Study Title: PLUG: a single-arm study - Feasibility study investigating the Prevention of post-operative gastro-oesophageal anastomotic Leaks with the Use of a surgical adhesive, BioGlue

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Sponsor:	Portsmouth Hospitals NHS Trust
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We are asking through the patient support group

PLUG

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1. AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made

2. SYNOPSIS

Study Title	Feasibility study investigating the Prevention of post-operative gastro-oesophageal anastomotic Leaks with the Use of a surgical adhesive, BioGlue – the PLUG trial: a single-arm trial
Internal ref. no.	PHT/2019/72
Problem statement	A leak from the gastro-oesophageal anastomosis in the post-operative period following an oesophagectomy is a serious, and unfortunately not uncommon, complication (1) (2). Leaks are known to prolong stay, worsen long term outcomes and have significant morbidity as well as mortality and need for return to theatre (3) (4). For patients suitable for resection in the form of oesophagectomy, current evidence shows that minimally invasive oesophagectomy, with a laparoscopic and thoracoscopic approach, gives better outcomes (5) (6). This study will use a pre-existing surgical adhesive in a novel way, to supplement standard gastro-oesophageal anastomotic techniques with BioGlue, with the aim of assessing technical feasibility of using the product in this operation, monitoring for additional complications, and observing rates of anastomotic leak. BioGlue is a mix of purified bovine serum albumin (BSA) and glutaraldehyde which are mixed at the time of application, within the applicator tip. BioGlue reaches full strength within two minutes. The BioGlue has been used widely, particularly in cardio-thoracic and vascular surgery and has been in circulation since 1998 (7). It is licensed for use in the alimentary system but, as yet, there has not been documented use in oesophagogastric anastomoses.. The study will be conducted at a single centre, and include patients undergoing an elective oesophagectomy for cancer.
Research question / hypothesis	Is it technically feasible to use BioGlue as an additional measure to supplement standard procedure in the creation of a gastro-oesophageal anastomosis in the context of a minimally invasive oesophagectomy? Are there any additional complications observed as a result of using BioGlue? What is the observed anastomotic leak rate in patients receiving BioGlue?
Study Design	Single-arm trial. Patients undergoing minimally invasive oesophagectomy for treatment of cancer will have BioGlue applied to the oesophago-gastric anastomosis in addition to the standard anastomotic technique.
Study Participants	Inclusion Criteria: 1. aged 18 years and above

	2. planned for elective minimally invasive oesophagectomy at Queen Alexandra Hospital 3. Able to provide informed consent Exclusion criteria: 1. Previous adverse reaction to BioGlue or one of its constituent ingredients.
Planned Sample Size	30
Follow-up duration	6 weeks post-surgery
Planned Study Period	1 year
Primary Objective	To assess whether it is technically feasible to use BioGlue at the anastomosis for oesophagectomy
Secondary Objectives	To describe adverse events up to 6 weeks post-surgery. To quantify the leak rate. To describe surgical process indicators and surgical outcomes.
Primary Endpoint	Technical feasibility of applying the BioGlue
Secondary Endpoints	Post-operative complications up to six weeks, graded with the Clavien-Dindo scale Anastomotic leak rate All-cause mortality up to 6 weeks follow up Operative duration Time to discharge from hospital Unplanned return to ITU Unplanned return to theatre Unplanned return to surgical high care unit Acceptability of the product to the surgeons and the theatre team (assessed using qualitative methods) Number of CT scans Use of antibiotics (duration, indication and type)
Intervention (s)	Application of adhesive BioGlue in addition to standard anastomotic formation in patients undergoing minimally invasive oesophagectomy.

3. ABBREVIATIONS

AE	Adverse event
BSA	Bovine serum albumin
CPET	Cardiopulmonary exercise testing
CT	Computed tomography
ITU	Intensive treatment unit
MDT	Multi-disciplinary team
MIO	Minimally invasive oesophagectomy
NHS	National Health Service
PPI	Public patient involvement
PRA	Patient research ambassador
QAH	Queen Alexandra Hospital, Portsmouth Hospitals NHS Trust
RCT	Randomised controlled trial
SAE	Serious adverse event
TMG	Trial management group
TOG	Trials oversight group

4. BACKGROUND AND RATIONALE

1. Oesophagectomy is the surgical treatment of oesophageal malignancy

The incidence of adenocarcinoma of the oesophagus has been observed to be rapidly increasing in the UK and the western world although incidence of squamous cell carcinoma of the oesophagus has been steadily declining. Cancer of the oesophagus (all types) is the sixth most common cancer in men and the ninth most common cancer in women worldwide with an observed six-fold increased incidence in men (8). The management of carcinoma of the oesophagus remains challenging (9). If a patient presents with malignancy which can be treated with curative intent, the surgical option is oesophagectomy. This was traditionally performed as an open operation but has progressed over the last 25 years and is now quite widely offered as a minimally invasive procedure – with laparoscopic and thoracoscopic stages (10). Within QA all oesophagectomies are undertaken with the aim of completion using minimally invasive techniques.

2. Anastomotic leaks are a major cause of perioperative morbidity and have a significant financial impact

One of the major risks of oesophagectomy is of a leak from the gastro-oesophageal anastomosis. Leak rates from the gastro-oesophageal anastomosis are quoted by NICE as 20%, which correlates with similar international figures e.g. The Dutch National database (1) (11). An anastomotic leak leads to prolonged in-hospital stay, can require an unplanned return to theatre, return to ITU and is associated with mortality as well as morbidity (2). Increases in mortality ranging from 18.2-35% have been quoted in the literature (12). As well as the distress, pain and other negative outcomes for the patients, the need for re-operation, return to ITU and increased length of stay come at significant financial cost. A Dutch team showed that a minor complication increases the cost of surgery for oesophageal cancer from an average of €23,476 to €31,529 and a major complication to increase the cost to an average of €59,167. Specifically, they showed the average cost of a patient who had suffered an anastomotic leak to be €44,268 (€20,792 higher than when the patient suffer no complications) (13).

3. BioGlue is already used, licensed and has been shown to be safe

BioGlue is a mix of purified bovine serum albumin (BSA) and glutaraldehyde which are mixed at the time of application, within the applicator tip. BioGlue has been used since 1998 with its main applications in cardiothoracic and vascular surgery. Despite its regular safe use, there are risks associated with its application which (as described in the product literature) include: inflammatory and immune response, allergic reaction, mineralization of tissue, local tissue necrosis, luminal obstruction, thrombosis and thromboembolism, pulmonary emboli, injury to normal tissue, and possible transmission of infectious agents from material of animal origin. Mr Nicholas Carter within QA had used BioGlue uneventfully in bariatric surgery (14) (15) (16) (17).

4. There is no documented use of this material in the context of preventing anastomotic leaks following oesophagectomy

There is no evidence of an existing completed or uncompleted study which is investigating the use of this material in the way this study proposes. There have been some small studies looking into the use of certain surgical adhesives in the context of preventing anastomotic leaks and a systematic review of these showed overall beneficial outcomes in the intervention groups, but not of this type of adhesive (11). There is a single arm prospective study in recruitment stage investigating the use of Porcine Fibrin Sealant (Bioseal®) to reinforce gastro-oesophageal anastomoses in patients undergoing oesophagectomy [Study of Porcine Fibrin Sealant in Preventing Cervical Anastomotic Leakage for Esophageal or Junctional Carcinoma. (PLACE020). Yang Hong, Sun Yat-sen University. NCT03529266]. Our trial of a different material will add valuable information in the attempt to reduce the incidence of post-operative anastomotic leaks following oesophagectomy.

5. Why use this product in this way now?

As outlined, the risk of anastomotic leak is high and is associated with high levels of morbidity and mortality. There have been a very large number of studies attempting to find the best surgical technique for creation of the gastro-oesophageal anastomosis to prevent leaks. Although a number of different techniques have been shown to be safe, there are few which have shown a significant benefit to changes in surgical technique (18) (19). There are numerous surgeons around the world attempting to reduce the risk of this major operation and this is a novel approach to an ongoing complex challenge.

5. PRELIMINARY STUDIES AND EXPERIENCE OF INVESTIGATORS

There have not been any preliminary studies in the use of BioGlue by the investigators. Mr Nicholas Carter has used the product uneventfully in a small number of bariatric cases but the data from this series has not been published.
Peter May-Miller is a surgical research fellow at Portsmouth Hospitals NHS Trust and is involved in a number of ongoing surgical trials within the Trust and the region.

6. AIMS AND OBJECTIVES

This study aims to investigate if the use of BioGlue, in addition to standard technique, is technically feasible and safe to provide evidence to allow for a larger randomised controlled study with the aim of investigating the effect on anastomotic leaks.

6.1 Primary Objective

To assess whether the use of BioGlue in addition to standard anastomotic technique is techincally feasible in the context of the reinforcement of an oesophago-gastric anastomosis following oesophagectomy.

6.2 Secondary Objectives

1. To describe adverse events up to 6 weeks post-surgery
2. To quantify the leak rate
3. To describe surgical process indicators and surgical outcomes

7. STUDY DESIGN

7.1 Summary of Study Design

This is a feasibility study to investigate the use of BioGlue (a mix of purified bovine serum albumin (BSA) and glutaraldehyde) to reinforce the anastomosis created during a minimally invasive oesophaegectomy. The study will be undertaken at a single centre and consecutive patients will be included up to a total of 30. Patients will receive the standard follow up following oesophagectomy, with a telephone consultation one week after discharge and then clinic appointments at two- and six-weeks. For the purposes of the study, all participants will also be reviewed by the study team six-weeks after the day of surgery. Patients will then continue to be followed up as normal, but outside of the bounds of this study.
The results from this study can guide the researchers in the further use of this product in the wider context of a randomised controlled trial.

7.2 Primary and Secondary Endpoints/Outcome Measures

Primary endpoints:

The technical feasibility of applying the BioGlue.

Secondary endpoints:

1. Post-operative complications up to six weeks, graded with the Clavien-Dindo scale
2. Anastomotic leak rate
3. All-cause mortality up to 6 weeks follow up
4. Operative duration
5. Time to discharge from hospital
6. Unplanned return to ITU
7. Unplanned return to theatre
8. Unplanned return to surgical high care unit
9. Acceptability of the product to the surgeons and the theatre team (assessed using qualitative methods)
10. Number of CT scans
11. Use of antibiotics (duration, indication and type)

8. STUDY PARTICIPANTS

8.1 Study Setting

This is a single centre, prospective, interventional, feasibility study. All patients who are found to have operable oesophageal cancer will be offered to be involved in the study. Patients will be seen in the specialist upper GI cancer clinic following MDT discussion at which point they will be informed of the study and given information to read. Consent for involvement in the study will be taken either at pre-assessment clinic, on the day of staging laparoscopy, or on the day of oeophagectomy. Potential participants will have the opportunity to ask questions at any appointment or by contacting the research team directly. All participants will then be monitored closely as is standard for patients undergoing this type of operation.

8.2 Overall Description of Study Participants

Participants with oesophageal cancer who are undergoing elective oesophagectomy.

8.3 Eligibility Criteria

Inclusion Criteria

1. NHS patients undergoing elective minimally invasive oesophagectomy.
2. Aged 18 years and above.
3. Able to provide informed consent

Exclusion Criteria

1. Previous adverse reaction to BioGlue or one of its constituent ingredients

9. SAMPLING

All patients who are referred to the QAH and are found to have a diagnosis of oesophageal cancer which is deemed amenable to surgery following MDT discussion will be given the opportunity to take part in the trial.
Currently, around 70 oesophagectomies are performed at our centre annually. Recruitment is estimated to be completed within 12 months.

10. STUDY PROCEDURES

10.1 Recruitment

Patients will be recruited from a single site, Queen Alexandra Hospital. All elective patients who attend the Upper GI clinic at Portsmouth Hospitals NHS Trust having been found to have oesophageal cancer and are suitable for, and willing to undergo, oesophagectomy will be approached to take part in the study.
These patients will be approached for recruitment whilst attending the Upper GI clinic.

10.2 Screening and Enrolment

Patients will be screened for eligibility at first surgical visit for this study using inclusion & exclusion criteria (9.3) on a screening log (online). If they are potentially eligible, the surgeon will introduce the option of joining this study during this consultation to the patient, giving them the participant information sheet.

All patients will undergo standard pre-operative assessment of fitness e.g. CPET and then diagnostic laparoscopy in the pre-operative period. They will have the opportunity to contact the research team in the time between their initial attendance in the clinic and the day of surgery. Additionally, they have the opportunity to ask questions in person when they attend for their diagnostic laparoscopy.

On the day of surgery patients will be enrolled onto the study. The research team will ascertain that the patient has understood what the study involves before consenting them. If the patient agrees to be included in this study, they will be asked to sign a consent form and a Case Report Form (CRF) with a Participant Study ID (initials+number) created at this point with a record made in the patient's notes and a standard letter to patient's GP.

10.3 Randomisation

In this feasibility study the patients will not be randomised. The intervention will be applied to all patients who consent.

10.4 Study Assessments

The baseline information will be collected on the CRF following informed consent. Data will include:

(i) Socio-demographic variables: age, gender, work/hobbies involving physical activity
(ii) Physical examination: weight, height, BMI,
(iii) Medical history: ASA (American Society of Anaesthesiologists physical status classification), and co-morbidities, current medication and allergies;
(iv) Clinical history/examination: symptoms and symptom duration, endoscopy/CT/ laparoscopic findings

Data collected during surgery will include:

- the date of surgery
- operation duration
- any difficulty in the application of the BioGlue – specifically if there were areas at which the BioGlue was not able to be applied
- intra-operative complications
- any specific concerns about the perfusion or state of the gastric conduit or anastomosis
- any deviation from standard post-operative protocol

Following surgery patients will be admitted to ITU. They will be managed identically to patients who have not been included in the study, with initially continuous recording of the observations. Decisions about change in care or progression with diet or drains will be made by an appropriately experienced consultant surgeon. A standardised Enhanced Recovery Protocol is followed.
Progression in the post-operative phase will be based on the patients clinical and biochemical findings and if necessary guided by imaging.

Up until the day of discharge all patients will have at least once daily clinical review by the surgical team. The majority of anastomotic leaks occur fairly early in the post-operative phase and almost all before discharge. Following discharge from hospital patients will be followed up as standard with a phone call one week after discharge and then in the outpatient clinic at 2 and 6 weeks. In addition to normal post-operative follow up, participants in the study will all be seen at six-weeks following their surgery.

Assessment of technical feasibility will be done using qualitative methods consisting of short interviews with surgeons post-operatively which will be subsequently analysed. Specifically we are interested in the surgeons' views on difficulties with the product, acceptability and any suggestions for improving the product or surgical technique.

10.5 Discontinuation/Withdrawal of Participants from Study Treatment

Patients withdrawing consent from the study will continue to have data which has already been collected used in the post-operative analysis. Once the surgery has occurred, there is no option for the removal of BioGlue and patients will be managed in the standard way.

Any patient who does not undergo surgery will not be included in the trial. Where surgery is abandoned intraoperatively for a surgical or anaesthetic reason, prior to the formation of the anastomosis, the patient will be withdrawn from the trial. This situation will be exceptionally uncommon.

10.6 Definition of End of Study

The end of the study is 6 weeks post-operatively following the last patient's operation.

11. INTERVENTIONS

11.1 Description of Study Intervention / Treatment

The surgical procedure performed is routine other than the addition of the BioGlue (mixture of purified bovine serum albumin and glutaraldehyde) to the anastomosis using the laparoscopic applicator tip. Detailed description of the surgical technique is included as appendix 3.

The procedure is performed under general anaesthetic using keyhole surgery in two stages, by two Consultant Surgeons. In the abdominal stage the stomach is mobilized from its attachments and lymph node dissection performed. The gastric conduit is then constructed using the greater curve of the stomach and relies on the right gastroepiploic arcade for its blood supply. The distal oesophagus is then freed from the hiatus and visible attachments in the posterior mediastinum. A feeding jejunostomy is constructed prior to closing the abdomen and moving to the chest. In the thoracic stage oesophagus is mobilized from surrounding thoracic tissue, and gastric conduit delivered into the chest. Approximation of the conduit and the oesophagus is then assessed and when happy the oesophagus divided, and specimen removed through an extraction site.

The anastomosis is an end to side linear stapled gastro-oesophageal anastomosis. A bougie catheter is inserted down the oesophagus and an enterotomy is made onto the bougie on the distal, postero-lateral side using diathermy. The mucosa at this opening is then sutured with two stitches to prevent retraction. A gastrotomy is then created on the mesenteric side of the stomach at least 5cm from the tip of the conduit. The blades of linear stapling gun are inserted into the two enterotomies created, one in the oesophagus and one in the gastric conduit. The gun is fired creating a 3-4cm window between oesophagus and stomach, and the remaining enterotomy closed with two layers of sutures.

The BioGlue will then be prepared as per manufacturers instructions. The glue will be applied using the laparoscopic applicator tip to cover the closed enterotomy and staple lines of the gastro-oesophageal anastomosis. It will not be used to cover the staple line of the gastric conduit. Surgeons will aim to apply a 2-3mm thick coating of the BioGlue 5-10mm either side of the anastomotic suture/staple line, as advised by manufacturers. Great care will be taken to avoid application of BioGlue to other tissues in the thorax; such as placing unfolded saline soaked swabs in the operative field to catch any spillage. If this does occur, then it will be at the discretion of the operating surgeons as to whether to remove this BioGlue or not once hardened, as removal of the glue can damage the underlying tissues, and its application should not cause harm to the structures exposed during the procedure. Application of the BioGlue will be videoed and the file saved for study records.

11.2 Adherence to Study Treatment

The surgical steps and techniques will be standardised between all surgeons participating in this study as described above. All of the surgeons participating in the study are experienced Consultants in Upper Gastro-Intestinal Surgery, and routinely perform minimally invasive oesophagectomies. The Principal Investigator (PI) will initially demonstrate to the other surgeons taking part in the study how to assemble the BioGlue laparoscopic applicator and apply the BioGlue to the gastro-oesophageal anastomosis in the described manner. The PI

will then move to supervising the other surgeons applying the BioGlue to the anastomosis once they are familiar with the technique. When the PI is confident that a surgeon taking part in the study is competent to apply the BioGlue independently it will be signed off in the study competency log. All surgeons participating in this study are proficient in complex laparoscopic surgery and it is expected that they should all be able to attain competency early on in the study.

11.3 Accountability of the Study Treatment

The chief investigator is accountable for the study treatment. BioGlue is produced and distributed by Cryolife and the product will be kept and stored as per the manufacturer's instructions within the theatre complex at QAH.

11.4 Concomitant Medication / Therapies

Operative and post-operative analgesia and anti-emetics will be prescribed according to standard operative protocols. If the patient is readmitted for complications or further therapy, this will be recorded as an adverse event (AE) or serious adverse event (SAE).

12. ASSESSMENT OF SAFETY (IF APPLICABLE)

12.1 Definitions

Adverse Event:

Any untoward medical occurrence, unintended disease or injury, or any untoward clinical signs (including an abnormal laboratory finding) in participants, users or other persons concerned with the medical device. These may, or may not be, considered related to the investigational material (i.e. BioGlue), related procedure or comparator. If the AE is considered to have a reasonable causal relationship with the material, then it is considered to be an Adverse Device Effect (ADE).

To fully address the potential adverse events following oesophagectomy we must include the established complications from surgery. Participants would be at risk of these complications irrespective of whether they receive the intervention or not. They will all be considered an expected adverse event and include (2):

- Pneumonia.
- Atrial dysrhythmia.
- Anastomotic leak.
- Gastric conduit necrosis.
- Chyle leaks.
- Recurrent laryngeal nerve injury.

BioGlue's manufactures CryoLife, detail the potential local and systemic adverse effects of the device in their product literature. These complications are specific to the adjunctive use of BioGlue during soft tissue repair, and include:

- Failure of product to adhere to intended tissue.
- Application of adhesive to unintended tissue.

- Inflammatory and immune response.
- Allergic reaction.
- Mineralization of tissue.
- Local tissue necrosis.
- Damage to normal vessels or tissue.
- Blood vessel, bronchial or luminal obstruction.
- Thrombosis, thromboembolism and pulmonary embolism.

CryoLife provide reference to evidence in the literature of these events in experimental animal and human studies investigating its use on cardiac or pulmonary tissue. They do not provide any reference to its use or effects on the alimentary tract (7). Literature review as part of the protocol development has found a number of studies assessing its use and safety on the alimentary tract, none of which have reported these complications. Systematic review of the use of tissue adhesives in gastro-oesophageal anastomosis identified a number of studies in animals and humans (11). None of the above complications were reported; however, it must be noted that the only outcomes measured were collagen synthesis, bursting pressure and anastomotic leak. An RCT comparing the application of BioGlue to reinforce the staple line in stapled haemorrhoidopexy vs standard procedure, found it reduced post-operative complications. Participants who received BioGlue did not have any anastomotic leak, thrombosis, haemorrhage or anal stenosis; all of which occurred in the standard treatment group, and are potential complications detailed in manufactures instructions for use (17). A systematic review of tissue adhesives in gastro-intestinal anastomosis found a range of evidence from animal and human clinical studies, on a number of tissue adhesive products. BioGlue was investigated in 3 of the 48 studies. The review identified no local complications from any of the tissue adhesives, such as tissue damage, luminal stenosis/blockage, injury to nerves, blood vessels, heart or lung parenchyma, or intra-abdominal solid organs (20). All of these review articles highlight the variability between studies and poor overall quality of evidence. Nonetheless the potential complications discussed in the manufacturer's literature have not been found to be significant in any of these studies and provides reassurance that BioGlue is highly likely to be safe in this application.

Participants in the study are at risk of these reactions, however they are so uncommon we believe that with such a small study group it is unlikely to cause any of them harm. The manufacturers instruction for use provides warnings for use of BioGlue in certain situations to avoid these reactions:

- Could contact or obstruct circulating blood flow.
- Could obstruct circulating air or luminal fluid flow.
- Contact with nerves, eyes or unintended tissue.
- Not to be used in presence of infection and used with caution in contaminated areas.
- Exercise caution with repeated exposure due to hypersensitivity reaction. Sensitisation has been observed in animal studies.

We do not expect or intend to use BioGlue in any of these situations, thus minimising any risk of adverse reactions.

BioGlue contains material of animal origin, which may be capable of transmitting infectious agents. CryoLife, Inc. is a U.S. FDA-registered medical device establishment (Registration #

1063481) and human cells, tissues, and cellular and tissue-based product establishment. It is also certified to the international quality standards (ISO 13485:2016) for the design, manufacture, and distribution of tissues and medical devices. BioGlue has been developed and manufactured in accordance with these national and international standards to ensure such risks are minimised.

Any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the investigational medical device will be considered an adverse device effect.

Serious adverse event:

A serious adverse event is any untoward medical occurrence that:

- Results in death
- Is life-threatening

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

- Requires inpatient hospitalisation or prolongation of existing hospitalisation,
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect.
- Other important medical events*

*Other events that may not result in death, are not life threatening, or do not require hospitalisation, may be considered a serious adverse event when, based upon appropriate medical judgement, the event may jeopardise the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.

12.2 Reporting Procedures for Serious Adverse Events

A serious adverse event (SAE) occurring to participant should 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' – that is, it resulted from administration of any of the research procedures; and 'unexpected' – that is, the type of event is not listed in the protocol as an expected occurrence. Reports of related and unexpected SAEs should be submitted within 15 days of the Chief Investigator becoming aware of the event, using the NRES report of serious adverse event form.

12.3 Recording and Reporting Procedures for All Adverse Events

AEs will be recorded on the relevant section of the CRF.

Information recorded will include:

- date of onset
- severity

- frequency
- treatment provided
- assessment of causality with the device
- whether or not the AE was expected or unexpected

All AEs must also be documented in the patient's medical records and must be followed up until resolution. If the AE should result in any lasting secondary disease this will be recorded accordingly when completing the study.

The sponsor's SOP for the reporting of all Adverse Events will be followed in the timeline set out in this procedure.

13. DATA HANDLING AND RECORD KEEPING

13.1 Data Collection Forms

Once a patient is recruited, the data will initially be collected on a paper-based CRF kept securely in the research office when not used for data collection. It will be transcribed prospectively onto an online CRF. Source data/documents (i.e. patient notes) are kept within QAH as per standard procedure and can be accessed as required through the standard mechanisms. CRFs will be stored for a maximum of 15 years after the study has been completed.

13.2 Data Management

All study data will be entered on a bespoke Microsoft Access database. The participants will be identified by a study specific participant number and/or code in any database. The name and any other identifying detail will NOT be included in any study data electronic file. The database will be stored securely on a secure hospital file storage area network with automated backups and will be password protected.

Data variables will include basic demographic data, operative details including operative duration and details regarding the application of the glue, post-operative course and specifically any complications, AE and SAE.

The database will be maintained for 10 years following study completion.

14. DATA ANALYSIS

14.1 Description of Analysis Populations

Analyses will be as per intention-to-treat i.e. all participants will be included.

14.2 Analysis of Endpoints

Primary endpoints are qualitative outcomes and outside of the remit of a statistical analysis plan.

Secondary endpoints will be described appropriately for use in informing future controlled analysis.

Time to event outcomes (operative duration, time to discharge) will be presented with the number of events experienced and the median time to event.

Indicator variables where the outcomes takes an occurrence/non-occurrence status are Anastomotic leak rate (leak/no leak), All-cause mortality up to 6 weeks follow up (death/ no death), Unplanned return to ITU (return/no return), Unplanned return to theatre(return/no return), and Unplanned return to surgical high care unit (return/no return). In all cases the proportion in each category will be reported, along with the standard error for the proportion.

Categorical variables with more than one category (Clavien-Dindo scale of post-operative complications) will similarly be presented with the proportion in each category reported. The number of CT scans will be treated as a multi category categorical variable in this case, since the number of scans during the study is likely to be relatively low. The use of antibiotics will also be treated as a multicategory categorical variable, although as well as the proportion using each antibiotic, the median duration of use will also be reported.

14.3 Procedure for Dealing with Missing, Unused and Spurious Data

There will be no imputation of missing values.

14.4 Procedures for Reporting any Deviation(s) from the Original Statistical Analysis Plan

Minor alterations can be made by agreement with the CI and documented accordingly.

14.5 Interim analysis and criteria for early study termination

As this is a feasibility study assessing the ease and safety of application of the glue, there will be no planned interim analysis. Due to the small number of patients needed for the study, and the acceptable leak rate of 20%, it is entirely possible that consecutive participants suffer an anastomotic leak through chance alone. Each anastomotic leak will be reviewed as a serious adverse event. If there are any concerns that a leak has been caused by the BioGlue applied (for example, the anastomosis has become abnormally adherent to structures in the chest at re-operation) then a serious adverse device effect has occurred, and the study paused while this is reviewed. If there are 5 consecutive anastomotic leaks in a row, this will trigger an internal review and an independent data monitoring committee formed and convened to review the study. If there are more SAEs than expected, raised by the research team inputting data, this will be highlighted to the PI. Early termination of the study can then be considered by the PI.

15. ETHICS

15.1 Participant Confidentiality

The study staff will ensure that the participants' anonymity is maintained. The participants will be identified only by initials and a participant's ID number on the CRF and any electronic database. All documents will be stored securely and only accessible by study staff and authorised personnel. The study will comply with the Data Protection Act and GDPR which requires data to be anonymised as soon as it is practical to do so.

15.2 Other Ethical Considerations

There will be no inclusion of patients who are unable to consent as outlined above.

15.3 Declaration of Helsinki

The study protocol will be carried out in accordance with the declaration of Helsinki.

15.4 ICH Guidelines for Good Clinical Practice

All investigators and research staff working on the study will have a current Good Clinical Practice training certificate.

16. PATIENT PUBLIC INVOLVEMENT (PPI)

16.1 Study design

The study was presented to the patient research ambassador (PRA) meeting in April 2019. The PRA group within the PHT Research Design Service are an active and invaluable group of lay persons who are or have been involved in research within the trust. The main comments following discussion of the proposed study were:

1. The intended cohort is a group who are already dealing with a new serious diagnosis. As such, all information should be clear and concise. A suggested format was a brief PIS followed by a more detailed description for those who wanted to know more.
2. At the initial meeting to discuss the study, it was suggested that patients would want to know in just a few words what the main potential benefits and the main risks are without much technical detail.
3. Clarity is needed regarding the fact that the product contains animal derived ingredients.
4. Extra visits to the hospital for follow up were viewed in general as a positive impact of the study, the group felt that following major surgery, patients would feel that an additional review would be attractive.
5. As allergy is a possible complication of the glue, should patients be tested for reaction before it is used?
    a. Based on a literature search "BioGlue" AND ("allergy" OR "allergic" OR "hypersensitivity") across PubMed, Medline and EMBASE, there is only one case study example of allergic reaction to BioGlue (21). Given the

product's use for over 20 years, allergy testing would not be indicated for the patients in this study.

The PIS, consent form and lay summary were also read by and discussed with the chair of the OPA-SPLASH group for patients with and carers of those with gastro-oesophageal cancer. The language in particular was discussed and edited accordingly. The main other point was to be clear about the way in which results of the study will be distributed to the participants.

16.3 Dissemination

The PRAs and SPLASH patients will assist with dissemination of the findings of this study via their meetings and social media, and through the National OPA website. They will help to identify routes of dissemination that are likely to be accessed by patients with this condition.

17. FINANCING AND INSURANCE

17.1 Research Costs

Research costs have been calculated by the Sponsor's finance officer. The sponsor will cover the costs of study delivery and CryoLife will provide the cost of the BioGlue and laparoscopic applicator tips.

17.2 Excess Treatment Costs

The BioGlue and laparoscopic applicator tips have been provided by CryoLife Europe Ltd. Guildford, Surrey.

17.3 Study Sponsorship

Portsmouth Hospitals NHS Trust will act as the study sponsor.

18. TIMETABLE AND ORGANISATIONAL CHART

- Approvals — Month 1
- Piloting of data collection tool and subsequent review — Month 2
- Data collection period – first inclusions — Month 3
- Data collection period – last inclusions — Month 15
- Data collection period – last follow-up visits — Month 17
- Data entry — Month 3-17
- Analysis — Month 18
- Writing up reports / publications / dissemination — Month 19 onwards

19. DISSEMINATION AND OUTCOME

The research will be disseminated:

1. Locally via our annual R&I conference
2. Nationally presented in Association of Upper Gastro-intestinal Surgeons of Great Britain and Ireland (AUGIS) and/or Association of Surgeon of Great Britain and Ireland (ASGBI)
3. Internationally presented at European Society of Surgical Oncology (ESSO) conference
4. Published in a reputable peer-reviewed surgical journal
5. Lay summaries available on R&I website and sent directly to all participants

The study results will inform the need for and the design of a large multicentre randomised controlled trial on the use of BioGlue to investigate it's impact on the post-operative anastomotic leak rate.

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21. APPENDIX 1 SCHEDULE OF PROCEDURES

	First Clinic Appointment	Day of Surgery	Week 1 Post Discharge	Week 2 Post Discharge	Week 6 Post Discharge
Introduction to study	X				
Consent		X			
Oesophagectomy[1]		X			
Application of Bioglue		X			
Telephone Consultation[1]			X		
Clinic Appointment[1]				X	X
Research Team Follow Up					X

[1]Standard Care

22. APPENDIX 3 DETAILED STEPS OF OESOPHAGECTOMY

All oesophagectomies are performed as dual consultant cases. The abdominal phase is performed laparoscopically with the patient supine and with legs in fins and the bed positioned with 20 degrees head up. Flotron boots and prophylactic low molecular weight heparin are administered. Three 10mm and one 5mm trocars are used. Initial 10mm trocar is just left of the midline approximately equidistant between umbilicus and xiphoid process. One 10mm port is placed two finger breadths below the costal margin in the left mid clavicular line and the other is in the same horizontal plane just lateral to the falciform ligament. The 5mm port is placed laterally on the patient's right. The operating surgeon stands between the patient's legs with the assistant seated on the patient's right.

Access to the lesser sac is gained via division of the gastro-colic ligament and the right gastro-epiploic arcade is identified. Great care is taken never to handle the arcade. Dissection is continued along the greater curve of the stomach using the harmonic scalpel continuing well outside the epiploic arcade. The short gastric arteries are divided and posterior gastric arteries are divided to gain access to the right crus. Dissection is then continued along the greater curve towards the pylorus. The stomach is then grasped posteriorly to rotate the arcade over in a cephalad direction, so it is not in danger of being damaged. The omental vessels crossing the gastro omental ligament are divided and the

plane between the colonic and gastric mesentery is opened to release the hepatic flexure of the colon. The dissection of the omentum is continued onto the duodenum. The duodenum is not routinely kocherised unless major concerns over conduit length. The lesser omentum is incised and dissection continued to the right crus. Anterior dissection around the crura reveals the pericardial fat pad which is taken with the specimen. Posterior gastric dissection continues by grasping the lesser curve mesentery containing the left gastric artery and reflecting the stomach anteriorly and cephalad. Lymph node dissection routinely includes stations 1-9 and 11p. We don't believe wider dissection to include stations 8p and stations 12 convey oncological benefit in lower oesophageal cancers and increases morbidity with higher incidence of abdominal chyle leak. The left gastric artery is divided between hem-o-lok clips. Dissection continues posteriorly to cleanly identify the aorta and this plane is followed posteriorly into the posterior mediastinum. The oesophagus is now slung with a jakes catheter and the two ends brought opposed with a hem-o-lok. This is used to manoeuvre the oesophagus around the hiatus in order to continue the hiatal dissection up the level of the inferior pulmonary vein. The conduit is fashioned starting on the lesser curve at the incisura. We try to preserve at least two branches of the right gastric artery. A tape measure is cut and placed inside the abdomen. A gastric conduit measuring 4.5cm in diameter is measured using the tip of a sterile marker pen all the way to the fundus. The conduit is fashioned normally with 1 single green Ethicon GST 60 and 4-5 fires of a GST Gold 60. At this point, the conduit is usually still attached by a small 1cm cuff of tissue. If there is a large Hiatus hernia or a bulky tumour which is making the hiatal dissection more tiresome, then we disconnect the conduit completely and complete the hiatal dissection. The conduit can then be reattached with an ethibond suture and the tumour now placed into the left chest to make way for the thoracic dissection. If the hiatus is patulous, a figure of 8 ethibond suture is used posteriorly as a hiatal repair to help protect against future hiatal herniation. Abdominal drains are not routinely used. A feeding jejunostomy is placed. The Nathanson's liver retractor is removed and a Johan is placed into the tract to help with placement of the feeding tube. The proximal jejunum is anchored with 4 quadrant vicryl rapide on a straight needle. The needle is grasped intraabdominally with an endoclose (Hamdan, Harper, Klimach, & Singh, 2016). Whilst fashioning we reduce the intraabdominal pressure to 6cm water.

The thoracic dissection is performed thoracoscopically or robotic assisted thoracoscopically in the left lateral position as for open Ivor Lewis Oesophagectomy. The prone position offers a better and more natural view in the chest and makes the anastomosis more ergonomic. However, we prefer the access in the left lateral position in case of an emergency thoracotomy (however, as yet, this has not been necessary). We break the table slightly to open the rib spaces and rotate towards the surgeon slightly for ergonomics. The surgeon stands as for an Open oesophagectomy with the assistant on the opposite side. Access is gained via a 12mm optiport in the 8th rib space approximately in the mid scapular line. Insufflation pressures are set at 6-8 mm Hg depending on lung position and compliance. A further working 12mm port is placed one rib space higher approximately 6-10cm anteriorly. A 5mm port is placed just behind the tip of the scapula and a 5mm retraction port is placed in the 5th space mid clavicular line. The "endoflex" lung retractor is used via this port to retract the lung. Ventilation is set to high frequency and low volume and this allows sufficient access to the mediastinum without the need for a double lumen endotracheal tube. The pleura is incised either side of the oesophagus in a caudal-cephalad fashion. The azygos vein is exposed leaving a flap of pleura as this is often used at the end of the procedure to tuck some omentum or top of gastric conduit under it. The vein is divided with a GST 60 white cartridge. Oesophageal mobilisation continues inside the thoracic duct but following the line

of the left pleura and along the pericardium and inferior pulmonary vein. The trachea and right bronchus are identified and subcarinal nodes dissected. Tonsil swabs are then used to protect the right bronchus and trachea. The Jakes catheter is manipulated out of the left chest and repositioned around the oesophagus to use for retraction. The oesophagus is retracted towards the assistant to identify the left bronchus and dissection carefully continue onto the tonsil swab which protects the right airway. The vagi are divided at this point and oesophagus mobilised to the azygous vein. A medial pocket is created between the oesophagus and trachea to allow space for the top of the conduit during the anastomosis. The conduit is now delivered into the chest and checked for blood supply and length. If satisfactory, the oesophagus is divided with GST Green 60 with the head of the gun angled vertically in a posterior-anterior orientation. The conduit is now detached from the specimen and the specimen is extracted by extending the camera port to 3-4cm and using the Alexis wound retractor. Once the specimen is out, the laparoscopic cap is used and port replaced. The anastomosis is a end to side linear stapled. A 34 French orogastric tube (OG tube) is placed to tent the distal end of the oesophagus. The assistant can now exchange the lung retractor with a Johan to grasp the staple line of the oesophagus. Hook diathermy is used to cut onto the bougie on the posterior/lateral side of the oesophagus. The incision is the diameter of the OG tube as this allows much easier introduction of the linier stapler. The cut edge of the mucosa is opposed the serosa (to prevent mucosal retraction) using a 3/0 Maxon suture. We do this in two places: at the midpoint of the cut edge and at the far posterior corner where the cut edge meets the staple line. We have found these sutures to be invaluable. The conduit is delivered and assessed again for length and blood supply. A gastrotomy is made on the mesenteric side at least 5cm from the tip of the conduit. It is stretched to permit entry of the stapler cartridge. A green or gold GST 60 cartridge is used with the cartridge surface inserted into the conduit and gun clamped (this avoids the gastrotomy stretching when making the join). The assistant then holds the anterior edge of the oesophageal staple line and the bougie is slowly withdrawn to permit entry of the staple gun. A 3-4cm anastomosis is then fashioned. The tip of the conduit should lie medially in the plural pocket between the trachea and oesophagus. The anastomosis is checked and the enterotomy closed with two 3/0 V-loc sutures which meet in the middle of the anastomosis. The sutures cross and a second layer of horizontal mattress sutures completes the anastomosis. It is at this point when the BioGlue will be applied to cover the formed anastomosis. We routinely perform an endoscopy to check the join and correctly site the nasogastric tube. A paravertebral catheter is placed in the 6th rib space and loaded with 30ml 0.5% Marcaine (bupivacaine hydrochloride). Apical and basal chest drains are placed.