CLINICAL STUDY PROTOCOL

This protocol has regard for the HRA guidance.

FULL STUDY TITLE: Open label randomised controlled trial of intensive surveillance vs. standard postoperative follow-up in patients undergoing surgical resection for oesophageal and gastric cancer

SHORT STUDY TITLE: Surveillance After Resection of Oesophageal aNd Gastric cancer (SARONG) trial

Version 2.0 05 Dec 2023

Study website: https://sarong.octru.ox.ac.uk/

Contents

1 RESEARCH REFERENCE NUMBERS

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2 ORGANISATIONAL INFORMATION

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Conflict of Interest statement:	None of the protocol authors/contributors have declared a potential conflict of interest.
Confidentiality Statement:	In accordance with the NIHR Open Access policy, the protocol will be published and made freely and openly accessible to all.

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4 PROTOCOL APPROVAL/SIGNATURE PAGE

This protocol has been approved by the Sponsor, Chief Investigator and Lead Statistician. Approval of the protocol is documented in accordance with OCTRU Standard Operating Procedures.

All parties confirm that findings of the study will be made publicly available through publication or other dissemination tools without any unnecessary delay and that an honest, accurate and transparent account of the study will be given; and that any important deviations and serious breaches of Good Clinical Practice (GCP) from the study as planned in this protocol will be explained.

5 LAY SUMMARY/PLAIN ENGLISH SUMMARY

There are over 15,800 new cases of gullet (oesophageal) or stomach cancer diagnosed every year in the UK, with over 12,300 deaths per year attributed to these cancers. Currently, most patients with cancer of the gullet and stomach are treated with surgery with or without additional chemo- or radio-therapy. In recent years there have been improvements in survival from these two cancers, due to better therapies, less invasive surgery and earlier detection. Despite these improvements, in around two-thirds of patients treated with surgery, the cancer will return and lead to death within three years.

At present there is very little evidence as to how gullet and stomach cancer patients should be followed up after surgery and whether different methods of follow-up could improve survival. Currently, national and international guidelines do not provide consistency in their recommendations for follow-up after surgery.

The SARONG study will investigate if regular radiological scans can lead to earlier detection of a cancer returning, at a stage when it may be more readily treatable. This means that participants who agree to take part will be allocated by chance to either more intensive surveillance (including regular radiological scans and a camera test (endoscopy)) or the current standard of care. The study aims to recruit at least 952 participants in the UK over a 32-month period from at least 24 NHS hospitals. Patients undergoing surgery for gullet or stomach cancer will be invited to participate in the study up to 12 weeks after this surgery.

(i) The intensive surveillance group will receive a review in clinic or by telephone with a member of the surgical team, and a radiological scan at 6, 12, 18, 24, 30 and 36 months after randomisation. They will also receive endoscopy at 12 months after randomisation.

(ii) The standard care group will receive a review in clinic or by telephone at 6 and 12 months. After this they will be either discharged to their local doctor or receive a review in clinic with a member of the surgical team every year.

The main aim of this study will be to determine whether earlier detection of cancer through more intensive follow-up results in improved survival and better quality of life for patients with gullet or stomach cancer.

Consultation with patient groups and charities, including Heartburn Cancer UK, Oesophageal and Stomach Cancer Patient Support group, Action against Heartburn, and GUTS charity UK, has taken place and patients will continue to be integral to the organisation and running of the study. The findings will be presented at national and international meetings, published in a high-impact scientific journal and disseminated with a broader social media strategy. All participants taking part in the study will be informed of the findings via the study website. We anticipate the results of the study may have significant practice-changing impact for patients undergoing follow-up after surgery for gullet and stomach cancer.

6 STUDY SYNOPSIS

Full Study Title:	Open label randomised controlled trial of intensive surveillance vs. standard postoperative follow-up in patients undergoing surgical resection for oesophageal and gastric cancer	
Short Title:	Surveillance After Resection of Oesophageal aNd Gastric cancer (SARONG) trial	
Study Acronym:	SARONG	
Study Design:	SARONG is a multicentre, parallel group, two-arm, open-label superiority randomised controlled trial (RCT)	
Study Participants/Target Population:	The SARONG study will recruit adults (aged 16 years or over) receiving surgical resection for curatively intended treatment of oesophageal or gastric cancer with or without neoadjuvant/adjuvant chemo(radio)therapy	
Eligibility criteria:	**Inclusion:** 1. Patients who have undergone surgical resection for curatively intended treatment of oesophageal or gastric cancer (adenocarcinoma and squamous cell carcinoma) with or without neoadjuvant/adjuvant chemo(radio)therapy or immunotherapy (or in combination) 2. Aged 16 years or over 3. Patients willing and able to give informed consent **Exclusion:** 1. Patients with other cancers undergoing treatment or surveillance for this cancer	
No. of study arms	2	
Intervention	Intensive surveillance (including radiological scans (chest, abdomen and pelvis) and clinical review) every 6 months for 36 months post-randomisation along with an endoscopy at 12 months post-randomisation.	
Comparator	Standard of care follow-up for 36 months, comprising clinical review at 6 and 12 months post-randomisation.	
Planned sample size:	952 participants (476 per trial arm)	
Target no. of centres:	At least 24 NHS Hospitals in the UK	
Follow-up duration:	Each participant will be followed-up for 36 months from randomisation	
	Objective	**Outcome Measure**
Primary objective and outcome measure	To assess whether intensive surveillance, including regular radiological investigations and an endoscopic investigation after completing curatively intended treatment, improves survival in patients with oesophageal or gastric cancer.	All-cause mortality at 3 years post-randomisation, defined as death from any cause. Participants who have not been observed to die during the course of the study will have their survival time censored at their last known follow-up date.

Refer to the OBJECTIVES AND OUTCOME MEASURES section of the main protocol for full study objectives and outcome measures.

7 ABBREVIATIONS

AE	Adverse Event
AR	Adverse Reaction
AUGIS	Association of Upper Gastrointestinal Surgeons for Great Britain and Ireland
CA	Cancer Antigen
CEA	Carcinoembryonic Antigen
CI	Chief Investigator
CI	Confidence Interval
CONSORT	Consolidated Standards of Reporting Trials guideline
CRF	Case Report Form
CT	Computerized Tomography
ctDNA	circulating tumour DNA
CTU	Clinical Trial Unit
CWS	Cancer Worry Scale
DMC	Data Monitoring Committee
DSMC	Data & Safety Monitoring Committee
ENSURE	European multi-centre cohort study
ESMO	European Society for Medical Oncology
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GP	General Practitioner
HEAP	health economics analysis plan
HQIP	Healthcare Quality Improvement Partnership
HRA	Health Research Authority
HRQoL	Health-Related Quality of Life
ICER	Incremental Cost Effectiveness Ratio
ICF	Informed Consent Form
IDMC	Independent Data Monitoring Committee
ISDE	International Society for Diseases of the Esophagus
ISRCTN	International Standard Randomised Controlled Trials Number
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
NCAPOP	National Clinical Audit and Patient Outcomes Programme
NCCN	National Comprehensive Cancer Network
NCIMI	National Consortium for Intelligent Medical Imaging
NCRAS	National Cancer Registration and Analysis Service
NCRI	National Cancer Research Institute
NHS	National Health Service
NOGCA	National Oesophago-Gastric Cancer Audit

NRES	National Research Ethics Service
OCTRU	Oxford Clinical Trials Research Unit
ONS	Office of National Statistics
OOSO	Oxfordshire Oesophageal and Stomach Organisation
OPA	Oesophageal Patient Association
OR	Overall Response
OUH	Oxford University Hospitals NHS Trust
PET-CT	Positron Emission Tomography-CT
PI	Principal Investigator
PICs	Participant Identification Centres
PIS	Patient Information Sheet
PPI	Public and Patient Involvement
QA	Quality Assurance
QALY	Quality Adjusted Life Year
QC	Quality Control
RCT	Randomised Clinical Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SDV	Source Data Verification
SFQ	Site Feasibility Questionnaires
SITU	Surgical Intervention Trials Unit
SMD	Standardised Mean Difference
SOC	System Organ Class
SOP	Standard Operating Procedure
TIDieR	Template for Intervention Description and Replication
TMF	Trial Master File
TMG	Trial Management Group
TNF	Tumour Necrosis Factor
TSC	Trial Steering Committee
UEG	United European Gastroenterology
UK NICE	United Kingdom National Institute for Health and Care Excellence

8 BACKGROUND INFORMATION AND RATIONALE

Oesophageal and gastric cancer current surveillance strategy evidence

There are over 15,800 new cases of oesophageal or gastric cancer diagnosed per year in the UK, with over 12,300 deaths attributed to these cancers annually [1,2]. The mainstay of curative treatment for oesophageal and gastric cancer is surgical resection, either with or without oncological adjunctive therapy. Despite some improvements in the survival for patients with oesophageal or gastric cancer, attributed to the improved early detection and greater utilisation of multimodal treatment [3-5], approximately 60% of patients with locally advanced and localised disease treated with curative intent will develop tumour recurrence and die within 3 years of completing treatment [4,6–8].

In the absence of robust scientific evidence, it is unsurprising that national or international guidelines fail to reach consensus on a common surveillance strategy after the treatment of oesophageal or gastric cancer. The National Comprehensive Cancer Network (NCCN) advocates regular cross-sectional imaging with computerised tomography (CT) for patients with locally advanced disease (cT2-4 N any) [9]. In contrast, the European Society for Medical Oncology (ESMO) guidelines state that neither routine imaging nor endoscopic surveillance is advocated [10]. The United Kingdom National Institute for Health and Care Excellence (UK NICE) guidelines based upon a lack of evidence currently state, 'for people without symptoms or evidence of residual disease after treatment for oesophago-gastric cancer with curative intent, do not offer routine clinical follow-up or radiological surveillance solely for the detection of recurrent disease' [11].

There has yet to be a randomised controlled trial (RCT) that has compared survival between oesophago-gastric cancer patients undergoing different surveillance protocols. This RCT is timely as there is considerable interest in the oesophago-gastric cancer community in pursuing this. NICE have highlighted that follow-up is one of the key areas for research in upper gastrointestinal cancer and have posed the key research question, 'is routine use of CT and tumour markers effective in detecting recurrent disease suitable for radical treatment in asymptomatic people who have had treatment for oesophago-gastric cancer with curative intent?' [11]. In order to answer this question, a national RCT is required.

UK current surveillance strategy

The UK NICE guidelines state, 'for people without symptoms or evidence of residual disease after treatment for oesophago-gastric cancer with curative intent, do not offer routine clinical follow-up or radiological surveillance solely for the detection of recurrent disease'[11]. A questionnaire study that we undertook of 27 oesophago-gastric UK specialist centres published online in August 2021 found that 43% of centres did not have a specific routine post-operative surveillance protocol [12]. Moreover, only 16% of centres provide routine radiological follow-up while 13% provide routine endoscopic follow-up. Upon further questioning, the most significant factor determining the intensity of surveillance was clinical presentation (82%), followed by pathologic staging (43%), margin status (36%), weight trajectory (36%) and patient preference (36%). Furthermore, there were widely different beliefs around the prognostic influence of intensive surveillance, with 31% in agreement that intensive surveillance may improve overall survival through the earlier detection of local recurrence, while 34% were not in favour of intensive surveillance, and 49% felt intensive surveillance may increase patient's anxiety. Given the significant variation in opinion, there was a

near unanimous willingness (94% agreement) to participate in an RCT to empirically evaluate the prognostic value of intensive surveillance after oesophageal and gastric cancer resections [12].

Why is this research important in terms of improving the health and/or wellbeing of the public and/or to patients and health and care services?

As stated by the current UK NICE guidance, the potential benefits to patients and the NHS of this research are clear: 'Detection of early recurrence potentially suitable for radical treatment offers the possibility of increased survival. However, the best methods of detecting recurrence are unclear and there is currently no evidence to determine whether early detection leads to improved overall survival. Studies examining the role of screening in this scenario would show whether routine surveillance in asymptomatic people was effective at detecting recurrence and improving overall survival' [11]. A large majority of patients who undergo curatively intended treatment (including extensive surgery) for oesophageal or gastric cancer die from tumour recurrence within 3 years of treatment, often due to late presentation with widely disseminated recurrence.

In addition to assessing mortality and recurrence, it is vital to also capture the impact of surveillance strategies upon wellbeing after curatively intended treatment. Previous investigations have suggested that routine clinical and radiological surveillance does reduce patients fear around cancer recurrence and provide them with reassurance, improving their overall Health-Related Quality of Life (HRQoL) [13]. Thus, following close consultation with charities and patient groups, we have ensured that this research will evaluate not only the potential prognostic benefits of a structured follow-up regime, but also the potential impacts upon patient anxiety and quality of life.

The cost-benefit of an intensive surveillance programme after oesophageal and gastric cancer treatment has not been previously studied. Thus, we have endeavoured to incorporate a robust cost-effectiveness analysis to better understand the financial costs associated with the two strategies that will be compared.

Systematic review of surveillance studies

We have completed a systematic review and meta-analysis to assess the available evidence investigating the usefulness of surveillance protocols in patients who had undergone oesophageal or gastric cancer surgery [14]. There were no RCTs, however, 15 cohort studies that described a surveillance protocol for post-operative patients with a surveillance period of at least 12 months were included. We noted that there was a large degree of heterogeneity in the structure of surveillance protocols between studies. Random-effects analysis demonstrated a statistically significant higher detection of recurrence (Overall Response (OR) 2.76, 95% Confidence Interval (CI) 1.78-3.97, P=0.01) and post-recurrence survival (Standardised Mean Difference (SMD) 14.15, 95% CI 1.40-27.26, P=0.03) with imaging-based planned surveillance post-oesophagectomy. However, the detection of recurrence (OR 0.73, 95% CI 0.11-5.12, p=0.76) and post-recurrence survival (SMD 6.42, 95% CI -2.16-18.42, P=0.14) were not significantly different with planned surveillance for gastric cancer. We concluded that an RCT is required to; (1) evaluate the potential survival benefits of intensive surveillance strategies, (2) to determine the optimal surveillance protocol and (3) to appropriately tailor it towards the target population [14].

European Investigation of Surveillance after Resection for Esophageal cancer (ENSURE study)

We undertook a European multi-centre cohort study (ENSURE). In phase 1 of this study, we surveyed 27 high-volume European centres and identified there was a large degree of heterogeneity in how centres undertook surveillance, with 37% performing intensive surveillance with annual computerised tomography (CT) or Positron Emission Tomography-CT (PET-CT). This survey also established a wide range of beliefs regarding the merits or not of an intensive surveillance strategy. Importantly, however, a high level of agreement (92%) was reached regarding the need for an RCT to study this issue.

In phase 2, 4972 patients were recruited from 20 centres, of which 47% were subject to an intensive surveillance strategy with CT or PET-CT every 6 to 12 months for the first five years after treatment. Intensive surveillance was independently associated with an increased detection of isolated local or anastomotic recurrence, and an improved overall survival (P=0.012) [15].

The results from ENSURE are important in the development and providing the rationale for this present RCT because:

(i) The survey established that there is widespread heterogeneity in surveillance protocols in Europe, and the vast majority of centres agreed there is a need for an RCT examining this issue. (ii) Intensive surveillance was associated with increased detection of isolated or anastomotic recurrence and improved overall survival.

Barriers to intensive surveillance after curatively intended treatment

The ENSURE study identified three key barriers to intensive surveillance strategies after curatively intended treatment of oesophageal or gastric cancer [15]:

(i) Uncertainty whether additional surgical or oncological treatment of recurrence improves survival

Historically, there has been an impression that the detection of recurrence or metastases in oesophageal or gastric cancer treatment will have little role in improving survival. However, we performed a systematic review and meta-analysis for the management of gastric cancer patients with liver metastases which showed that surgical resection of metastases improved overall survival (P<0.001) [16]. We have also undertaken a systematic review of oligometastatic disease in oesophageal cancer which has demonstrated improved overall survival if treated actively [17]. Furthermore, the ENSURE study suggests that intensive surveillance is associated with an increased detection of isolated local or anastomotic recurrence and that surgical treatment, with or without chemoradiotherapy, improved overall survival [15].

(ii) High costs of intensive surveillance

Regular radiological and endoscopic centred surveillance is costly. In the absence of an empirically proven survival benefit, the financial cost may be deemed to be prohibitive to establishing a nationally mandated surveillance programme. As such, undertaking a cost-effectiveness analysis of a structured surveillance pathway compared to standard care will be a key outcome measure for this RCT.

(iii) Potential impact upon Health-Related Quality of Life (HRQoL) and specifically anxiety from intensive surveillance

The ENSURE study, which is described above, consisted of 4972 patients from 20 centres and included an analysis of HRQoL. On multivariable analysis, intensive surveillance was not associated

with global health status (P=0.160), emotional functioning (P=0.209) or financial difficulties (P=0.627). However, patients undergoing intensive surveillance did exhibit greater anxiety scores (P=0.016) but also reduced dysphagia scores (P=0.006) [15]. As part of the patient involvement prior to this clinical study, we also conducted a survey study of 107 former oesophageal or gastric cancer patients, to specifically ask about potential increases in anxiety associated with intensive surveillance. We found that only 17% of respondents felt that intensive surveillance may be likely to increase their anxiety. Furthermore 78% of patients felt that intensive surveillance would be reassuring for them regarding their ongoing cancer care and monitoring for recurrence. Given these disparate findings, we believe that an analysis of HRQoL, including anxiety, will be a key secondary outcome measure within this RCT.

Definition of alarm symptoms for standard care

We have undertaken a Delphi consensus process from 24 high-volume international oesophago-gastric cancer centres to define the critical symptomatic threshold that should stimulate further endoscopic or radiological investigation for cancer recurrence. The symptoms that reached at least 80% consensus for investigation were; dysphagia to solid food, dysphagia to liquids, vomiting, abdominal pain, chest pain, regurgitation of foods, unexpected weight loss and progressive hoarseness of voice [20]. Investigations triggered by the presence of these symptoms, along-with deviations from this assigned pathway, will be recorded locally and entered onto the case report form (CRF) every 6 months during the surveillance period. Significant deviations from the established symptomatic threshold, defined as more than 10% of patients in the control arm in a 6-month period, will trigger feedback and monitoring of the participating centre.

Use of imaging techniques for active surveillance

CT scans of the chest, abdomen and pelvis will be performed at 6 monthly intervals for 3 years post-randomisation.

Timing of intervention follow-up

The timing of intensive surveillance was based upon two previous studies:

1. The ENSURE cohort study suggested a timing of the intensive surveillance with CT (every 6-12 months) and an endoscopy at 12 months was prognostically important.

2. In systematic review of surveillance studies, 11 out of 15 studies utilised an intensive surveillance protocol with a CT or PET-CT at least every 6-12 months for the first two to three years after surgery

The final decision for the intervention follow-up was made to include clinical follow-up and CT every 6 months for 3 years and an endoscopy at 12 months post-randomisation.

9 OBJECTIVES AND OUTCOME MEASURES

9.1 Aim

The aim of the SARONG study is to determine whether intensive surveillance after completing curatively intended treatment improves survival and HRQoL in patients with oesophageal or gastric cancer.

9.2 Primary objective and outcome measure

Objective	Outcome measure	Time point(s) of evaluation of this outcome measure (if applicable)	Data required	Source data (including location)
To assess whether intensive surveillance, including radiological investigations and an endoscopic investigation after completing curatively intended treatment, improves survival in patients with oesophageal or gastric cancer.	All-cause mortality defined as death from any cause. Participants who have not been observed to die during the course of the study will have their survival time censored at their last known follow-up date.	3 years post-randomisation of the last included participant.	Date of randomisation. Date of death. Date last known alive if not dead.	Participant's medical notes.

9.3 Secondary objectives and outcome measures

Objectives	Outcome measures	Time point(s) of evaluation of this outcome measure (if applicable)	Data required	Source data (including location)
1. To determine the impact of intensive surveillance upon the detection and treatment of cancer recurrence.	a) Disease-specific mortality, defined as known oesophageal or gastric cancer recurrence at the time of death.	3 years post-randomisation of the last included participant.	Cause of death Date of death Last date known alive and oesophageal or gastric cancer recurrence free.	Participant's medical notes.
	b) Pattern of tumour recurrence, defined as the incidence of loco-regional or distant recurrence.	3 years post-randomisation of the last included participant.	Site of recurrence as defined as loco-regional, distant or mixed.	Participant's medical notes including CT reports.
	c) Treatment of tumour recurrence,	3 years post-randomisation of	Treatment of recurrence as	Participant's medical notes.

	ie. the requirement for chemotherapy, surgery, immunotherapy, radiotherapy, chemoradiotherapy, best supportive care or other as determined by the clinical team at the treating site.	the last included participant.	allocated, along-with compliance to and completion of treatment.	
	d) Rates of oligometastatic (one site) tumour recurrence.	3 years post-randomisation of the last included participant.	Site of recurrence as defined as oligometastatic.	Participant's medical notes including CT reports.
	e) Rates of multi-metastatic (several sites) tumour recurrence.	3 years post-randomisation of the last included participant.	Site of recurrence as defined as multi-metastatic.	Participant's medical notes including CT reports.
2. To determine the impact of surveillance upon health-related quality of life.	HRQoL, including anxiety or depression and worry of cancer returning as measured by the following validated questionnaires: EQ-5D-5L, EORTC QLQ-C30 and QLQ-OG25 and Cancer Worry Scale (CWS).	At baseline, 6, 12, 18, 24, 30 and 36 months post-randomisation.	EQ-5D-5L EORTC QLQ-C30 EORTC QLQ-OG25 CWS.	Participant-reported outcome (questionnaires administered and data collected centrally).
3. To assess the cost-effectiveness of routine clinical, radiological investigations and an endoscopic investigation compared with the current practice, led by clinical symptomatic follow-up.	Incremental cost per quality adjusted life year (QALY).	Healthcare Resource usage data to be collected at baseline 6, 12, 18, 24, 30 and 36 months post-randomisation.	EQ-5D-5L Healthcare Resource use questionnaires Date of death.	Participant-reported outcome (questionnaires administered and data collected centrally) Participant's medical records for resources used in secondary care.

9.4 Use of core outcome sets

There is a newly developed core outcome set for gastric cancer surgery [21], however this has not been validated as yet and is not applicable to this surveillance study. We have thus included common core outcomes where applicable.

10 STUDY DESIGN AND SETTING

The SARONG study is a multi-centre, open-label, two-arm, parallel design, superiority randomised controlled trial. 952 patients (476 in each of two trial arms) will be recruited from approximately 24 sites in the UK. Participants will be randomised to either intensive surveillance (including radiological scans) every 6 months for 36 months and an endoscopy at 12 months post-randomisation or standard care follow-up for 36 months.

A study flow chart is provided in APPENDIX 1 – STUDY FLOW CHART.

10.1 Recruiting sites/site types

Participants will be recruited from approximately 24 NHS oesophago-gastric centres across the United Kingdom.

10.2 Collection of outcome data and follow-up assessments

All clinical follow-up visits will either be face-to-face appointments or by telephone consultation in accordance with local site practice and the participant's randomised allocation. Participants will be sent all HRQoL questionnaires and healthcare resource use questionnaires via email with a link to complete questionnaires online, with an option to complete the questionnaires via telephone call from the Surgical Intervention Trials Unit (SITU) post if the patient expresses this as a preference. HRQoL questionnaires will be administered in English. Non-native English speakers will be permitted to use support to complete the questionnaires as needed.

Clinical outcomes and resource usage in secondary care will be collected by local study teams and recorded in the case report form in the REDCap database. Refer to section STUDY ASSESSMENTS/PROCEDURES for details of the data being collected in the study and the timepoints and methods for this data collection.

Participating study centres will describe the indication for further investigations and if this met the defined symptomatic threshold (see section 14.2.1 Definition of alarm symptoms) or was a protocol deviation.

Data on all-cause 3-year mortality will be collected from the participant's medical record and validated against National Oesophago-Gastric Cancer Audit (NOGCA) [22] and Office of National Statistics (ONS). The process of validation will begin after 12-months of recruitment and then continue every 6 months during the study. Data regarding timing, centre and treatment of recurrence, and 3-year disease specific mortality will be recorded on the CRF by the local centre study team using the participant's medical record. Specific approval has been gained from the audit to support the SARONG study and integration of this data within the national audit processes. Data on treatment of recurrence will be collected from the participating centres on the CRF.

Any discrepancies identified between centre-reported data collected on the case report form and data derived from the registries will be discussed with the participating site to verify the correct data. Data discrepancies will be handled in accordance with the study-specific data management and monitoring plan.

Refer to section17 STUDY ASSESSMENTS/PROCEDURES for full details of outcome data collection and follow-up assessments.

10.3 Duration of participant involvement

Participants will be in the study for approximately 36 months from randomisation to last protocol visit. Mortality and recurrence data will be collected for 36 months after the last participant is randomised, this data will be collected from medical records and in the case of all-cause mortality validated against NOCGA and NCRAS.

10.4 Post-study treatment/care and follow-up

Following a participant's final protocol visit, they will receive standard care from their participating institution.

10.5 Central review procedures

10.5.1 Quality assurance of radiology reporting

During the internal pilot phase (see Internal pilot/Decision Points), all CT scans from participating centres will be sent by the local centre team to a central repository housed within the secure Oxford University Hospitals NHS Foundation Trust's Secure Data Environment server (OUH NHSFT SDE). Images will be sent for participants in both arms of the study; any CT scans for images taken as part of standard care in the standard care arm will be requested. All images will be identifiable only by the participant's Study ID. These will be transferred securely by e-mail from a nhs.net e-mail address. If the files are unable to be transferred via email, another secure service, approved by the affected site, and compliant with the relevant OCTRU SOP will be used. Images will be re-reviewed by a senior Oxford consultant radiologist, with discrepancies discussed with the local radiology reporting lead at the participating site to ensure standard (internal audit) during this internal pilot phase.

Following the internal pilot phase, each site will be requested to send a randomly selected 10% of all CT images every 6 months to the secure OUH NHSFT SDE server. The radiological lead at Oxford will direct the quality assurance program to validate these reported radiological images, with any discrepancies discussed with the local radiology reporting team. Images will be either reported as positive, indeterminant or negative for recurrence. Within the positive recurrence group, oligometastatic recurrence will be characterised and classified according to current European recommendations [23]. Indeterminant lesions will be further investigated and characterised as per local participating centre protocols.

10.6 Use of NHS England data (including data from registries)

The NOGCA is commissioned by the Healthcare Quality Improvement Partnership (HQIP) as part of the National Clinical Audit and Patient Outcomes Programme (NCAPOP). The data processes and validation of the entered data has been well established for patients receiving surgery for oesophageal and gastric cancer since 2012. This national audit is used by all oesophago-gastric specialist cancer centres in England and Wales for the entry of oesophageal and gastric cancer patients undergoing treatment both curative and palliative.

Participants from the SARONG study will be consented for linkage of their data to the Office of National Statistics (ONS) and NOGCA datasets. Locally collected data from participant medical records will be checked against mortality data from ONS, and from NOGCA.

Patients that decline to take part in the study will continue to have their data collected as part of their normal clinical surveillance and recorded within NOGCA. Data will also be collected regarding

additional radiological and endoscopic imaging during surveillance, to evaluate if a change in surveillance protocols has been observed within participating centres during the study, in non-study participants. Thus, the external validity of the study findings will be tested through comparison of the SARONG study data, with NOGCA data from non-participating patients and centres.

10.7 Health Economics

A cost-utility analysis to assess the cost-effectiveness of implementing an intensive surveillance after oncological treatment compared with current practice will be conducted.

Participants will be asked to complete a resource use questionnaire which will collect healthcare (primary care appointments, prescribed and over the counter medications, hospital admissions outside of their participating institution, contact with other healthcare professionals) and non-healthcare resource use (social and informal care, travel costs and time off work) of participants in both arms of study. The questionnaires will be administered to patients at baseline and at 6, 12, 18, 24, 30 and 36-months post-randomisation. Secondary care resource usage at the participating institution will also be collected from the participant's medical records.

The EQ-5D-5L instrument will be used to measure HRQoL at baseline and at 6, 12, 18, 24, 30 and 36-months post-randomisation.

Refer to section 20.12 for full details of the health economic analysis.

10.8 Expected recruitment rate

Each of the 24 oesophago-gastric centres planned to take part in the SARONG study currently undertake 50 to 150 oesophageal or gastric resections per year. It has been conservatively estimated that 35% of eligible patients will consent to take part in the study. We estimate that we will open at least 1-2 sites per month starting in June 2023 and that all sites will be open to recruitment within 15 months. Therefore, we are expecting 32 months of recruitment across 24 NHS sites. The expected recruitment rate for this study is 2-3 patients per month / per site based on a staggered opening of sites and assuming a recruitment of 35% of eligible participants.

11 TRANSLATIONAL STUDY/MECHANISTIC STUDY

Machine learning on computerised tomography images for detection of tumour recurrence

Anonymised CT images will be used to create a repository of CT scans, which will be used to test the accuracy of a recurrence identification model [15].

12 PARTICIPANT ELIGIBILITY CRITERIA

Participant eligibility will be confirmed by a suitably qualified and experienced individual who has been delegated to do so by the Principal Investigator.

12.1 Timing of eligibility assessment

Eligibility will be assessed upon initial entry into the study and checked at the point of randomisation.

12.2 Overall description of trial participants

The SARONG study will recruit adults aged 16 years and over who have undergone surgical resection for curatively intended oesophageal and gastric cancer with or without neoadjuvant/adjuvant chemotherapy or radiotherapy or immunotherapy (or in combination).

Written informed consent must be obtained before any study specific procedures are performed.

The Investigator (or designee) will determine patient eligibility based on the following criteria.

12.3 Inclusion Criteria

A patient will be eligible for inclusion in this study if all of the following criteria apply:

1. Has undergone surgical resection for curatively intended treatment of oesophageal or gastric cancer (adenocarcinoma and squamous cell carcinoma) with or without neoadjuvant/adjuvant chemotherapy or radiotherapy or immunotherapy (or in combination).
2. Aged 16 years or over
3. Willing and able to give informed consent

12.4 Exclusion Criteria

A patient with not be eligible for the trial if **ANY** of the following apply:

1. Has other cancers undergoing treatment or surveillance for this cancer

12.5 Rationale for inclusion and exclusion criteria

The vast majority of patients in the UK with oesophageal or gastric cancer are over the age of 16 years. Those under 16 years of age, will typically have a specific genetic mutation (for example CDH1), which is often associated with other cancers requiring treatment and formal surveillance. Patients undergoing treatment or surveillance for another cancer will be excluded from inclusion.

12.6 Protocol waivers to entry criteria

Protocol adherence is a fundamental part of the conduct of a research study. There will be no waivers regarding eligibility i.e. each participant must satisfy all the eligibility criteria. Changes to the approved inclusion and exclusion may only be made by a substantial amendment to the protocol.

Before entering a patient into the study, the Principal Investigator or designee will confirm eligibility. If unsure whether the patient satisfies all the entry criteria and to clarify matters of clinical discretion investigators must contact the study office, who will contact the Chief Investigator or designated clinicians as necessary. If in any doubt the Chief Investigator must be consulted before entering the patient. Details of the query and outcome of the decision must be documented in the TMF/ISF.

12.7 Clinical queries and protocol clarifications

Every care has been taken in drafting this protocol. Contact the Study Office for clarification if any instructions seem ambiguous, contradictory or impractical. Clinical queries must also be directed to the Study Office. All clinical queries and clarification requests will be logged, assessed and a written response provided. Minor administrative corrections or clarifications will be communicated to all trial investigators for information as necessary. For urgent safety measures or changes that require protocol amendment see section 24.8.

12.8 Compliance with NIHR INCLUDE guidance

Data provided by CRUK describe that the incidence rate for oesophageal and gastric cancer is highest in people over 75-years-old, every year 4 in 10 (41%) of all new oesophageal cancer cases and each year half (50%) of all new stomach cancer in the UK are diagnosed in people aged 75 years and over (2016-2018). The prevalence of both cancers is higher in deprived areas in both genders. Stomach

cancer incidence rates for persons are lower in the Asian ethnic group, higher in the Black ethnic group, and similar in people of mixed or multiple ethnicity, compared with the White ethnic group, in England. Incidence rates for oesophageal cancer are lower in the Asian and Black ethnic groups, compared with the White ethnic group, in England (2013-2017) [24]. Therefore, we believe that the under-served groups for this study are associated with two main demographics factors; age extremes and different ethnic minority groups and social and economic factors such as patients living in deprived areas.

The study includes anyone who has been treated with surgery for both these cancers and is eligible to take part of the study. We do not foresee any differences between our study population and the broader population with oesophageal and gastric cancer undergoing surgery.

We will promote a patient-oriented retention method where participants can choose their preferred method of communication for follow up questionnaires. During the first post-operative visit (baseline) with the local study team, if the patient decides to take part in the study, we will ensure that participants can decide how to receive their questionnaires over the three years of the study (for example, electronically, by telephone or by mail).

This will allow us to accommodate the needs of the elderly, populations with limited access to technology, or other vulnerable populations, with the provision of postal or telephone follow up. The use of electronic questionnaire follow ups will also allow convenience for many participants, and the ability to use any other accessible technologies they may use in daily life (e.g. screen readers, increased font size).

13 SCREENING AND RECRUITMENT

13.1 Participant Identification

Participants will be recruited from oesophago-gastric centres and referring hospitals within the NHS in the United Kingdom

The following methods will be used to identify potentially eligible participants:

- Identification during routine clinical or ward visits.
- Searching of clinic records/hospital database by the usual care team to identify individuals that may be eligible

A poster advertising the study may be displayed in electronic and paper formats as allowed in participating centre. All advertising material will be approved prior to use.

13.1.1 Identification of participants during routine clinical visits

Potentially eligible patients identified during routine clinic visits will be provided with a Patient Information Sheet (PIS) by a member of their usual care team (who may also be a member of the study team) and asked to consider the study. Where their usual care clinician is not a member of the local study team potential participants will be asked if it would be acceptable for their name to be passed to the local study team to make contact (this may be in person in clinic or via telephone or video call), or potential participants may be given the PIS and asked to call the number on it if they wish to find out more about the study. When a potential participant is approached for permission for their details to be passed onto the local study team – if this permission is given this should be recorded in their clinical notes.

The initial approach about this study will usually take place after surgery. Patients will be consented for inclusion in the study and eligibility confirmed at least 24 hours after the initial approach and within approximately 12 weeks of their surgery. Randomisation will take place after the baseline data are collected. Consent will be taken in clinic electronically, or obtained using remote eConsent.

13.1.2 Identification of participants via clinic records/hospital database

Potentially eligible participants will be identified by searching of clinic records/hospital databases by those in the clinical care team only. Any patients who are thought to fulfil the inclusion/exclusion criteria will be approached about the study after surgery within approximately 12 weeks.

13.2 Use of screening logs

A screening log must be kept of all patients considered for the study including any that are subsequently excluded; the reason for exclusion must be recorded on this form.

Screening logs will be used to record information about the number of patients considered and/or approached for the study and if provided, the reasons for declining participation.

13.3 Use of social media

Twitter/X feeds may be utilised to promote the study, and acknowledge when milestones are met (e.g. sites open to recruitment, first recruitment at a site etc).

14 STUDY INTERVENTION AND COMPARATOR

14.1 Intensive surveillance follow-up (intervention)

Participants randomised to the intervention arm will receive intensive surveillance for three years. Participants will have a clinical review with a CT scan of the chest, abdomen and pelvis every 6 months up to 36 months. An endoscopy will also be performed 12 months post-randomisation.

14.2 Usual care (comparator/control)

Participants randomised to the comparator arm will receive standard care follow-up following their surgery. Standard care comprises of a clinical review at 6 and 12 months and after 12 months, participants are either discharged to primary care or clinically reviewed annually by the treating centre, with targeted investigations as needed. Targeted investigations are recommended in the event of new onset alarm symptoms (see section 14.2.1 below).

14.2.1 Definition of alarm symptoms

Participants randomised to the control arm will undergo further endoscopic or radiological investigation for cancer recurrence at the discretion of local centre if they experience any of the following symptoms:

- dysphagia to solid food
- dysphagia to liquids
- vomiting
- abdominal pain
- chest pain
- regurgitation of foods
- unexpected weight loss
- progressive hoarseness of voice

Investigations triggered by the presence of these symptoms, along-with deviations from this assigned pathway, will be collected on the CRF and for participants in both study arms during the follow-up period. Significant deviations from the established symptomatic threshold, defined as more than 10% of patients in the control arm from centre in a 6-month period, will trigger feedback and monitoring of the participating centre.

15 INFORMED CONSENT

15.1 Consent Procedure

Informed consent will be sought and if a person approached is willing to give consent it will be obtained by a member of the study team listed on the delegation log before they undergo any interventions/assessments related to the study. A member of the local study team will explain the details of the study in addition to the already presented PIS, ensuring that the potential participant has sufficient time to consider participating or not. A member of the local study team (authorised to do so on the delegation log) will answer any questions that the potential participant has concerning study participation.

The Investigator who obtains consent must be suitably qualified and experienced. All delegates must be authorised by the site Principal Investigator to obtain consent. The Investigator is responsible for ensuring that the study consent procedures comply with current applicable GCP Regulatory and ethical requirements. Informed consent discussions and outcomes must be well documented in the medical record. The Investigator must be satisfied that the patient has made an informed decision before taking consent.

15.2 Completion of the Informed Consent Form (ICF)

The Informed Consent Form will usually be offered to participants in clinic as an electronic form on a tablet device (with the consent form being filled in directly on the study database, REDCap.) Where it is not possible for a consent form to be completed in clinic (for example, if a participant has only had telephone appointments), remote electronic consent may be used.

A copy of the fully signed ICF will be given to the participant; where electronic consent is used and the participant has an email address they are willing to provide, an electronic version of the signed ICF will be automatically emailed to them. If the participant does not have/does not provide an email address the local study team will be able to print a copy of the signed ICF and provide this to the participant. Consent forms will be e-mailed securely to the participant. The electronic signed consent form will be held securely in the study database. A copy will be downloaded from the study database and should be placed in the participant's medical record.

Remote eConsent (using REDCap) will be obtained in accordance with OCTRU's standard operating procedures for obtaining consent. Where remote consent will be used, potential participants will be asked to provide an e-mail address for receiving consent documents prior to obtaining written informed consent. Potential participants will receive a unique link via e-mail to an electronic consent form which may then be completed remotely, once completed this form will be sent, via e-mail, to the participant as a PDF document. A member of the local study team will be required to countersign all consent forms completed remotely, in the same way as for paper forms and verify the identity of the participant. Participants that do consent to study participation will receive a copy of the fully completed consent form via e-mail once this has been countersigned.

15.3 GP notification

Participants will be made aware as part of the informed consent process that if they consent to take part in the study their GP will be informed of their participation in the study. Explicit consent will be obtained from the participant for this and an approved GP letter will be sent by the local centre to the participant's GP informing them of their participation in the study together with study information.

15.4 Re-consenting

Should there be any subsequent amendment to the final protocol, which might affect a participant's participation in the study, continuing consent will be obtained using an amended consent form which will be signed by the participant.

15.5 Participants who lose capacity during the study

Participants that lose capacity during the study will be withdrawn from the study.

16 RANDOMISATION AND BLINDING

16.1 Timing of randomisation

Participants will be randomised once informed consent has been given, eligibility for participation has been confirmed and baseline questionnaires have been completed.

16.2 Randomisation procedure

Participants will be randomised by the local study team via a centralised validated computer randomisation program through a secure (encrypted) web-based service, RRAMP (https://rramp.octru.ox.ac.uk), provided by the Oxford Clinical Trials Research Unit (OCTRU), accessed via the SARONG REDCap study database.

Participants will be randomised in a 1:1 ratio to one of the following treatment arms:

Arm	Details
Follow-up with intensive surveillance (intervention arm)	Intensive surveillance (including radiological (CT) scans) every 6 months for 36 months and endoscopy at 12 months post-randomisation
Usual care follow-up (control arm)	Standard of care follow-up for 36 months

Upon randomisation of a participant the OCTRU SARONG study office and a member of the site research team will be notified by an automated email.

Full details of the randomisation procedure will be stored in the Randomisation and Blinding Plan in the confidential statistical section of the Trial Master File (TMF).

16.3 Randomisation methodology

Consenting participants will be allocated randomly (1:1) to either the intensive surveillance arm or standard of care.

Randomisation will be performed using a minimisation algorithm to ensure balance between the two treatment groups using stratification factors:

- Recruiting centre

- Age (<50 years, 50-70 years, >70 years)
- Pathological TNM Stage (I & II, III & IV)

The first few participants will be randomised using a simple randomisation schedule, prepared by the trial statistician, to seed the minimisation algorithm, and a non-deterministic probabilistic element will be included to prevent predictability of treatment allocation. The randomisation schedule will be designed by the OCTRU study statistician.

16.3.1 Justification for stratification factors

Patient age and pathological TNM stages are potential confounding factors affecting overall survival (primary outcome of the study), and thus are included within the minimisation algorithm.

16.4 Back-up randomisation procedure

As randomisation is not time-critical there is no back-up randomisation procedure.

17 STUDY ASSESSMENTS/PROCEDURES

The study flow chart can be found in Appendix 1 of this protocol.

Endoscopy and CT scans require hospital attendance, however other assessments could be undertaken electronically/over the telephone.

17.1 Overview

The below table shows scheduled assessments including sampling for the study. Please refer to the Data Management and Sharing plan for more details of clinical visit windows and questionnaire distribution.

PROCEDURE	BASELINE	RANDOMISATION	POST-RANDOMISATION					
	After surgery within 12 weeks		6 Months	12 months	18 months	24 months	30 months	36 months
All Participants								
Screening/check eligibility	X							
Informed consent & confirm eligibility	X							
Baseline data collection	X							
HRQoL questionnaires (EQ-5D-5L, EORTC QLQ-C30, EORTC QLQ-OG25, CWS)	X		X	X	X	X	X	X
Healthcare Resource Use Questionnaire	X		X	X	X	X	X	X
Outcome data collection			X	X	X	X	X	X
Control group (usual care)								
Clinic visit or telephone call[$]	X		X	X				
Intervention group (intensive surveillance)								
Clinic visit or telephone call	X		X	X	X	X	X	X
Endoscopy +/- biopsy^				X				
CT scan			X	X	X	X	X	X

^ Biopsies will be performed according to each hospital's standard practice where an abnormality is visualised.

[$]After 12 months participant will follow standard of care in local centre, either discharge to primary care physician or continued clinical follow-up. Patients in this group will be evaluated for trigger symptoms (described above) in this group.

17.2 Data Collection

17.2.1 Baseline (within 12 weeks postoperatively) data collection

Sourced/collected by local study team *Completed at hospital by local study team member from medical notes or with participant*	**Direct patient report**
• Participant demographics • Blood test results • Clinical staging results including CT findings before surgery • Neoadjuvant therapy utilised • Surgery performed and postoperative complications • Intended adjuvant therapy • Postoperative complications • Pathological staging of cancer	• Health-related quality of life questionnaires* ○ EQ-5D-5L (unmodified) ○ EORTC QLQ-C30 ○ EORTC QLQ-OG25 ○ Cancer Worry Scale (CWS) • Healthcare Resource use questionnaire

*QoL questionnaires will be completed prior to randomisation.

17.2.2 Follow-up assessments/subsequent visits

6, 12, 18, 24, 30 and 36 months post-randomisation

Sourced/collected by local study team *Completed at hospital by local study team member from medical notes or with participant*	**Direct patient report**
• Blood test results • CT-scan results (intervention arm only) • Further radiological or endoscopic investigations • Reason for further investigation (both arms) • Locoregional or distant tumour recurrence • Date of mortality and cause of mortality • Treatment of tumour recurrence • Endoscopy results (Intervention arm only) # • Resource use in secondary care # collected at 12 month time-point only	• Health-related quality of life questionnaires ○ EQ-5D-5L (unmodified) ○ EORTC QLQ-C30 ○ EORTC QLQ-OG25 ○ CWS • Healthcare Resource use questionnaire

Questionnaire administration

Questionnaires will be sent at the time points specified above and according to the schedule set out in the Data Management Plan, and with 2 follow up reminders. For participants who have failed to return questionnaires, the central research team will check their clinical status with the local study team and then attempt to obtain the data over the telephone using the relevant script for that questionnaire, detailed below. Participants with limited English who are unable to complete these

over the telephone may be offered additional electronic or postal forms, to complete at home to allow them to access their support networks directly.

EQ-5D-5L: The self-complete version for use in REDCap will be used for participants completing the questionnaire electronically. The self-complete version on paper may also be used. Where participants have failed to return questionnaires, the central research team will check their clinical status with the local study team and then attempt to obtain the data over the telephone using the EQ-5D-5L telephone interviews scripts.

Where necessary, permission for use of all validated questionnaires used in this study have been obtained.

Self-reported Healthcare Resource Use Questionnaire: The Healthcare Resource Use Questionnaire in REDCap will be used for participants completing the questionnaire electronically. The Healthcare Resource Use Questionnaire on paper may also be used. Where participants have failed to return questionnaires, the central research team will check their clinical status with the local study team and then attempt to obtain the data over the telephone.

17.2.3 Endoscopy (intervention/active surveillance arm only)

Participants randomised to the intervention arm (intensive surveillance) will have an upper GI endoscopy with or without biopsy at 12 months post-randomisation. Biopsies will be performed if an abnormality is visualised according to each hospital's standard practice, and as per standard of care pathway.

17.2.4 CT scans (intervention/active surveillance arm only)

Participants randomised to the intervention arm (intensive surveillance) will have a chest, abdomen and pelvis CT scan performed every 6 months for 36 months post-randomisation.

17.2.5 Further endoscopic/radiological investigation – both arms

Participants randomised to either arm will undergo further endoscopic or radiological investigation for cancer recurrence if they report any of the following symptoms during clinical review either within the study or outside of the study as part of normal clinical practice:

- dysphagia to solid food
- dysphagia to liquids
- vomiting
- abdominal pain
- chest pain
- regurgitation of foods
- unexpected weight loss
- progressive hoarseness of voice.

17.3 Withdrawal of Participants

17.3.1 Withdrawal of consent by the participant

Withdrawal of consent means that a participant has expressed a wish to withdraw from the study altogether, or from certain aspects of the study only. The type of withdrawal will be collected on the Withdrawal CRF.

Participants may also be withdrawn from the study (or aspects of the study) by their clinician if they believe the participant needs to be withdrawn.

The Withdrawal CRF should be completed to document the reasons for withdrawal, and state who made the decision to withdraw. Discussions and decisions regarding withdrawal should be documented in the participant's medical notes. Investigators should continue to follow-up any SAEs and should continue to report any SAEs to resolution in the CRF in accordance with the safety reporting section.

Where a participant expresses a wish to withdraw from the study, the study team will determine which aspect(s) of the study the participant wishes to withdraw from; all other aspects of the study/follow-up will be continued. The local study team should discuss with the patient if they accept subsequent data (including routine care data) to be collected as part of the study. This data as a minimum would be data from medical records, ONS and NOGCA for the analysis of mortality as the primary outcome of the trial.

The aspects of the study that the participant may request to withdraw from are as follows:

- No longer willing to receive study intervention
    - participants would have no more CT scans than standard of care, but would continue active follow-up to complete the study questionnaires and allow continued collection of data from medical records that is recorded as part of routine standard care).
- No longer willing to complete study questionnaires
    - this refers to the health-related quality of life questionnaires and Healthcare Resource Use questionnaires sent directly to participants by the study office
- No longer willing to have standard of care data from the medical record provided to the study
- No longer willing for standard of care data from Health data providers e.g. NHS digital, to be provided to the study
    - this refers to data from ONS and NOGCA

Data collected up to the point of withdrawal will be used in the study analysis, or beyond depending on the specific type of withdrawal described above.

17.4 Communication with trial participants by the central trial team

Participants will be notified to completed study questionnaires by e-mail, or where they have selected to receive postal questionnaires these will be posted to the participant. Participants will receive an initial e-mail and up to two reminder messages. Participants that do not complete their study questionnaires may be telephoned by a member of the central study team to collect outcome data.

18 SAFETY REPORTING

The study will be run in accordance with OCTRU's Standard Operating Procedures (SOPs) and operational policies, which all adhere to applicable UK regulatory requirements.

An independent Data and Safety Monitoring Committee (DSMC) and Trial Steering Committee (TSC) will be appointed. The DSMC will monitor data arising from the trial, review confidential interim reports of accumulating data, and recommend whether there are any ethical or safety reasons why the trial should not continue. The TSC will monitor the trial's progress and will provide independent advice. Both committees will comprise independent clinicians, statisticians, health service researchers

and patient representatives. Additionally, the study may be monitored, or audited by sponsor or host sites in accordance with the current approved protocol, GCP, relevant regulations and standard operating procedures.

18.1 Definitions

18.1.1 Safety reporting period

Safety reporting will begin from randomisation and will end when the participant has reached their main follow-up time point at 36 months post-randomisation.

18.1.2 Adverse Event (AE)

An adverse event is any untoward medical occurrence in a clinical study participant.

Note: An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom or disease temporarily associated with the trial procedures, whether or not considered related to the procedures.

18.1.3 Serious Adverse Event (SAE)

A serious adverse event is any untoward medical occurrence that:

- results in death
- is life-threatening
- requires inpatient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability/incapacity
- may have caused a congenital anomaly/birth defect

Other 'important medical events' may also be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardise the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.

Note: The term "life-threatening" in the definition of "serious" refers to an event in which the participant 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.

18.2 Reporting Procedures

It is important to consider the natural history of oesophago-gastric cancer affecting each participant enrolled, the expected sequelae of the illness, and the relevance of these complications to the study treatment. All eligible participants have a poor prognosis, and due to the complexity of their condition are at increased risk of experiencing multiple adverse events. Consequently, only Serious Adverse Events (SAE) will be recorded in this study. This is limited to serious adverse events, which might reasonably occur as a consequence of the study surveillance (i.e. not events that are part of the natural history of the primary disease process or expected complications of oesophagogastric cancer).

SAEs, as defined above (and unless excluding from reporting – see below), experienced by a participant from randomisation until their completion of the study must be reported in the participant's medical notes, on the study CRFs, and reported to the CTU using the SAE Reporting Form, within 24 hours of observing or learning of the SAE(s). The SAE form will be kept on REDCap to enable direct data entry. All sections of the SAE Reporting Form must be completed. The CTU is automatically notified of the SAE report through the database. A paper SAE form should be used as a back-up if the SAE form is not available electronically.

18.3 Review of SAEs by the Sponsor/CTU Nominated Person

An appropriately qualified person will review the SAE and raise any queries with the reporting site. If the site has not provided an assessment of causality and has not responded to the query, it will be assumed that the event reported is related to the study procedures/intervention. The site will be encouraged to respond and if a response is not provided the CI will be consulted by the CTU and the CTU will complete the Sponsor part of the SAE report.

A SAE occurring to a participant will be reported to the Research Ethics Committee (REC) that gave a favourable opinion of the study where in the opinion of the Chief Investigator the event was 'related' (resulted from administration of any of the research procedures) and 'unexpected' in relation to those procedures. Reports of related and unexpected SAEs should be submitted within 15 working days of the Chief Investigator becoming aware of the event, using the Health Research Authority (HRA) report of serious adverse event form.

18.3.1 Events exempt from being reported as SAEs

The following hospitalisations are not considered a SAE:

- a visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered an important medical or life-threatening event)
- admissions as per protocol for a planned medical/surgical procedure
- admissions for planned chemotherapy and/or radiotherapy and any related sequelae
- routine health assessment requiring admission for baseline/trending of health status (e.g. routine colonoscopy)
- medical/surgical admission other than to remedy ill health and planned prior to entry into the study
- admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (e.g., lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason)
- admission for administration of anticancer therapy in the absence of any other SAEs (applies to oncology protocols)
- non-surgical sequelae which can result from any operative procedure or a diagnosis of malignancy (for example, but not limited to: pneumonia, urinary tract infection, pulmonary embolism, deep vein thrombosis)
- unplanned admissions resulting from pre-existing co-morbidities recorded at baseline

18.4 Death during the study

Death due to disease under study is to be recorded on the Death CRF form providing the death is not unexpected or if a causal relationship with the study intervention is suspected. The investigator must clearly state whether the death was expected or unexpected and whether a causal relationship to the study intervention is suspected.

18.5 Elective admissions and supportive care

Elective admissions to hospital for patient convenience or for planned procedures or investigations or treatment as specified in this protocol and standard supportive care are not SAEs, and do not require SAE reporting.

19 PREGNANCY

Pregnancy testing is carried out as appropriate, as part of NHS Standard of Care prior to radiological scans. In the event a patient becomes pregnant within the study they will be withdrawn from the intervention (if applicable) and follow their standard clinical care. Patients will be offered the option of withdrawal from all active follow-up i.e. completion of questionnaires but allow continued collection of data from medical records that is recorded as part of routine standard care. This will allow them to be followed up by site until the end of the pregnancy.

20 STATISTICAL CONSIDERATIONS

20.1 Statistical Analysis Plan (SAP)

The statistical aspects of the study are summarised here with details fully described in a statistical analysis plan that will be drafted early in the trial and finalised prior to the final data lock. The SAP will be written by the Trial Statistician in accordance with the current OCTRU SOPs. The TSC and DSMC will review and, if necessary, provide input on the SAP.

A summary of the planned statistical analysis is included within this section.

20.2 Sample Size/Power calculations

We aim to recruit 952 participants over 32 months from at least 24 NHS centres. Data from the ENSURE study [15] indicated all-cause mortality rates in the standard-of-care arm of 55% at 3-years. Based on discussions with clinicians and patient representatives, a 10% absolute improvement in overall survival would be clinically meaningful to patients and would lead to change clinical practice. An absolute improvement in survival of 10% was also used in the recent CROSS and Neo-AEGIS trials [5,25]. The sample size calculations were based on a comparison of the survivor functions in the two groups using a two-sided log-rank test. The sample size was calculated based on statistical power of 90%, two-sided alpha=0.05 with a 3-year recruitment period and 3-year follow-up period and an expected all-cause 3-year mortality in the control group of 55% and an assumed improvement to 45% in the intervention group. This correspond to a hazard ratio of 0.749, assuming hazard rates are proportional. Allowing for a 10% loss to follow-up based upon average estimates from MAGIC and OEO2 trials in the UK [26, 27], 952 patients would need to be recruited to this trial, with approximately 273 all-cause mortality events occurring in the control arm and 229 events in the intervention arm.

Since the proposed translational sub-studies are intended to be hypothesis generating, no formal sample size calculations have been performed.

20.3 Choice of primary outcome/justification for the follow-up period

Following oesophageal and gastric cancer surgery, approximately 90% of cancer recurrences will occur in the first 3 years post surgery, with an often poor survival due to late presentation [15, 28, 29]. Thus the follow-up period of 3-years has been chosen to establish the value of intensive surveillance in detecting the vast majority of cancer recurrences at an earlier and potentially treatable stage.

20.4 Description of Statistical Methods

Results will be reported in line with the CONSORT statement.

All analyses will be carried out on the intention-to-treat population (i.e. all patients will be analysed in the group that they were randomised to regardless of the actual treatment received). It is not anticipated there will be any protocol deviations, however, in the event that any occur, we will

repeat the primary analysis for the per protocol population (patients excluded from the per-protocol population will be pre-specified in the SAP).

Standard descriptive statistics will be used to describe the demographics between the two follow-up regimens; reporting means and standard deviations or medians and inter-quartiles ranges as appropriate for continuous variables and numbers and percentages for binary and categorical variables. All comparative outcomes will be presented as summary statistics and reported together with 95% confidence intervals. All tests will be carried out at a 5% significance level.

It is anticipated that all statistical analysis will be undertaken using Stata (StataCorp LP, www.stata.com) or other well validated statistical software.

Primary outcome

The primary outcome is overall survival. An event is defined as death from any cause. Participants who have not died during the trial will have their survival time censored at their last known alive date. This includes participants who withdraw from the trial.

The primary outcome will be analysed using time-to-event methodology. Cox Proportional Hazards models will be used adjusting for minimisation factors (centre, age and pathological TNM stage). The hazard ratio and 95% confidence intervals will be reported. The assumption of proportional [11] hazards will be examined and if proportional hazards are not present alternative methods will be considered. Supplementary analysis will additionally adjust for other important prognostic factors, which will be pre-specified in the SAP. Kaplan Meier survival curves will be presented graphically and unadjusted log-rank tests will be undertaken for completeness. Disease specific survival and locoregional or distant tumour recurrence will be analysed using the same time-to-event techniques as for the primary outcome. HRQol outcome measures (EORTC QLQ-C30 and QLQ-OG25 and CWS) will be compared between intervention arms as the dependent variable in a mixed-effects linear regression model with adjustment for the corresponding baseline score and the stratification factors. A random effect will be included to account for any heterogeneity is the response due to recruitment centre and fixed effects will be included to adjust for age and TNM stage, timepoint and a time-by-intervention interaction which will be included to take account of the repeated measures nature of the outcomes.

20.5 Inclusion in analysis

All randomised participants will be included in the primary intention-to-treat population and they will be analysed as randomised regardless of intervention received.

A per protocol population will be defined in the statistical analysis plan and will be analysed to provide supplementary evidence in support of the primary analysis.

20.6 Subgroup analysis

Subgroup analyses of patients by pathological tumour stage will be undertaken to understand the potential difference in outcomes seen with surveillance in more advanced tumour stages.

20.7 Interim analyses

Given the nature of the primary outcome and the planned study length, no formal comparative interim analyses are planned. However, accumulating data will be reviewed regularly by the Data

Safety and Monitoring Committee (DSMC), including reviewing data by treatment arm and patient safety.

20.8 Stopping Rules

There are no formal stopping rules planned.

20.9 Level of Statistical Significance

5% significance will be used throughout and differences between the intervention arms will be reported using 95% confidence intervals.

20.10 Procedure for accounting for missing, unused and spurious data

The procedure for handling spurious or missing data will be described in the SAP. The trial will attempt to collect data as completely as possible. There will be no missing data for the primary outcome as patients who have not died will be censored at their last known alive date and therefore included in the analysis.

20.11 Procedures for reporting any deviation(s) from the original statistical analysis plan

Any changes or deviation from the original SAP will be described and justified in the final report and/or publications, as appropriate.

20.12 Health economics analysis

A cost-effectiveness analysis will be conducted by the health economists at the University of Oxford.

We will conduct a within trial cost-utility analysis to assess the cost-effectiveness of implementing an intensive structured follow-up after oncological treatment compared with current practice. As described above, the structured follow-up includes clinical reviews, CT scans and endoscopy for up to 36 months whereas current practice consists of clinical symptomatic follow-up.

We will use an NHS and Personal Social Services perspective for the base-case analysis and a societal perspective will be presented in the sensitivity analysis [30,31]. The primary outcome measure used in the health economics study will be the incremental cost per QALY. We will follow good practice guidelines when undertaking the economic evaluation analysis [30-32].

Data on resource use will be collected for healthcare (primary care appointments, prescribed and over the counter medications, hospital admissions, contact with healthcare professionals) and non-healthcare resource use (social and informal care, and time off work) of patients undergoing the two arms of trial. The questionnaire will be administered at baseline (4-8 weeks after surgery), 6, 12, 18, 24, 30 and 36-months post-randomisation. The resources used will be valued using national cost databases such as NHS Reference costs and Prescription Cost Analysis.

The EQ-5D-5L instrument [33] will be used to measure HRQoL at baseline (4-8 weeks after surgery), 6, 12, 18, 24, 30 and 36-months post-randomisation. The EQ-5D-5L instrument will be valued using NICE recommendations at the time of the analysis, either using a UK value set or converted into the EQ-5D-3L using a cross-mapping algorithm [34] and valued using the UK set for EQ-5D-3L [35]. QALYs will be calculated using the area under the curve approach, which involves estimating the average EQ-5D utility between each follow-up time, and weighting it by survival time. We will report descriptive statistics (means, SD as a minimum) for healthcare resource use, costs, and EQ-5D utilities at each follow-up time point.

We will test for baseline difference in healthcare resource use and utilities between the trial arms and if required adjust for these differences using the most appropriate recommended method [36]. All costs and effects will be discounted at 3.5% following NICE guidelines.

We will follow best practice methods for addressing missing data in cost-effectiveness studies [37]. Missing data on participant characteristics at baseline will be imputed following guidelines. Incremental cost effectiveness ratio (ICER; cost per QALY) will be estimated by dividing the difference in costs by the difference in QALYs of the two treatments under analysis and will be depicted on the cost-effectiveness plane. The ICER will be compared against the threshold used to establish value for money in the NHS (currently in the region of £20,000 to £30,000 per QALY) [30]. We will estimate the joint uncertainty around incremental costs and QALYs and in cost-effectiveness using a bootstrapping approach take accounts for the imputed data. From these bootstrapped results, we will calculate the probability that the intensive structured follow-up for up to 3 years after oncological treatment is more cost-effective than the current practice led by clinical symptomatic follow-up for different threshold values per QALY gained [38]. These will be calculated by estimating the proportion of bootstrap replicates with a net monetary benefit (NMB) above 0 for each threshold value, where the NMB is given by the product of the mean difference in QALYs and the threshold value minus the mean difference in costs.

The robustness of results will be evaluated in a sensitivity analysis.

20.13 Internal pilot/Decision Points

An internal pilot phase to assess the feasibility of recruitment will be conducted after 9 months of recruitment. This timepoint was chosen to ensure that a minimum of 9 centres are open to recruitment and at least 2 participants/centre/month are being recruited. Recruitment is expected to last for 32 months, however there will be a formal review after the internal pilot phase. Stop-go criteria for this pilot phase are given in table 1 together with the progression guidance.

Table 1: Stop-go criteria for internal pilot phase

Progression guidance	Participants recruited	Centres recruiting
Continue with study – no action required	>108 participants	≥9 centres open
Continue with study – action required: • Review recruitment strategies* and modify/ monitor closely • Report to TSC	66-108 participants	6-8 centres open
Stop	<66 participants	<6 centres open

* Consider extending study to other countries including; Sweden, Denmark, Norway and Finland, as agreement and funding in place for study in Scandinavia. These countries have agreed to participate at any point if recruitment is a challenge within the SARONG study; funding for recruitment in Scandinavian countries has already been obtained.

The Trial Management Group (TMG) will closely monitor the progression criteria during the internal pilot, and together with the Trial Steering Committee (TSC) and Data and Safety Monitoring Committee (DSMC) will perform a full review towards the end of the internal pilot. The TSC and funder will make the final decision to terminate the study.

The internal pilot trial will mirror the procedures and logistics undertaken in the main definitive trial. Data from the internal pilot trial will contribute to the final analysis.

Should a decision be made to stop the trial all trial participants will be followed up per protocol. It is intended that the trial will progress seamlessly from the internal pilot phase to the main recruitment phase.

21 DATA MANGEMENT

The data management aspects of the study are summarised here with details fully described in the Data Management Plan. See section on patient confidentiality for information on management of personal data.

21.1 Source Data

Source documents are where data are first recorded, and from which participants' CRF data are obtained. These include, but are not limited to, hospital records, laboratory records, participant, patient-reported outcome measures that are submitted directly to the coordinating centre and correspondence. The SARONG study will validate data concerning mortality against the NOGCA and ONS datasets every 6 months for the duration of follow-up beginning 12 months after recruitment begins. This data will be sent directly to the trial statistician for validation processes.

21.2 Location of source data

Sections 9.2 and 9.3 outlines the source data for the trial.

21.3 Case report forms (CRFs)

The Investigator and study site team will ensure that data collected on each participant is recorded in the CRF as accurately and completely as possible. Details of all protocol evaluations and investigations must be recorded in the participant's medical record for extraction onto the CRF. All appropriate laboratory data, summary reports and Investigator observations will be transcribed into the CRFs from the relevant source data held in the site medical record(s).

All documents will be stored safely in confidential conditions. On all study-specific documents, other than the signed consent, the participant will be referred to by the study participant number/code, not by name.

CRF entries will be considered source data if the CRF is the site of the original recording (e.g. there is no other written or electronic record of data).

21.4 Non-CRF data

All study data will be recorded on the CRFs. Imaging data will be stored in the Oxford University NHS Foundation Trust Secure Data Environment (OUH NHSFT SDE) server for radiology quality assurance processes described below.

21.5 Access to Data

To ensure compliance with regulations, direct access will be granted to authorised representatives from the Sponsor and host institution to permit study-related monitoring and audits. The data submitted by study participants directly via the clinical database (i.e. electronic patient reported outcomes) will also be made available to the participating centre; this is detailed within the PIS so that participants are aware of who will have access to this data.

21.6 Data Recording and Record Keeping

The CRFs will be designed by members of the study management team which will include the Chief Investigator, study statisticians and study manager.

Data will, wherever possible, be collected in electronic format with direct entry onto the study database by local study team or participants. Electronic data collection has the major advantage of building "data logic" into forms, minimising missing data, data input errors and ensuring the completeness of consent and assent forms. REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies, providing 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources.

All data entered directly onto the server. All electronic patient-identifiable information, including electronic consent forms, will be held on a server located in an access-controlled server room at the University of Oxford. The data will be entered into a GCP compliant data collection system and stored in a database on the secure server, accessible only to members of the research team based on their role within the study. The database and server are backed up to a secure location on a regular basis.

Personal identifiable data will be kept separately from the outcome data obtained from/about the participants (both paper and electronic). Participants will be identified by a study ID only.

Direct access to source data/documents will be required for study-related monitoring and/or audit by the Sponsor, research team or NHS Trust as required.

Personal identifiable data will be destroyed as soon as it is no longer required – the time point for destruction is detailed in the study data management plan and is in accordance with OCTRU standard operating procedures which comply with the UK GDPR Data from paper questionnaires or captured during phone calls to participants will be entered into the study database by suitably trained central office or local study team. Full details will be recorded in the Data Management Plan. The participants will be identified by a unique study specific number in any data extract. Identifiable data will only be accessible by members of the study team with a demonstrated need (managed via access controls within the application) and only used to communicate with the participant (e.g. sending follow-up reminders for online form completion or telephone follow-up).

22 QUALITY ASSURANCE PROCEDURES

A rigorous programme of quality control will be implemented. The trial management group will be responsible for ensuring adherence to the study protocols at the study centres. Quality assurance (QA) checks will be undertaken by OCTRU to ensure integrity of randomisation, study entry procedures and data collection. The OCTRU has a QA team who will monitor this study by conducting audits (at least once in the lifetime of the trial, more if deemed necessary) of the Trial Master File and compliance with requirements in OCTRU SOPs. Furthermore, the processes of obtaining consent, randomisation, registration, provision of information and provision of treatment will be monitored by the study unit staff. Written reports will be produced for any oversight committees as applicable, informing them if any corrective action is required. Additionally, the study may be monitored, or audited by sponsor or host sites in accordance with the current approved protocol, GCP, relevant regulations and standard operating procedures.

A study-specific data management and monitoring plan will be in place prior to the start of the study.

22.1 Risk Assessment

This protocol is designed to deliver a risk-adapted approach to conducting the study. A risk assessment has been conducted and a monitoring plan will be prepared before the trial opens. The known and potential risks and benefits to participants have been assessed in comparison to those of standard of care. A risk management strategy is in place and will be reviewed and updated as necessary throughout the trial or in response to outcomes from monitoring activities. Monitoring plans will be amended as appropriate.

22.2 Study monitoring

Monitoring will be performed by the central study team according to a study-specific monitoring plan. Data will be evaluated for compliance with the protocol, completeness and accuracy according to a study-specific data management plan. The investigator and institutions involved in the study will permit study-related monitoring and provide direct on-site access to all study records and facilities if required. They will provide adequate time and space for the completion of monitoring activities.

Study sites will be monitored centrally by checking incoming data for compliance with the protocol, consistency, completeness and timing. The case report data will be validated using appropriate set criteria, range and verification checks. The study site must resolve all data queries in a timely manner. All queries relating to key outcome and safety data and any requiring further clarification will be referred back to the study site for resolution.

Note: 'in a timely manner' means within no more than 7 working days of the data query unless otherwise specified.

Study sites will also be monitored remotely and/or by centre visit, as necessary, to ensure their proper conduct of the study. Study Office staff will be in regular contact with centre personnel to check on progress and deal with any queries that they may have. Any monitoring reports / data discrepancies will be sent to the site in a timely fashion. The Investigator is expected to action any points highlighted through monitoring and must ensure that corrective and preventative measures are put into place as necessary to achieve satisfactory compliance, within 28 days as a minimum, or sooner if the monitoring report requests.

22.3 Audit

All aspects of the study conduct may be subject to internal or external quality assurance audit to ensure compliance with the protocol, GCP requirements and other applicable regulation or standards. Such audits may occur at any time during or after the completion of the study. Investigators and their host Institution(s) should understand that it is necessary to allow auditors direct access to all relevant documents, study facilities and to allocate their time and the time of their staff to facilitate the audit visit.

22.4 Trial committees

22.4.1 Trial Management Group (TMG)

A Trial Management Group (TMG) will be established for the study and operate in accordance with a study-specific TMG charter. The TMG will manage the trial, including the clinical and practical aspects and will meet approximately monthly to assess progress. Other specialities/ individuals will be invited as required for specific items/issues.

22.4.2 Data and Safety Monitoring Committee (DSMC)

An independent Data & Safety Monitoring Committee (DSMC) will be established for this study. The DSMC will adopt a DAMOCLES based charter, which defines its terms of reference and operation in relation to the oversight of the study. The DSMC will meet regularly throughout the study at time-points agreed by the Chair of the Committee and the Chief Investigator. At a minimum this will be on an annual basis. The DSMC will review the safety data generated and make recommendations as to whether the protocol should be amended to protect patient safety. Recommendations of the DSMC will be discussed between the CI, TSC, and the Sponsor.

22.4.3 Trial Steering Committee (TSC)

The TSC, which includes independent members, provides overall supervision of the study on behalf of the funder. The TSC will act in accordance with a TSC charter which will outline its roles and responsibilities. Full details including names will be included in the TSC charter. Meetings of the TSC will take place at least once a year during the recruitment period. An outline of the remit of the TSC is to:

- Monitor and supervise the progress of the trial towards its interim and overall objectives
- Review at regular intervals relevant information from other sources
- Consider the recommendations of the DSMC
- Inform the funding body on the progress of the study

The TSC will consider, and act, as appropriate, upon the recommendations of the DSMC.

23 IDENTIFICATION AND MANAGEMENT OF PARTICIPATING CENTRES

23.1 Identification of recruitment centres

Recruitment centres will be selected based on suitability to conduct the study. Potential sites will be invited to complete a Site Feasibility Questionnaire (SFQ) which will be used by the Trial Management Group/Coordinating Centre to assess suitability of the site for the study; the suitability assessment will primarily be based on the resources available at site and the feasibility of meeting recruitment targets.

23.2 Study site responsibilities

The Principal Investigator (the PI or lead clinician for the study centre) has overall responsibility for conduct of the study but may delegate responsibility where appropriate to suitably experienced and trained members of the study site team. All members of the study site team must complete the delegation provided prior to undertaking any study duties. The PI must counter sign and date each entry in a timely manner, authorising staff to take on the delegated responsibilities.

23.3 Study site set up and activation

The Principal Investigator leading the investigational study site is responsible for providing all required core documentation. Mandatory site training which is organised by the study office (see below) must be completed before the site can be activated. The study office will check to confirm that the site has all the required study information/documentation and is ready to recruit. The site will then be notified once they are activated on the study database and are able to begin recruiting patients.

23.4 Training

Training in the study processes will be administered at site initiation visits (delivered face to face or online) by the central study team.

23.5 Study documentation

The study office will provide an electronic Investigator File to each investigational site containing the documents needed to initiate and conduct the study. The study office must review and approve any local changes made to any study documentation including patient information and consent forms prior to use. Additional documentation generated during the course of the study, including relevant communications must be retained in the site files as necessary to reconstruct the conduct of the study.

24 ETHICAL AND REGULATORY CONSIDERATIONS

24.1 Declaration of Helsinki

The Investigator will ensure that this trial is conducted in accordance with the principles of the Declaration of Helsinki.

24.2 Guidelines for Good Clinical Practice

The Investigator will ensure that this trial is conducted in accordance with relevant regulations and with Good Clinical Practice.

24.3 Ethical conduct of the study and ethical approvals

The protocol, patient information sheet, informed consent form and any other information that will be presented to potential study participants (e.g. advertisements or information that supports or supplements the informed consent process) will be reviewed and approved by an appropriately constituted, independent REC, HRA and host institution.

24.4 Public and Patient Involvement (PPI)

The SARONG patient co-investigator has been involved in the design of the study from the outset and is included as a co-applicant, and is a member of Action Against Heartburn, Action against Heartburn. The PPI co-applicant will lead the PPI advisory group and their input into the trial, and will sit on the Trial Management. Extensive feedback on this study has been sought from patient representatives, and key stakeholders from the clinical community. This trial was presented to Action for Heartburn charity, Heartburn Cancer UK, National Cancer Research Institute (NCRI) Oesophago-Gastric subgroup and GUTS charity UK, all of whom recognised merits in the proposed research and have provided additional letters of support. Patients taking part in the study will be informed of the findings via the study website and a wider dissemination strategy. Representatives from the Oesophageal Patient Association (OPA), Oxfordshire Oesophageal and Stomach Organisation (OOSO), Oesophageal and Gastric cancer patient support group in Guildford, Action against Heartburn, Heartburn Cancer UK and GUTS charity UK, will all be part of the trial PPI advisory group during the trial (please see PPI section for full details).

Patients taking part in the study will be informed of the findings via the study website and social media.

24.5 NHS Research Governance

Once HRA & HCRW approval is in place for the study, centres will confirm capability and capacity to participate in the study.

24.6 Protocol amendments

All amendments will be generated and managed according to the study office standard operating procedures to ensure compliance with applicable regulation and other requirements. Written confirmation of all applicable REC and local approvals must be in place prior to implementation by Investigators. The only exceptions are for changes necessary to eliminate an immediate hazard to study participants (see below).

It is the Investigator's responsibility to update patients (or their authorised representatives, if applicable) whenever new information (in nature or severity) becomes available that might affect the patient's willingness to continue in the trial. The Investigator must ensure this is documented in the patient's medical notes and the patient is re-consented if appropriate.

24.7 Protocol Compliance and Deviations

Protocol compliance is fundamental to GCP. Prospective, planned deviations or waivers to the protocol are not allowed. Changes to the approved protocol need prior approval unless for urgent safety reasons.

A study related deviation is a departure from the ethically approved study protocol or other study document or process (e.g. consent process) or from Good Clinical Practice (GCP or any applicable regulatory requirements. Deviations from the protocol will be captured within the study database either using a protocol deviation form or via suitably designed fields within the CRF which will be extracted from the study database and reviewed regularly by the TMG. Deviations will be handled and reviewed in a timely manner in accordance with a trial-specific Data Management and Monitoring Plans.

The Investigator must promptly report any important deviation from Good Clinical Practice or protocol to the study office. The TMG will adjudicate which are to be classified as important deviations. Examples of important deviations are those that might impact on patient safety, primary/ secondary endpoint data integrity, or be a possible serious breach of GCP (see serious breach 24.10 below).

24.8 Urgent safety measures

The Sponsor or Investigator may take appropriate urgent safety measures to protect study participants from any immediate hazard to their health or safety. Urgent safety measures may be taken without prior authorisation. The study may continue with the urgent safety measures in place. **The Investigator must inform the study office IMMEDIATELY if the study site initiates an urgent safety measure:**

The notification must include:

- Date of the urgent safety measure;
- Who took the decision; and
- Why the action was taken.

The Investigator will provide any other information that may be required to enable the study office to report and manage the urgent safety measure in accordance with the current regulatory and ethical requirements for expedited reporting and close out. The study office will follow written procedures to implement the changes accordingly.

24.9 Temporary halt

The Sponsor and Investigators reserve the right to place recruitment to this protocol on hold for short periods for administrative reasons **or** to declare a temporary halt. A temporary halt is defined a formal decision to:

- Interrupt the treatment of participants already in the study for safety reasons;
- Stop recruitment on safety grounds; or
- Stop recruitment for any other reason(s) considered to meet the substantial amendment criteria, including possible impact on the feasibility of completing the study in a timely manner.

The study office will report the temporary halt via an expedited substantial amendment procedure. The trial may not restart after a temporary halt until a further substantial amendment to re-open is in place. If it is decided not to restart the trial this will be reported as an early termination.

24.10 Serious Breaches

A "serious breach" is a breach of the protocol or of the conditions or principles of Good Clinical Practice which is likely to affect to a significant degree –

(a) The safety or physical or mental integrity of the trial subjects; or

(b) The scientific value of the research.

In the event that a serious breach is suspected the Sponsor must be contacted within 1 working day. In collaboration with the C.I., the serious breach will be reviewed by the Sponsor and, if appropriate, the Sponsor will report it to the approving REC and the relevant NHS host organisation.

24.11 Study Reports

This protocol will comply with all current applicable REC and Sponsor reporting requirements.

24.12 Transparency in Research

Prior to the recruitment of the first participant, the study will have been registered on a publicly accessible database (ISRCTN), which will be kept up to date during the study, and results will be uploaded to the registry within 12 months of the end of the study declaration. In addition, the lay summary from the final report will be published alongside the study research summaries on the HRA website.

24.13 Participant Confidentiality

The study will comply with UK General Data Protection Regulation (GDPR) and Data Protection Act 2018, which will require data to be de-identified as soon as it is practical to do so. Personal data on all documents will be regarded as confidential. The processing of the personal data of participants will be minimised by making use of a unique participant study number on all study documents and any electronic databases. All documents will be stored securely and only accessible by study staff and authorised personnel. The study staff will safeguard the privacy of participant's personal data. See section 21 for more details.

The patient's name and NHS/CHI number (where available) will be collected to allow the patient to be contacted or information about their health status to be obtained from NHS England and other central NHS registries for longer term follow beyond the study.

Participants who have indicated that they are willing to be approached for future studies for which they may be eligible, will have their consent forms retained in order that they may be approached in the future. The consent forms will be stored securely, whether as paper or electronic versions, and accessible only by study staff and authorised personnel.

The Investigator site must maintain the patient's anonymity in all communications and reports related to the research.

24.14 End of study

The end of study is the point at which all the data has been entered and all queries resolved in the REDCap database, and all laboratory outcomes have been analysed. The minimum time this will be is 3 years after the last patient is randomised plus time for entering and cleaning the data.

The Sponsor and the Chief Investigator reserve the right to terminate the study earlier at any time. In terminating the study, they must ensure that adequate consideration is given to the protection of the participants' best interests.

25 EXPENSES/PAYMENTS TO PARTICIPANTS

There is no study funding to reimburse participant expenses incurred for attending additional research visits in excess of standard of care.

PPI was extensively involved and did not feel that this needed to funded as part of the trial. This was discussed within workshops with Oxfordshire oesophageal and stomach patient organisation (OOSO).

26 SPONSORSHIP, FINANCE AND INSURANCE

26.1 Sponsorship

The Sponsor will provide written confirmation of Sponsorship.

26.2 Funding and support in kind

Funder(s)	Financial and non-financial support given
National Institute for Health Research – Health Technology Assessment	Reference Number: NIHR134344

26.3 Insurance

The University has a specialist insurance policy in place which would operate in the event of any participant suffering harm as a result of their involvement in the research (Newline Underwriting Management Ltd, at Lloyd's of London). NHS indemnity operates in respect of the clinical treatment that is provided.

27 CONTRACTUAL ARRANGEMENTS

Appropriate contractual arrangements will be put in place with all third parties.

This study is subject to the Sponsor's policy requiring that written contracts/agreements are agreed formally by the participating bodies as appropriate.

28 PUBLICATION AND DISSEMINATION

The Sponsor will retain ownership of all data arising from the study.

Publication and dissemination of study results and associated study publications (e.g. the study protocol, SAP, health economics analysis plan (HEAP) and secondary analyses) will be in accordance with the OCTRU Standard Operating Procedure and irrespective of study findings.

The study protocol will be published in an open-access peer-reviewed journal in accordance with the Standard Protocol Items: Recommendations for Interventional Trials statement (SPIRIT, www.spirit-statement.org/). The study results will be published in an open-access journal, in accordance with the NIHR's policy on open-access research. The study will be reported following the Consolidated Standards of Reporting Trials guideline (CONSORT) including any applicable extensions to this. The Template for Intervention Description and Replication (TIDieR) statement will be used for reporting the intervention.

28.1 Study results

All data will be presented such that no individual participants can be identified. Dissemination of results will include the following methods:

Conference: The results of this study will be disseminated to the clinical community via presentations at national and international meetings. Traditional conference dissemination will focus on presentations to include the key professional stakeholders. It is expected that findings from this project will be presented at national (National Cancer Research Institute (NCRI) and Association for Upper Gastrointestinal Surgeons for Great Britain and Ireland (AUGIS)) and international (United European Gastroenterology (UEG), International Society for Diseases of the Esophagus (ISDE) conferences, and ESMO) conferences.

Publications: Results will be published in peer-reviewed journals. Where possible, plain English summaries will be published alongside the full paper, along with links to other digital media on the study website to explain the study result in an accessible format – i.e. an explainer video and infographic.

Policy Makers: Given the potential involvement of over 24 sites in the UK, and the positions held by co-applicants and collaborators within the national and international oesophageal and gastric cancer community, the results will rapidly reach Multi-Disciplinary Teams, ensuring the trial findings improve practice and service delivery for oesophageal and gastric cancer patients within the NHS. Should intensive surveillance prove of significant benefit, it is anticipated that it will be integrated into the standard of care (NICE guidance) within the UK for patients with oesophageal or gastric cancer.

Public Dissemination: All participants will be asked informed at the time of recruitment that the trial results will be made available on the study website. The results summary for patient dissemination will be written collaboratively with clinicians and patient representatives. The trial website, Twitter or other social media etc. will be used to ensure the results of SARONG are communicated to the wider community once they are available.

The wider public will be alerted via links with relevant organisations/charities, and the Research Media Offices. Engagement with the NIHR Dissemination Centre will also be sought, to ensure global awareness of study findings. Moreover, the University of Oxford and Oxford University Hospitals

NHS Trust have professional communication officers. It is anticipated that together these individuals, and NIHR equivalents, we will agree upon effective communication strategies including co-ordinated press releases, interviews etc.

To ensure a broad campaign we will target a range of social media outlets (e.g. Twitter) with the explainer video and infographic. We will seek to engage the NHS Dissemination centre and seek to publish 'digital story' as part of the 'NIHR Signal'.

28.2 Implementation into National and International guidelines

Should intensive surveillance prove advantageous, it is expected that the NICE guidelines will be updated. Currently three quarters of all oesophago-gastric centres in the UK have agreed to participate in the trial, ensuring the results of this trial will confer a high degree of external validity within the UK. Nick Maynard and Tim Underwood (coinvestigators) are current president and research leads for the AUGIS, and are committed to producing a national guideline regarding surveillance after oesophago-gastric cancer treatment, which will be informed by the results of this study. Furthermore the European Society for Diseases of the Esophagus and the International Society for Diseases of the Esophagus have agreed to endorse and utilise the guidelines that will be developed following completion of this study.

28.3 Authorship

Authorship of any publications arising from the study will be determined in accordance with the ICMJE guidelines and any contributors acknowledged accordingly.

All publications arising from this trial must acknowledge the funder, OCTRU, SITU and the Sponsor.

29 DEVELOPMENT OF A NEW PRODUCT/PROCESS OR THE GENERATION OF INTELLECTIAL PROPERTY (IP)

Considering the objectives of the study, we do not believe that any patentable or commercialisable intellectual property will be generated. Outputs of the work will be disseminated as described (via publications, presentations) and impact felt (via altering standard care).

Ownership of IP generated by employees of the University vests in the University. The University will ensure appropriate arrangements are in place as regards any new IP arising from the study.

30 ARCHIVING

During the study and after study closure the Investigator must maintain adequate and accurate records to enable the conduct of a clinical study and the quality of the research data to be evaluated and verified. All essential documents must be stored in such a way that ensures that they are readily available, upon request for the minimum period required by national legislation or for longer if needed.

It is the University of Oxford's policy to store data for a minimum of 3 years. Investigators may not archive or destroy study essential documents without written instruction from the study office.

Study data and associated metadata will be retained electronically in a suitable format in a secure server area maintained and backed up to the required standard. Access will be restricted to the responsible Archivist and will be controlled by a formal access request. On completion of the minimum mandatory archiving period the TMF and associated archived data sets will be destroyed or transferred as appropriate, according to any data sharing requirements.

30.1 Sponsor Trial Master File

All paper and electronic data including the Trial Master File and study database will be archived in accordance with the OCTRU standard operating procedures and retained for at least 3 years after completion of the study.

30.2 Investigator Site File and participant medical records.

The Investigator Site Files will be archived at site. The medical files of study participants must be retained for at least 3 years and in accordance with the maximum period of time permitted by the participating site. Sites should comply with the documentation retention specified in the clinical trial agreements issued by the trial Sponsor.

31 REFERENCES

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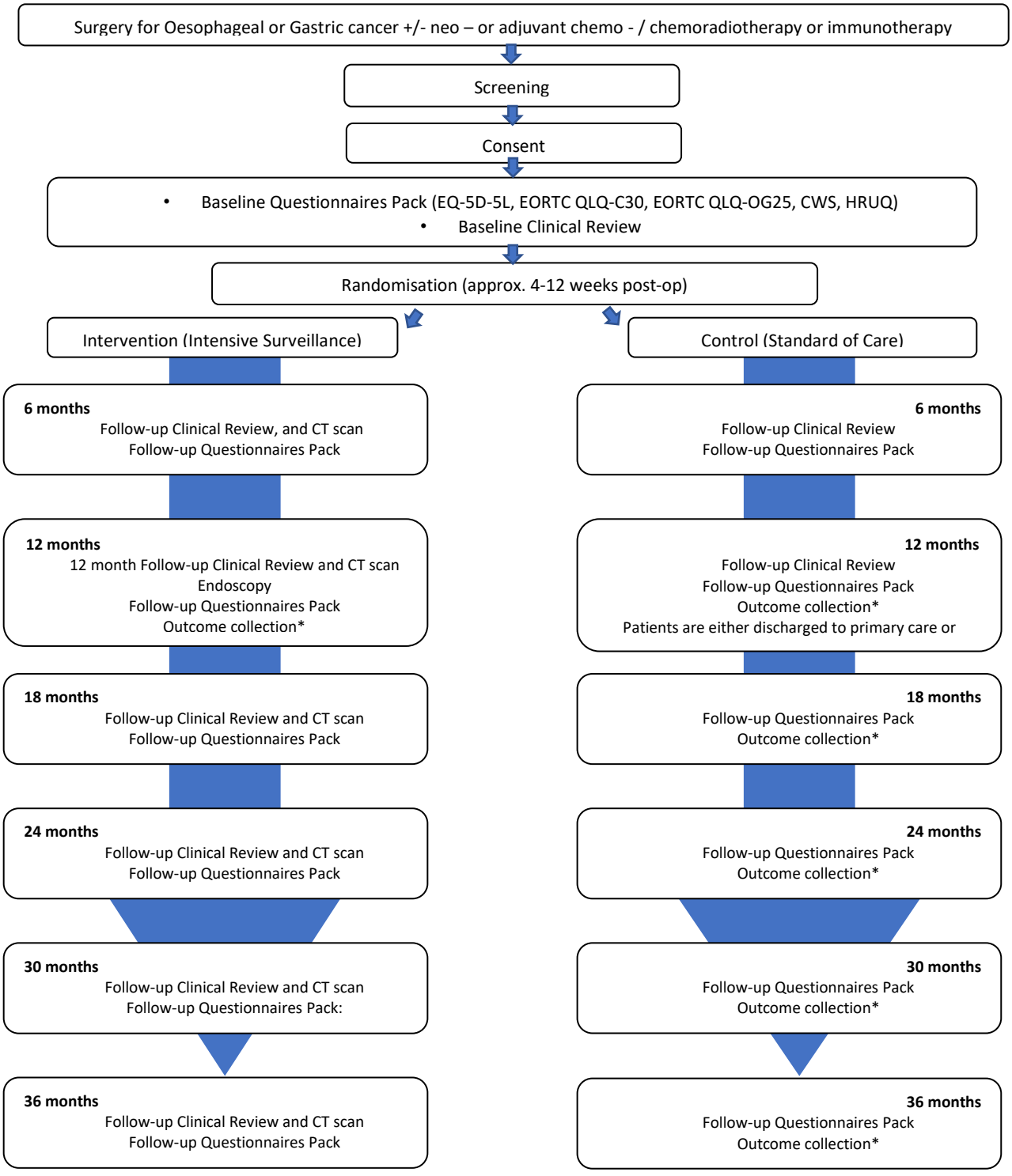
32 VERSION HISTORY

Previous versions of this protocol and a summary of the changes made are provided in the table below:

Protocol version no.	Protocol date	Summary of key changes from previous version
N/A		1st version of the protocol.
2.0	05Dec2023	The changes from the previous version are the following: - modification of timelines for screening, consent and randomisation - change of name of the Lead Statistician - clarification of consent documentation - correction of minor typographical errors

APPENDIX 1 – STUDY FLOW CHART



* Outcome collection (Completed by Sites):
All-cause mortality (Primary Outcome)
Disease-specific mortality (Secondary Outcome)
Pattern and treatment of recurrence (Locoregional, distant or mixed) (Secondary Outcome)
Detection of oligometastatic vs. multi-metastatic disease (Secondary Outcome)
Cost-effectiveness, resource use in secondary care (Secondary Outcome)

Follow-Up Questionnaires Pack:

EQ-5D-5L, EORTC QLQ-C30, EORTC QLQ-OG25, CWS, HRUQ