VALUE

Understanding the variation of modern endoscopic ultrasound use in patients with oesophageal cancer (**VALUE**): a multi-methods study.

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FUNDER

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Protocol Information

This protocol describes the VALUE trial and provides information about procedures for entering participants. The protocol should not be used as a guide for the treatment of other non-trial participants; every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the trial, but sites entering participants for the first time are advised to contact Southampton Clinical Trials Unit to confirm they have the most recent version.

Compliance

This trial will be conducted in compliance with the approved protocol and will adhere to the principles of GCP guidelines, the current Data Protection Regulations, the Sponsor's (and any other relevant) SOPs, and other regulatory requirements as appropriate.

TABLE OF CONTENTS

CONTACT AND RESPONSIBILITIES 1
TABLE OF CONTENTS 3
LIST OF ABBREVIATIONS 5
KEYWORDS 5
TRIAL SYNOPSIS 6
TRIAL SCHEMA 7
SCHEDULE OF OBSERVATIONS AND PROCEDURES 8
1. INTRODUCTION 10
1.1 BACKGROUND 10
1.2 RATIONALE FOR CURRENT TRIAL 11
2. TRIAL OBJECTIVES AND ENDPOINTS 12
2.1 PRIMARY TRIAL OBJECTIVE AND ENDPOINT 12
2.2 TABLE OF ENDPOINT/OUTCOMES 12
3. OVERALL TRIAL DESIGN 13
4. SELECTION AND ENROLMENT OF PARTICIPANTS 13
4.1 CONSENT 13
4.2 INCLUSION CRITERIA 14
4.3 EXCLUSION CRITERIA 14
5. TRIAL PROCEDURES 14
5.1 RECRUITMENT 14
5.1.1 PARTICIPANT IDENTIFICATION 14
5.2 SCREENING PROCEDURES 14
5.3 SCREEN FAILURES 15
5.4 PAYMENT 15
5.5 REGISTRATION PROCEDURES 15
5.6 PRE EUS 15
5.7 POST EUS 15
5.8 TREATMENT 15
5.9 END OF STUDY 15
5.10 TRIAL DISCONTINUATION AND PARTICIPANT WITHDRAWAL 15
5.10.1 DISCONTINUATION OF TRIAL INVOLVEMENT 15
5.10.2 WITHDRAWAL 16
5.11 DEFINITION OF END OF TRIAL 16
6. QUALITATIVE STUDY 16
6.1 PATIENT INTERVIEWS 17
6.1.1 ELIGIBILITY CRITERIA 17
6.1.2 SAMPLING 17
6.1.3 RECRUITMENT 17
6.1.4 DATA COLLECTION 17
6.2 CLINICIAN INTERVIEWS 17
6.2.1 ELIGIBILITY 17
6.2.2 SAMPLING 18
6.2.3 RECRUITMENT 18
6.2.4 DATA COLLECTION 18
6.2.5 PATIENT AND CLINICIAN QUALITATIVE DATA ANALYSIS 18
7. SAFETY 19
8. STATISTICS AND DATA ANALYSES 19
8.1 SAMPLE SIZE 19

8.2 INTERIM ANALYSIS 19
8.3 STATISTICAL ANALYSIS PLAN (SAP) 19
8.3.1 PRIMARY ENDPOINT 19
8.3.2 SECONDARY ENDPOINT 19
9. REGULATORY COMPLIANCE 19
9.1 CLINICAL TRIAL AUTHORISATION 19
9.2 DEVIATIONS AND SERIOUS BREACHES 20
9.2.1 PROTOCOL COMPLIANCE 20
9.2.2 SERIOUS BREACHES 20
10. ETHICAL CONSIDERATIONS 20
10.1 RESEARCH ETHICS COMMITTEE (REC) REVIEW AND REPORT 20
10.2 SPECIFIC ETHICAL CONSIDERATIONS 20
10.3 INFORMED CONSENT PROCESS 20
10.4 DATA PROTECTION AND CONFIDENTIALITY 21
11. SPONSOR 21
11.1 INDEMNITY 21
11.2 FUNDING 21
11.3 SITE PAYMENTS 21
11.4 PARTICIPANT PAYMENTS 21
12. TRIAL OVERSIGHT GROUPS 22
12.1 TRIAL MANAGEMENT GROUP (TMG) 22
12.2 TRIAL STEERING COMMITTEE (TSC) 22
12.3 INDEPENDENT DATA MONITORING COMMITTEE (IDMC) 22
13. DATA MANAGEMENT 22
13.1 DATA SHARING REQUESTS FOR RESULTS THAT ARE AVAILABLE IN THE PUBLIC DOMAIN 23
14. MONITORING 23
14.1 CENTRAL MONITORING 23
14.2 CLINICAL SITE MONITORING 23
14.2.1 SOURCE DATA VERIFICATION 23
14.3 SOURCE DATA 24
14.4 AUDITS AND INSPECTIONS 24
15. RECORD RETENTION AND ARCHIVING 24
16. PUBLICATION POLICY 24
17. REFERENCES 24
18. APPENDICES 26
18.1 APPENDIX 1 ECOG PERFORMANCE STATUS 26
19. SUMMARY OF SIGNIFICANT CHANGES TO THE PROTOCOL 26

LIST OF ABBREVIATIONS

CI	Chief Investigator
CRF	Case Report Form
CRT	Chemoradiotherapy
CT	Computed Tomography
DMEC	Data Monitoring and Ethics Committee
DMP	Data Management Plan
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EUS	Endoscopic Ultrasound
FNA	Fine Needle Aspiration
GCP	Good Clinical Practice
IDMC	Independent Data Monitoring Committee
ISF	Investigator Site File
MDT	Multi-Disciplinary Team
MHRA	Medicines and Healthcare products Regulatory Agency
NCI	National Cancer Institute
PET	Position Emission Tomography
PI	Principal Investigator
PID	Patient Identifiable Data
PIS	Participant Information Sheet
PPI	Patient & Public Involvement
QoL	Quality of Life
REC	Research Ethics Committee
RfPB	Research for Patient Benefit
SAP	Statistical Analysis Plan
SCTU	Southampton Clinical Trials Unit
SOC	Standard of Care
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
UHS	University Hospital Southampton NHS Foundation Trust
UKIOG	United Kingdom and Ireland Oesophagogastric Cancer Group

KEYWORDS

Oesophageal cancer, endoscopic ultrasound; diagnosis; staging; metastases; patient care management.

TRIAL SYNOPSIS

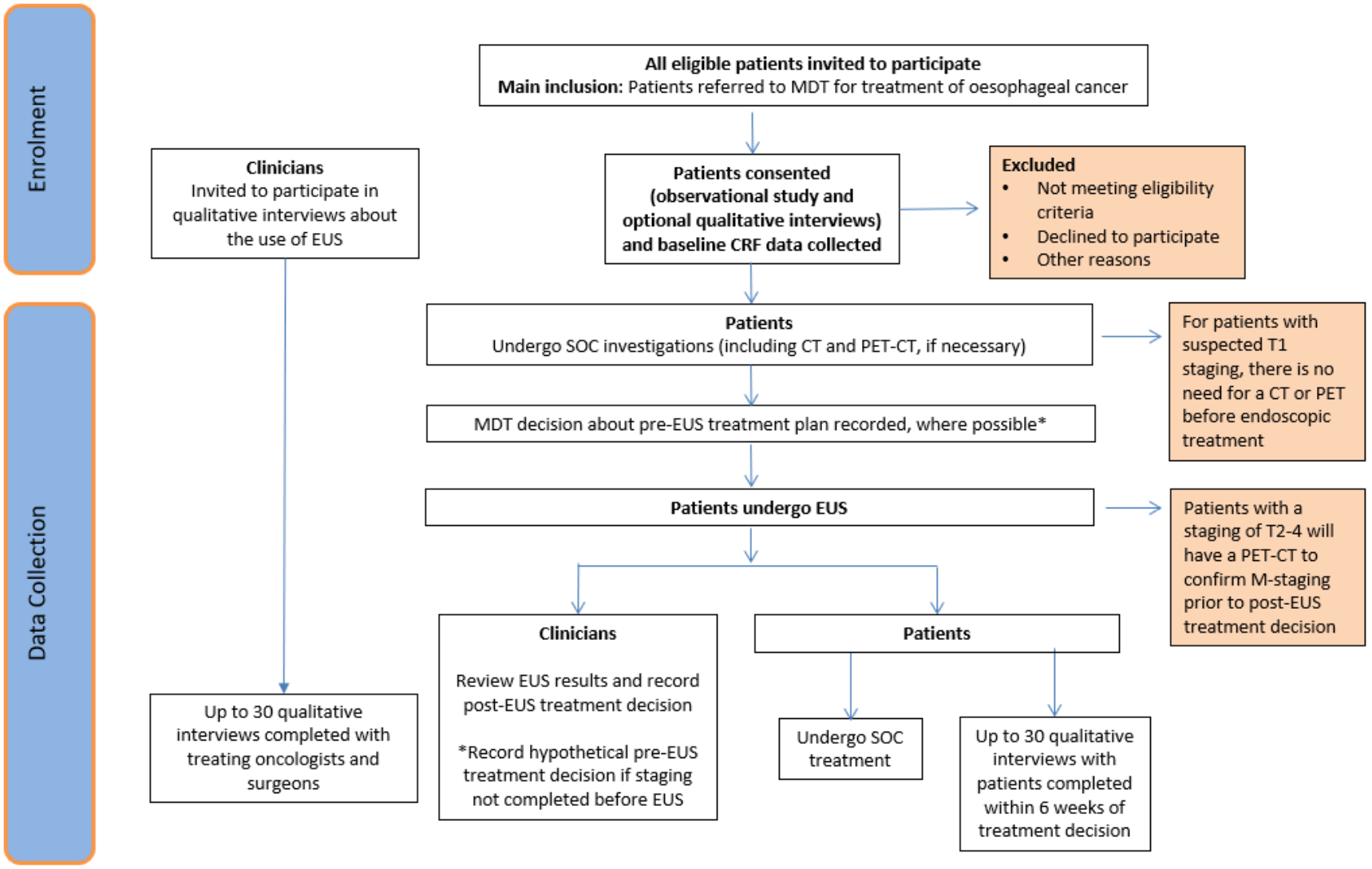
Short title	VALUE
Full title:	Understanding the variation of modern endoscopic ultrasound use in patients with oesophageal cancer (VALUE): a multi-methods study

Population:	Patients with confirmed oesophageal cancer who are being referred for EUS examination
Primary Objective:	To determine the proportion of cases in which endoscopic ultrasound (EUS) changes disease management.
Secondary Objectives:	To identify factors that clinicians and patients consider when deciding whether EUS should be used. To determine the reasons why EUS changed the management. To determine time from diagnosis to treatment decision before and after EUS.
Rationale:	Over 9,000 UK patients are diagnosed with oesophageal cancer annually. Shared decision-making about treatment options is heavily influenced by radiological staging, which inform clinicians of the likely disease extent, in combination with histopathology, and patient factors. Staging may include computed tomography (CT), positron emission tomography (PET), and EUS, which provide complementary information, yet each are affected by limitations. EUS use around the UK varies significantly and, since the introduction of PET-CT in staging pathways, the added value of EUS in staging and treatment pathways has been questioned. VALUE aims to understand this variation in practice and determine how often and why EUS changes treatment decisions. VALUE will also evaluate patient and clinician opinions, experiences and attitudes about EUS.
Trial Design:	This is a prospective, multi-centre, mixed-methods, observational cohort study.
Sample size:	180 patients will be recruited from clinical centres in the UK. In addition, for the qualitative study the following will be interviewed regarding EUS: • Up to 30 clinicians (e.g., oncologists and surgeons) • Up to 30 patients
Treatment/Intervention:	Non-interventional study

URL for Database:	https://www.imedidata.com

Primary Trial Endpoints:	% of patients where treatment plan changes post EUS.
Secondary Trial Endpoints:	• To identify factors that clinicians and patients consider when deciding whether EUS should be used. • Reasons why EUS changed the management. • Time from diagnosis to treatment decision before and after EUS
Total Number of Sites:	This study will open to recruitment at 11 sites

TRIAL SCHEMA



VALUE Flow Diagram v2 30-Sep-2024

SCHEDULE OF OBSERVATIONS AND PROCEDURES

Visit:	Screening (to be taken from patient notes)	Pre-EUS[k]	Post EUS	Within 6 weeks of EUS	Within 6 months of Registration – Treatment Information
Informed Consent[a]	X[f]				
Registration	X[f]				
Eligibility evaluation	X[f]				
Medical History	X[f]				
ECOG PS	X[f]				
MDT/Clinician Determined (Pre-EUS) Hypothetical Treatment Plan	X[f]				
TNM Staging (from CT if applicable)[b]	X[f]				
PET-CT (if applicable, to confirm disease is potentially curable)		X[g]			
Details of reason(s) why EUS requested			X[h]		
EUS Report[c]			X[h]		
Post EUS Treatment Plan **agreed with patient**			X[h]		
Details of reason(s) why EUS +/- FNA changed treatment plan			X[h]		
EUS Complications			X[i]		
Details of Treatment (surgery/CRT/Chemo etc)					X[i]

QUALITATIVE STUDY	Screening (Post MDT)		Post EUS visit	Within 6 weeks of EUS	Treatment
Qualitative interview patients[d]				X[d]	
Qualitative Interview clinicians[e]		X			

a – patients can be consented remotely prior to EUS or on the day of EUS. The Participant/legal representative is free to withdraw consent at any time without providing a reason. When withdrawn, the participant will continue to receive standard clinical care. Follow up data will continue to be collected (unless the participant/legal representative has specifically stated that they do not want this to happen).
b – Patients will need a CT for eligibility but will still need a PET-CT following this. If a patient is suspected of having a T1 tumour, then CT or PET-CT is not mandated. All other patients should be clinically staged with a CT, with a PET-CT to confirm M-stage and whether disease remains potentially curable. Staging laparoscopy may be used for junctional tumours if peritoneal disease is suspected, as per standard local practice. If patient is confirmed to have M1 disease, then please refer to section 5 of the protocol. Similarly, if the total disease length means the patient is no longer suitable for radical treatment, please refer to section 5.

c – details of the report will be collected on the trial database.
d – up to 30 patients who consented to the optional qualitative study will be contacted by the SCTU qualitative researcher for an interview lasting up to 60 minutes about their experience of EUS. This interview will take place within 6 weeks of the patients' EUS.
e – up to 30 clinicians who agreed to take part in the qualitative study will be contacted by the SCTU qualitative researcher for 30-minute interview about the use of EUS once patient interviews have commenced so themes can be discussed.
f – Data collected from patient notes.
g – to be entered unless not completed when staging is suspected to be a T1 tumour.
h – Data collected from patient notes
I – EUS complications should be recorded if the complication occurs within the first 2 weeks following the procedure.
i – Data collected from patient notes
k – the pre-EUS treatment plan can be added after the EUS has taken place.

1. INTRODUCTION

1.1 BACKGROUND

Over 9,000 patients are diagnosed with oesophageal cancer in the United Kingdom (UK) annually. The prognosis of these patients is poor, with an overall 5-year survival rate of 15%[1]. Most patients (60%) present with advanced disease and palliation is the only treatment option. Accordingly, oesophageal cancer has considerable unmet research need[2].

The VALUE trial is a prospective observational study investigating EUS in the modern era of oesophageal cancer staging. A quantitative study component will examine how often and why EUS changes treatment decisions after initial staging with CT and, in most cases, PET-CT. A qualitative study component will explore both clinician and patient attitudes and opinions towards the utility of EUS in the staging pathway.

EUS is an invasive procedure combining upper gastrointestinal endoscopy with ultrasonography. An ultrasound probe located at the end of the endoscope allows direct visualisation of the oesophageal wall layers and adjacent tissues providing local assessment of the depth of tumour invasion and lymph nodes. This assessment informs local tumour (T-) and node (N-) staging which are important prognostic indicators of survival[3]. Patients undergoing EUS require sedation and there are risks of complication. EUS is a specialist investigation requiring many years of dedicated training to perform competently.

VALUE aims to recruit patients with oesophageal cancer who are deemed to have potentially curable disease and who are fit for, and wish to have, radical treatment, and who receive EUS as part of their standard of care staging pathway. Patients with a range of disease status (T1-T4; N0-N3) will be considered for recruitment to allow diverse consideration of the reasons whether EUS impacts treatment decisions in current clinical practice (see section 1.2 for further rationale). Patients with suspected T1 tumours are not required to have CT or PET-CT, as per NICE guidelines[3]. VALUE will also recruit clinicians who regularly care for oesophageal cancer patients in a multi-disciplinary setting to gather their opinions regarding the use of EUS in this patient population.

A systematic review[4], updating a prior review[5], found that current evidence concerning the impact of EUS on the management and outcome of oesophageal cancer patients in modern staging with PET-CT was of limited quality. In total, 18 studies with 11,836 patients were included. Overall, 2,805 patients (23.7%) underwent EUS compared to 9,031 (76.3%) without. However, only 19.7% of all patients also had PET-CT for staging. Reported change of management by EUS varied widely from 0% to 56%.

EUS use in oesophageal cancer patients across the NHS is also reported to vary widely. Considerable variation in EUS practice was found in a survey of oesophageal cancer multi-disciplinary team (MDT) leads across the UK[6]. Eighty-seven of 97 UK NHS trusts responded. 29% recommended EUS for all potentially curable patients whereas 46% requested EUS after PET-CT on a case-by-case basis. 20% reported both a lack of utility and concerns about treatment delay. Overall, 63% and 43% routinely use EUS for radiotherapy and surgical planning, respectively. Further, data from the National Oesophago-Gastric Cancer Audit (NOGCA) all describe the reported decline in EUS use from 62% of all patients in 2013, to 39% in 2019, and 18.6% to 2021[7]. In 2020/21, EUS was used in 23.6% of patients who had a curative treatment plan.

The Cancer of Oesophagus or Gastricus-New Assessment of Technology of Endosonography (COGNATE)[8] trial randomised patients between EUS with CT, and CT alone. EUS led to improved quality-adjusted survival. However, since COGNATE, oesophageal cancer staging has been transformed by PET-CT, a cross-sectional nuclear imaging test usually performed prior to EUS[9]. PET-CT has greater sensitivity for distant metastases than CT[10], and therefore identifies more patients unsuitable for radical treatment, meaning that local staging with EUS becomes less critical in these patients[11].

This conclusion is supported by data from a large retrospective cohort study by Findlay et al[12] which included 953 patients, of which 798 had EUS, and 918 had PET-CT. The authors found that patient management was changed by EUS in 11% of cases, but when probability thresholds were calculated, the utility of EUS in the majority of patients (71.8% staged T2-T4a) was minimal (0.4%), concluding that the risk of EUS exceeded its benefit. However, these data have not been validated outside of this single-centre study but does question the value of EUS in the modern staging pathway.

In summary, the use of PET-CT for oesophageal cancer staging is increasing[7], and use of EUS declining, which supports the modern tendency of clinicians to favour non-invasive cross-sectional imaging. However, evidence supporting the basis for this recent change in practice is limited.

1.2 RATIONALE FOR CURRENT TRIAL

The incidence of oesophageal cancer has increased in recent decades and is expected to continue growing[13]. Oesophageal cancer treatment planning is complex and requires multi-disciplinary input to decide upon the treatment most likely to deliver the best outcome for each patient. For instance, quality of life (QoL) is only regained 2 years after oesophagectomy[14]. However, 2-year survival after oesophagectomy is only 70%[15] and recurrence rates are 20%[16]. Therefore, patient selection for radical treatment must improve.

Shared decision-making about treatment options in oesophageal cancer is heavily influenced by radiological staging, which inform clinicians of the likely disease extent[17], in combination with histopathology, and patient factors. Radiological staging may include CT, PET, and EUS which provide complementary information, yet each are affected by limitations. These tests determine whether radical treatment is attempted, using either curative surgery or definitive chemoradiotherapy, or if palliation is most appropriate.

The reliance on complex multi-modality imaging means that staging pathways are susceptible to diagnostic delays, therefore any investigation extending the pathway perceived to have little or no value should be omitted. More than ever, high-quality evidence concerning the effectiveness of cancer investigations is needed during the recovery from the COVID-19 pandemic. Delays in cancer diagnostics are well-documented, therefore optimisation of these pathways must be addressed and informed by high-quality evidence. Further, health care costs are rising[18], particularly in patients treated with radical intent, which requires intensive and expensive health-care resources.

EUS is a relatively safe procedure although there are risks of complication such as adverse reactions to sedation and oesophageal perforation, which is potentially life-threatening, if severe. However, EUS use is established in the NHS and continues to serve an important purpose in many diseases. As described in section 1.1, there is an increasing trend to use non-invasive cross-sectional imaging in place of EUS, but the evidence for the clinical effectiveness of this approach is limited. There is a risk that patients who have EUS omitted from their staging pathways receive sub-optimal treatment decisions in the absence of important information that the EUS may have provided. Conversely, patients who receive EUS may be exposed to an unnecessary invasive procedure with no benefit.

Therefore, the evidence base for EUS in the NHS is outdated, its use varies considerably across the UK, and its value should be questioned given the potential impact of the intervention on patients and the delivery of care. Not all patients receive EUS due to conflicting views concerning its modern clinical effectiveness[6]. Existing NICE guidance[9] recommends that EUS is only used to guide ongoing management decisions. However, this guidance can be interpreted differently. The lack of high-quality evidence hinders definitive guideline development, which drives variation in clinical practice and inequality to service access.

Furthermore, UK EUS services are severely affected by workforce shortages so existing resources must be used pragmatically[19]. The problems of inconsistent radiological staging causing varied patient selection for radical treatment and unequal access to diagnostic tests must be addressed.

Patient views must also be considered, and literature review reveals a lack of patient engagement regarding EUS in oesophageal cancer. One prospective single-centre study published in 1999 examining EUS across different tumour sites investigated patient acceptance using independent questionnaires. In patients able to remember the EUS examination (42%), 90% found it tolerable, and 83% were willing to have repeated EUS[20]. This sparse evidence must be updated and specifically related to the modern oesophageal cancer staging pathway.

In summary, the evidence concerning EUS in oesophageal cancer is limited and mostly low-quality. Wide variation in practice around the UK is documented. Clinician and patient factors concerning its use must be better understood to determine its utility in the NHS and standardise practice ensuring equal access for all patients.

Therefore, the evidence suggests:
1) a need to investigate the current clinical effectiveness of EUS in oesophageal cancer, and
2) a need to explore the factors associated with its use by accessing clinical and patient opinion.

The VALUE trial will address these research needs by creating a better understanding of how and why EUS is, and should be, used. Solutions to these problems would have clear demonstrable benefit to patients and the NHS. Effective staging pathways would enhance patient selection for radical and palliative treatments with better outcomes for both groups and consequent health economic benefits. If high-quality evidence suggests clinical and cost-effectiveness, patients with oesophageal cancer from across the UK should have equal access to EUS. Conversely, if EUS is not effective, then patients should not undergo an invasive test with potential complications, and NHS resources could be re-distributed to other patients in need.

We anticipate that this research will identify important factors that clinicians and patients evaluate when considering EUS use and determine the frequency that EUS changes treatment decisions in the modern staging pathway. The results will assist the creation of effective standardised staging pathways that are accessible to every patient.

2. TRIAL OBJECTIVES AND ENDPOINTS

2.1 PRIMARY TRIAL OBJECTIVE AND ENDPOINT

This study is designed to determine whether the proportion of cases in which EUS changes management is larger than 5%.

2.2 TABLE OF ENDPOINT/OUTCOMES

	Objective	Outcome Measures	Summary method(s)
Primary	To determine if using EUS changes management.	% of cases treatment plan changes following EUS	Descriptive statistics
Secondary	To identify factors that clinicians and patients consider	Clinician and patient perceptions and decision-making experiences of EUS	Thematically analysed one-to-one interviews

	when deciding whether EUS should be used. To determine the reasons why EUS changed the management. To determine time from diagnosis to treatment decision before and after EUS	Reason for treatment change Time between diagnosis and treatment decision, pre- and post-EUS	Descriptive statistics Descriptive statistics

3. OVERALL TRIAL DESIGN

This is a prospective, multi-centre, mixed-methods, observational cohort study.

4. SELECTION AND ENROLMENT OF PARTICIPANTS

4.1 CONSENT

The Principal Investigator (PI) retains overall responsibility for the conduct of the research at their site, including the taking of informed consent of participants. They must ensure that any person delegated responsibility to participate in the informed consent process is duly authorised, trained, and competent to participate.

Consent to enter the trial must be sought from each participant only after a full explanation has been given, a participant information sheet offered, and time allowed for consideration. Signed participant consent must be obtained prior to the participant being registered on the trial specific database.

Signed participant consent can be obtained with the PI or delegated individual on the day of or before the EUS (as long as completed prior to the procedure). The patient can complete the consent form remotely or in person. They can be sent the PIS and consent form by post or email, and they will be guided through the consent process via a telephone or video call with an appropriately delegated individual. This call will be documented in the patient notes. Once the patient has completed the consent form, they will return the completed form either by post or email to the site team, or they can bring the form with them to their next clinic visit. Once the researcher who went through the consent process with the patient receives the consent form it must be signed and dated by them. The patient will be asked to reconfirm their consent verbally when they are next seen in clinic, and this should be recorded in the patient notes.

The right of the participant to refuse to participate without giving reasons must be respected.

All participants are free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing further treatment. Participants must be provided with a contact point where they may obtain further information about the trial.

Upon completion of the informed consent form, a copy will be given to the participant, a copy stored in the participant's medical notes, the original filed in the site trial file and a copy of the consent form be sent to the SCTU via SafeSend to monitorSCTU@soton.ac.uk.

4.2 INCLUSION CRITERIA

1. Patients aged 16 or above with first diagnosis of biopsy-confirmed oesophageal cancer
2. Referred for EUS examination as part of standard of care investigations
3. Tumour location in the oesophagus, or gastro-oesophageal junction (Siewert types I-III)
4. MDT decision that patient is potentially curable with radical treatment (e.g., endoscopic treatment, surgery +/- neoadjuvant therapy, or definitive chemoradiotherapy)
5. Eastern Cooperative Oncology Group (ECOG) performance status 0-2
6. Either:
   Clinical staging of T1 disease (CT and PET-CT are not required)
   Or:
   Clinical staging of T2-T4, N0-N3, M0 disease confirmed by CT scan
7. Adenocarcinoma or squamous cell carcinoma (SCC) histopathological cell type

4.3 EXCLUSION CRITERIA

8. Recurrent or residual disease
9. Known distant metastatic disease
10. Previous oesophagectomy or oesophageal radiotherapy
11. Unable to undergo EUS examination
12. Other histopathological cell type

5. TRIAL PROCEDURES

5.1 RECRUITMENT

5.1.1 Participant Identification

Patients will be recruited through MDTs at participating secondary care centres in the UK. Those deemed suitable for the study will be approached by their direct care team to participate. Screening logs will be maintained and returned to SCTU on a monthly basis.

5.2 Screening Procedures

All patients will have the following data collected from notes at screening to confirm eligibility:

- Informed consent (can be taken remotely)
- Eligibility Evaluation
- Medical History relevant to the treatment decision e.g., any medical conditions that directly impact the treatment options available to the patient
- Eastern Cooperative Oncology Group (ECOG) performance status 0-2
- Clinical staging of disease by CT scan (if applicable)
- Patients may undergo PET/CT before EUS referral or before consent. Patients who have definite M1 disease on PET/CT, or a total length of disease deemed unsuitable for planned radical treatment by the MDT are not eligible.
- Both medical history and the ECOG performance status can be taken from documented clinical notes up to 6 months in advance of screening. We ask that these are checked again at screening to confirm nothing has changed that would stop the patient from taking part in the trial.

5.3 Screen Failures

Screen failures will be recorded on a screening log, along with the reason for screen failure. Details will be collected on their initials, year of birth and reason for screen failure. The screening log should be scanned and emailed to value@soton.ac.uk on a monthly basis.

5.4 Payment

Only patients who take part in the qualitative interview will be reimbursed for their time, as detailed in the patient information sheet.

5.5 REGISTRATION PROCEDURES

Patients will be screened for eligibility, consented and registered on the trial specific RAVE database. **The patient must be consented before the EUS procedure.**

5.6 Pre EUS Data Collection

- Disease characteristics and TNM Staging from CT and PET-CT. Note, for patients with suspected T1 staging, there is no requirement for CT or PET-CT staging, and for relevant patients, PET-CT can be performed after EUS.
- MDT Determined Pre-EUS Hypothetical Treatment Plan

For patients where the PET-CT result is reviewed by the MDT with or after the EUS result, the above data, including the hypothetical treatment plan, should be entered into the database *ignoring the EUS result*.

5.7 Post EUS Data Collection

The following information should be entered onto the RAVE electronic Case Report Form (eCRF) following the EUS procedure.

- EUS report (details of what is recorded in the report should be recorded in Rave)
- Post EUS Treatment Plan agreed with patient.
- EUS complications (bleeding, infection, damage to teeth, aspiration, adverse reaction to sedation, perforation). Any complications occurring within the first 2 weeks following EUS should be recorded on RAVE.
- If Treatment Plan changed, details of reason(s) why EUS +/- FNA changed Treatment Plan should be recorded.

5.8 Treatment

Details of the actual treatment the patient receives should be recorded in RAVE, this could include surgery, chemoradiotherapy (CRT) or chemotherapy. Data to be added within 6 months of registration.

5.9 End of Study

End of study details in the database can be entered once the patient has started treatment following EUS.

5.10 TRIAL DISCONTINUATION AND PARTICIPANT WITHDRAWAL

5.10.1 Discontinuation of Trial Involvement

Participants may be discontinued from the trial:

- If the participant meets an exclusion criterion (either newly developed or not previously recognised) that precludes further trial participation

The data to be collected at the time of trial discontinuation will include the following:

- Treatment data

Full details of the reason for trial discontinuation should be recorded in the End of Study eCRF and participant's medical record.

5.10.2 Withdrawal

The participant/legal representative is free to withdraw consent from the trial at any time, without providing a reason, and without their medical care or legal rights being adversely affected.

Participants may be withdrawn from the study either at their own request or at the discretion of the Investigator. The participants will be made aware that this will not affect their future care. Participants will be made aware (via the information sheet and consent form) that should they withdraw the data collected to date cannot be erased and may still be used in the final analysis.
Full details of the reason for trial discontinuation should be recorded in the End of Study eCRF and medical record.

5.11 DEFINITION OF END OF TRIAL

The end of trial is defined as being when the last participants data has been collected and all data required to answer the study objective has been received and reviewed.

6. QUALITATIVE STUDY

A researcher with experience of qualitative research will carry out semi-structured interviews remotely (over the telephone or by video call) as per participant preference.
All participants will receive information about the optional interviews in a participant information sheet and be provided with a contact telephone number and email address to enable them to proactively reach out and ask questions. The consent form will have a section for those who wish to participate in the interviews to provide contact details. A brief of the interview purpose and opportunity to ask questions will also be offered prior to interview start.

Microsoft Teams will be used for all phone and video recordings using end-to end encryption. (https://learn.microsoft.com/en-us/microsoftteams/teams-end-to-end-encryption). At the participant's discretion the camera can be turned on or off for the video interview.
Once completed the recorded interview will be moved and deleted from the web call server (e.g., Microsoft Stream) to a secure University network and sent for transcription (section 6.2.5). All identifiers (e.g., name and organisation) mentioned during the interview will be removed during transcription analysis to maintain participant anonymity. Any quotes used during write-up of the findings will use pseudonyms.
The original audio interview will be deleted once the transcript has been error checked. The transcript will remain stored on a secure University Network and will be archived with other study documentation in line with SCTU policy.

6.1 Patient interviews

Patient interviews will be up to 60 minutes with up to 30 trial participants who have optionally consented to interviews.

6.1.1 Eligibility criteria

- Capacity to consent
- Consented to participate in the observation study.
- Patients who underwent EUS in the last 6 weeks

6.1.2 Sampling

Purposive sampling of up to 30 patients from participating sites will be interviewed to reach information of power. Interviews will initially be with locally advanced (T2+ and/or N1+) patients. If information of power is deemed to be reached prior to 20 interviews, sampling will subsequently be directed to early-stage patients to compare similarities and differences between groups. If information of power is not reached prior to 20 interviews, sampling will focus on late-stage patients only to optimise the depth and transferability of findings. A conscious effort will be made to sample ethnic minority patients from the baseline demographic data collected in the eCRF as they are known to be currently under-represented in cancer research.

6.1.3 Recruitment

Patients will be invited (via information sheet and informed consent form) to participate in an optional interview in conjunction with the observational study. Following the sampling criteria, patients will be contacted by the qualitative researcher anytime between consent and six weeks after EUS by phone or email (patient preference) to provide an opportunity to ask questions and confirm willingness to participate before scheduling an interview. Consent will be confirmed prior to interview recording.

6.1.4 Data collection

For reporting purposes demographic data including age, sex, post code and education level will be confirmed/ collected at interview. Interviews will be scheduled prior to treatment initiation or early in the first neoadjuvant chemotherapy cycle (usually 4-6 weeks after EUS) and completed up to 6 weeks after EUS to mitigate the attrition of memory. Our patient representatives' feels this is an unproblematic window for patients who want to take part.

A topic guide has been developed to explore patients' experiences and factors influencing acceptability of EUS. The interview will focus on patient's understanding of EUS, the procedure, and perspectives on how widely they feel it should be used.

Patient interviews will commence before clinician interviews so that themes can be presented and discussed with clinicians to understand if/how the information impacts their EUS related decision-making.

See section 6.2.5 for data analysis.

6.2 Clinician interviews

Clinician interviews will be up to 30 minutes with up to 30 clinicians who have consented to interview.

6.2.1 Eligibility

- Clinicians (e.g. surgeons, clinical oncologist) responsible for deciding whether to use EUS as part of treatment planning at the time of interview.

6.2.2 Sampling

Purposive and snowball sampling will be used to recruit up to 30 clinicians for semi-structured interviews over 12 months to reach information of power.

6.2.3 Recruitment

The following recruitment strategies will be used to identify eligible participants.

1. Invite investigators from recruiting sites.
An invitation email with the participant information sheet (PIS) will be sent to clinicians (identified by the CI and co-apps) eligible to participate.

2. Ask investigators to identify other eligible clinicians
Clinicians may cascade information and pass on contact details to the qualitative interviewer or share the contact details of the interviewer.

3. Advertise through appropriate networks including other UK NHS sites, who the research team already have links and through the UKIOG and Royal Colleges.

Clinicians can send an expression of interest to the interviewer who will respond with a PIS and opportunity to ask question. Upon acceptance to interview, the qualitative researcher will schedule a mutually convenient date and time and audio-recorded consent will be received prior to interview.

6.2.4 Data collection

For reporting purposes demographic and professional data including age, sex and job role will be collected at interview. Interviews with clinicians will focus on the organisational, patient, and experiential factors to the use of EUS.

Key questions will explore:

- The oesophageal cancer staging pathway currently in place at the clinician's institution or region, and how EUS fits into this.
- Factors which they consider when deciding whether to use EUS for staging, including the availability of resources, clinical indication and case complexity, and the wishes of patients.

For clinicians that use EUS routinely or regularly, we will explore how they use the results of EUS in subsequent treatment decisions.

6.2.5 Patient and clinician qualitative data analysis

Interview data will be transcribed verbatim by a University approved service (e.g. McGowan Transcripts) and analysed using an inductive thematic approach. Analysis will take place in parallel to data collection to allow for further exploration of topics of interest in relation to the research question. A coding frame will be developed from themes derived from the data[21] with constant comparison to identify factors that influence contrasting attitudes towards the use of EUS.
Where possible, patients' individual understanding of the reason they received EUS from interview data will be compared with the respective information the clinicians entered on the eCRF to explore insight into the adequacy of the consent process for EUS. Iterative refinement of codes and themes will occur through discussion with the research team.

NVivo qualitative data management software will facilitate management of the dataset. Independent quantitative and qualitative analyses will be performed initially, with subsequent integration of the two data sets to enrich the interpretation of findings.

7. SAFETY

No specific therapeutic intervention is proposed: this study consists only of obtaining diagnostic and clinical treatment information about patients and, for a small minority, qualitative interviews about diagnostic tests. We do not anticipate any safety events with this trial. All patients will have contact details for their local clinical team and should they experience any untoward reaction to their standard care investigations local procedures will apply.

8. STATISTICS AND DATA ANALYSES

8.1 SAMPLE SIZE

The sample size is based on estimating the proportion of cases that EUS (when recommended) changes MDT decisions regarding treatment. We will test the observed proportion against a null hypothesis of 5% (which is considered to be too small to be of clinical use) using an alternative hypothesis of 10% (which is considered to be the level at which EUS may be beneficial). With 180 participants, we have 85% power based on a one-sided test with 5% type I error rate. (in STATA 17: `sampsi 0.05 0.1, onesided onesample power(0.85)`). Patients found to have metastatic disease on a PET scan conducted after enrolment into the trial will be excluded and replaced.

8.2 INTERIM ANALYSIS

No interim analysis is planned.

8.3 STATISTICAL ANALYSIS PLAN (SAP)

8.3.1 Primary Endpoint

We will compare the proportion of cases where EUS changes MDT decision against a null hypothesis of 5% with a one-sided test. We will also present 90% confidence intervals around the estimated proportion using the Wilson method.

8.3.2 Secondary Endpoint

Where management was changed, we will tabulate reasons why using descriptive statistics.

We will calculate the time from treatment decision prior to EUS to treatment decision post EUS to get a measure of delay generated by waiting for an EUS. We will investigate whether patient and/or centre factors are associated with longer delay using cox regression methods with centre as a shared frailty.

9. REGULATORY COMPLIANCE

9.1 CLINICAL TRIAL AUTHORISATION

This trial is not considered to be a clinical trial of a medicinal product, so clinical trial authorisation from the UK Competent Authority the Medicines and Healthcare products Regulatory Agency (MHRA) is not required.

9.2 DEVIATIONS AND SERIOUS BREACHES

9.2.1 Protocol Compliance

A protocol deviation is any noncompliance with the trial protocol, GCP, or Manual of Procedure requirements. Any deviation occurring at sites should be reported to the SCTU and the local R&D Office immediately. As a result of deviations SCTU will advise of and/or undertake any corrective and preventative actions as appropriate. Deviations from the protocol which are found to frequently recur are not acceptable, will require immediate action and could potentially be classified as a serious breach.

9.2.2 Serious Breaches

A "serious breach" is a breach which is likely to effect to a significant degree – The safety or physical or mental integrity of the participants of the trial, or the scientific value of the trial.

Any serious breaches of the protocol or of the principles Good Clinical Practice which is likely to affect to a significant degree the safety or physical or mental integrity of the research participants, or the scientific value of the research will be reported to the REC and the Sponsor.

10.ETHICAL CONSIDERATIONS

The trial will be conducted in accordance with the recommendations for physicians involved in research on human participants adopted by the 18th World Medical Assembly, Helsinki 1964 as revised and recognised by governing laws and EU Directives. Each participant's consent to participate in the trial should be obtained after a full explanation of the study has been. The right of the participant to refuse to participate in the trial without giving reasons must be respected.

10.1 RESEARCH ETHICS COMMITTEE (REC) REVIEW AND REPORT

The trial protocol has received the favourable opinion of a Research Ethics Committee or Institutional Review Board (IRB) in the approved national participating countries.

An annual progress report will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the trial is declared ended.

Within one year after the end of trial, the Chief Investigator will submit a final report with the results, including any publication/abstracts, to the REC.

10.2 SPECIFIC ETHICAL CONSIDERATIONS

We do not envisage any specific ethical issues with this study.

10.3 INFORMED CONSENT PROCESS

Informed consent is a process that is initiated prior to an individual agreeing to participate in a trial and continues throughout the individual's participation. In obtaining and documenting informed consent, the investigator should comply with applicable regulatory requirements and should adhere to the principles of GCP.

Discussion of objectives, risks and inconveniences of the trial and the conditions under which it is to be conducted are to be provided to the participant by appropriately delegated staff with knowledge in obtaining informed consent with reference to the patient information leaflet. This information will emphasise that participation in the trial is voluntary and that the participant may withdraw from the trial at any time and for any reason. The participant will be given the opportunity to ask any questions that may arise and provided

the opportunity to discuss the trial with family members, friend or an independent healthcare professional outside of the research team and time to consider the information prior to agreeing to participate.

10.4 DATA PROTECTION AND CONFIDENTIALITY

SCTU will preserve the confidentiality of participants taking part in the study. The principal investigator must ensure that participant's anonymity will be maintained and that their identities are protected from unauthorised parties. On eCRFs participants will not be identified by their names, but by an identification code.

All Investigators and trial site staff must comply with the requirements of the Data Protection Act 2018 with regards to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles.

Qualitative Interviews

As part of clearly outlining the purpose of the interview, the non-medical expertise of the interviewer will be made clear upon the interviewers first contact with the patient. As supported by discussion with PPI representative it is anticipated that patients might feel fearful and anxious at this time. The safeguarding of participants well-being will be optimised through a sensitive approach to questioning and signposting to resources of support where required (e.g., local healthcare facility).

11.SPONSOR

SCTU, Chief Investigator and other appropriate organisations have been delegated specific duties by the Sponsor and this is documented in the trial task allocation matrix.

The duties assigned to the trial sites (NHS Trusts or others taking part in this study) are detailed in the Organisational Information Document.

11.1 INDEMNITY

For NHS sponsored research HSG (96) 48 reference no.2 applies. 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 study. 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.

11.2 FUNDING

NIHR RfPB are funding this study with support from SCTU core.

11.3 SITE PAYMENTS

The payments assigned to the trial sites (NHS Trusts or others taking part in this study) are detailed in the Non-Commercial Agreement.

This trial is adopted onto the NIHR portfolio. This enables Trusts to apply to their comprehensive local research network for service support costs.

11.4 PARTICIPANT PAYMENTS

Participants in the observational study will not be paid for participation. Participants in the qualitative study will be reimbursed for their time as detailed in the participant information sheet.

12. TRIAL OVERSIGHT GROUPS

The day-to-day management of the trial will be co-ordinated through the SCTU and oversight will be maintained by the Trial Management Group and the Trial Steering Committee.

12.1 TRIAL MANAGEMENT GROUP (TMG)

The TMG is responsible for overseeing progress of the study, including both the clinical and practical aspects. The Chair of the TMG will be the Chief Investigator of the study.

The VALUE TMG charter defines the membership, terms of reference, roles, responsibilities, authority, decision-making and relationships of the TMG, including the timing of meetings, frequency and format of meetings and relationships with other trial committees.

12.2 TRIAL STEERING COMMITTEE (TSC)

The TSC act as the oversight body on behalf of the Sponsor and Funder. The TSC will meet at least yearly and have at least one further teleconference meeting during the year. The majority of members of the TSC, including the Chair, should be independent of the trial.

The SCTU TSC charter defines the membership, terms of reference, roles, responsibilities, authority, decision-making and relationships of the TSC, including the timing of meetings, frequency and format of meetings and relationships with other trial committees.

12.3 INDEPENDENT DATA MONITORING COMMITTEE (IDMC)

An IDMC is not required for this trial.

13.DATA MANAGEMENT

Participant data will be entered remotely at site and retained in accordance with the current Data Protection Regulations. The PI is responsible for ensuring the accuracy, completeness, and timeliness of the data entered.

The participant data is pseudo anonymised by assigning each participant a participant identifier code which is used to identify the participant during the trial and for any participant- specific clarification between SCTU and site. The site retains a participant identification code list which is only available to site staff.

The PIS and Informed Consent Form will outline the participant data to be collected and how it will be managed or might be shared, including handling of all Patient Identifiable Data (PID) and sensitive PID adhering to relevant data protection law.

Trained personnel with specific roles assigned will be granted access to the eCRF. ECRF completion guidelines will be provided to the investigator sites to aid data entry of participant information.

Only the Investigator and personnel authorised by them should enter or change data in the eCRFs. When requested, laboratory data must be transcribed, with all investigator observations entered into the eCRF. The original laboratory reports must be retained by the Investigator for future reference.

A Data Management Plan (DMP) providing full details of the trial specific data management strategy for the trial will be available and a Trial Schedule with planned and actual milestones, CRF tracking and central monitoring for active trial management created. Timelines for key tasks will be specified in the DMP and shared with sites during the Site Initiation Visits.

Data queries will either be automatically generated within the eCRF, or manually raised by the trial team, if required. All alterations made to the eCRF will be visible via an audit trail which provides the identity of the person who made the change, plus the date and time.

At the end of the trial after all queries have been resolved and the database frozen, the PI will confirm the data integrity by electronically signing all the eCRFs. The eCRFs will be archived according to SCTU policy and a PDF copy including all clinical and Meta data returned to the PI for each participant.

Pseudonymised results and clinical data may be stored in a secure data environment, following the end of the trial. No identifiable information for the study participants will be stored within the secure data environment.

Data may be requested from the Data Access Committee at SCTU. Any request will be considered on a regular basis.

13.1 Data Sharing requests for results that are available in the public domain

In order to meet our ethical obligation to responsibly share data generated by clinical trials, SCTU operate a transparent data sharing request process. As a minimum, anonymous data will be available for request from three months after publication of an article, to researchers who provide a completed Data Sharing request form that describes a methodologically sound proposal, for the purpose of the approved proposal and if appropriate a signed Data Sharing Agreement. Data will be shared once all parties have signed relevant data sharing documentation.

Researchers interested in our data are asked to complete the Request for Data Sharing form (CTU/FORM/5219) [template located on the SCTU web site, www.southampton.ac.uk/ctu] to provide a brief research proposal on how they wish to use the data. It will include the objectives, what data are requested, timelines for use, intellectual property and publication rights, data release definition in the contract and participant informed consent etc. If considered necessary, a Data Sharing Agreement from Sponsor may be required.

14.MONITORING

14.1 CENTRAL MONITORING

Data stored at SCTU will be checked for missing or unusual values (range checks) and checked for consistency within participants over time. Any suspect data will be returned to the site in the form of data queries. Data queries on eCRFs will be raised to site either automatically or manually by STCU staff via the database. Sites should respond to queries on the database and provide an explanation/resolution to any discrepancies within the required timeframe. Queries and responses are recorded within the database audit trail. There are a number of monitoring principles in place at SCTU to ensure reliability and validity of the trial data, which are detailed in the trial monitoring plan. Informed Consent Forms will be monitored centrally.

14.2 CLINICAL SITE MONITORING

As detailed in the Trial Monitoring Plan

14.2.1 Source Data Verification

On receipt of a written request from SCTU, the PI will allow the SCTU direct access to relevant source documentation for verification of data entered onto the eCRF (taking into account data protection regulations). Access should also be given to trial staff and departments (e.g., pharmacy).

The participants' medical records and other relevant data may also be reviewed by appropriate qualified personnel independent from the SCTU appointed to audit the study, including representatives of the

Competent Authority. Details will remain confidential, and participants' names will not be recorded outside the trial site without informed consent.

14.3 SOURCE DATA

Source documents are where data are first recorded, and from which participants' eCRF data are obtained. These include, but are not limited to, hospital records (from which medical history and previous and concurrent medication may be summarised), clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence.

The PI is responsible for maintaining the Investigator Source Location Agreement (CTU/FORM/5245) to detail site specific source data location information.

14.4 AUDITS AND INSPECTIONS

The trial may be participant to inspection and audit by UHS (under their remit as Sponsor), SCTU (as the Sponsor's delegate) and other regulatory bodies to ensure adherence to the principles of GCP, Research Governance Framework for Health and Social Care, applicable contracts/agreements and national regulations.

15. RECORD RETENTION AND ARCHIVING

Trial documents will be retained in a secure location during and after the trial has finished.

The PI or delegate must maintain adequate and accurate records to enable the conduct of the trial to be fully documented and the trial data to be subsequently verified. After trial closure the PI will maintain all source documents and trial related documents. All source documents will be retained for a period of 15 years following the end of the trial.

Sites are responsible for archiving the Investigator Site File and participants' medical records.

The Sponsor is responsible for archiving the TMF and other relevant documentation.

16. PUBLICATION POLICY

Data from all centres will be analysed together and published as soon as possible.

Individual investigators 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 investigators, and if there are named authors, these should include the Chief Investigator, Co-Investigators, Trial Manager, and Statistician(s) involved in the trial. Named authors will be agreed by the CI and Director of SCTU. If there are no named authors, then a 'writing committee' will be identified.

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18. APPENDICES

18.1 Appendix 1 ECOG performance Status

GRADE	PERFORMANCE STATUS
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out light work or sedentary nature, e.g., light housework, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work; up and about more 50% of waking hours.
3	Capable of only limited self-care confined to bed or chair more than 50% of waking hours.
4	Completely disabled; cannot carry out any self-care; totally confined to bed and chair.

19. SUMMARY OF SIGNIFICANT CHANGES TO THE PROTOCOL

Protocol date and version	Summary of significant changes
v1 29-Jan-2024	Initial protocol submission
v2 05-Mar-2024	Changes requested following REC review
v3 30-Sep-2024	Changes to inclusion criteria and removing the need for CT and PET-CT for staging of T1 disease. For T2-4 disease, CT is necessary for entry to trial, with a PET-CT later but not necessary as for previous version.
v4 18-Feb-2025	Changes to screening and pre/post-EUS procedures and data collection. The study schema has been updated to reflect these changes.