Full Title: A randomised controlled trial investigating the use of PuraBond® (3-D Matrix) in transoral resections of primary oral or oropharyngeal mucosal lesions

Short Title: PuraBond® and Pain following Resection of Oral or Oropharyngeal mucosal lesions (PuraBond® PROOF)

IRAS 322447
NCT05773781

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Clinical Trial Protocol

Version: 0.7
Date: 26th October 2023
IRAS Number: 322447
Funder: 3-D Matrix
Funder No: TBC
Name of Sponsor: University of Liverpool
Sponsor No: UoL001737

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the study in compliance with the approved protocol and will adhere to the principles outlined in the Declaration of Helsinki, the Sponsor's SOPs, and other regulatory requirement.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the investigation without the prior written consent of the Sponsor

I also confirm that I will make the findings of the study 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 discrepancies from the study as planned in this protocol will be explained.

Authorised by:

Mrs Karen Jennings-Wilding	Mr Jason Fleming
Senior Clinical Research Governance Manager	*Chief Investigator*
Date:	Date:

General Information

This protocol describes the PuraBond® PROOF clinical trial and provides information about the procedures for entering participants into the trial, study processes, safety reporting and governance requirements The protocol should not be used as a guide, or as an aide-memoire for the treatment of other patients. Every care has been taken in drafting this protocol; however, corrections or amendments may be necessary. These will be circulated to the known Investigators in the trial following receipt of required approvals. Problems relating to the trial should be referred, in the first instance, to the chief investigator.

Compliance

This trial will adhere to the conditions and principles of Good Clinical Practice which apply to all clinical trials. It will adhere to the principles outlined in the UK Policy Framework for Health and Social Care Research. It will be conducted in compliance with the protocol, the Declaration of Helsinki (South Africa, 1996), the Data Protection Act 2018 and the UK GDPR as amended from time to time and any successor legislation in the UK and any other directly applicable regulation relating to data protection and privacy as well as any other regulatory requirements as appropriate.

Funding

The trial is being funded by 3-D Matrix, UK.

Key Study Contacts

Chief Investigator	Mr Jason Fleming Senior Clinical Lecturer, University of Liverpool, Liverpool, UK. Consultant ENT/ Head and Neck Surgeon, Aintree University Hospital, LUHFT, Liverpool. Jason.fleming@liverpoolft.nhs.uk; Jason.fleming@liverpool.ac.uk; 0151 529 5259
Study Co-investigators	Dr Randa Ghazal Asswad Clinical Research Fellow, Aintree University Hospital, LUHFT Liverpool. Randa.Ghazal-Asswad@liverpoolft.nhs.uk; R.ghazalasswad@doctors.org.uk; 0151 529 5259 Mr Andrew Schache Reader/Hon Consultant Oral & Maxillofacial (Head & Neck) Surgeon, Liverpool Head and Neck Centre, Department of Molecular and Clinical Cancer Medicine and Liverpool University Hospital NHS Foundation Trust. schache@liverpool.ac.uk 0151 529 5283
Sponsor	The University of Liverpool is the research Sponsor for this Study. It is recognised that as an employee of the University the Chief Investigator has been delegated specific duties, as detailed in the Sponsorship Approval letter. For further information regarding the sponsorship conditions, please contact: Mrs Karen Jennings-Wilding Senior Clinical Research Governance Manager Sponsor@liverpool.ac.uk

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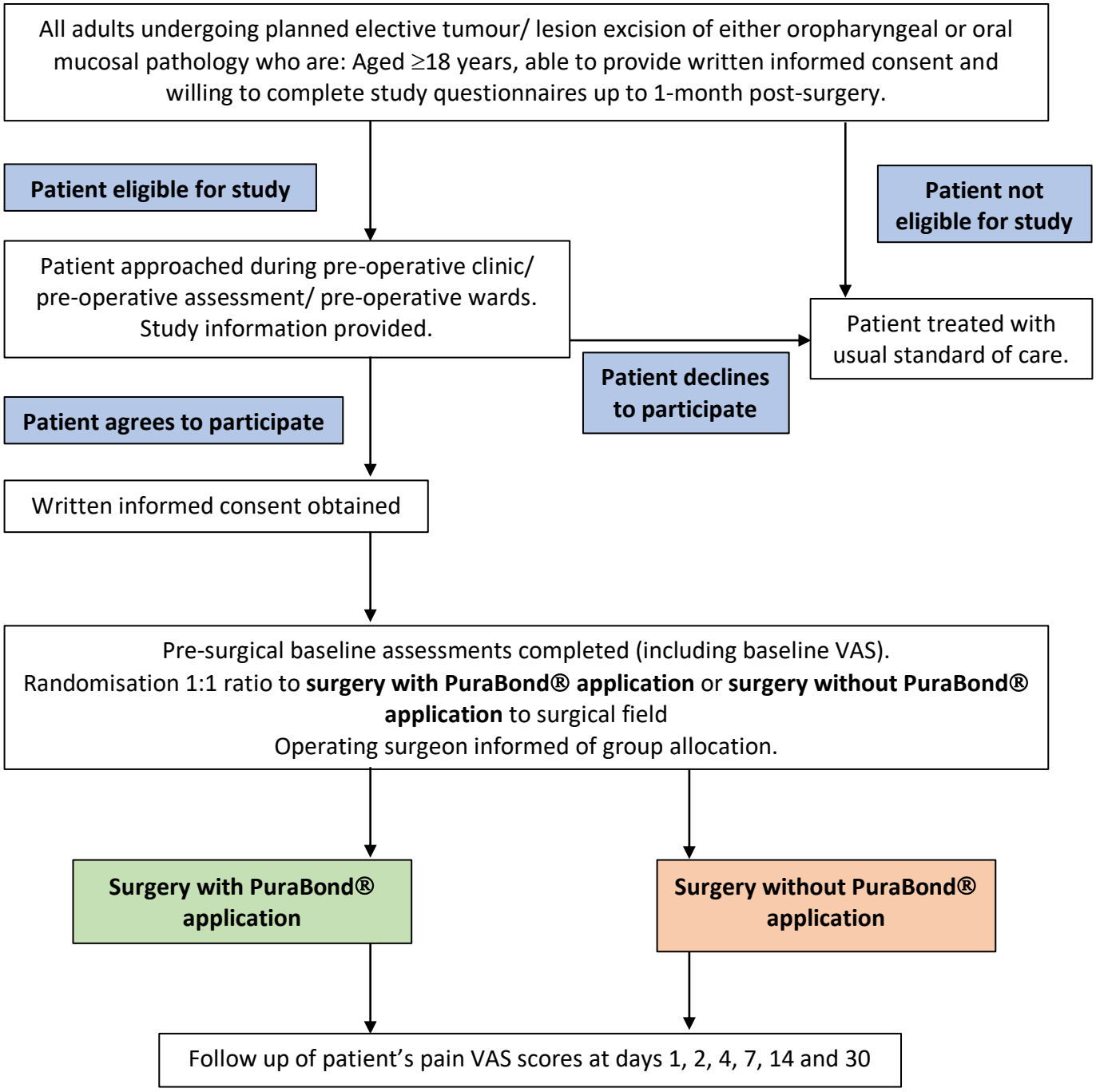
1 Trial Schema



2 Trial synopsis

Study title	A randomised controlled trial investigating the use of PuraBond® (3-D Matrix) in transoral resections of primary oral or oropharyngeal lesions
Study acronym	PuraBond® PROOF
Funder	3-D Matrix, UK
Chief investigator	Mr Jason Fleming
Sponsor	University of Liverpool
Trial design	Non-CTIMP Single site, parallel group randomised controlled trial
Study participants	64 suitable patients
Setting	Aintree University Hospital LUHFT at Liverpool Head and Neck Centre, UK. A large tertiary UK centre with a track record of successful recruitment to clinical trials and significant head and neck case load.
Main eligibility criteria	Inclusion: • Patient and disease factors are deemed suitable for transoral surgery under general anaesthetic. • Decision to treat with primary transoral resection or local excision biopsy. • Aged 18 or over. • Written informed consent provided. • Clinically suspected or histologically confirmed primary dysplasia or malignancy of the oral cavity or oropharynx OR histologically confirmed diagnosis of squamous cell carcinoma in a cervical lymph node of unknown primary. • Patient considered fit for surgery. Exclusion: • Lesions undergoing incisional or punch biopsy only. • Surgery with planned primary closure or local/ distant flap reconstruction. • Inability to provide written informed consent. • Medical contraindication to a general anaesthetic or to PuraBond® use.
Interventions	Two existing operative techniques: i) PuraBond ® application to surgical field ii) No PuraBond ® application to surgical field.
Follow up duration	1 month
Planned Study Period	TBD
Objectives	To test the hypothesis that in adult patients undergoing surgical excision procedures for mucosal pathology of the oral cavity or oropharyngeal subsites, the use of PuraBond ® intraoperatively on the surgical bed significantly reduces acute pain at 30 days post randomisation. To compare the effectiveness of its use on the incidence of post-operative complications and important clinical outcomes.

3 Background, rationale and objectives

3.1 Background and rationale

Head and Neck Cancer (HNC) describes a host of different malignancies originating from various anatomical sites including the oral cavity, pharynx and larynx, with 90% of tumours being squamous cell carcinomas. In the UK, HNC is the eighth most common cancer type accounting for an estimated 12,422 new cases annually [1].

One particular subtype of HNC is oropharyngeal squamous cell carcinoma which relates to the structures of the oropharynx including the tonsils, base of tongue (BOT), soft palate and walls of the oropharynx. In 2018, the global incidence of oropharyngeal cancer (OPC) was just over 92,000 new cases [2]. Both premalignant oral lesions and OPC are treated with surgical excision and healing by secondary intention [3]. Surgery within this anatomical area means pain is an important side effect and as with all surgical procedures, intra-operative and post-operative bleeding is also a known consequence.

Developed by the company 3-D Matrix, PuraBond® (also known as PuraStat®; 3-D Matrix Ltd, Tokyo, Japan) is a novel haemostatic agent [4]. It utilises RADA16, a synthetic peptide normally viscous in consistency, that is organised in β-sheet nanofibers in acidic environments. However, upon exposure to biological fluids such as blood these sheets cross-link creating a stable interwoven transparent hydrogel 3-D matrix. This hydrogel acts as a barrier to prevent further blood flow from the operative wound site. Thus, its use controls local surgical haemorrhage and prevents post-operative re-bleeding. Its use as a haemostatic agent has been demonstrated in various surgical fields including endoscopic resection of gastrointestinal lesions, cardiac surgery and laparoscopic colorectal operations [5,6,7]. These studies confirmed PuraBond® as an effective operative haemostat. Packaged in a prefilled syringe, use of PuraBond® is thus practical within busy operating theatres. It was approved for use in the European Union (EU) in 2014 (with the United Kingdom a member state at this time) as a CE marked class III medical device. It is currently actively being used within routine head and neck cancer operations in Liverpool University Hospital Foundation Trust (LUHFT), although current use is variable and largely depends on surgeon preference.

Transoral approaches in head and neck surgery have become more common given they offer a minimally invasive approach to surgery, thus removing the need for external incisions in the neck. This surgical approach can involve using either a carbon dioxide laser or a robotic approach. A recent UK case series from Birmingham reported on the use of PuraBond® in thirteen oropharyngeal cancer cases treated with Transoral Robotic Surgery (TORS) [8]. No cases of primary or secondary haemorrhage post-operatively were recorded and all patients resumed oral diet on day one post operatively. The authors also alluded to better patient outcomes including swallowing, pain and length of stay in hospital. Although, the use of PuraBond® as a haemostatic agent is well documented, its impact on pain management is a clinically important factor of interest as pain directly impacts patient recovery. Yet this factor has not been studied within the parameters of a randomised control trial. The formation of the hydrogel barrier insulates the wound bed thus it may also reduce pain stimulus to the operative site. A clinical trial such as PuraBond® PROOF is needed to provide gold-standard evidence to support such findings and impact clinical management. This will provide real world evidence of PuraBond® use on pain outcomes in head and neck surgery.

3.2 Study objectives

The aim of this study is to assess whether intraoperative use of the haemostatic agent PuraBond® is associated with decreased levels of pain postoperatively following wide local excision procedures for oral or oropharyngeal mucosal lesions. We hypothesise that patients treated with such agents will have better post-operative pain scores compared to those treated without.

4 Study design

PuraBond® PROOF is a prospective, single centre, parallel group randomised controlled trial (RCT). Patients eligible for the study must have clinically suspected or histologically confirmed dysplasia or malignancy in the oral cavity or oropharyngeal subsites. Their primary lesion must be considered resectable via a transoral approach. After informed consent, patients will undergo baseline assessment of pain levels prior to surgery and demographic data will be collected. Surgery may or may not involve laser use to the primary site.

Suitable patients will be stratified prior to randomisation by lesion site (oral cavity or oropharynx) and whether or not the surgical technique will involve laser resection. Depending on which arm the participant is allocated to, PuraBond® may or may not be applied to the surgical bed intraoperatively. It is important to note that both treatments are routinely used in these operations and PuraBond® use will fall completely within its license in this study.

Using surgical site and technique to clinically stratify patients is important as standard post operative analgesia management differs between these groups (see table below). It is important that data collected from this trial represents real world evidence and thus, pre and post operative analgesia agents used will be recorded by analysing patient's prescriptions rather than. restricting analgesia prescriptions and changing current standard of care. This means this trial will not lack generalisability and will not limit the relevance of its results to real world practice.

Medication	Oropharyngeal surgery		Oral cavity surgery
	TOLR	No laser used	
Paracetamol	✓	✓	✓
Ibuprofen	✓	✓	✓
Codeine	✓	✓	✓
Morphine	✓	Not routinely used	Not routinely used
Oxycodone	**X**	Not routinely used	Not routinely used
Chlorhexidine	**X**	**X**	✓
Gelclair®*	✓	**X**	✓
Benzydamine 0.15% solution	✓	✓	✓
Pregabalin	✓	**X**	**X**

*Please note: Patients enrolled in PuraBond® PROOF will not be prescribed Gelclair® post operatively. Gelclair® is a viscous gel used orally that may confound any results of PuraBond use. It is a product licensed for treatment of oral mucositis in in oncology, hence use in our patient cohort is considered off label.

4.1 Study setting

This will be a single centre study undertaken at Liverpool University Hospitals NHS Foundation Trust (LUHFT) in Liverpool Head and Neck Centre. LHNC is the largest UK NHS/ University head and neck collaboration delivering research-driven high-quality patient care. It has developed a

large clinical trial portfolio with multiple international and national clinical trials supported at the centre. Thus, it provides an ideal clinical setting to ensure adequate patient recruitment into the study due to the large number of surgical head and neck operations conducted daily as well as research expertise.

Suitable patients will be identified by screening both daily operative lists at the centre as well as head and neck outpatient clinic lists and MDT. Suitable patients will then be approached by a member of the research team to confirm eligibility as well as discuss and provide information on the study and potential participation. All trial procedures including identification, recruitment, surgery and follow up will be undertaken within LUHFT.

5 Trial entry

5.1 Identification of participants

Patients will be identified directly from clinical lists of patients undergoing a predetermined list of surgical procedures involving either the oral cavity or oropharyngeal sites (see section 6). Patients will be identified by members of their normal clinical team or study team. Patients who appear to fulfil the inclusion criteria will be referred to the research team for confirmation. Eligibility will be formally confirmed by the CI, site PI, study co-investigators or delegates, who have access to, and a full understanding of, the patient's medical history. Once eligibility is confirmed the patient will be approached by a suitably delegated member of the trial team who will inform them of the trial. This may occur in a variety of settings e.g., in surgical clinics, pre-operative clinics and on pre-operative wards.

5.2 Screening procedures

Patients are eligible for the trial if they are undergoing surgical excision of either suspected or confirmed dysplasia or malignancy of an oral or oropharyngeal subsite, all inclusion criteria are met (see section 5.3) and none of the exclusion criteria apply (see section 5.4). The patient`s written informed consent must be obtained before registration and any trial related procedures are undertaken (see section 12).

5.3 Inclusion criteria

Patients are eligible for the trial if **all** of the following criteria are met:

- Patient and disease factors are deemed suitable for transoral surgery under general anaesthetic.
- Decision to treat with primary transoral resection or local excision biopsy.
- Aged 18 or over.
- Written informed consent provided.
- Clinically suspected or histologically confirmed primary dysplasia or malignancy of the oral cavity or oropharynx OR histologically confirmed diagnosis of squamous cell carcinoma in a cervical lymph node of unknown primary.
- Patient considered fit for surgery.

5.4 Exclusion criteria

Patients are not eligible for the trial if **any** of the following criteria apply:

- Lesions undergoing incisional or punch biopsy only.
- Surgery with planned primary closure or local/ distant flap reconstruction.
- Inability to provide written informed consent.

- Medical contraindication to a general anaesthetic or to PuraBond® use.

6 Surgery

Surgery should only be carried out through the transoral route. Depending on the lesion subsite, suitable procedures include:

Oral cavity
Excision of a lesion from free oral mucosal surfaces with planned healing by secondary intention.

Oropharynx:
- Tonsillectomy
- Tongue base mucosectomy
- Lateral oropharyngectomy
- Tongue base resection
- Soft palate excision

It is important to note that all surgical procedures undertaken will be standard of care and agreed on before and regardless of trial participation. PuraBond® is already in use in head and neck surgery at LUHFT depending on the operating surgeon's preference and is currently on the recognised supplier list for the trust.

7 Registration and randomisation

Following clinical assessment, participants will be randomised to one of two trial arms using the method of minimisation. Randomisation will be performed centrally by the LCTC. Patient eligibility must be established prior to randomisation (see section 5.1) and patients must confirm their consent by providing a signed informed consent form (see section 12.1). Details of the trial enrolment will be recorded in the participant's electronic patient record. This will include confirmation of eligibility and the date of enrolment into the trial.

At registration the participant will be given a unique participant trial number. At randomisation the participant will be allocated to a treatment arm. To register or randomise a patient the relevant registration or randomisation case report form (CRF) should be completed and the LCTC contacted. Participants will be randomised centrally by a computer in a 1:1 ratio to either have PuraBond® applied to the surgical field or not intraoperatively. A minimisation algorithm will be used within the online randomisation system to ensure balance in the treatment allocation over the three following clinical variables:

- Surgical subsite: oral cavity or oropharynx
- Surgical operation: concurrent neck procedure (yes or no)
- Surgical technique: laser use (yes or no)

The operating surgeon will be informed by LCTC regarding the patient's treatment arm allocation. Due to the packaging of PuraBond® within pre-filled and labelled syringes, attempts to completely blind clinicians intraoperatively are not feasible. However, the patient, the assessors of postoperative outcomes and the study co-investigators will be blinded.

8 Trial endpoint assessments

The aim of the PuraBond® PROOF trial is to determine whether PuraBond® application intraoperatively on the surgical field significantly reduces postoperative pain in head and neck transoral operations. Assessment of secondary clinical outcomes such as hospital stay and time till oral intake alongside post operative complications are also important points to record consequently. The study will also briefly consider any health economic benefits of PuraBond® use.

Details of the assessments required are included in the CRF and are outlined below in the schedule of trial assessments (see section 8.4). With regards to the timing of assessments, the date of transoral surgery and thus whether PuraBond® is applied or not is classified as day 0.

8.1 Baseline (pre-operative assessments)

Pre-operative clinical investigation and preparation will be as per trust guidelines. Upon obtaining informed patient consent for participation in the study, the following data will be recorded:

- Informed Consent (written)
- Compliance to inclusion/exclusion criteria
- Assignment of unique patient ID
- Sex and age in years (on the day of surgery)
- Height in centimetres
- Weight in kilograms
- Diagnosis and indication for surgery
- Surgical plan

8.2 Intra-operative assessments

On the day of the operation (day 0), the following data will be recorded:

- Baseline VAS pain score
- Surgical plan
- WHO performance score
- Surgeon's survey

8.3 Post-operative assessments

8.3.1 *Post-operative discharge*

On discharge day, the following data will be recorded:

- Length of stay in hospital (days)
- Intraoperative complications
- Time till commencement of oral intake

8.3.2 *Post-operative follow up*

A patient phone call may be conducted on days 1,2,4,7,14 and 30 to remind them to fill in their VAS pain scores. A scheduled patient phone call on day 30 will collect the following data:

- Reoperation within 30 days
- Post operative complications

- Readmission to hospital within 30 days

They will be asked to return their VAS pain CRF to the study team via a pre-paid envelope provided.

8.4 Schedule of trial assessments

Assessment/ Procedure	Screening and baseline	Surgery (Day 0)	Day of discharge	Follow up					
				POD 1	POD 2	POD 4	POD 7	POD 14	POD 30
Eligibility (inclusion/ exclusion criteria)	x								
Written informed consent	x								
Registration	x								
Assignment of a unique participant identification number	x								
WHO performance score	x	X							
Randomisation		x							
Pain VAS score		x	**x**	x	x	x	x	x	x
Participant demographics – age, gender etc.	x								
Diagnosis and proposed surgery	x	x							
TOLR/ transoral surgical excision		x							
Surgeon's survey		x							
Return to theatre within 24 hours				x					
Length of hospital stay			x						
Readmission to hospital within 30 days									x
Return to theatre within 30 days									x
Intra operative complications			x						
Post operative complications				x	x	x	x	x	x
Time till oral intake			x	x					x

9 Adverse effects and safety reporting

9.1 Definitions

PuraBond® PROOF is a non-CTIMP study as defined by the MHRA due to PuraBond® being a class III CE marked medical device not a drug. Thus, the following definitions are applicable to this study:

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a patient or clinical study subject, including unfavourable and unintended signs, including abnormal laboratory results, symptoms or a disease associated with treatment.
Serious Adverse Event (SAE)	Any AE that: • Results in death • Is life-threatening • Requires hospitalisation, or prolongation of existing inpatients' hospitalisation • Results in persistent or significant disability or incapacity • Is a congenital anomaly or birth defect.
Suspected Unexpected Serious Adverse Event (SUSAE)	Any SAE, the nature and severity of which is not consistent with the Reference Safety Information (RSI) for the trial treatments – transoral surgery or PuraBond® application to the surgical field.

Medical judgement should always be exercised in deciding whether an AE is serious in other situations. Important AEs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

9.2 Reporting procedures

Any questions concerning adverse event reporting should be directed to the CI in the first instance.

9.2.1 *Adverse Events (AE)*

An AE has been defined above (see section 9.1). It may or may not be related to the transoral surgical procedure or PuraBond® application to the surgical field. Any AE should be recorded, this can be done on the designated CRF and in the patient electronic hospital medical records.

A list of expected complications of transoral surgery include:

- Teeth, lip, gum injury
- Cutaneous or intraoral laser injury
- Pain
- Haemorrhage
- Surgical site infection
- Velopharyngeal insufficiency
- Difficulty swallowing
- Lingual or hypoglossal nerve injury

- Pharyngocutaneous fistula

A list of expected complications of PuraBond® application include:
- Irritation/inflammation, or disruption of blood components, due to the low pH of the product.
- Thromboembolism following migration of thrombus resulting from haemostatic effect.
- Embolization of gelled product following migration into blood vessels before or after gelation.

The above listed complications can be used as the RSI when assessing the expectedness of SAEs causally to the trial treatments.

9.2.2 *Serious Adverse Events (SAE)*

All SAEs (see section 9.1) must be reported immediately with 24 hours of knowledge of the event apart from a hospitalisation because of expected complications of transoral surgery or PuraBond® application as defined above (see section 9.2.1) which will not require expediated reporting.

A SAE form should be completed and sent to either the CI or study co-investigators (see SAE reporting form). All SAEs should also be reported to the relevant NHS research ethics committee where in the opinion of the CI, the event was both related to the study (it resulted from the administration of any of the research procedures) and unexpected (an event that is not listed in the protocol as an expected occurrence). These should be sent within 15 days of the CI becoming aware of the event. The CI should also inform the sponsor regarding any SAE.

10 Data management

The University of Liverpool, as Sponsor, has overall responsibility for the security, maintenance, and integrity of the study. The study's CI and study co-investigators are responsible for data held locally at LUHFT and for ensuring all data provided is subject to written informed consent.

10.1 Data collection and study database

Data will be collected according to the study protocol and by approved, delegated members of the study team only. Data will be recorded on the designated CRF and then transcribed over onto a specifically designed electronic data capture system. The REDCap (Research Electronic Data Capture) database that will be used in this study is encrypted and password protected. Only approved and delegated study team members will be given access to the study's REDCap database for data insertion. Access to this database is controlled by means of user identifiers and passwords, thus an audit trail will be available. Participants will be assigned a unique study identification number on registration, and this will be used on subsequent CRFs and database reporting, thus maintaining the strictest patient confidentiality.

10.2 Training

All members of the study team will be educated on the trial protocol at a departmental meeting. This will allow members of staff the opportunity to ask questions to ensure they are confident and comfortable with all aspects of the study protocol. Furthermore, the CI and study co-investigators will confirm surgeon credentialing through prior experience with PuraBond® before any surgery is performed. Study team members that are approved to use REDCap will undergo further training on how to use this database.

10.3 Patient data

All data collected for the study will be pseudonymised using unique identification numbers. Thus, a master patient identification list will be created and held securely on the password-protected encrypted NHS servers at LUHFT, ensuring it is securely and confidentially stored on site. Direct access to patient identifiable data, including access to the master patient identification list to enable reversal of pseudonymisation, will be granted to specific individuals or authorised representatives, and regulatory authorities only on request for monitoring, audit and inspection purposes.

11 Trial management

11.1 Trial committees

11.1.1 *Patient and public involvement group*

Patient involvement and advice will be sought from some members of the Merseyside regional head and neck cancer patient and carer support group. This includes patients who have previously undergone head and neck surgery at the study setting. Their input on key study elements will be incorporated into the study protocol. Furthermore, their involvement in reviewing the study PIS is vital.

11.1.2 *Trial oversight*

The Trial Management Group (TMG) will consist of the CI, study co-investigators and representatives from LCTC. This group will be responsible for the daily running of the trial. A small independent Trial Steering Committee will be convened for this study on the basis that the surgery performed and PuraBond® intervention are already in routine clinical use and both treatment arms are considered standard of care (see appendix 2). No Independent Data Management Committee (IDMC) is being proposed for this study.

11.2 Risk assessment

Given both treatment arms are already used throughout the UK and in head and neck surgical operations at the study site of LUHFT, the risk to all the study participants is no higher than that of standard care. In fact, a case series on PuraBond® use in transoral surgery reported no significant adverse events. A higher evidence study, such as PuraBond® PROOF, is needed to prove efficacy. A trial risk assessment will be performed to identify the potential hazards associated with the trial and their likelihood of occurring.

PuraBond® is a class III CE marked medical device not a drug, it is being used within its license for this study. The following risks have been identified for PuraBond® use:

- Irritation/inflammation, or disruption of blood components, due to the low pH of the product.
- Thromboembolism following migration of thrombus resulting from haemostatic effect.
- Embolization of gelled product following migration into blood vessels before or after gelation.

It is important to stress that such side effects would be the same for participants enrolled onto the study as for those patients not enrolled in the study but are treated with PuraBond® routinely as per the operating surgeon's preference. The level of risk that a trial participant would be exposed to is the same of that they would encounter outside of the trial as its use is standard of care.

11.3 Participant withdrawal

By consenting to this trial, participants are accepting of the trial interventions, assessments and follow up data collection requirements. However, at time of informed consent, patients will be reminded that their participation is voluntary, and they retain the right to withdraw from the study without reason and without prejudicing any further treatment. The sample size calculation accounts for some participant withdrawal, so it is not anticipated that it will be necessary to replace participants who decide to withdraw.

If a participant does decide to withdraw from this study, they can do so at any time by informing the CI or any other member of the research study team by calling 0151 529 5259. The contact details of the study team are recorded on the PIS. The investigator will need to clarify whether the participant wishes to withdraw from all or only particular trial components. If the latter is requested, then follow up data collection for which the participant previously consented to may continue. Should any participant wish to withdraw fully from the study, any data collected prior to withdrawal may be retained and used in trial analysis as specified by the study protocol. If following randomisation, the participant does not go on to have their surgery they should be withdrawn from the trial.

11.4 Lost to follow up

If a participant is lost to follow up, the study team will attempt to contact the participant to obtain information on their status in the first instance. Otherwise, the patient will be considered withdrawn from the study (see section 11.3).

11.5 Protocol/ GCP non-compliance

The CI should report any non-compliance to the trial protocol or the conditions and principles of GCP to the sponsor as soon as they become aware of it.

11.6 End of trial

The end of the trial is defined as the date of final data capture to meet the trial endpoints.

11.7 Archiving

The Trial Master File (TMF) will be held in a secure locked personal office of the CI which itself is located in a secure staff only access department area at LUHFT. Essential documents pertaining to the trial shall not be destroyed without permission from the Sponsor. Electronic copies of the study documents will also be archived on the password-protected encrypted NHS server at LUHFT for a minimum of 10 years.

12 Statistical considerations

12.1 Randomisation

After confirmation of eligibility, randomisation will take place by contacting LCTC. Participants will be randomised using minimisation to ensure balanced treatment allocation by several clinically important stratification factors including lesion site and surgical technique. A randomisation allocation ratio of 1:1 will be used.

12.2 Outcome measures

12.2.1 *Primary outcome measures*

The primary outcome of this study will be pain following procedure. This will be measured using the visual analogue scale (VAS) which is a validated pain rating scale first used by Hayes and Patterson in 1921 [9]. Self-reported pain severity is recorded by marking a point on a 10cm line that represents a continuum between 'no pain' at one end and 'worst pain' at the other. VAS pain scores preoperatively and on days 1, 2, 4, 7, 14 and 30 postoperatively will be recorded.

12.2.2 *Secondary outcome measures*

This will include data on:

- Post-operative analgesia usage (including drug used, dose, route and frequency)
- Post-operative complications by Clavien Dindo Classification including wound infection and bleeding rates
- Length of stay in hospital
- Readmission to hospital within 30 days post operatively
- Bleeding events including primary (24 hours post operatively) and secondary (day 1 to 30 post operatively) haemorrhage
- Return to operating room within 24 hours post operatively
- Return to operating room within 30 days post operatively
- Surgeon survey regarding ease of PuraBond® use
- Time taken to normal oral dietary intake (days)
- Any health economic benefits of PuraBond® use.

12.3 Sample size calculation

To achieve a power of 80% with a significance level of 0.05, 32 patients will be needed in each treatment arm. A comparative study looking at pain scores following corticosteroid use in transoral robotic surgery reported a standard deviation in VAS pain scores of 2.0 [10]. A 1.2-point difference in VAS pain scores between intervention and control groups would be significant [10,11]. Analysis will be conducted using analysis of Covariance techniques which include pre-surgical pain scores.

The following sample size calculation was conducted for our continuous pain VAS outcome measure:

$$n = \frac{2\,[(a+b)^2]\sigma^2}{\delta^2}$$

Where: n = the sample size in each group arm, a = the conventional multiplier for alpha (1.96 for 5% alpha), b =the conventional multiplier for power (0.84 for 80% power), σ= standard deviation and δ= the difference you wish to detect.

$$n = \frac{2\,[(1.96 + 0.84)^2]2^2}{1.2^2}$$

$$n = \frac{62.72}{1.96} = 43.5\ patients\ per\ overall$$

$$= 87\ patients\ in\ total$$

To account for the study using pre-surgical pain scores in the final analysis, the sample size is adjusted using a design factor based on the correlation between pre- and post-surgical pain scores. Here a conservative estimate of 0.3 is used. A final sample size, including 5% inflation for patient attrition is then given by:

87*(1-0.3)*1.05 = **64 patient (32 per treatment group)**

12.4 Statistical analysis

All data will be collected using the trial CRF and will be included in the final analysis. A detailed statistical analysis plan will be developed before the analyses are conducted. The following statistical considerations will be used in this study:

Data Summaries:
Continuous data are summarised as median (inter-quartile ranges) and categorical data are summarised as frequencies of counts (percentages). All VAS pain scores will be recorded to 1 decimal point.

Missing Data:
Missing data are assumed to be rare given the study methodology and short follow up period, and analyses are thus planned on a complete case basis.

Levels of Significance:
Statistical significance will be determined using the $p<0.05$ significance level with all results presented alongside two-sided 95% confidence intervals.

Patient groups for analysis:
All analysis will be carried out on an intention to treat basis, retaining patients irrespective of any protocol violations.

Analysis of the primary outcome:
Analysis of the primary outcome will be carried out using Analysis of Covariance (ANCOVA) techniques. Here the post-operative pain score will be analysed as the primary outcome with the pre-surgical pain score being included as an adjusting covariate. Results will be presented in terms of the difference in means (95% confidence) intervals between the two groups.

13 Informed consent, ethical and regulatory considerations

13.1 Informed consent

Before any trial related procedures are undertaken, the patient's written informed consent must be obtained using the PuraBond® PROOF trial Informed Consent Form (ICF), which follows the PIS. Please note, only when written informed consent has been obtained from the patient and they have been registered into the trial can they be considered a trial participant.

The patient's consent to participate in the trial should be obtained by those delegated to do so such as members of the study team, research nurses or qualified members of their direct clinical team, all after a full explanation has been given. All patients must be informed of the objectives of the study, the trial design, the possible adverse events, the procedures, and personal implications of study participation. They will be informed of the strict confidentiality of their patient data, but that their medical records may be reviewed for trial purposes by authorised individuals other than their treating physician.

Patients will be provided with adequate time after being given the trial PIS to consider and discuss participation and have the opportunity to ask questions. This will be defined using patient and public involvement and engagement (PPIE) data (see PPIE survey). The study team will conduct a PPIE exercise with previous head and neck surgery patients that are part of the Merseyside & Cheshire Head & Neck Cancer Support Group. During the consent process, the investigator should determine that the patient is fully informed of the trial and their participation, in accordance with the principles of Good Clinical Practice. Patients should always be asked to sign a consent form. One copy should be given to the participant, but the original copy should be kept in the investigator site file and a further copy should be kept with the participant's hospital notes. At the time of signing the ICF, each participant must be given the names and contact details of study site staff for reporting adverse events and medical emergencies.

The right of the patient to refuse to participate in the trial without giving reasons will be respected and participants are free to withdraw from the study at any time before the last trial data collection point, that takes place at one-month postoperatively, without giving reasons and without prejudicing any further treatment.

13.2 Ethical approval

The relevant ethical approval will be obtained from the research ethics committee (REC) for the study and all associated documents before any activity commences on the study. All study amendments must be reviewed by the sponsor to assess if they are substantial or non-substantial. All substantial amendments to the protocol will be submitted to the relevant bodies and approval received before implementation. Informed written consent will be obtained from all participants. The right of a patient to refuse participation or withdraw from the study without giving reasons must and will be respected.

13.3 Confidentiality and data protection

All information collected during this study will be kept strictly confidential. Information will be held anonymously and securely on an electronic data capture system. A REDCap database will be created and utilised to collect study data. This will be compliant with the relevant data protection laws and any data published will be anonymous.

14 Publication

The study team is committed to transparent communication of findings. Thus, data will be analysed and published as soon as possible. The results of this trial will be disseminated through presentations at scientific meetings, and in scientific articles in peer-reviewed medical journals.

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APPENDIX 1: Abbreviations and glossary

PuraBond® PROOF	PuraBond® and Pain following Resection of Oral or Oropharyngeal lesions
AE	Adverse Event
AR	Adverse Reaction
AUH	Aintree University Hospital
CI	Chief Investigator
CRF	Case Report Form
CTIMP	Clinical Trial of an Investigational Medical Product
GCP	Good Clinical Practice
HNC	Head and Neck Cancer
ICF	Informed Consent Form
IDMC	Independent Data Management Committee
LCTC	Liverpool Clinical Trials Centre
LHNC	Liverpool Head and Neck Centre
LUHFT	Liverpool University Hospital Foundation Trust
MDT	Multidisciplinary Team
MHRA	Medicines and Healthcare products Regulatory Agency
NHS	National Health Service
PIS	Participant Information Sheet
PPIE	Patient and Public Involvement and Engagement
RCT	Randomized control Trial
REC	Research Ethics Committee
REDCap	Research Electronic Data Capture
RSI	Reference Safety Information
SAE	Serious Adverse Event
SUSAE	Suspected Unexpected Serious Adverse Event
TLM	Transoral Laser Microsurgery
TMF	Trial Master File
TMG	Trial Management Group
TOLR	Transoral Laser Resection
TORS	Transoral Robotic Surgery
TSC	Trial Steering Committee
VAS	Visual Analogue Scale

APPENDIX 2: TSC members

Chairman:
Mr Dejo Olaleye
Consultant ENT/ Head and Neck Surgeon, University Hospitals Leicester.

Panel members:

- Mrs Pippa Mather
  Principal Head and Neck Oncology Dietician, Guy's Hospital London.
- Mr Jason Fleming
  CI of PuraBond® PROOF. Consultant ENT/ Head and Neck Surgeon, Aintree University Hospital, LUHFT, Liverpool. Senior Clinical Lecturer, University of Liverpool.
- Mr Michael McGovern
  Lay member who is a patient representative of the Merseyside regional head and neck cancer patient and carer support group.
- Mr Richard Jackson
  Medical statistician. Senior Lecturer at the department of Health Data Science, University of Liverpool

Invited attendees:

- 3D Matrix representative.
- Sponsor/ LCTC representative.