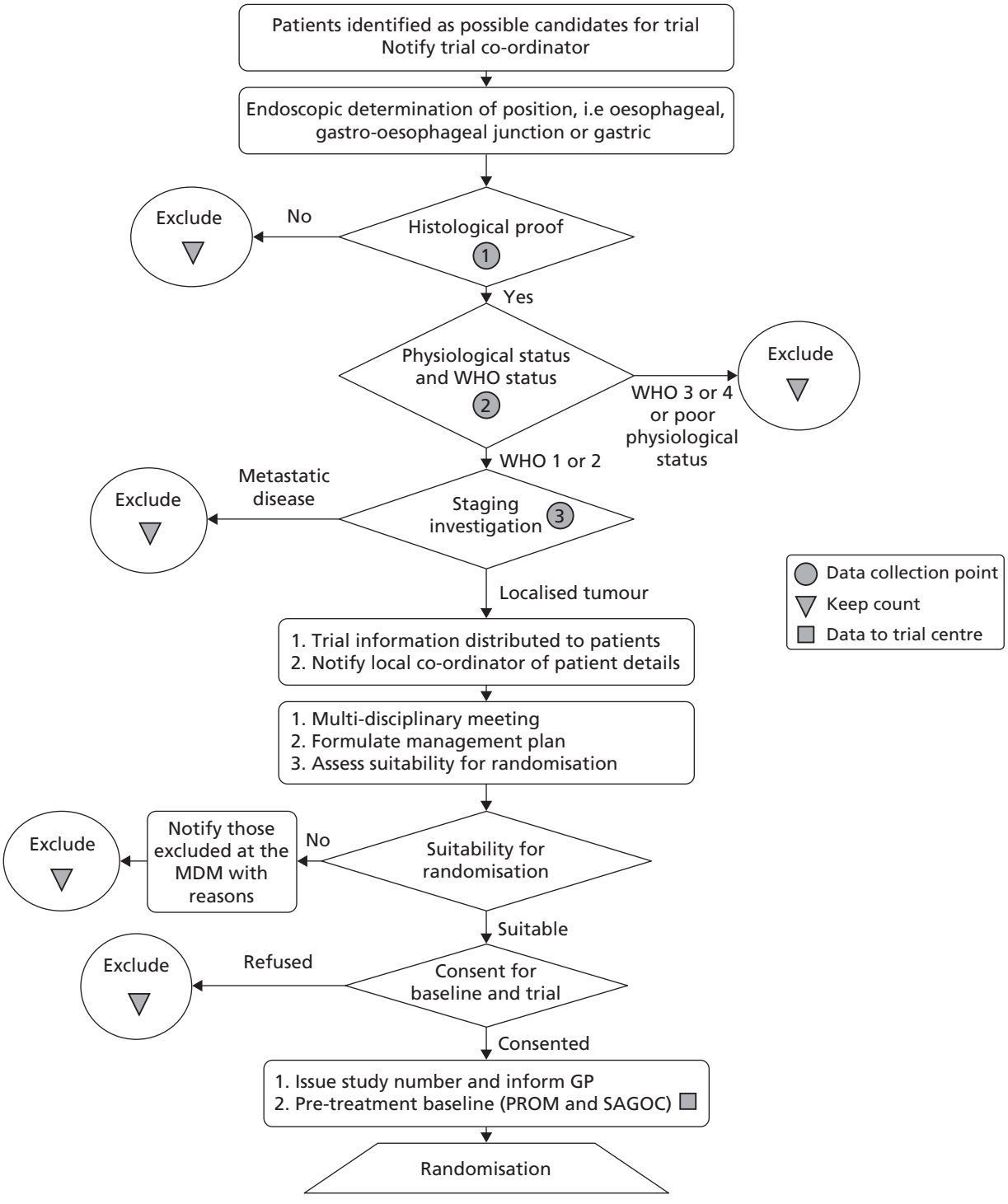

FIGURE 3 Trial design: start to randomisation.

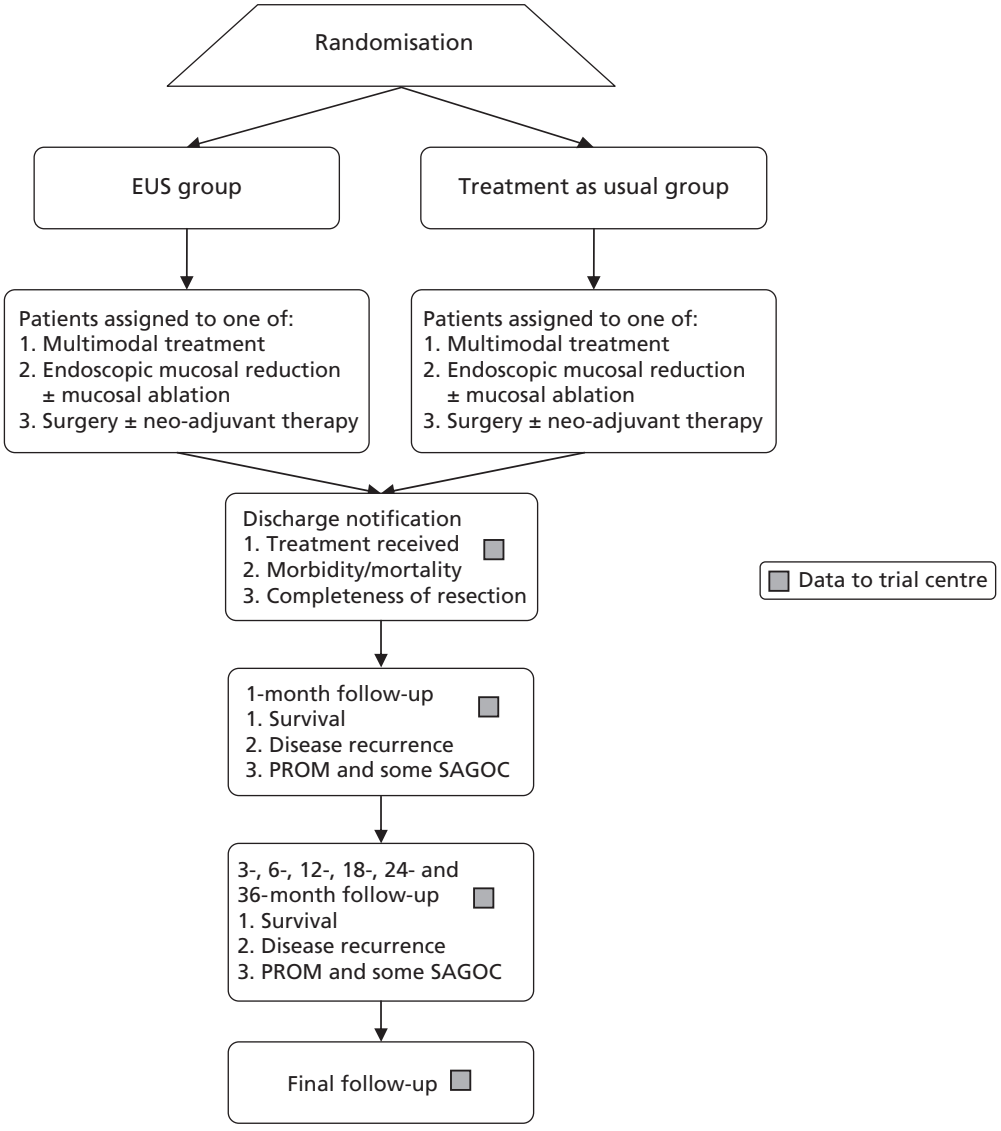

FIGURE 4 Trial design: randomisation to conclusion.

Inclusion and exclusion criteria

To be randomised patients should be fit for both surgery and chemo-radiotherapy and free of metastatic disease. Their ASA grade should be 1 or 2 (*Figure 1*) and their WHO performance status also 1 or 2. Following initial staging clinicians will identify all eligible patients but may exclude patients from the trial for clinical reasons. To ensure there is no bias we shall monitor all such exclusions and the corresponding reasons.

Randomisation

We shall randomise consented eligible patients by telephone to the COGNATE office in Bangor after stratification for centre and tumour location viz gastric, oesophageal, or at the gastro-oesophageal junction. As only patients with a good performance status will be randomised there is no need to stratify for performance status.

Follow up

Median life expectancy with GOC is 18 months. We shall follow patients until death or the end of data collection 12 months after the end of recruitment. We shall collect data at the time of discharge from hospital after initial treatment and thereafter every three months.

Ethical considerations

The value of EUS in the staging of patients with GOC is not proven. The only ethical means of evaluating this investigation is therefore a randomised controlled trial.

Risks and benefits

The technique of EUS is safe and carries the same risk to the patient as an endoscopy. It has the potential to improve staging of gastric and oesophageal tumours, particularly the T stage, and thus provide prognostic information which may guide management. However it is not clear how staging influences management or whether EUS improves management decisions. Accordingly there is potential for patients to be assigned to a management plan which may disadvantage them. Therefore we shall carefully monitor the quality of treatment under the surveillance of the COGNATE Data Monitoring and Ethics Committee (DMEC), with the intention of detecting increased morbidity or mortality in any treatment or any centre at an early stage. If EUS can improve the selection of treatment, this will benefit, not only individual patients, but also the population of patients with GOC, as it will encourage better targeting of resources. However if COGNATE shows that EUS does not improve selection, the number of procedures will fall, releasing resources for GOC and other patients.

Patient information and informed consent

Before randomisation we shall ask eligible patients with GOC to participate in the COGNATE trial. We shall explain the process of randomisation to patients, together with the nature of EUS. We shall stress that the subsequent choice of treatment is identical in both groups.

Data storage

All data will identify each patient only by a unique trial number. Each trial centre will keep its own index linking trial numbers to patients' names and addresses separate from the laptop computers used to store and transfer trial data, and protect that index by key and password. Those in Bangor analysing the data will have no access to these local indices.

Sample size

We aim to consent, randomise and follow up a total of 400 patients. As there is no easy means of calculating the power of this sample for the primary outcome of quality-adjusted survival, we calculate power for two simple but plausible scenarios. First if we assume no difference between groups in quality of life (as measured for example by FACT-GE) a log-rank test using a 5% significance level would yield 80% power of detecting a hazard ratio of 0.6, equivalent to a difference between 60% and 73% in survival at 12 months (derived from SAGOC data by analogy with *Figure 2*). Secondly if we assume no difference between groups in survival, a t test using a 5% significance level would yield greater than 80% power of detecting a 'small' effect size of 0.3 in quality of life. As the groups are more likely to differ in both survival and quality, the power of our primary analysis of quality-adjusted survival will be correspondingly greater. At worst to consent, randomise and follow up only 220 patients will yield 80% power to detect a hazard ratio of 0.5 (equivalent to a difference between 60% and 78% in survival at 12 months) or an effect size of 0.4 in quality of life, still a 'small' effect.

Outcome measures

We shall use the following measures to compare the two randomised groups:

1. *Primary outcome measure:* Quality adjusted survival
   We shall ask patients to attend follow-up clinics after 1, 3, 6, 12, 18, 24 and 36 months and assess their quality of life through the EuroQol EQ-5D and the Functional Assessment of Cancer Therapy

(FACT), in particular the general module FACT-G,[34] the oesophageal module FACT-E and the gastric module FACT-Ga. As FACT-E and FACT-Ga have many questions that are common or similar, the FACT team have permitted and encouraged us to combine them into a gastro-oesophageal module provisionally called FACT-GE. Two of us with substantial experience of validating patient-assessed outcome measures (ITR & DKI) are concurrently revalidating FACT-GE using the methods described by Streiner & Norman.[35] At worst we shall adjust survival by the EQ-5D in traditional fashion. If FACT-GE proves more responsive to change than EQ-5D, as we expect, we shall adjust survival by FACT-GE. We shall therefore complete our concurrent validation of FACT-GE and finalise the COGNATE analysis plan before starting the definitive analysis.

2. *Secondary outcome measures*:
   a. Quality of treatment:
      i. Complete resection rate. This will include pathological data on both EMR and resected tumours. For patients treated with EMR we shall record residual tumours and any additional treatment.
      ii. Pathological reporting of resected specimens according to the SAGOC recommendations,[36] under the surveillance of the DMEC.
      iii. Treatment-related morbidity and mortality according to the SAGOC definitions.[36] In particular mortality will include deaths in hospital following treatment or within 30 days of treatment.
   b. Survival – to 12 months for those last randomised and to 48 months for those first randomised.
   c. Quality of survival – FACT-G and FACT-GE.

3. *Health economics*:
   Within COGNATE we shall assess whether EUS is more cost-effective than conventional staging in the diagnosis and treatment of GOC by estimating the incremental cost-effectiveness ratio of EUS relative to conventional staging. We shall estimate differences in the cost of patients' care between the two groups and relate this to differences in effectiveness in the form of quality adjusted survival. Following COGNATE we shall use SAGOC data on the prognosis of patients with GOC to model the long-term costs and benefits of EUS.
   a. Measurement of effectiveness. For the purpose of estimating the cost-effectiveness ratio, we shall measure effectiveness in Quality Adjusted Life-Years (QALYs). Nevertheless we shall set this calculation within a broader cost-consequence analysis that will include the full range of primary and secondary outcomes of the trial, for example generating both cost per life-year gained and cost per QALY gained.
   b. Measurement of costs. We shall analyse COGNATE from the perspective of the NHS, covering the major direct costs of health care resources used by patients in the trial. These costs will include initial treatment and subsequent investigation, treatment and palliation, and other major elements of primary and secondary care. The local co-ordinators at each of the sites uses an electronic database to record the main uses of NHS resources by trial patients throughout the study period. We shall also ask NHS finance departments at each site to provide unit costs for procedures received by patients in the trial. Finally we shall compare the putative costs of the treatment plans proposed after initial staging in each group with that adopted following EUS in the experimental group, and the actual costs of treatment in each group.
   c. Sensitivity and threshold analysis. We shall conduct sensitivity and threshold analyses based on the observed distributions of outcomes and costs, to test whether, and to what extent, the incremental cost-effectiveness ratio of EUS relative to conventional staging is sensitive to key assumptions in our analysis. We shall use 'bootstrapping' to estimate skewed costs in unbiased fashion and cost effectiveness acceptability curves to interpret findings.
   d. Generalisability and policy implications. We shall compare the findings of this economic evaluation, in particular the estimated cost per QALY, including confidence intervals, with those available from other studies at the end of our trial. This approach will enable us to place the cost-effectiveness of the diagnosis and treatment of GOC, both with and without EUS, within the range of estimated health gains 'per NHS pound' for other conditions.

Statistical analysis

Primary analysis will be by "intention to investigate by EUS". This reflects the essentially pragmatic nature of the trial, and its primary goal of assessing health technology to inform decisions in the real world. We shall also undertake secondary analysis by "EUS received" to explore the implications of documented clinical decisions to diverge from the allocated algorithm. The primary survival analysis will use site and stage as covariates, especially if there is any evidence of baseline imbalance between groups despite stratification and remote randomisation. We shall analyse secondary outcome measures by general linear models, again allowing us to use covariates, notably site and stage, when appropriate.

Trial management

The COGNATE Trial has a Steering Committee comprising an independent chair, two independent members and four members of the COGNATE trial executive group (TEG). Lead clinicians in each centre report to the Trial Steering Committee (TSC) through the TEG. The independent DMEC also reports to the TSC (*Figure 5*).

Composition of Trial Steering Committee

Robert Heading, Consultant Gastroenterologist, Royal Infirmary, Edinburgh (chair).
Hugh Gilmour, Consultant Pathologist, University of Edinburgh (independent member).
Toni Lerut, Professor of Thoracic Surgery, University of Leuven (international member).
COGNATE team – Kenneth Park, Ian Russell, Grant Fullarton, Shona Campbell.

Composition of Data Monitoring and Ethics Committee

Hugh Gilmour, Consultant Pathologist, University of Edinburgh (chair).
Marion Campbell, Statistician, Health Services Research Unit, University of Aberdeen.
David Kirby, Chair of Oesophageal Cancer Patients Group.

Project timetable and milestones

Timetable

Our initial plan was to conduct COGNATE over a period of 60 months from February 2004 through January 2009. However a combination of factors beyond the control of the co-ordinating centre (discussed with the visiting party from NCCHTA in April 2006) has slowed both recruitment and expenditure. In these circumstances we are actively considering applying for a 'no-cost extension' through October 2009. The following timetable displays the current timetable without brackets and the potential extension in brackets:

1. Start of funding: 01/02/04
2. Detailed design & pilot study to ensure consistency of staging investigations & treatment options, and that randomisation and data collection are robust.
3. Start of recruitment: 01/02/05
4. End of recruitment: 31/07/08
5. End of follow-up to ensure minimum of 12 months for all trial participants: 31/07/09
6. Analysis and draft report covering all patients – 31/01/10

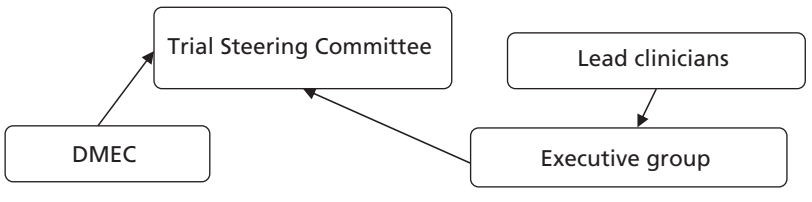

FIGURE 5 Trial management.

Recruitment

Over the two years 2005 and 2006 eight centres joined the original six centres. On closing the recruitment of centres at the end of 2006 we revised our power calculations and recruitment targets in the light of the numbers of patients with GOC seen in the original centres over the first 23 months of recruitment. From SAGOC we estimate that one third will be eligible for inclusion. From our feasibility study of recruitment we estimate that 90% of these will consent to randomisation.

Expertise and responsibilities of applicants

- Prof Ken Park (KGMP) is consultant surgeon in the upper gastrointestinal surgical unit at Aberdeen Royal Infirmary. He is co-chair of the Scottish Audit of Gastro-Oesophageal Cancer (SAGOC). He is responsible for the clinical management of COGNATE. He also acts as lead clinician in Aberdeen. As co-chief investigator with ITR, he sits on the Trial Steering Committee.
- Prof Ian Russell (ITR) specialises in the design, conduct and analysis of pragmatic randomised trials. Since October 2002 he been Director of the Institute of Medical and Social Care Research (IMSCaR) at University of Wales Bangor, which includes centres devoted to clinical trials, the economics of health, public health, and social care. IMSCaR enjoys a close relationship, both organisational and geographical, with the University Department of Psychology (RAE rating 5*), which has particular strengths in clinical and health psychology. ITR is responsible for the technical management of COGNATE and for supervising the trial team in Bangor. As co-chief investigator with KGMP, he sits on the Trial Steering Committee.
- Mr Stephen Attwood (SEAA) is consultant surgeon with the Northumberland NHS Trust with a particular interest in gastro-intestinal cancer. He has written extensively on endoscopic techniques and has pioneered endoscopic ablative treatment. He advises the trial executive group.
- Prof Hugh Barr (HB) is consultant surgeon at Gloucester Royal Infirmary and Dean of the Postgraduate Medical School of Cranfield University. He has an international reputation for treatment of gastric and oesophageal cancer. He is lead clinician in Gloucester.
- Dr Shona Campbell (SC) is consultant radiologist at the University Hospital of Leicester. She has a longstanding interest in endoscopic ultrasonography. She is lead clinician in Leicester and sits on the Trial Steering Committee.
- Dr Rhiannon Edwards (RTE) is Director of the Centre for the Economics of Health within IMSCaR at the University of Wales Bangor. She specialises in economic evaluation and modelling. She leads the economic evaluation of EUS in COGNATE. She will use SAGOC data to develop a broader model of the implications of COGNATE findings for the effectiveness of EUS across the NHS.
- Mr Grant Fullarton (GMF) is consultant surgeon with North Glasgow University NHS Trust. He has a particular interest in upper gastro-intestinal surgery and endoscopic techniques. He acts as lead clinician in Glasgow. As the representative of the largest centre he sits on the Trial Steering Committee.
- Prof Fiona Gilbert (FJG) is an academic radiologist in the Department of Radiology, University of Aberdeen, with expertise in the design and management of trials in radiology. She is co-chair of SAGOC. She has a particular interest in the quality of pre-operative staging investigations, and will monitor the quality of these investigations across COGNATE.
- Dr David Ingledew (DKI) is Senior Lecturer in Psychology at the University of Wales Bangor. He is a health psychologist and psychometrician with expertise in the development and validation of health-related measurement scales. He will contribute to the development, validation and analysis of patient-assessed outcome measures, including quality of life.

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