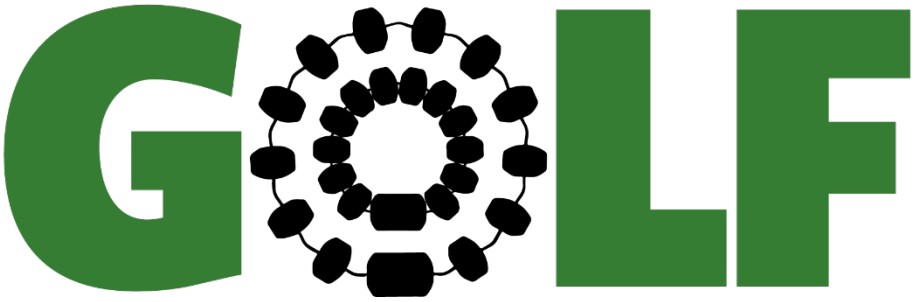
NUFFIELD DEPARTMENT OF SURGICAL SCIENCES

SITU
SURGICAL INTERVENTION TRIALS UNIT

CLINICAL STUDY PROTOCOL

This protocol has regard for the HRA guidance.



FULL STUDY TITLE: Double-blind randomised controlled trial for treatment of Gastro-Oesophageal reflux disease; LINX management system vs. Fundoplication

SHORT STUDY TITLE: LINX vs Fundoplication

STUDY ACRONYM: GOLF

Version: 3.0 10 April 2025

Study website: golftrial.org

UNIVERSITY OF OXFORD

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UKRI Medical Research Council
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1 RESEARCH REFERENCE NUMBERS

Sponsor Protocol Number:	PID17751
Funder Reference(s):	NIHR152268
Ethics Reference Number:	24/WA/0154
IRAS Number:	331404
Registry:	International Standard Randomised Controlled Trial Number (ISRCTN): insert ISRCTN number here
CPMS ID:	58022

2 ORGANISATIONAL INFORMATION

Chief Investigator (CI):	**Prof Sheraz R Markar** Associate Professor & Director of Surgical Interventional Trials Unit University of Oxford Refer to the KEY STUDY CONTACTS section for contact details.
Sponsor:	University of Oxford Refer to the KEY STUDY CONTACTS section for contact details.
Clinical Trials Unit:	The study is managed by Surgical Intervention Trials Unit (SITU) Botnar Research Centre University of Oxford Old Road Headington Oxford OX3 7LD situ@nds.ox.ac.uk
Funder:	The study is funded by the National Institute for Health and Care Research (NIHR). Refer to Funding and support in kind section for full details of all funding sources.
Co-applicants:	The following are co-applicants on the study grant and have contributed to the study design and development of the protocol: **Professor Jesper Lagergren (Joint Lead Applicant)** Professor in Upper Gastrointestinal Cancer and Lead of Programme in Gastrointestinal Cancer School of Cancer and Pharmaceutical Sciences King's College London jesper.lagergren@kcl.ac.uk

	Mr Ahmed Ahmed Senior Clinical Lecturer Department of Surgery and Cancer Imperial College London a.ahmed07@imperial.ac.uk **Professor Nick Maynard** Clinical lead for oesophagogastric surgery and President of AUGIS Oxford University Hospitals NHS Foundation Trust Nick.Maynard@ouh.nhs.uk **Mr James Gossage** Consultant in Upper Gastointestinal Surgery Guy's and St Thomas' NHS Foundation Trust James.Gossage@gstt.nhs.uk **Professor Natalie Blencowe** Linder Foundation Associate Professor in Clinical Trials University of Bristol Natalie.Blencowe@bristol.ac.uk **Dr Nicola Mills** Senior Research Fellow in Health Services Research Population Health Sciences University of Bristol nicola.mills@bristol.ac.uk **Dr Filipa Landeiro** Senior Researcher Health Economics Research Centre University of Oxford filipa.landeiro@dph.ox.ac.uk **Professor Jane Blazeby** Professor of Surgery Bristol Population Health Science Institute University of Bristol J.M.Blazeby@bristol.ac.uk **Mr T. Martyn Hill** Trial Statistician Surgical Interventional Trials Unit University of Oxford martyn.hill@nds.ox.ac.uk **Ms Amy Taylor** Trials Unit Operational Lead Surgical Interventional Trials Unit University of Oxford

	amy.taylor@nds.ox.ac.uk **Professor Tim Underwood** Professor of Gastrointestinal Surgery University of Southampton T.J.Underwood@soton.ac.uk **PATIENT AND PUBLIC CONTRIBUTORS** **PPI co-applicant** **Mrs Mimi McCord** Chairman, Trustee & Director Heartburn Cancer UK
Additional protocol contributors:	**Dr Begum Zeybek-Saglam** Trial Manager Surgical Interventional Trials Unit University of Oxford Contributed to protocol development and design of study procedures **Dr Nainika Menon** Clinical Research Fellow, University of Oxford nainika.menon@nhs.net
Conflict of Interest statement:	None of the co-applicants/protocol contributors listed above 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.

3 KEY STUDY CONTACTS

Study Office/Coordinating centre for general queries	**GOLF study team** Surgical Intervention Trials Unit (SITU) Botnar Research Centre University of Oxford Old Road Headington Oxford OX3 7LD +44 (0) 7584 039433 golf@nds.ox.ac.uk
Chief Investigator (CI)	**Professor Sheraz Markar** Director of Surgical Interventional Trials Unit Nuffield Department of Surgical Sciences University of Oxford +44 (0) 1865 235673

	sheraz.markar@nds.ox.ac.uk
Sponsor:	**University of Oxford** Research Governance, Ethics & Assurance Team (RGEA) Boundary Brook House Churchill Drive Headington Oxford OX3 7GB 01865 616480 RGEA.Sponsor@admin.ox.ac.uk
Lead Study Statistician	**Mr T. Martyn Hill** Surgical Intervention Trials Unit (SITU) Botnar Research Centre University of Oxford Old Road Headington Oxford OX3 7LD martyn.hill@nds.ox.ac.uk
Trial Steering Committee (TSC) Chair:	Professor Alex Phillips Consultant Oesophago-Gastric Surgeon Newcastle Hospitals NHS Foundation Trust awphillips@doctors.org.uk Other members of the TSC are detailed within a study specific TSC charter.
Data and Safety Monitoring Committee (DSMC) Chair:	Professor Marion Campbell Professor of Health Services, University of Aberdeen m.k.campbell@abdn.ac.uk Other members of the DSMC are detailed within a study specific DSMC charter.

4 PROTOCOL APPROVAL/SIGNATORIES

This protocol has been approved by the Sponsor, Chief Investigator and Lead Study Statistician. Approval of the protocol is documented in accordance with University of Oxford 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 GCP from the study as planned in this protocol will be explained.

5 LAY SUMMARY/PLAIN ENGLISH SUMMARY

Severe heartburn and regurgitation (reflux disease) is a common condition in which acidic juice from the stomach passes back into the gullet (oesophagus). It typically occurs due to weakening of the ring of muscle surrounding the bottom of the oesophagus (the lower oesophageal sphincter). Reflux disease can have a severe impact upon individuals' quality-of-life and lead to complications,

including ulceration and narrowing of the oesophagus. The most serious complication is a change in the inner lining (mucosa) of the oesophagus, called Barrett's oesophagus, that increases the risk of developing oesophageal cancer.

In most cases, reflux disease can be controlled with self-help measures and medication. However, there are instances in which surgery is recommended. The current best surgical treatment for reflux disease is called a fundoplication. This operation, which is carried out through keyhole (laparoscopic) surgery, tightens the lower oesophagus to prevent reflux. Fundoplication has an excellent safety profile and produces an improvement in the quality of life of most patients. However, many patients suffer from gas bloating, difficulty swallowing and a recurrence of their reflux symptoms after fundoplication.

As an alternative to fundoplication, some surgeons have started to use a device called LINX, through a similar keyhole procedure. LINX is a magnetic device that wraps around the lower part of the oesophagus to prevent reflux. Some studies suggest that LINX may cause fewer complications than fundoplication, with a similar improvement in quality-of-life. However, there is a need to generate more conclusive evidence to compare LINX with fundoplication in the surgical treatment of reflux disease.

In order to meet this need, we have designed a multi-centre study which aims to determine whether the LINX procedure achieves similar reflux control and improves symptoms when compared to fundoplication. We intend to measure (1) quality of life, (2) complications related to the operation, including the need for additional treatment, (3) the financial cost effectiveness and (4) measure the presence of acid that has refluxed into the lower oesophagus.

The study aims to include 460 patients who will be randomly allocated to receive either fundoplication or the insertion of the LINX device. This study will be conducted across at least 16 UK and 7 other European large specialist surgical centres. Patients participating in the study will be followed up at regular intervals (6 weeks, 6 months, 12 months and 24 months) to assess which treatment option offers the best results over time after treatment. We will implement a quality assurance programme within participating study centres to ensure that the procedures are completed to a high-quality standard. As part of this, all procedures will be recorded and assessed.

We anticipate that the study results, which will incorporate a patient and public involvement programme, will inform national and international guidelines for the surgical treatment of reflux disease.

6 STUDY SYNOPSIS

Full Study Title:	Double-blind randomised controlled trial for treatment of Gastro-Oesophageal reflux disease; LINX management system vs. Fundoplication
Short Title:	LINX vs Fundoplication
Study Acronym:	GOLF

Study Design:	The GOLF study is a multi-centre, pragmatic, two-arm, double-blind, phase III, randomised controlled trial (RCT). A QuinteT Recruitment Intervention (QRI) is incorporated into the study to understand and address any challenges to recruitment.
Study Aim	To determine whether the LINX procedure achieves similar reflux control and improves postoperative symptoms, specifically gas bloating and inability to belch when compared to fundoplication at 24 months after surgery.
Study Participants/ Target Population:	The GOLF study will recruit adults aged 18 and above with GORD insufficiently controlled by medical therapy or intolerance to medical therapy being considered for anti-reflux surgery. Refer to section OBJECTIVES AND OUTCOME MEASURES of the main body of the protocol for full eligibility criteria.
Eligibility criteria:	Inclusion: 1. Age 18 years and above. 2. Willing and able to give informed consent. 3. Patients with GORD insufficiently controlled by medical therapy or intolerance to medical therapy being considered for anti-reflux surgery. 4. Symptomatic and objectively defined GORD; endoscopy with appearances or biopsies consistent with reflux oesophagitis, or 24-hour pH study or BRAVO test of the oesophagus consistent with GORD. 5. No hiatal hernia or hiatal hernia <5cm in length. 6. Adequate lower oesophageal motility as defined by preoperative oesophageal manometry study. Oesophageal manometry will show a mean contractile amplitude of >30 mm Hg or DCI > 450 mmHg-s-cm in 70% of swallows. Exclusion: 1. Unsuitable for surgical intervention due to medical conditions precluding general anaesthesia. 2. Suspected or known allergies to titanium, stainless steel, nickel, or ferrous materials. 3. Previous anti-reflux or gastric surgery. 4. Previous or planned neurosurgical intervention 5. Oesophageal manometry showing complete absence of lower oesophageal contractility.
No. of study arms:	2
Intervention(s):	Laparoscopic magnetic sphincter augmentation procedure (LINX).

Comparator:	Laparoscopic fundoplication including a total or partial fundic wrap around the distal oesophagus.	
Planned Sample Size:	460 participants (230 per trial arm).	
Target no. of research sites:	At least 16 NHS Hospitals in UK and 7 non-UK Hospitals in Europe.	
Countries of recruitment:	UK, Austria, France, Germany, Italy and Switzerland.	
Planned recruitment duration:	Recruitment is expected to last for 24 months.	
Follow-up duration:	Each participant will be followed up for 24 months from randomisation.	
Primary objective and outcome measure:	**Objective**	**Outcome Measure**
	To determine whether the LINX procedure achieves similar reflux control and improves postoperative symptoms, specifically gas bloating and inability to belch when compared to fundoplication at 24 months after surgery.	Control of reflux
Additional objectives and outcome measures:	Refer to the OBJECTIVES AND OUTCOME MEASURES section of the main body of the protocol for full study objectives and outcome measures.	

7 ABBREVIATIONS

AE	Adverse Event
AR	Adverse Reaction/Response
CI	Chief Investigator
CRF	Case Report Form
CTU	Clinical Trials Unit
DCI	Distal Contractile Integral
DSMC	Data and Safety Monitoring Committee
GCP	Good Clinical Practice
GORD	Gastro-oesophageal reflux disease
GP	General Practitioner
HRA	Health Research Authority
ICF	Informed Consent Form
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trials Number
LOS	Lower oesophageal sphincter
NHS	National Health Service
NIHR	National Institute for Health and Care Research
NHSR	National Hiatal Surgery Registry
PI	Principal Investigator
PIS	Participant information sheet
PPI	Patient and Public Involvement
QA	Quality Assurance
QRI	QuinteT Recruitment Intervention
PROMS	Patient Reported Outcome Measures
REC	Research Ethics Committee
RDSF	Research Data Storage Facility
RGEA	Research Governance, Ethics & Assurance Team
SAE	Serious Adverse Event
SFTP	Secure File Transfer Protocol
SITU	Surgical Intervention Trials Unit
SQA	Surgical Quality Assurance
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Response/Reaction
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee

8 BACKGROUND INFORMATION AND RATIONALE

8.1 Why is this research needed now?

Gastro-oesophageal reflux disease (GORD) represents a significant burden on the Western healthcare system, affecting up to 20% of adults, with a rising prevalence.[1,2] Not only does this have a negative impact on a patient's health related quality of life (HRQL), but GORD is also associated with an increased risk of complications including inflammation and strictures, and developing Barrett's oesophagus and oesophageal adenocarcinoma.[3] The dominating treatment of GORD is anti-reflux medication (mainly with a proton pump inhibitor), with surgery reserved as an alternative therapy, mainly for resistant symptoms or complications from GORD.[4] A large UK randomised clinical trial (RCT, REFLUX) showed, surgery (laparoscopic fundoplication) offers the most effective symptom control at five years follow-up, as well as being the most cost-effective treatment strategy compared to medical therapy.[4,5] Recent evidence has also emerged which suggests that long-term medication with proton pump inhibitors (PPIs) may be associated with an increased risk of serious side-effects, e.g. dementia, renal pathology, infections, fractures and gastric cancer.[6]

Laparoscopic fundoplication is currently the gold standard surgical treatment for managing GORD, which can either be performed as a total or partial wrap of the gastric fundus around the distal oesophagus. According to several international guidelines there is no convincing evidence at present to suggest total or partial wrap to be superior to the other.[7-9] Laparoscopic fundoplication has an excellent safety profile with a 30-day mortality risk of 0.03%.[10] Later side-effects of surgery are mainly gas bloating and inability to belch (up to 85%), dysphagia (3-24%), diarrhoea (18-33%) and recurrence of reflux symptoms (10-62%).[9] In addition, a proportion of patients may require endoscopic or surgical intervention, and those with post-operative recurrence of GORD may require secondary fundoplication or reintroduction of anti-reflux medication.[11] Our research has shown that approximately 5% of patients undergoing fundoplication in England may require secondary surgery and 60% of patients use anti-reflux medication within 12months of primary anti-reflux surgery.[10]

In 2007, a magnetic sphincter augmentation device (LINX) was introduced as an alternative intervention to fundoplication, requiring less extensive dissection and less disruption of the hiatal anatomy.[12,13] The LINX device is laparoscopically placed around the distal oesophagus and comprises titanium beads with magnets in the centre that augment lower oesophageal tone and thus prevent reflux.[14] The beads are interlinked with independent titanium wires to form a flexible and expandable ring with a 'Roman arch' configuration. Each bead can move independently of the adjacent beads, creating a dynamic implant that mimics the physiological movement of the oesophagus without limiting its range of motion. The strength of the magnetic core contained in each bead is calibrated by mass to provide a resisting force that precisely augments sphincter function. For reflux to occur, the intraluminal pressure must overcome both the patient's native lower oesophageal sphincter (LOS) pressure and the magnetic bonds of the device, creating a resistance to opening, mimicking the natural physiology. The LINX device, while augmenting the LOS, can double in diameter, to accommodate a large, swallowed bolus or the escape of elevated gastric pressure associated with belching or vomiting.

The most common complication of the LINX device is dysphagia, requiring dilatation at the site of the device in 5-11% of patients.[13-15] There have been a few reports of endoluminal erosions (0.1%) that required device removal, although no long-term sequalae have been noted.[13,15] A small RCT

comparing the LINX device to high doses of proton pump inhibitor (PPI) demonstrated that patients receiving the LINX device had substantially improved GORD-HRQL scores compared to those in the medication group.[16] In non-randomised comparative studies patients have also reported favourable outcomes with LINX compared to laparoscopic fundoplication.[15] Aside from its ease of insertion, the LINX device is also appealing in terms of symptom control, shorter operation time and reduced hospital stay, and lower burden of post-operative care.[17] In 2021, a prospective multi-centre observational registry-based study compared the LINX procedure (n=465) with laparoscopic fundoplication (n=166) in 631 patients and showed substantial improvements in GORD-related HRQL scores at 3 years both after LINX (from 22.0 to 4.6) and laparoscopic fundoplication (from 23.6 to 4.9).[18]

Some upper gastrointestinal surgeons have feared placing foreign material around the oesophagus for the treatment of GORD since the poor results seen with the Angelchick prosthesis, which often resulted in oesophageal erosions and fistulae, prompting device removal.[19] The Angelchick prosthesis was a large silastic 'C'-shaped rigid ring utilised as an anti-reflux device in the 1980s and 1990s.[20] However, there are important structural differences between the Angelchick (rigid) and LINX (dynamic) devices. In contrast to the Angelchick device, the LINX forms a flexible and expandable dynamic ring, which responds to changes in intraluminal oesophageal pressure, and can double in diameter to permit large food boluses. To date, long-term data from LINX implantation[21] identified only 6 erosions from 335 cases within 12 years of surgery, with the majority seen in the early part of the centre's learning curve. The long-term safety of the LINX device is also supported by the latest guidelines of the National Institute for Clinical Excellence (NICE).[22]

We conducted the national UK ARROW study (Audit & Review of Anti-Reflux Operations & Workup), a multicentre prospective audit to investigate the current management of patients undergoing anti-reflux surgery in the UK.[23] This survey study included responses from 155 surgeons across 57 institutions in the UK performing a median of 40 anti-reflux surgeries annually. When analysing surgical technique, 98% of surgeons offered fundoplication, with 75% offering total posterior fundoplication and 48% performing partial posterior fundoplication. Within the NHS, 5% of surgeons performed LINX procedures compared to 17% of surgeons in the private sector. Further feedback from this survey study highlighted the lack of RCTs concerning the surgical management of GORD.

The latest NICE guidelines in 2023 stated there were 'no major safety concerns' about laparoscopic insertion of a magnetic titanium ring for GORD.[22] Although NICE do allow the use of the LINX device in clinical practice, they encourage research in this area, and particularly comparative trials with other anti-reflux surgery were recommended.

8.2 What is the knowledge gap this research will address?

Laparoscopic fundoplication is primarily performed to improve the HRQL in patients suffering with GORD. Despite reasonable acid control, the side-effects of this operation - predominantly gas bloating and inability to belch and difficulty swallowing - can have a substantial adverse impact upon patients' HRQL. The LINX procedure may offer an alternative with less debilitating side effects while maintaining good reflux control.[15] Recent NICE guidelines have highlighted the need for a well-designed RCT comparing the LINX procedure with laparoscopic fundoplication.[22]

8.3 Surgical Quality Assurance and video analysis

Surgical quality assurance (SQA) involves directing the performance and behaviours of practitioners and institutions undertaking surgical interventions toward more appropriate standardised

procedures and acceptable health outcomes.[24,25] In this study, we propose that SQA will identify key steps in the procedure and the degree to which they should be standardised, and subsequently delineate how well they are performed within the trial. Through this, SQA allows for better standardisation of the procedure; analysis of their quality; and monitoring of outcomes. Traditional methods of SQA involve analysing operative notes to understand the course of the procedure, and in more recent years analysis of intraoperative photographs.[24] Previous studies have confirmed that post-operative outcomes are largely dependent on intraoperative events and have a strong correlation with factors such as surgical skill and technique; how well the individual steps of a procedure are adhered to and completed and the management of unexpected events. This has led to the widespread incorporation of SQA in large-scale RCTs to ensure that the intraoperative technique and events are generalisable. For example, in the recent completed ROMIO trial (Randomised Oesophagectomy–Minimally Invasive or Open), our research team (JB and NB) have used SQA in three categories, namely trial entry criteria for surgeons and centres; standardisation of surgical techniques; and monitoring of surgeons and/or units.[26] We have previously published regarding current methodology of SQA and the importance of SQA associated with clinical outcome from oesophago-gastric cancer and bariatric surgery.[27,28]

More recent work appraising SQA has highlighted the wealth of information that intraoperative video recording can provide about how an operation was performed, reducing the incidence of recall bias, inaccurate or incomplete details, and blind spots. For example, Birkmeyer et al described a wide variation in the technical abilities of surgeons and demonstrated that surgeon skill was highly correlated with patient outcomes.[29] More technically proficient surgeons (as rated by video analysis) also had the lowest complication rates. In another study, Chhabra et al reviewed intraoperative videos submitted by 30 surgeons performing laparoscopic sleeve gastrectomy on 6915 patients, specifically the technical approaches to 5 controversial aspects of laparoscopic sleeve gastrectomy for obesity.[30] On blinded analysis, they noted substantial variation in how these five steps were performed, and showed a strong correlation with total weight loss, reflux severity, and the incidence of postoperative haemorrhage and staple line leak. In their commentary, Dimick et al highlighted the value of operative videos compared to operative notes, which may describe which staplers are used for an anastomosis, but not usually how well the anastomosis was fashioned. In contrast, intraoperative videos provide a visual recount of the procedure that can be revisited easily to correlate it with the post-operative outcomes.[30] Thus, video analysis captures these details in a more detailed and objective manner than other forms of SQA, and especially when compared to an operative report recorded by the operating surgeon.

To our knowledge, no studies have evaluated the utility of video analysis for SQA in procedures for the treatment of GORD. Our study is novel in being the first RCT to use video-based SQA to link intraoperative events and surgical quality to patient reported outcome measures, specifically in a surgical setting. Our hypothesis is that the laparoscopic LINX procedure will achieve reflux control equivalent to fundoplication and with fewer side effects. We propose that this will be due to less disruption of hiatal anatomy and less mobilisation of the gastric fundus with surgical dissection. Video-based SQA will enable us to dissect the procedure into smaller, key individual steps; appraise how well they are performed, specifically the assessment of disruption to the hiatal anatomy; and identify how the variation in surgical technique can affect the outcomes. Furthermore, our analysis will involve identifying the quality of particular key steps that are most impactful in controlling reflux symptoms and avoiding side effects such as gas bloating and inability to belch at 24 months after

surgery. This will enable us to validate our hypothesis and accelerate the safe adoption of the LINX procedure.

8.4 Review of existing evidence and preliminary results

We conducted a systematic review and meta-analysis of the laparoscopic LINX procedure versus laparoscopic fundoplication, which included 6 cohort studies, comprising 1099 patients, 632 receiving LINX and 467 receiving fundoplication.[15] There were no statistically significant differences between the groups in requirement for postoperative antireflux medication, GORD-HRQL scores, dysphagia or reoperation. However, when compared to fundoplication, LINX was associated with significantly less gas bloating (pooled odds ratio [OR] 0.34; 95% confidence interval [CI] 0.16-0.71) and a greater ability to belch (OR 12.34; 95% CI 6.43-23.7). This review suggested that LINX achieves good GORD symptomatic control similar to that of fundoplication, with the benefit of less gas bloating and better ability to belch. The safety of the LINX device also appears acceptable with only 3.3% of patients requiring device removal The local site within the NHS or in the event of emergency the NHS treating local authority will remove the device. The LINX is an accepted standard of care within the NHS and thus device removal is an accepted potential outcome. For details of device removal for non-UK sites please refer to Appendix 3.1 LINX Device Removal.

A further systematic review from our research group evaluated the introduction of LINX against the established IDEAL (Idea, Development, Exploration, Assessment and Long-term follow-up) framework for novel surgical procedures and devices.31 A series of 39 published articles included within this review clearly identified a lack of standardised surgical quality assurance regarding how the LINX should be implanted, and lack of consensus regarding results that should be evaluated to meaningfully assess patient benefit. This review identified several existing IDEAL 2b studies, and therefore a well-designed and pragmatic RCT that provides information relevant for patients and the NHS is required before there is further intervention creep, and LINX is further incorporated into clinical practice without robust evidence.

We recently led a multidisciplinary group that developed the joint United European Gastroenterology (UEG) and European Association of Endoscopy Surgery (EAES) guidelines on surgical management of GORD.[32] Through a process of systematic review, network meta-analysis and Delphi consensus, different constructions of fundoplication (posterior total, posterior partial, anterior 90^0 or anterior $>90^0$) were compared. We identified a lack of high-quality evidence in this area, but the guidelines suggested posterior partial fundoplication is similar to a posterior total fundoplication in terms of reflux control,[32] and also highlighted the lack of evidence from RCTs comparing the LINX procedure to fundoplication.

9 OBJECTIVES AND OUTCOME MEASURES

9.1 Aim

The aim of the study is to determine whether the LINX procedure achieves similar reflux control and improves postoperative symptoms, specifically gas bloating and inability to belch, when compared to fundoplication at 24 months after surgery in an RCT.

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
To determine whether the LINX procedure achieves similar reflux control when compared to fundoplication	Gastro-oesophageal reflux	24 months postoperatively	GORD-HRQL	Participant reported outcome

9.3 Secondary objectives and outcome measures

Objective	Outcome measure	Time point(s) of evaluation of this outcome measure (if applicable)	Data required	Source data (including location)
To determine whether the LINX procedure improves postoperative symptoms, specifically gas bloating and inability to belch	Gas bloating and inability to belch	24 months postoperatively	GORD-HRQL and Foregut Symptom Questionnaire	Participant reported outcomes
To compare the prevalence and severity of reflux, gas bloating and inability to belch	Gastro-oesophageal reflux, gas bloating and inability to belch	6 weeks, 6, and 12 months postoperatively	GORD-HRQL and Foregut Symptom Questionnaire	Participant reported outcome
To compare the prevalence and severity of regurgitation and dysphagia	Regurgitation and dysphagia	6 weeks, 6, 12 and 24 months postoperatively	GORD-HRQL	Participant reported outcomes
To compare global health-related quality of life (HRQL)	Global HRQL	6 weeks, 6, 12 and 24 months postoperatively	EQ-5D-5L	Participant reported outcomes
To compare utilisation of anti-	Anti-GORD medications including Proton pump	6 weeks, 6, 12 and 24 months postoperatively	Utilisation of anti-GORD medications	Participant reported outcomes

GORD medications	inhibitors and H2 antagonists		GORD-medication questionnaire	
To objectively assess lower oesophageal acid exposure	Acid exposure time and DeMeester score	12 months postoperatively	24-hour pH-measurement or BRAVO test	Participant's medical records
To objectively assess complication rates between each procedure	Complication rates as Clavien Dindo 3 or above	30-day, 90-day and 12 months postoperatively	Postoperative outcomes including complications and reintervention.	Participant's medical records
To assess cost-effectiveness of both treatments	Incremental cost per quality adjusted life year (QALY)	6 weeks, 6, 12 and 24 months postoperatively	Resource use questionnaire	Participant's medical records for resources For hospital and patient

9.4 Additional mechanistic objectives outcomes

Objective	**Outcome measure**	**Time point(s) of evaluation of this outcome measure (if applicable)**	**Data required**	**Source data (including location)**
To annotate all procedural videos	a) Careful documentation of every operative task, step, and phase	After surgery and 30-day complications described above	Annotated surgical videos	Surgical videos
	B) Identification of technical errors or technique modifications			
	c) Whether these errors are consequential or inconsequential			
To compare annotated videos with data relating to post-operative complications and patient reported symptoms (focusing on gas-bloat, inability to	Technical errors from surgical videos and HRQL from 24 months	After surgery and long-term HRQL data from 24 months described above.	Annotated surgical videos AND Postoperative outcomes including complications	Surgical videos and HRQL data from 24 months

belch, dysphagia and persistent reflux)			and reintervention and GORD-HRQL	

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

Our previous research identified the majority (94%) of anti-reflux surgery patients who require reoperation or go back onto anti-GORD medications will do so within 24 months of surgery. Thus, the follow-up period of 24 months has been chosen to establish the value of the laparoscopic LINX procedure over laparoscopic fundoplication. The GOLF study will be embedded within the National Hiatal Surgery Registry, which will permit longer than 2 years of follow-up with a planned report at 5 and 10 years after surgery. This will allow the GOLF trial to also formally assess the long-term outcome and safety of the LINX procedure compared with fundoplication.

10 STUDY DESIGN AND SETTING

The GOLF study is a multi-centre, pragmatic, two-arm, double-blind, phase III, randomised controlled trial (RCT). An embedded QuinteT Recruitment Intervention will be used to understand, monitor and address barriers to participation.

The study will recruit 460 patients (230 in each of two arms) recommended for anti-reflux surgery with GORD from at least 16 UK and 7 non-UK European large upper gastro-intestinal surgical centres. Patients will be randomised 1:1 to receive either laparoscopic LINX procedure or fundoplication.

The primary outcome is assessment of symptomatic GORD using the GORD-HRQL questionnaire at 24 months following surgery, and core secondary outcomes are prevalence of inability to belch and gas bloating at 24 months also assessed by GORD-HRQL. Patients will be followed-up either in clinic, via telephone or electronically at baseline, 6 weeks, 6, 12 and 24 months after surgery.

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

10.1 Recruiting sites/site types

Participants will be recruited from at least 16 UK and 7 non-UK European specialist anti-reflux surgical centres.

Refer to section 24 for information on identification and management of sites.

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. Participants will be sent all HRQL questionnaires via email with a link to complete questionnaires online, with an option to complete the questionnaires via telephone call from the study team or via post if so requested. HRQL questionnaires will be administered in English in UK and non-native English speakers will be permitted to use support to complete the questionnaires as needed. HRQL questionnaires will be administered in approved translated versions at each non-UK European site.

Clinical outcomes and resource usage will be collected by site 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.

The GOLF study will be embedded within the National Hiatal Surgery Registry, which will permit longer than 2 years of follow-up with a planned report at 5 and 10 years after surgery at UK sites only. This will allow the GOLF trial to also formally assess the long-term outcome and safety of the LINX procedure. Refer to section STUDY ASSESSMENTS/PROCEDURES for full details of outcome data collection and follow-up assessments.

10.3 Countries of recruitment

UK, Switzerland, Germany, Italy, France and Austria. We will also consider extending the trial to other UK centres and other countries, including Sweden, Netherlands and Spain at any point if recruitment is a challenge within the GOLF trial.

10.4 Duration of participant involvement

Participants will be in the study for approximately 24 months from randomisation to last protocol visit.

10.5 Post-study treatment/care and follow-up

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

For all patients in both study arms postoperative care will consist of:

- Discharge on the same day or the following day based upon the participating centres' usual practice, with criteria for discharge that the patient is tolerating at least a liquid diet.
- All patients will be provided with specific dietary advice sheets, but the contents will depend on the procedure performed.
- Control group (fundoplication); Patients will be advised to remain on a largely liquid diet for 2 weeks after surgery, with advancement of diet to solids after this period, in line with the local centre's protocols.
- Intervention group (LINX); Patients will be provided with a specific diet which will include eating between five and eight small regular meals per day for the first 2 weeks after surgery and minimise the amount of dry food intake (APPENDIX 2 – DIET ADVICE FOR LINX)
- Clinical follow-up by telephone, video call or face-to-face will be typically performed with a surgeon (consultant or trained registrar) at 4 to 6 weeks, and 3 months after surgery, depending on the local institutions pattern of clinical practice.

We will assess the degree of unblinding this may have caused with administering the Bang Blinding Index questionnaire to participants.

10.6 Central review procedures

Not applicable for this study.

10.7 Use of Registry/NHS Digital data – UK Sites Only

The GOLF study will be embedded within the National Hiatal Surgery Registry, which will permit longer than 2 years of follow-up with a planned report at 5 and 10 years after surgery. This will allow the GOLF trial to also formally assess the long-term outcome and safety of the LINX procedure. This will be applicable to UK sites only.

10.8 Expected recruitment rate

We estimate that we will open at least 2-4 sites per month starting in month 4 (with recruitment starting in month 7) and that all sites will be open to recruitment within 8 months. Therefore, we are expecting 24 months of recruitment across at least 16 UK sites and 7 non-UK sites. Assuming staggered opening of recruitment sites, we will need to recruit an average of 1-3 patients per month and site assuming a recruitment of 50% of eligible participants, which we consider feasible.

10.9 Equality, diversity and inclusion for study participants

Provided patients satisfy the eligibility criteria, we will offer the same opportunity of taking part in this study regardless of age, gender including gender reassignment, sexual orientation, marital status, ethnicity, religion or belief, geographical location, socioeconomic status or access to healthcare.

We will promote a patient-oriented retention method where participants can choose their preferred method of communication for follow up questionnaires. During the first visit with the site 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 two years of the study (for example, electronically or by paper).

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 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).

10.10 End of study

The end of study is the point at which all CRF and non-CRF data relating to the trial primary and secondary outcomes has been entered/received (or collected if non-CRF data) and all queries resolved. The study will stop randomising participants when the stated number of patients to be recruited is reached. The minimum time before reaching end of study will be 24 months after the last patient is randomised plus time for entering and clearing the data. As stated above for UK sites the GOLF study will be embedded within the National Hiatal Surgery Registry, which will permit longer than 2 years of follow-up with a planned report at 5 and 10 years after surgery.

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.

24 months after the surgery, patients will be unblinded (i.e informed via letter or email about which operation they received) and then they will be followed-up according to the standard of care in their treating hospital.

10.11 The Quintet Recruitment Intervention (QRI) – UK sites only

The GOLF study includes an integrated QuinteT Recruitment Intervention (QRI), led by the QuinteT team at the University of Bristol. The aim of the QRI is to understand/assess the recruitment process and how it operates in each recruiting site, so that sources of recruitment difficulties can be identified and suggestions made to change aspects of design, conduct or training that could then

lead on to improvements in recruitment and informed consent[33]. The QRI team will engage with sites prior to their opening to recruitment to consider anticipated recruitment challenges and suggestions to minimise. The team will also develop and disseminate general recruitment strategies informed by QRI findings from previous studies (e.g. approaches to explain randomisation) and tailored to GOLF. Once recruitment begins, the QRI will investigate and address recruitment issues in 'real-time' through two iterative phases:

10.11.1 Phase 1: Understanding recruitment issues

Mixed methods will be used to identify and understand issues impacting upon recruitment[34]. A flexible approach will be taken using one or more of the following:

a. Semi-structured (remote) interviews with i) members of the TMG and co-ordinating study team, ii) staff involved in study recruitment ('recruiters'), and possibly iii) eligible patients who have been approached to consider the study. Interviews with key TMG members and a diverse sample of recruiters will explore their perspectives on GOLF, and experiences of recruitment. Key topics will cover perspectives on the study design and protocol; views about the evidence on which the study is based; perceptions of uncertainty/equipoise in relation to the RCT treatment arms; views about how the treatment arms and protocol are delivered in their clinical centre; methods for identifying eligible patients; views on eligibility; and examples of actual recruitment successes and difficulties. Interviews with a maximum variation sample of patients approached about the study may also take place if further information is needed to elucidate the reasons underpinning recruitment issues. These interviews will explore views on the presentation of study information, understandings of study processes (e.g. randomisation), and reasons underlying decisions to accept or decline the study.

b. Recording recruitment discussions: recruiters' discussions with eligible patients will be recorded (with consent) to provide direct insight into how the study is being presented. We will pay particular attention to whether the study interventions are described in a clear, accurate and balanced way (i.e. equipoise issues); ways in which recruiters manage patients' expectations and preferences, and approaches to explaining study processes such as randomisation and follow-up.

c. Mapping of recruitment pathways and screening log analyses: anonymised information about each patient screened for GOLF, including whether they were eligible, approached and randomised (with reasons if not), will be captured in detailed screening logs and compared across sites. Recruitment pathways for each site will be mapped from staff interviews, noting processes for screening and identifying eligible patients, steps taken to confirm eligibility, when/how patients are approached, and the staff involved in these activities. This information will be compared with screening log figures to identify bottlenecks in recruitment pathways.

d. Attendance at TMG and investigator meetings: the QRI researcher will attend TMG and investigator meetings to gain an overview of study conduct and overarching challenges. This can elucidate new lines of enquiry and add new dimensions to challenges that have emerged through other data collection methods.

e. Review of study documentation to ensure that study documents are unbiased and clear. As the study progresses, the PIS and consent form(s) will be compared with interviews and recorded appointments to identify any disparities or improvements that could be made.

10.11.2 Phase 2: Development and implementation of recruitment intervention strategies

The QRI team will feedback findings from QRI Phase 1 to the chief investigator (CI) and trial management group (TMG), working closely together to then design and implement tailored actions to address identified issues. Actions are likely to include individual, centre or study wide feedback and training on recruitment issues such as how to present the study design more clearly to improve levels of understanding, how to approach patients' treatment preferences; and facilitating discussions around issues of clinical pathways and eligibility assessment, equipoise, and team-working. Group feedback sessions will use anonymised extracts from recorded consultations to illustrate how recruiters' communication can influence patients' responses to invitations of study participation and to share examples of good recruitment practice. Actions may also entail developing/adapting recruitment tips documents to address identified issues and suggesting changes to patient facing study material if proving misleading/confusing.

10.11.3 Iterative nature of QRI phases

Both QRI phases will run iteratively for the duration of recruitment. New avenues of enquiry will emerge throughout the conduct of the QRI and thus both phases will run cyclically throughout the period of recruitment. Lessons learnt from the first centres to open will be shared up-front with subsequent centres opening later in the study's timeline.

10.11.4 QRI data analyses

Interviews and recruitment consultations will be recorded, transcribed in full or parts and, along with recruitment screening logs and observations, subject to simple counts, content, thematic and targeted conversation analyses. Preliminary analysis will be used to inform training and further data collection. Members of the QRI team will independently analyse a proportion of transcripts to assess the dependability of coding and will meet regularly to review coding and descriptive findings, agree further sampling and training strategies, and discuss theoretical development – all in close collaboration with the CI.

11 SUB-STUDIES

11.1 Translational "Surgical Quality Assurance" Sub-Study

Surgical quality assurance (SQA) is an important component of this trial because LINX is a newer surgical procedure and because there is (inter)national variation in fundoplication techniques. The SQA will help to ensure the procedures are also completed to a good surgical standard, to maximise internal and external validity and facilitate accurate interpretation of trial results and replication of the successful intervention across wider clinical practice. The inclusion of detailed SQA in this trial is novel in seeking to identify the key surgical steps and how well they are performed as potential mechanistic explanations for patient reported outcome measures within this trial.

The SQA programme will comprise the five phases presented below. Phases 1-3 will occur before the trial starts, phase 4 is the mechanistic work and phase 5 involves ongoing monitoring of adherence to the intervention protocol during the trial.

11.1.1 Surgeon training

If participating surgeons have not previously undertaken the LINX procedure, adequate training will be provided. This specific training programme will include:

- Guidance regarding counselling of patients before surgery regarding the risks and benefits of the LINX procedure.
- Provision of video and educational materials including guidance on sizing and implantation of the device and a step by step written and video-guided description of the technique.
- Prompt sheet for postoperative patient consultations, which will provide specific adverse features to be aware of that may require further investigations, and advice on further counselling of patients and advancing oral intake.
- Each participating surgeon who has not previously undertaken a LINX procedure, will be paired with a consultant surgeon from the investigating team experienced in implanting the device, who will act as a mentor during this initial phase. The mentor will be available to answer any questions about the pre, intra- and postoperative management of patients undergoing the LINX procedure.

11.1.2 Credentialing of centres and surgeons

Each participating centre will be required to have an annual caseload of at least 15 anti-reflux procedures and include a minimum of two surgeons involved in the trial. Only surgical consultants who have previously performed a minimum of 20 laparoscopic fundoplications and regularly perform anti-reflux surgery (or trainees under direct supervision) will be eligible to participate. Surgeons will be required to be willing to undertake either procedure. Prior to beginning the trial, surgeons will each be asked to submit two videos of them performing fundoplication and LINX. However, surgeons who have already performed 20 LINX procedures will be allowed to join the trial without the need to upload any credentialing videos. This will allow Observed Clinical Human Reliability Analysis (OCHRA) to be performed on their technique to ensure they are of a sufficient standard and are beyond any potential proficiency gain curve.[35]

11.1.3 Standardisation of surgical techniques

An existing typology will provide a framework for deconstructing fundoplication and LINX procedures into their component parts. These will be based on best available evidence and where evidence does not exist, on the consensus opinion of surgeons. At the end of this process, operative demonstration videos will be developed, that describe each technical step of fundoplication and the LINX procedure, and detail those that are mandatory or optional as agreed within the trial. These videos will be provided to all participating centres and surgeons to ensure standardisation of techniques during the trial, with deviations recorded.

11.1.4 Mechanistic work

All procedures in both arms of this study will be video recorded and stored in a central repository at the University of Bristol Research Data Storage Facility (RDSF). A nominated local site study team member will be assigned at each site to complete data uploads. Both laparoscopic and robotic techniques are accepted as standards of care and only intraoperative videos will be which will have no patient identifiable information. Mechanistic research will involve annotation of videos to enable

a) documentation of every operative task, step, and phase,

b) identification of technical errors or technique modifications, and

c) whether technical errors or technique modifications are consequential or inconsequential.

Each operation will therefore have a ‘fingerprint’ which collectively will enable assessment of the uniformity of surgical approach. Annotated videos will then be compared with data relating to post-operative complications and symptoms (focusing on gas-bloat, dysphagia and persistent reflux).

Videos will be assessed by a trained clinical research fellow who is blinded to which surgeon did the operation and to the postoperative complications and symptoms to ensure validity of the video analysis. Particular steps that will be focused upon within the analysis will include division or non-division of short gastric vessels, mobilisation and length of intra-abdominal oesophagus, length of wrap in the case of fundoplication and extent of hiatal dissection including disruption of the phreno-oesophageal ligament. Anti-reflux surgery is primarily performed for relief of symptoms and thus this study provides a unique area for patient reported outcomes research, and identifying the performance of key surgical steps and how they underpin patient reported outcomes.

11.1.5 Monitoring adherence to the intervention protocols

All procedures undertaken during the trial will be videoed using existing laparoscopic technology. OCHRA Analysis will be performed to ensure adherence to the intervention protocol (above) and that a high quality of surgery is maintained. Feedback regarding adherence to the intervention protocol and standards of surgery will be provided regularly throughout the trial. The novelty in this SQA programme will be in providing regular feedback to participating surgeons based upon video analysis during the trial, thus minimising any learning curve effects seen during the trial and ensuring standardisation and high surgical performance.

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 local 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 study participants

The GOLF study will recruit adults aged 18 years and over with GORD insufficiently controlled by medical therapy being considered for anti-reflux surgery.

Written informed consent must be obtained before any study specific procedures are performed with the exception of recording study discussions as part of the QRI (see section 15.1). Participant eligibility will be confirmed by a suitably qualified and experienced individual who has been delegated to do so by the Principal Investigator (PI) based on the below criteria.

12.3 Inclusion Criteria

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

- Age 18 years and above.
- Willing and able to give informed consent
- Patients with GORD insufficiently controlled by medical therapy or intolerance to medical therapy being considered for anti-reflux surgery.
- Symptomatic and objectively defined GORD; endoscopy with appearances or biopsies consistent with reflux oesophagitis, or 24-hour pH study or BRAVO test of the oesophagus consistent with GORD.
- No hiatal hernia or hiatal hernia <5cm.
- Adequate lower oesophageal motility as defined by preoperative oesophageal manometry study. Oesophageal manometry will show a mean contractile amplitude of >30 mm Hg or

DCI > 450 mmHg-s-cm in 70% of swallows. Patients with weaker peristalsis should be counselled regarding the risk of post-operative dysphagia.

12.4 Exclusion Criteria

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

- Unsuitable for surgical intervention due to medical conditions precluding general anaesthesia.
- Suspected or known allergies to titanium, stainless steel, nickel, or ferrous materials.
- Previous anti-reflux or gastric surgery.
- Previous or planned neurosurgical intervention
- Oesophageal manometry showing complete absence of lower oesophageal contractility.

12.5 Rationale for inclusion and exclusion criteria

The inclusion and exclusion criteria above have been selected based upon current manufacturer guidance upon patient selection for the LINX procedure and furthermore discussion with expert surgeons who have a substantial experience with the LINX procedure. This to ensure the patient has symptomatic objectively defined GORD, and the motility of the lower oesophagus is sufficient to propel a food bolus beyond the LINX device or fundoplication.

12.6 Pre-study screening tests or investigations

In the GOLF study, preoperative assessment for all patients will consist of:

- Clinical assessment of indications for surgery including volume reflux (especially affecting sleep, or during physical activities that involve stooping), break-through symptoms of heartburn despite optimal medical therapy, and intolerance of medications (mainly PPIs).
- Upper GI endoscopy.
- Oesophageal manometry with 24-hour pH study or BRAVO test.

12.7 Protocol waivers to entry criteria

Protocol adherence is a fundamental part of the conduct of a randomised 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 criteria may only be made by a substantial amendment to the protocol.

Before entering a patient onto the study, the principal investigator or designee, as listed on the delegation log, will confirm eligibility. If unsure whether the potential participant satisfies all the entry criteria and to clarify matters of clinical discretion investigators should contact the GOLF study office, who will contact the Chief Investigator as necessary. If in any doubt the Chief Investigator must be consulted before recruiting the patient. Details of the query and outcome of the decision must be documented in the Investigator Site File (ISF)/Trial Master File (TMF).

12.8 Clinical queries and protocol clarifications

Every care has been taken in drafting this protocol. Contact the GOLF 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 study investigators for information as necessary. For urgent safety measures or changes that require protocol amendment see section 25.7.

13 SCREENING AND RECRUITMENT

13.1 Participant Identification

Participants will be recruited from hospitals in the UK and other European countries regularly performing anti-reflux surgery.

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

- Identification during routine clinic visits

Posters advertising the study will be displayed in electronic and paper formats as allowed in participating sites in surgical and gastroenterology clinics. All advertising material will be approved prior to use.

13.1.1 Identification of participants during routine clinic visits

Potentially eligible patients identified during routine clinic visits will be provided with a Participant Information Sheet (PIS) by a member of their usual care team (who may also be a member of the site study team) and asked to consider the study. Where their usual care clinician is not a member of the site study team potential participants will be asked if it would be acceptable for their name and contact details to be passed to the site study team who will make contact at a later time point (this may be in person in a clinic or via telephone or video call in accordance with local site practice) or during a further routine clinic visits, 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 site study team – if this permission is given this should be recorded in their clinical notes.

Patients will be invited to have their discussions about the study recorded (as part of the QRI component) until they have reached a decision about participation in GOLF. An encrypted audio recording device for recording recruitment discussions will be supplied to sites by the researchers at the University of Bristol. Alternatively, sites may use a Sponsor/Trust-approved recording or video-conferencing tool.

13.2 Re-screening if a potential participant does not meet inclusion/exclusion criteria first time round

Not applicable for this study. Re-screening of ineligible patients is not permitted.

13.3 Use of screening logs

A screening log (within the REDCap study database) will be used to record information about the number of patients screened, eligible, approached and randomised[36], along with reasons why not, where applicable. Personal identifiable data will not be recorded on the screening log; a screening number will be assigned to each patient screened.

14 STUDY INTERVENTION AND COMPARATOR

14.1 Laparoscopic or robotic LINX procedure (intervention)

The laparoscopic insertion of a magnetic ring, such as the LINX device, has been part of the NICE guidelines for treating gastro-oesophageal reflux disease, and therefore standard of care in the NHS

since 2017.
Participants randomised to laparoscopic or robotic magnetic sphincter augmentation (LINX procedure) will receive surgical treatment under general anaesthesia, with placement of the LINX device around the distal oesophagus. The LINX device comprises titanium beads with magnets in the centre.

14.2 Laparoscopic or robotic fundoplication (comparator)

Participants randomised to laparoscopic or robotic fundoplication will receive surgical treatment for managing GORD including a total or partial fundic wrap behind or in front of the distal oesophagus and gastro-oesophageal junction.

15 INFORMED CONSENT

15.1 Consent for recording of study discussions and patient interview (QRI component)

Patient participants: Information about the recording of study discussions and possibility of a research interview is contained in the main study PIS. Consent for these aspects of GOLF is separate to consent for participating in the main study. Patients may decline the QRI component and participate in GOLF, or vice versa. It is beneficial if as many consultations during the patient pathway as possible can be recorded, therefore consent to recording will be requested at the earliest possible opportunity. This may be verbal consent (recorded on the QRI verbal consent form) in the first instance (remote or face-to face consultation) if the patient has not received the PIS, with a view to obtaining written informed consent subsequently. This will be on the understanding that the data will not be uploaded/submitted or used until written consent has been obtained. A copy of the signed QRI ICF for patients will be given to the participant. The original signed ICF will be retained at the study site and participant QRI consent will be recorded in the GOLF study database.

Staff participants: Consent from staff to record their consultations and/or participate in a research interview as part of the QRI will be discussed and sought during site set up. Staff may consent to both consultation recording and interview, to only one of these aspects, or to no aspects of the QRI. Where the recruiting member of staff has not consented to participate in the study discussion recordings, their patients will not be invited to have their discussions recorded. A copy of the signed QRI ICF for HCPs will be given to the participant and a copy retained by the QRI team. The original signed form will be retained at the study site.

15.2 Consent Procedure for the main GOLF study

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

15.3 Time allowed to decide to take part

Potential participants will be given the participant information sheet before, at or shortly after their initial outpatient clinical visit. They will then be followed up by a member of the study team within 1 month of being given the participant information sheet, either with an in-person or telephone discussion to discuss if they wish to participate in the GOLF study.

15.4 Completion of the Informed Consent Form

The patient and the Investigator (or authorised designee) must personally sign and date the current approved version of the informed consent form.

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), however paper consent forms will also be made available for use in situations where electronic consent is not possible or suitable. 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 via a secure link sent directly to the participant's specified email address, may also be used. For details of completion of the informed consent form during the study for non-UK sites, please see the Appendix 3.2 Completion of Informed Consent Form.

Where consent forms are completed electronically signatures will be either achieved by a finger tracing across a tablet device, or using an electronic stylus on a tablet device or using a mouse dragging the cursor across the screen – all methods are to be used as if signing with a traditional pen.

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 site study team will be able to print a copy of the signed ICF and provide this to the participant. A copy of the electronic consent form downloaded from the study database should be placed in the Investigator Site File and a copy in the participant's medical record.

15.5 Individuals lacking capacity to consent

Individuals lacking capacity to consent to study participation will not be eligible to enter the study.

15.6 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.

15.7 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.

15.8 Participants who lose capacity during the study

Participants who lose capacity during the study will be withdrawn from the study for further follow-up with HRQL questionnaires, however their data already collected will be retained within the study and routinely collected data regarding resource utilisation will continue to be collected. This data will be included within the final analysis.

15.9 Timing of randomisation

Randomisation will take place once informed consent has been given and eligibility for participation has been confirmed. At the end of the screening visit, participants who meet all the eligibility criteria

and are keen to proceed with the study should be randomised once informed consent is in place. Queries on eligibility must be resolved before randomisation and participants who do not meet all the eligibility criteria must not be randomised.

15.10 Randomisation procedure

Randomisation should take place once informed consent has been given. Participants will be randomised by the site study team via a centralised validated computer randomisation program through a secure (encrypted) web-based service, accessed via the GOLF REDCap study database.

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

Arm	Treatment
Laparoscopic/robotic LINX procedure (intervention arm)	Laparoscopic/robotic insertion of the LINX device at the level of the gastro-oesophageal junction, with or without repair of the oesophageal hiatus.
Laparoscopic/robotic Fundoplication (comparator arm)	Laparoscopic/robotic partial or total posterior or anterior fundoplication, with or without repair of the oesophageal hiatus.

Upon randomisation of a participant, an email will be sent to the PI performing the randomisation confirming treatment allocation and a member of the site study 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 TMF.

15.11 Randomisation methodology

Consented participants will be allocated randomly (1:1) to either the laparoscopic/robotic LINX procedure or laparoscopic/robotic fundoplication. Randomisation will be performed using a minimisation algorithm to ensure balance between the two treatment groups using stratification factors:

- Age (<40, 40-60, >60 years)
- Sex
- Co-morbidity at baseline according to the well-validated Charlson Co-morbidity Index
- Body mass index (BMI)
- Preoperative DeMeester score (a composite score system of acid exposure during ambulatory pH monitoring used to objectively define GORD)
- Country of treatment

The participants will be randomised by the randomisation software programmed by the clinical data personnel. The trial statistician will place the details in the Randomisation and Blinding Plan and confirm that the randomisation is nominal.

A delegated site study team member will enter the required information into the randomisation system which will then allocate the participant to either fundoplication or LINX intervention and an automatic email will inform the local PI of the allocation.

Following randomisation, the site study team will send a letter to the participant's GP informing them about their participation in the trial.

15.11.1 Justification for stratification factors

Each of the factors included in the stratification are important confounding variables that may be associated with the primary outcome of the study and thus were selected to ensure these are well balanced between the groups.

15.12 Back-up randomisation/registration procedure

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

16 STUDY ASSESSMENTS/PROCEDURES AND DATA COLLECTION

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

Follow-up BRAVO or pH manometry test require hospital attendance, however other assessments may be undertaken electronically/over the telephone.

16.1 Overview

The below table shows scheduled assessments for the study. Shaded timepoints require hospital attendance for samples – but other assessments at this time points could be undertaken electronically/over the telephone. Please refer to the Data Management and Sharing plan for more details of clinical visit windows and questionnaire distribution.

Table 2: Schedule of assessments - (Please note for non-UK sites resource use questionnaire and long-term follow-up via NHSR is not applicable)

	Assessments	Surgery discussion	Baseline		During operation	Post-op follow-up							Longer term follow-up¥	
						30 days	6 weeks	90 days	6 months	12 months	24 months	Ad-Hoc	60 months	120 months
All participants in both arms	Patient demographics		*	Randomisation										
	Upper GI endoscopy results‡		*											
	Oesophageal manometry with 24-hour pH study or BRAVO test.‡		*							*				
	Radiological imaging results‡§		*											
	GORD-HRQL^		*				*		*	*	*			
	EQ-5D-5L^		*				*		*	*	*			
	Foregut symptom questionnaire^		*				*		*	*	*			
	Complications and reintervention					*		*		*			*	*
	Resource use questionnaire (by hospital)		*				*		*	*	*			
	Resource use questionnaire (by patient)		*				*		*	*	*			
	Length of hospital stay					*								
	Utilisation of medications						*		*	*	*			
	Screening/check eligibility	*												
	Confirm eligibility	*												
	Informed consent±	*												
	Surgical videos₸				*									
	Bang Blinding index (by patients)						*		*	*	*			
	Bang Blinding index (by research nurse)										*			
	Collection/reporting of AEs"											*		
	Collection/reporting of SAEs											*		
	Withdrawal/Exclusion/Death notification Protocol Deviation/Statistical exclusion											*		

‡ Pre-op diagnostic assessment made by upper GI surgeon - as a part of SoC. Results from medical notes collected as a part of baseline assessment data - clinical visit on 12 month.
§ CT or contrast study results - only if performed as a part of Pre-op diagnostic assessment
¥ Study will be embedded within the National Hiatal Surgery Registry
₸ Part of the SQA mechanistic work (videos for both LINX and fundoplication surgery)
^ HRQL are given +/- 2 months for completion – except 6 weeks follow up (+/- 1 months for completion)
± eConsent or remote consent
" Ad-hoc up to 30 days only

Electronically/over the telephone/letter – completed by participant
Electronically – completed by research nurse/local clinical team
Electronically – completed by PI
Electronically – collected and completed by research nurse / local clinical team - additional clinical visit required

16.2 Study questionnaires

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 study 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. For details of study questionnaires and translations for non-UK sites, please see the Appendix 3.3 Study Questionnaires.

EQ-5D-5L: The self-complete version for use in REDCap will be used for participants completing the questionnaire electronically. Where participants have failed to return questionnaires; the study team will check their clinical status with the site study team and then attempt to obtain the data over the telephone using the EQ-5D-5L telephone interview scripts.

GERD-HRQL: The self-complete version for use in REDCap will be used for participants completing the questionnaire electronically. Where participants have failed to return questionnaires; the study team will check their clinical status with the site study team and then attempt to obtain the data over the telephone using the GERD-HRQL telephone interview scripts. THE GERD-HRQL is a well validated HRQL questionnaire for patients with GORD, with scores ranging from 0 to 50 with higher scores indicating worse symptoms.

Foregut symptom questionnaire: The self-complete version for use in REDCap will be used for participants completing the questionnaire electronically. Where participants have failed to return questionnaires; the study team will check their clinical status with the site study team and then attempt to obtain the data over the telephone using the foregut symptom questionnaire telephone interview scripts. Through this questionnaire patients will be asked about foregut symptoms including regurgitation, belching and vomiting, before and after treatment.

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 study team will check their clinical status with the site study team and then attempt to obtain the data over the telephone.

16.3 Data Collection

16.3.1 Baseline (Pre-randomisation)

Data sourced/collected by site study team *Completed at hospital by site study team member from medical notes or with participant*	**Data directly reported by participants**

• Participant demographics
• Upper GI endoscopy results
• 24-hour pH manometry OR BRAVO test results
• Radiological imaging results
• Resource use
	• Health-related quality of life questionnaires
	  ○ GERD-HRQL
	  ○ Foregut symptom questionnaire
	  ○ EQ-5D-5L (unmodified)
	• Resource use

16.3.2 Follow-up assessments/subsequent visits

30/90 days post-operatively

Data sourced/collected by site study team *Completed at hospital by site study team member from medical notes or with participant*	**Data directly reported by participants**
• Complications and reintervention • Length of hospital stay* *collected at 30 day time-point only	

6 weeks/6 months/12 months/24 months post-operatively

Data sourced/collected by site study team *Completed at hospital by site study team member from medical notes or with participant*	**Data directly reported by participants**

• 24-hour pH manometry OR BRAVO test*
• Complications and reintervention**
• Resource use
 	
*collected at 12-month time-point only
** collected also at 12 months
	• Utilisation of medications
	• Health-related quality of life questionnaires
	  ○ GERD-HRQL
	  ○ Foregut symptom questionnaire
	  ○ EQ-5D-5L (unmodified)
	• Resource use

16.4 Communication with study participants by the study team

Participants will be notified to complete study questionnaires by e-mail. Participants may be sent up to two reminder messages and/or where possible may be asked to complete questionnaires during a routine clinic visit. Participants that do not complete their study questionnaires may be telephoned to collect the data or request return of the questionnaire. Participants will receive an initial e-mail and up to two reminder messages by a member of the study team to collect outcome data.

16.5 Withdrawal

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 and the type of withdrawal will be collected on a Withdrawal CRF. All other aspects of the study/follow-up will be continued. The site study team should discuss with the patient if they accept subsequent data (including routine care data) to be collected as part of the study.

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

- No longer willing to receive study intervention
- No longer willing to complete study questionnaires
- No longer willing to agree to recording of study discussions and/or research interview as part of the QRI component
- No longer willing to attend study visits
- No longer willing to be contacted by the site study team to obtain CRF/outcome data
- No longer willing to have routine data from the medical record provided to the study
- No longer willing for routine data from health data providers e.g. NHSR, to be provided to the study

Where a participant wishes to withdraw from all aspects of study participation detailed above this will be recorded on the Withdrawal CRF as full withdrawal.

In addition to participant self-withdrawal, an investigator may decide to withdraw a participant from trial treatment for clinical reasons. Participants will still be asked to participate in the collection of follow-up data. The reason for withdrawal will be recorded on the study withdrawal case report form. Withdrawn participants will not be replaced as we have allowed for possible withdrawals and loss to follow-up in the estimated sample size.

The Withdrawal CRF should be completed to document the reasons for withdrawal and state who the decision to withdraw was made by. 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.

Completion of the Withdrawal CRF by the site study team will trigger a notification to the Study Office. Appropriate action will be taken by the study teams (centrally at the CTU and by the site study team at each participating site) to ensure compliance with the participant's withdrawal request. This may include marking future CRFs as not applicable and ensuring any relevant communications which the participant had consented to receive regarding their participation are no longer sent.

Data collected up to the point of withdrawal will be used/analysed as explained in the PIS, unless the participant specifically requests otherwise.

17 BLINDING AND CODE BREAKING

17.1 Blinding

The study will be double-blinded, i.e., the patients and the outcome assessors will be blinded to the trial treatment arm (LINX or fundoplication). Baseline GERD-HRQL and foregut symptoms are assessed at initial clinical assessment prior to randomisation. When randomised, the patient will not be informed which trial arm they have been allocated to. All postoperative symptomatic questionnaires will be collected electronically directly from blinded patients or by telephone interviews conducted by blinded research nurses. At 12 months after surgery randomised patients will undergo a 24-hour pH or Bravo and manometry investigations, by blinded assessors. All assessors will be informed these patients were part of the GOLF trial but will not be informed which procedure was performed. Success of blinding will be assessed using the Bang Blinding Index[37]. Table

provides an overview of the blinding status of all individuals involved in the conduct and management of the study.

Table 3: Blinding status of those involved in study conduct and management.

Role in study	Blinding status	Additional information
Participants	Blinded	All participants will be blinded to treatment allocation
Principal Investigator	Not blinded	Not possible due to the nature of the intervention. Following randomisation, an email will be sent to the PI (unblinded for participants they randomise only) performing the randomisation (as delegated) confirming treatment allocation.
Site research staff/ Research nurse	Blinded	The outcome assessors (trained research nurses) will be blinded to the trial treatment arm. All postoperative symptomatic questionnaires will be collected electronically directly from blinded patients or by telephone interviews conducted by blinded research nurses. Serious Adverse Event reports could results site staff become unblinded to a participant's treatment allocation if absolutely needed.
Chief Investigator	Not blinded	The Chief investigator will not be blinded to treatment allocation.
Database programmer	Not blinded	The database programmer is responsible for the management of randomisation system and the REDCap database and will have access to all unblinded datasets within both systems.
GOLF Study Management staff within SITU	Blinded	GOLF Study Management staff within SITU will remain blinded to treatment allocations as far as possible; there may be situations where site staff require support for randomisation and in these situations it is acknowledged that study management staff may become aware of treatment allocation but efforts will be made to ensure the blind where possible. Serious Adverse Event reports will be handled by the study team who may become unblinded to a participant's treatment allocation.
Data Management	Not blinded	Data management staff will have access to the unblinded datasets within the study randomisation system and database to ensure data quality and undertake central monitoring activities.
Study statistician and Senior Study Statistician	Not blinded	The study statistician and senior study statisticians will have access to treatment allocations or data needed for generating the Data and Safety Monitoring Committee (DSMC) closed reports and the final analysis.
Health Economist	Not blinded	

17.2 Code break/ unblinding

In the event a patient included in the trial seeks emergency medical attention for an urgent medical condition that might be related to either surgical procedure, or requires elective or emergency abdominal surgery, the treating physician and patient will be unblinded to support best patient care.

Participants will be provided with a Trial Card which will explain that they are part of the GOLF trial, that they may have had a LINX device implanted, also it will give the participant's study ID, site and PI along with the local site and out of hours contact details. Should the participant need urgent medical treatment, there will be sufficient ways for healthcare workers to contact the site or out of hours number in order to ascertain their trial allocation and therefore if the participant may safely receive specific clinical interventions (e.g., an MRI scan).

18 SAFETY REPORTING

The study will be run in accordance with University of Oxford Standard Operating Procedures (SOPs) and operational policies, which all adhere to all applicable UK regulatory requirements. For details of safety reporting for non-UK sites, please see the Appendix 3.4 Safety Reporting. An independent Data and Safety Monitoring Committee (DSMC) and a 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 if there are ethical or safety reasons why the trial should not continue. The TSC will monitor trial progress and provides independent advice. Both committees will comprise independent clinicians, statisticians, health service researchers and patient representatives from Heartburn Cancer UK. The project may be monitored by the Sponsor (University of Oxford) and progress reports will be submitted to NIHR.

18.1 Safety reporting period

Safety reporting for each participant will begin from randomisation and will end when the participant has reached their final main follow-up time point, at 24 months post-randomisation.

18.2 Definitions

An adverse event (AE)	Any untoward occurrence in a clinical study participant. *Note: An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom or disease temporarily associated with the study procedures, whether or not considered related to the procedures.*
Serious Adverse Event (SAE)	An AE that: • results in death • is life-threatening[1] • requires hospitalisation or prolongation of existing hospitalisation • results in persistent or significant disability or incapacity • is a congenital anomaly or birth defect; or • is otherwise considered medically significant by the Investigator[2]
Unexpected Serious Adverse Event	This is a term used to describe a serious adverse event related to the study (i.e. resulted from administration of any of the research procedures) and is unexpected (not listed in the protocol as an expected occurrence).

[1] 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

[2] Medical events that may jeopardise the participant or may require an intervention to prevent one of the above characteristics/consequences.

A distinction is drawn between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined using the criteria above. Hence, a severe AE need not necessarily be serious.

18.3 Expected adverse events

Potential expected adverse events are related to the surgical interventions under investigation and no additional risks are foreseen that occur as a result of taking part in the trial. The GOLF trial compares two standards of care within the NHS and thus consent for these surgical procedures will include consenting operative risks described below:

Bleeding, infection, blood clots, risk of general anaesthesia, injury to intra-abdominal organs including specific injury to the oesophagus, stomach or vagal nerve, reoperation, reintervention, death, long-term symptoms including dysphagia, gas bloating, inability to belch, change in bowel habit including diarrhoea, failure of surgical intervention to control symptoms or reflux.

18.4 Reportable SAEs

- Oesophageal or gastric erosion secondary to the LINX device
- Death within 90-days of surgery in either trial arm

18.5 Events exempt from recording as SAEs

- Reoperations within 90-days of surgery in either trial arm
- Endoscopic or radiological reintervention within 90-days of surgery in either trial arm
- Readmission within 30-days of surgery in either trial arm
- Migration of the LINX device within 90-days of surgery as documented by radiological or endoscopic imaging or direct surgical visualisation.

18.6 Procedure for collecting safety events from sites/participants

Complications that arise from surgery will be captured on the relevant CRFs for that time point and those which meet the definition of serious will be reported as SAEs on an SAE form to the trials Office. Only AEs that meet the criteria above and meet the definition of serious will be recorded.

SAEs, as defined above, experienced by a participant from their enrolment until their completion of the trial must be reported in the participant's medical notes, on the trial CRF, and reported to the CTU using the SAE Reporting Form, within 24 hours of observing or learning of the SAE(s). All sections of the SAE Reporting Form must be completed.

A SAE occurring to a participant will be reported to the 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 HRA report of serious adverse event form. For details of collecting safety events from participants during the study for non-UK sites, please see the Appendix 3.5 Collecting safety events from sites/participants.

18.7 Reporting of SAEs from sites to the study team

Only serious adverse events considered by the site PI, or appropriate delegate, to be related (possibly, probably, or definitely) to the study intervention/any of the research procedures will be reported immediately to the study team. Such events will be reported immediately to the study team as follows:

SAEs will be reported by the site study team using the SAE form within the REDCap study database within 24 hours of becoming aware of the event. 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. This should be e-mailed to golf@nds.ox.ac.uk within 24 hours of becoming aware of the event. The study team will acknowledge receipt of any SAEs reported via e-mail within one working day and provide the site with a unique SAE Log number.

18.7.1 Assessment of SAEs by the Principal Investigator (or delegate)

The Principal Investigator (or delegated individual) is responsible for assessing all reported serious adverse events for seriousness, causality and expectedness.

18.7.2 Relatedness/causality

The assessment of "relatedness" to the study intervention is the responsibility of the PI at site or an agreed designee according to the following definitions:

Relationship to intervention	Attribution (Causality)	Description
Unrelated	Unrelated	The AE is clearly NOT related to the intervention
	Unlikely	The AE is doubtfully related to the intervention
Related	Possible	The AE may be related to the intervention
	Probable	The AE is likely related to the intervention
	Definite	The AE is clearly related to the intervention

18.7.3 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 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.

18.8 Reporting of SAEs to the Research Ethics Committee (REC)

All intervention/study procedure related SAEs will be recorded and reported to the REC as part of the annual reports. All SAEs that are assessed as related and unexpected will be submitted to the REC within 15 days of the CTU/Sponsor becoming aware of the event. For details of reporting SAEs to the local research ethics committee for non-UK sites, please see Appendix 3.6 Reporting of SAEs to the Local Research Ethics Committee.

18.9 Unblinding of SAEs for reporting to the REC

Any serious unexpected SAEs related to the intervention that require reporting to the REC will be unblinded for reporting purposes. Unblinding will be performed, documented and communicated in accordance with University of Oxford Standard Operating Procedures.

18.10 Follow-up of Serious Adverse Events

If the SAE is a unexpected and related, then follow up information must be provided as requested by the study office. A follow-up report must be completed when the SAE resolves, is unlikely to change, or when additional information becomes available.

19 PREGNANCY

If a participant does become pregnant during their participation in the study, it does not need to be reported due to the nature of the intervention as concluded in the risk assessment of the study.

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 (SAP) that will be drafted early in the study and finalised prior to the final analysis data lock. The SAP will be written by the Study Statistician in accordance with the current University of Oxford 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

Sample size calculations are based on a hierarchical analysis, and non-inferiority between the study arms for reflux symptoms (GORD-HRQL) (primary outcome) and superiority in favour of the LINX procedure for gas bloating and inability to belch (core secondary outcomes).

Non-inferiority outcome: A non-inferiority margin was set at 2 scores in difference on GORD-HRQL based upon our previous systematic review,[15] co-investigator consensus and patient workshops. For a one-sided alpha level of 0.025 and expecting 10% of loss to follow-up, 230 patients per group will be necessary to show non-inferiority with 90% power.

Superiority outcomes: We assumed a two-sided alpha level of 0.05 and 10% of loss to follow-up for the superiority outcomes. Regarding post-operative gas bloating, meta-analysis prevalence's estimate of post-operative gas bloating of 30.1% for fundoplication and a meta-analysis of efficacy showed an odds ratio of 0.34 in favour of LINX,[15] which correspond to a 12.7% prevalence of gas bloating for LINX. Thus, a reduction of 17.4% of post-operative gas bloating from 30.1% to 12.7% is hypothesised. According to those parameters 144 patients per group will be necessary to verify that change with 90% power.

Sample size: We decided upon the larger number of patients needed for the primary outcome, i.e. a total of 460 patients (230 per group) which allows for a 10% of loss to follow-up.

20.3 Justification for the follow-up period

Our previous research identified the majority (94%) of anti-reflux surgery patients who require reoperation or go back onto their anti-GORD medications will do so within 24 months of surgery.[10]

Thus the follow-up period of 24 months has been chosen to establish the value of the laparoscopic LINX procedure over laparoscopic fundoplication.

20.4 Description of Statistical Methods

Results will be reported in line with the CONSORT statement and any appropriate extensions and will be described fully in a separate Statistical Analysis Plan.

Interim pilot study

At the end of the internal pilot the results will be checked to ensure that the targets for recruitment and centres have been met and whether the trial should continue. At that time an interim analysis will also be performed to display the results and inspect the efficacy. Should the adverse event rates rise above what is typically expected to be reported, this will be reviewed by the DSMC.

Full RCT

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.

The analysis of the GORD-HRQL will be performed by a linear mixed model. This model will produce as output an adjusted GORD-HRQL score based on the fixed and random effects. It will take into account, as the fixed effects, the intervention group, as well as the age, sex, BMI and preoperative DeMeester score. It will consider, as the random effects, a random intercept by centre. An interaction between the random intercept centre and the intervention will also be included in the model. The model will be run and the output adjusted GORD-HRQL scores will be compared.

The effect of the LINX on the GORD-HRQL will be tested and quantified through mean differences between groups, adjusted on the factors included in the model; the 97.5% unilateral confidence interval of the mean differences will be provided. A transformation of the primary criterion may be performed to fulfil the assumptions of the linear mixed model.

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

20.4.1 Primary outcome

Assessment of symptomatic GORD and HRQL will be using the GORD-HRQL questionnaire at 24 months following surgery.

20.4.2 Secondary outcome(s)

We will assess the following secondary outcomes:

- Prevalence of gas bloating at 24 months postoperatively.

- Prevalence of inability to belch at 24 months postoperatively.

Other secondary outcomes are:

- Prevalence of symptomatic GORD, inability to belch and gas bloating at 6 weeks, 6 and 12 months after surgery.
- Severity of dysphagia and regurgitation at 6 weeks, 6, 12 and 24 months postoperatively.
- Global HRQL, measured by EQ-5D-5L at 6 weeks, 6, 12 and 24 months postoperatively.
- Utilisation of anti-GORD medications at 6 weeks, 6, 12 and 24 months postoperatively.
- 24-hour pH-measurement at 12 months postoperatively.
- 30-day, 90-day, 12 and 24-month postoperative complication rates, including pneumonia, wound infection, reoperation and endoscopic reintervention.
- Cost-effectiveness of both treatments as measured by incremental cost per quality adjusted life year (QALY).

20.5 Inclusion in analysis

The principal analysis will be performed on the as randomised ("intention to treat") population, analysing participants with available outcome data in their randomised groups, regardless of adherence. The study will be reported in line with Consolidated Standards of Reporting Trials (CONSORT) guidelines.

20.6 Interim analyses

An interim analysis will be performed in month 14 to determine if any major benefit or efficacy is shown to either procedure compared to the other. If this recruitment target is met and efficacy is shown in the interim analysis, the trial will continue to recruit for a further 16 months. Data from the internal pilot phase will be included in the final analysis.

20.6.1 Stopping rules

An independent Data and Safety Monitoring Committee* (DSMC) will review the accumulating data at regular intervals and may recommend pausing or stopping the study in the event of safety concerns.

20.7 Level of Statistical Significance

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.

20.8 Procedure for accounting for missing data

The procedure for handling spurious or missing data will be described in the SAP. The study will attempt to collect data as completely as possible. The sample size calculation incorporated an inflation to account for 10% potential loss to follow-up.

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

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

20.10 Internal pilot/Decision Points

An internal pilot is planned that will progress seamlessly to the definitive study if predefined progression criteria are reached. Data from the internal pilot trial will contribute to the final analysis. The purpose of the internal pilot is to evaluate the willingness of patients to participate in terms of recruitment and randomisation to this RCT, and also the comparative efficacy of the procedures.

Stop-go criteria will be reviewed at month 14 (8th month of recruitment) to ensure a minimum 15 centres are active and recruiting 1-3 patients/centre/month, thus in total 121 patients being recruited to the RCT at this time-point. An interim analysis will be performed at this time-point to determine if any major benefit or efficacy is shown to either procedure compared to the other. If this recruitment target is met and efficacy is shown in the interim analysis, the trial will continue to recruit for a further 16 months. Data from the internal pilot phase will be included in the final analysis. The following stop-go criteria are proposed for review by the Trial Steering Committee (TSC) after 8 months of recruitment.

Stop-go criteria for the pilot phase are given in table 4 together with the definitions of how each will be measured.

Table 4: Stop-go criteria for internal pilot phase.

Target	**Actual recruitment in 8 months**		
15 centres with 121 patients recruited	121 patients and 15 centres open	80 – 120 patients and 8 to 14 centres open	<80 patients and <8 centres open
Stop-Go criteria	• Recruitment feasible • Proceed with study	• Review • recruitment strategies* • Report to TSC • Continue but modify and monitor closely	• Recruitment not feasible • Decision not to proceed

**Consider extending the trial to other UK centres and other countries, including Sweden, Netherlands and Spain. Centres from these countries have agreed to participate at any point if recruitment is a challenge with the GOLF trial.*

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 Monitoring Committee (DMC) will perform a full review towards the end of the internal pilot. The TSC and funder would make the final decision to terminate the study.

The internal pilot study will mirror the procedures and logistics undertaken in the main definitive study. It is intended that the study will progress seamlessly into the main phase, with internal pilot participants included in the final analysis. Should a decision be made to stop the study all study 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 HEALTH ECONOMICS – APPLICABLE TO UK SITES ONLY

We will conduct a within-trial analysis to assess the cost-effectiveness of laparoscopic LINX compared to fundoplication. 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.[38,39] The primary outcome measure used in the health economics study will be incremental cost per quality adjusted life year (QALY). We will follow good practice guidelines when undertaking the economic evaluation analysis.[38,39]

We will use a resource use questionnaire to collect all healthcare (primary care appointments, prescribed and over the counter medications, hospital admissions, contact with other healthcare

professionals) and non-healthcare resource use (time off work) of patients undergoing any of the procedures assessed in the trial. The questionnaire will be administered to patients at baseline, 6 weeks, 6, 12, and 24 months after surgery. The resources used will be valued using national cost databases such as NHS Reference costs and Prescription Cost Analysis.

The EQ-5D-5L instrument[39] will be used to measure HRQL at baseline, 6 weeks, 6, 12, and 24 months after surgery. The EQ-5D-5L instrument will be valued using NICE recommendations at the time of the analysis, using a UK value set or converted into the EQ-5D-3L with a cross-mapping algorithm[40] and valued using the UK set for EQ-5D-3L[41]. 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, standard deviation as a minimum) for resource use, costs, and EQ-5D utilities at each follow-up time point. We will describe baseline difference in resource use and utilities between the trial arms and adjust for these differences using the most appropriate recommended method.[41] 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.[43] 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 incremental cost-effectiveness ratio (ICER) will be compared against the threshold used to establish value for money in the NHS (currently between £20,000 and £30,000 per QALY).[38] 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 laparoscopic LINX is more cost-effective than the fundoplication for different threshold values per QALY gained.[44] 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.

22 DATA MANAGEMENT

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

22.1 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 medical records, laboratory records, participant, patient-reported outcome measures that are submitted directly to the coordinating centre and correspondence. Source data is outlined in section 9.

22.2 Location of source data

The location of source data in the study is listed in the tables within the section 9.

22.3 Case report forms (CRFs)

The Investigator and study site staff 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.

Source data to be recorded directly on the CRFs

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

22.4 Non-CRF data

All study data will be recorded on the CRF. The intraoperative video recording data will be securely electronically transferred from participating sites to the Secure Data Environment server within the University of Bristol Research Data Storage Facility (RDSF). This will be kept there for review of the surgical quality assurance processes described below and long-term secure storage for the study.

Following data generated will not be recorded on a study CRF/entered into the study REDCap database:

Table 5: Non-CRF data

Non-CRF data	Use of non-CRF data
Surgical videos to assess intraoperative surgical performance	Surgical videos will be stored securely at the University of Bristol Research Data Storage Facility (RDSF) to allow for monitoring of operative performance during the trial. At the end of the trial surgical videos stored at the university of Bristol will be destroyed. Surgical videos stored at the University of Oxford will be paired with clinical data from the trial in a translational piece of research described in section 11.1.

22.5 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, audits and inspections. The data submitted by study participants directly via the study database (i.e. electronic participant reported outcomes) will also be made available to the participating site that recruited the participant; this is detailed within the PIS so that participants are aware of who will have access to this data.

22.6 Data Recording and Record Keeping

The case report forms will be designed by members of the study team which will include the Chief Investigator, study statistician(s) and study manager.

Data will, wherever possible, be collected in electronic format with direct entry onto the study database by site staff 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 will be encrypted in transit between the client and 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 study team based on their role within the study.

The database and server are backed up to a secure location on a regular basis. Details of the data collected, where it is stored and who has access to it along with a fair processing statement will be available for the participants within the study participant information sheet. 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, NHS Trust or regulatory authorities 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 the University of Oxford standard operating procedures which comply with the UK GDPR Data captured during phone calls to participants will be entered into the study database by suitably trained central office or site 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)

Refer to section 26.5 for details about retention of participant identifiable data.

22.7 Electronic transfer of data

Any electronic transfer of data during the course of the study will be strictly controlled in accordance with the University of Oxford Standard Operating Procedure for Secure Information/Data Transfer.

22.8 Mechanistic study surgical video data

All operations within the GOLF trial will be performed with a minimally invasive approach, either laparoscopically or robotically, which will facilitate the recording of all surgical procedures. All surgical videos will be scored using a video-based analytical tool for fundoplication and the LINX procedure. This scoring will be fed back to surgeons during the trial to facilitate monitoring of

operative performance and good surgical practice within the trial. At the end of the trial data from the scoring of surgical videos will be paired with patient clinical outcome data, to evaluate which steps of surgical technique are critical in both procedures to determining the outcome of the patients. This will provide invaluable understanding for the future of clinical implementation of both techniques after the trial and future assessment of intraoperative surgical performance. All surgical videos will be analysed in collaboration between the University of Bristol group led by Professor Natalie Blencowe and the chief investigator Professor Sheraz R. Markar.

22.9 QRI data - UK sites only

GOLF-eligible patients will be given a unique identifying number (GOLF Study ID). All QRI-related data will be labelled by the reference number (with no personal information).

Study discussions and research interviews will be recorded using encrypted audio-recorders (or Sponsor/Trust-approved recording or video-conferencing tool) and transferred securely to and retained by the University of Bristol. If a video-conference platform is used to record discussions, only the audio file will be transferred and retained for analysis. Site staff will upload consultation audio files through the study's REDCap database which will be accessible to the University of Bristol's GOLF QRI team. If this is not possible, then an alternative Trust-approved secure encrypted electronic data transfer system will be used, or the QRI researcher will provide an encrypted device (memory stick or a second encrypted audio-recorder) to transfer the audio recordings from the recruiting site to the University of Bristol. Separate communication (via secure email) will confirm the password to the encrypted device.

Recordings will be transcribed by University of Bristol employees or University approved transcription services. The transfer of recordings and transcripts will adhere to the secure transfer of recordings/transcripts procedure specified by the University. Transcripts will be labelled with the study-assigned participant number and edited to ensure anonymity of respondents. Anonymised quotations and parts of voice modified recordings may be used by authorised members of the University of Bristol for training, teaching, research and publication purposes for GOLF and other similar studies to improve how such studies are explained to potential participants. Anonymised transcripts may also be made available by controlled access to researchers outside of the GOLF study and University of Bristol (if they secure the necessary approvals) for purposes not related to the GOLF study, subject to individual written informed consent from participants.

All data from the QRI will be stored securely on the University of Bristol servers for up to 20 years, adhering to the University's data storage policies. Information about how the data are stored and used is provided in the information leaflet, and participants will confirm they consent for their data to be used in this manner.

23 QUALITY ASSURANCE PROCEDURES

A rigorous programme of quality control will be implemented. The study management group will be responsible for ensuring adherence to the study protocols at the study sites. Quality assurance (QA) checks will be undertaken by SITU to ensure integrity of randomisation, study entry procedures and data collection. The University of Oxford has a QA team who may monitor this study by conducting audits (at least once in the lifetime of the trial, more if deemed necessary) of the Trial Master File. Internal audits for QA by the study team will be performed in accordance with the specifications of the Trial-specific Monitoring Plan. The University of Bristol may also conduct audits for the QRI

component of the study. 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.

23.1 Risk Assessment

This protocol is designed to deliver a risk-adapted approach to conducting the research. A risk assessment has been conducted and a monitoring plan will be prepared before the study 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 study or in response to outcomes from monitoring activities. Monitoring plans will be amended as appropriate.

23.2 Study monitoring

Monitoring will be performed by the 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 form 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 site visit, as necessary, to ensure their proper conduct of the study. Study Office staff will be in regular contact with site 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.

23.3 Audit and regulatory inspection

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 or inspections 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/inspectors direct access to all relevant documents, study facilities and to allocate their time and the time of their staff to facilitate the audit or inspection visit. Anyone receiving notification of a Regulatory Inspection or audit that will (or is likely to) involve this study must inform the Study Office without delay.

23.4 Trial committees

23.4.1 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.

23.4.2 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 annual basis. The DSMC will review the safety data generated, including all safety data 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.

23.4.3 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 study 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.

24 IDENTIFICATION AND MANAGEMENT OF PARTICIPATING SITES

24.1 Identification of recruitment sites

Recruitment sites 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.

24.2 Study site responsibilities

The Principal Investigator (the PI or lead clinician for the study site) has overall responsibility for the conduct of the study but may delegate responsibility where appropriate to suitably experienced and trained members of the site study team. All members of the site study team must complete

delegation log 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.

24.3 Study site set up and activation

The Principal Investigator leading the participating 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 participants.

24.4 Training

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

24.5 Study documentation

The study office will provide an electronic Investigator Site File to each participating site containing the documents needed to conduct the study. The study office must review and approve any local changes made to any study documentation including participant 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.

25 ETHICAL AND REGULATORY CONSIDERATIONS

25.1 Declaration of Helsinki

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

25.2 Guidelines for Good Clinical Practice

The Investigator will ensure that the study is conducted in accordance with relevant regulations and with the principles of Good Clinical Practice.

25.3 Ethical conduct of the study and ethical approvals

The protocol, participant 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 Research Ethics Committee (REC), HRA and host institution. For details of ethical conduct of the study and ethical approvals for non-UK sites, please see Appendix 3.7 Ethical conduct of the study and local ethical approvals.

25.4 NHS Research Governance in the UK

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

25.5 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 as applicable for the amendment type. 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 participants (or their authorised representatives, if applicable) whenever new information (in nature or severity) becomes available that might affect the participant's willingness to continue in the study. The Investigator must ensure this is documented in the participant's medical notes and the participant is re-consented if appropriate.

25.6 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 Trial Management Group (TMG). Deviations will be handled and reviewed in a timely manner in accordance with a study-specific Data Management and Monitoring Plan.

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 section 25.9).

25.7 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.

25.8 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 as 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 study 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 study this will be reported as an early termination.

25.9 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 study 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 in the UK. For details of serious breaches for non-UK sites, please see the Appendix 3.8 Serious Breaches.

25.10 Study Reports

This protocol will comply with all current applicable Research Ethics Committee and Sponsor reporting requirements.

25.11 Transparency in Research

Prior to the recruitment of the first participant, the study will be 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. A Final Report will be submitted to the REC containing a lay summary of the study results which will be published on the HRA website. For details of transparency in research for non-UK sites, please see the Appendix 3.9 Transparency in Research.

25.12 Use of social media

Social media (e.g., Twitter feeds or equivalent) may be utilised to promote the study, and acknowledge when milestones are met (e.g., sites open to recruitment, first recruitment ay a site etc).

26 PARTICIPANT CONFIDENTIALITY

26.1 Collection and use of personal identifiable information

Contact details (e.g. e-mail addresses/phone number) will be collected in this study for the following purposes, and where an activity is optional, only with the specific consent of the participant:

- Sending of follow-up questionnaires and any reminder messages
- Sending text messages regarding follow-up questionnaires
- Sending of responsive text messages

- Contact about future research
- Sending a copy of the completed consent form by e-mail (for any participants that consent electronically and wish to receive a copy by e-mail)
- Research interviews as part of the QRI
- Collection of outcome data from NHS Digital (NHS number). For details for non-UK sites, please see the Appendix 3.10 Collection and use of personal identifiable information.

The participant information sheet explains what contact details will be collected and how these will be used; explicit consent will be obtained for this.

Site staff at participating sites will ensure that contact details for study participants are up to date when participants attend for study visits.

Where remote eConsent is used, participants will be asked to give their permission verbally for a link to the consent documentation to be sent to their e-mail address or an e-mail address they provide.

26.2 Use of audio/visual recording devices

All surgical procedures will be recorded and stored as videos to assess intraoperative surgical performance as described above. These videos will be stored and transferred securely from local sites to the University of Bristol Research Data Storage Facility (RDSF) central repository and then also transferred and stored securely at the University of Bristol for the duration of the trial. Please refer to section 33.3. for details of the data retention period.

26.3 Storage and use of personal data

Personal data during the study will be stored and used in accordance with the University of Oxford Standard Operating Procedure for confidentiality, protection and breach of personal data in relation to research subjects. This ensures that all personal data collected during the study is recorded, handled and stored in such a way that is satisfies the requirements of the UK General Data Protection Regulation and requires data to be anonymised as soon as it is practical to do so.

All electronic patient-identifiable information will be held on a secure, password-protected database accessible only to authorised personnel. Paper forms with patient-identifiable information will be held in secure, locked filing cabinets within a restricted area. The processing of the personal data of participants will be minimised wherever possible by the use of a unique participant study number on study documents and in any electronic databases, such as REDCap in University of Oxford; and for stored video recordings and consultation recordings and staff/patient interviews in REDCap and in University of Bristol servers.

Personal data on all documents will be regarded as confidential. The study staff will safeguard the privacy of participant's personal data.

The use of all personal data in the study will be documented in a study-specific data management and sharing plan which details what and where personal data will be held, who will have access to the data, when personal data will be anonymised and how and when it will be deleted.

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

Data Breaches will be highlighted to the relevant site staff and reported as required by the UK GDPR and Data Protection Act 2018. This will also be deemed a protocol deviation. For details of storage

and use of personal data for non-UK sites, please see the Appendix 3.11 Storage and use of personal data.

26.4 Access to participants' personal identifiable data during the study

Access to participants personal identifiable data will be restricted to individuals authorised to have access. This includes a) members of the site study team at participating study sites with delegated responsibility by the site Principal Investigator and b) members of the study team involved in the conduct/management of the study where this is necessary for their role.

Research staff that are not part of the participant's direct healthcare team will not have access to personal identifiable data until the participant has given their consent to take part in the study or the participant has indicated to their direct healthcare team that they wish to be contacted by a member of the site study team – permission for this will be recorded in the participant's medical notes.

The participant information sheet clearly describes who will have access to the participants personal identifiable data during the study and explicit consent is obtained from study participants for such access.

Participants will be asked to consent to relevant sections of their medical notes and data collected during the trial being looked at by individuals from the University of Oxford, from regulatory authorities [and from the NHS Trust(s)], where it is relevant to their taking part in this trial; only authorised individuals will be granted access where this is necessary for their role. For details of access to participants' personal identifiable data during the study for non-UK sites, please see the Appendix 3.12 Access to participants' personal identifiable data during the study.

26.5 Destruction of personal identifiable data

Explicit consent for the storage and use of personal identifiable data (which includes consent forms) will be obtained from participants as detailed in the Participant Information Sheet and Informed Consent Form.

Personal identifiable data will be destroyed as soon as it is no longer required – the time point for this destruction is detailed in the study data management plan and is in accordance with Sponsor standard operating procedures which comply with the UK GDPR. For details of data destruction of personal identifiable data for non-UK sites, please see the Appendix 3.13 Destruction of personal identifiable data.

Personal identifiable data may be retained longer than the duration of study.

26.5.1 Participant Identification Log

The site study team must keep a separate log of enrolled patients' personal identification details as necessary to enable them to be tracked. These documents must be retained securely, in strict confidence. They form part of the Investigator Site File and are not to be released externally.

27 PUBLIC AND PATIENT INVOLVEMENT

27.1 PPI in study design and protocol development

We sought to understand the patient perspective on four key questions associated with the study design.

- What were positive and negative experiences that patients had following anti-reflux surgery?
- Would patients be willing to be randomised between the laparoscopic LINX procedure vs. fundoplication?
- Would patients be willing to be blinded (unaware) of which specific procedure they had had for the duration of the clinical trial?
- Which of the Health-Related Quality of Life (HRQL) tools did patients feel most accurately captured their symptoms before and after anti-reflux surgery?

To address each of these questions we undertook an electronic questionnaire study, which was sent to former patients who had received anti-reflux surgery (LINX procedure or fundoplication) from Oxford and London. We received responses from 86 patients to allow us to address each of the questions described above. As expected from the published literature and our own surgical experience there was a large degree of variation in patient experience following anti-reflux surgery. Similar to the published literature many patients following fundoplication had returned to taking their medical therapy (58%), compared to 32% following the LINX procedure. The most commonly reported side effects seen after fundoplication were gas bloating (44%), dysphagia (28%) and inability to belch (34%). There was overwhelming agreement from patients for the need for an RCT (88%) when presented with the results of our previous meta-analysis.[15] There was slightly less agreement (76%) that patients would be willing to be blinded to which specific procedure they had received for the duration of the clinical trial. Finally, the majority of patients (86%) felt that the GORD-HRQL tool captured the breadth of their symptoms and would be most appropriately utilised in the current trial.

Following this questionnaire study, we undertook two virtual patient workshops with former patients who had received anti-reflux surgery (LINX procedure or fundoplication) from Oxford and London and patient representatives from Heartburn Cancer UK and GUTS Charity UK.

Key outputs from these workshops included:

- Outcomes; there was absolute agreement that the main outcomes from this trial should be patient reported outcomes. The majority of patients also agreed that the GORD-HRQL tool does capture their pre- and postoperative symptoms adequately to be utilised in the trial.
- Blinding; there was mixed feelings as to whether blinding was absolutely necessary within the trial. However, consensus was gained in favour of blinding, once the primary outcome and key secondary outcomes were discussed. Furthermore, through these patient workshops, we developed and gained consensus upon the criteria for unblinding within the trial.
- Patient dissemination strategy; this was discussed at length as to how best to reach patients with the results of the trial. A combined strategy using the engaged patient groups, through their multi-media links was designed, along-with presentation at their quarterly meetings with updates from the trial.

Patients and the public will continue to be actively involved throughout the trial.

PPI advisory group: Representatives from the Heartburn Cancer UK, Oxfordshire Oesophageal and Stomach Organisation (OOSO), GUTS charity UK, and former anti-reflux surgery patients (both following LINX and fundoplication procedures) will all be part of the trial PPI advisory group during the trial, including the assessment after the pilot stage of the trial. Members of the PPI advisory group will be involved in the design and final approval of the participant information sheet, the family information sheet and consent form for the GOLF trial. Their involvement is vital to help make the language and the information content of these documents understandable to patients and families at a period of great stress, and to make them relevant to recruitment centres across the UK.

27.2 PPI during the study

Individuals from the PPI advisory group who agree to contribute to the management of the project will meet the Clinical Trials Unit (CTU) individually, to gain understanding of their previous involvement in clinical trials (if any). Appropriate training will be offered and participation will be tailored appropriately. The induction pack for PPI contributors on Trial Oversight Committees is invaluable preliminary reading.

A short video for potential participants describing the trial will be available on the CTU website. The lead applicants will explain the background and rationale for the trial, and what participation would entail. Patient/carer feedback for this will be vital, for which we will engage the PPI advisory group. Furthermore, a number of former patients have expressed a desire for involvement in writing of the participant information sheet, and relevant details for inclusion on the trial website. In addition, with appropriate permission, short videos will be made available of trial participants, providing their real life experience of inclusion (e.g. questions askes, assessments undertake, etc).

27.3 Dissemination of study results

As a NIHR funded project, the standard monograph will be produced. We will be working with our PPI advisory group and patient co-investigator to ensure any plain English parts of the monograph are phrased appropriately to ensure that the findings can be interpreted correctly by all audiences, and we would hope to produce an infographic if possible, to explain the findings.

With our patient co-applicant, and the PPI advisory group mentioned above, communication for patients/carers and the public will be developed. Newsletters, Facebook, Twitter etc. will be used to ensure the results of GOLF are communicated to the wider community once they are available. In addition, the GOLF study team will follow the Public Involvement Impact Assessment Framework to maximise PPI in the trial.

28 EXPENSES/PAYMENTS TO PARTICIPANTS

All research activity is conducted during routine standard of care visits; no payments will be made to study participants for taking part in this study

29 SPONSORSHIP, FINANCE AND INSURANCE

29.1 Sponsorship

The Sponsor will provide written confirmation of Sponsorship.

29.2 Funding and support in kind

The table below provides a summary of all funding and support in kind for the study.

Funder(s)	Financial and non-financial support given
National Institute for Health and Care Research (NIHR) Efficacy and Mechanism Evaluation (EME) Programme	NIHR152268

29.3 Insurance

The Sponsor (University of Oxford) 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. For details of insurance arrangements for non-UK sites, please see the Appendix 3.14 Insurance.

30 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.

The Sponsor will also set up written agreements with any other external third parties involved in the conduct of the study as appropriate.

31 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, statistical analysis plan (SAP), health economics analysis plan (HEAP) will be in accordance with University of Oxford Standard Operating Procedures 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 Template for Intervention Description and Replication (TIDieR) and CONSORT Non-Pharmacologic Treatment Interventions (CONSORT-NPT) Statements for reporting will be employed to ensure replication is possible.

31.1 Study results

All data will be presented such that no individual participants can be identified.

31.2 Dissemination of study results to participants

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 study will be presented nationally at the Association for Upper Gastrointestinal Surgeons for Great Britain and Ireland (AUGIS)) and internationally at the United European Gastroenterology

Week (UEGW), International Society for Diseases of the Esophagus (ISDE), and European Association of Endoscopic Surgery (EAES) conferences.

Publications: Results will usually be published in appropriate peer-reviewed, open access journals, as well as the NIHR Journals Library. 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. This will permit dissemination of the results beyond the realms of general surgery.

Public Dissemination: To ensure a broad campaign we will target a range of social media outlets (this may include an 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'.

All participating patients will be asked at the time of recruitment if they would like to receive a copy of the trial results. This document will be written collaboratively with clinicians and patient representatives and distributed accordingly. The wider public will be alerted via links with relevant organisations/charities, and the Research Media Offices. Engagement with the NIHR Dissemination Centre will ensure global awareness of study findings. Moreover, the University of Oxford, Oxford University Hospitals NHS Trust and University of Bristol have professional communication officers who will be engaged. It is anticipated that together with these individuals, and NIHR equivalents, we will agree upon effective communication strategies including co-ordinated press releases, interviews and possible articles for general practitioners and others for lay people.

Oxford Surgical Interventional Trials Unit (SITU) maintains a list of all ongoing and completed trials, with all publications on its website even when trial websites are archived. Given the potential involvement of at least 16 centres in the UK, and the positions held by co-applicants and collaborators within the national and international upper GI surgical community, the results will rapidly reach surgical teams, ensuring the trial findings will improve clinical practice and service delivery for GORD patients within the NHS and elsewhere. With our patient co-applicant, and the patient advisory group mentioned above, communication for patients/carers and the public will be developed. Newsletters and social media (Facebook, Twitter etc). will be used to ensure the results of GOLF are communicated to the wider community once they are available.

Implementation into National and International guidelines: Should the LINX procedure prove advantageous, it is expected that the NICE guidelines will be updated. Currently 16 upper GI surgical 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. Furthermore, the European Society for Diseases of the Esophagus and the European Association of Endoscopic Surgery have agreed to endorse and utilise the guidelines that will be developed following completion of this trial. Wider dissemination of the LINX procedure will facilitate the need for surgical training in the technique, similar to what was developed in the National Training Programme in Laparoscopic Colorectal Surgery (Lapco).[50] The broader advantage of the robustly developed SQA programme and mechanistic research outlined above will provide the technical material and scientific basis for development of such a national training programme.

31.3 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 study must acknowledge the contribution of participants, funder(s), SITU and the Sponsor.

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

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.

All results shall be owned by the Lead (as per standard NIHR terms), with the exception of the QRI work which is owned by Bristol. All collaborators including Bristol licence to use the Results for academic and non-commercial research purposes, including research projects funded by third parties (including commercial entities) provided that those parties gain or claim no rights. SQA methods developed during GOLF would be considered Results, and owned by Oxford as the lead, but with Bristol and other collaborators given an academic license.

33 ARCHIVING

33.1 Minimum Mandatory archiving period

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

The minimum mandatory archiving period for essential study documents for this study is 3 years following publication.

33.2 Archiving responsibilities/procedure

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 as specified above.

33.2.1 Sponsor Trial Master File

All paper and electronic data including the Trial Master File and study database will be retained and archived in accordance with Sponsor's standard operating procedures which are compliant with the UK GDPR.

33.2.2 Investigator Site File and participant medical records

The Investigator Site Files will be archived at the participating site. The medical files of study participants must be retained for maximum of five years after the study has finished or as per local Trust policy for medical notes retention. Sites should comply with the documentation retention specified in the clinical trial agreements issued by the trial Sponsor. For details of insurance arrangements for non-UK sites, please see the Appendix 3.15 Investigator Site File and participant medical records.

33.3 Retention of data sets

Trial data and associated metadata 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 mandatory

archiving period the TMF and associated archived data sets will be destroyed or transferred as appropriate, according to any data sharing requirements. Surgical video recordings and QRI-related data will be retained for up to 20 years by the University of Bristol.

34 DATA SHARING

The study statistician and health economist may retain copies of anonymised datasets for the purpose of data sharing in accordance with the study data sharing plan. University of Bristol researchers will collaborate on the surgical quality assurance and assessment of intraoperative videos as described above, and thus data will be securely shared with them. The University of Bristol Research Data Storage Facility (RDSF) is designed for bulk long-term storage. The RDSF is secure and backed up, preventing any loss of data. Remote data uploads will be sent via the Secure File Transfer Protocol (SFTP) a network protocol for securely accessing, transferring and managing large files and sensitive data. The SFTP protocol prevents any third party reading the exchanged data.

34.1 Retention of anonymised datasets

Upon completion of the trial, and with appropriate participant consent, anonymised research data may be shared with other organisations on request to the Chief Investigator and in accordance with the data sharing policies the Sponsor and funder(s).

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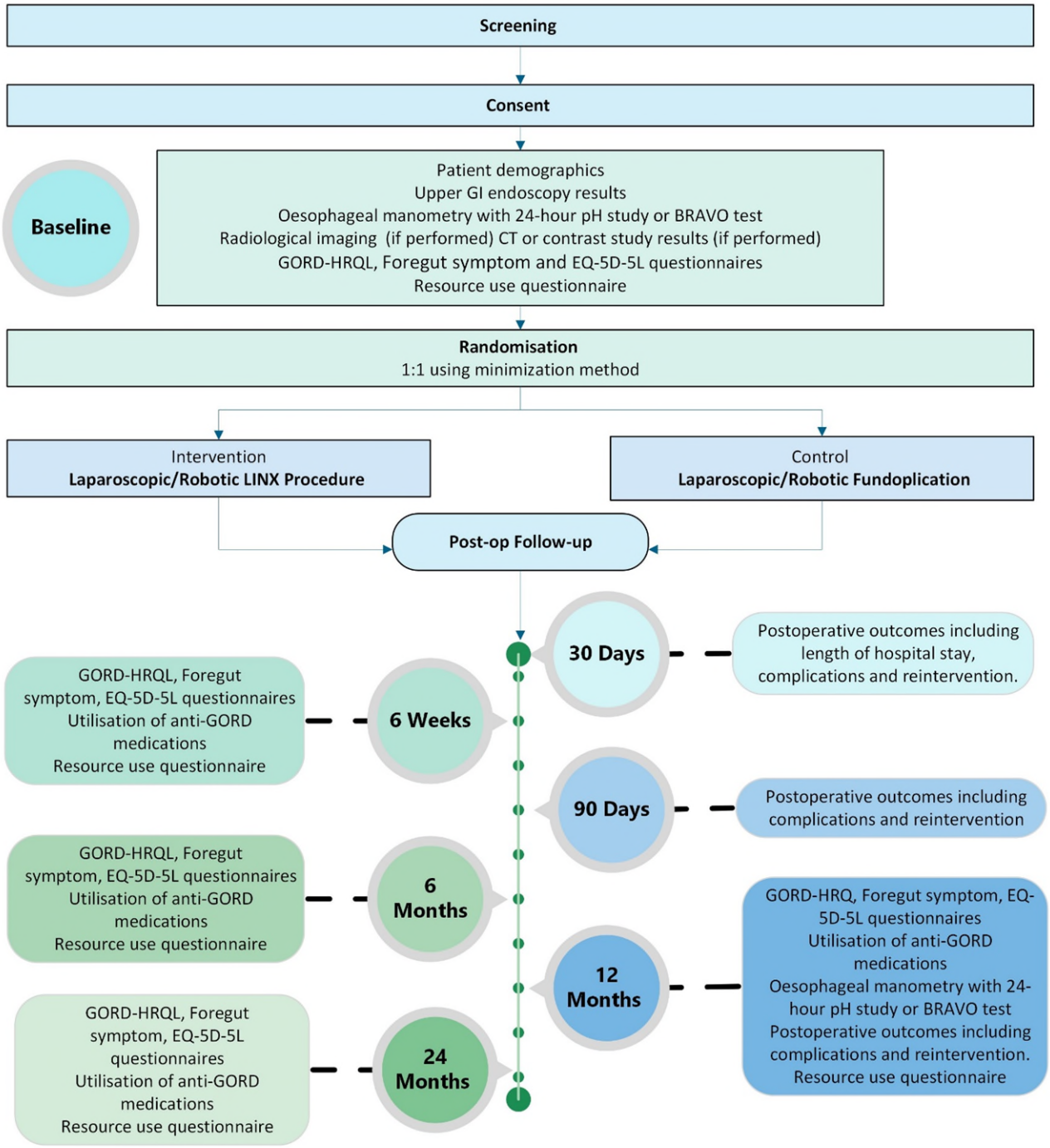
36 VERSION HISTORY

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 – delete if using template for an amendment
3.0	10 April 2025	The changes from the previous version are as follows:

		1. Correction of minor typographical errors 2. Modification to credentialling of surgeons to allow those who have already performed 20 LINX procedures to join trial without a need to upload videos.

APPENDIX 1 – STUDY FLOW CHART



APPENDIX 2 – DIET ADVICE FOR LINX

•We want people to resume a normal diet immediately following surgery and you will be asked to eat a sandwich or equivalent before you leave hospital following your surgery. It is important that you eat at least two- three normal (small) meals every day to ensure that the LINX is being exercised. We would also recommend snacking in-between meals

• If you are struggling slow down: one bite every 30 seconds if things are not going down easily.

• Swallowing may be temporarily worse around 2-4 weeks. It is important that you continue to eat regular food during this time, even if the food feels as though it is getting stuck.

There is not a specific list of foods to eat during recovery from LINX surgery. Each patient tolerates different consistencies at different times of their recovery, and some patients have no difficulty swallowing after surgery. Gradually increase your diet over the next weeks as your body permits. We do like foods though that add bulk. Physical therapy for the oesophagus – swallow something every few hours.

It is a normal healing process for the body to form scar tissue (capsule) around the oesophagus and LINX. It is essential that the scar tissue remains flexible for the LINX to function properly – so it needs regular stretching. To stretch the scar tissue please eat a normal diet immediately following surgery, as this will be equivalent to doing physio on your gullet. This can be uncomfortable at times, but is the most important part of your recovery, so keep doing it even if uncomfortable. You may also have 3-4 snacks between meals per day. Eat slowly – wait one minute in between each bite.

The oesophagus generates better pressures with semi-solid foods and exercise the LINX better than liquids. If liquids are not going down well, the first thing we recommend is taking a few crackers or soft mushy foods; the higher pressures from more solid foods will often help clear the liquids as well.

Warm or room temperature liquids tend to be more comfortable than cold. Cold liquids lead to the weakest pressures (meaning more difficult for things to go down). Small sips frequently are helpful to prevent dehydration. Sometimes a sip of carbonated beverage helps to pressurize and push food through. Not more than a sip.

APPENDIX 3 – SPECIFICATIONS FOR NON-UK SITES

Any change to the appendix will be subject to change by amendment.

Appendix 3.1 LINX Device Removal

Appendix 3.2 Completion of Informed Consent Form

Appendix 3.3 Study Questionnaires

Appendix 3.4 Safety Reporting

Appendix 3.5 Collecting safety events from sites/participants

Appendix 3.6 Reporting of SAEs to the Local Research Ethics Committee

Appendix 3.7 Ethical conduct of the study and local ethical approvals

Appendix 3.8 Serious Breaches

Appendix 3.9 Transparency in Research

Appendix 3.10 Collection and use of personal identifiable information

Appendix 3.11 Storage and use of personal data

Appendix 3.12 Access to participants' personal identifiable data during the study

Appendix 3.13 Destruction of personal identifiable data

Appendix 3.14 Insurance

Appendix 3.15 Investigator Site File and participant medical records