CONFIDENTIAL

Determining the Effectiveness of Fibrin Sealants in Reducing Complications in Patients Undergoing Lateral Neck Dissection: A randomised external pilot trial

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Study Protocol Approval

I, the undersigned, hereby approve this clinical study protocol:

Signature: _____ **Date:** 16.2.2018

Andrew Schache
Chief Investigator/Primary PhD Supervisor
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Signature: _____ **Date:** 14th February 2018

Richard Jackson
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Signature: _____ **Date:** 15/2/18

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Signature: _____ **Date:** 15 Feb 18

Alex Astor
Sponsor Representative
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Signed on behalf of sponsor

General Information

This document describes the DEFeND trial and provides information about procedures for entering patients into it. The protocol should not be used as an aide-memoir or guide for the treatment of other patients. Every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to the registered investigators in the trial, but centres entering patients for the first time are advised to contact the coordinating centre (North West Surgical Trials Centre (NWSTC) part of Liverpool Cancer Trials Unit (LCTU)) to confirm they have the most up to date version. Clinical problems relating to this trial should be referred to the relevant Chief Investigator via NWSTC/LCTU.

Statement of Compliance

This study is designed to comply with the guideline developed by the International Conference on Harmonisation (ICH) for Good Clinical Practice (GCP) and will be conducted in compliance with the protocol, NWSTC/LCTU Standard Operating Procedures and EU Directive 2001/20/EC, transposed into UK law as the UK Statutory Instrument 2004 No 1031: Medicines for Human Use (Clinical Trials) Regulations 2004.

UK Registration

This study will have Health Research Authority (HRA) Approval. All research sites will confirm capacity and capability to conduct the study and will sign a Research Site Agreement.

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Glossary

ABPI	Association of the British Pharmaceutical Industry
AE	Adverse Event
APTT	Activated Partial Thromboplastin Time
AR	Adverse Reaction
CI	Chief Investigator
CO_2	Carbon Dioxide
CRF	Case Report Form
CTIMP	Clinical Trial of Investigational Medicinal Product
CTU	Clinical Trials Unit
CV	Curriculum Vitae
DOB	Date of Birth
(E)CRF	Electronic Case Report Form
FDA	United States Food & Drug Administration
FS	Fibrin Sealant
GCP	Good Clinical Practice
GP	General Practitioner
HE	Health Economics
HRA	Health Research Authority
IB	Investigator's Brochure
ICER	Incremental Cost Effectiveness Ratio
ICF	Informed Consent Form
ICH	International Conference for Harmonisation
IDSMC	Independent Data and Safety and Monitoring Committee
IEC	Independent Ethical Committee
IMP	Investigational Medicinal Product
INR	International Normalised Ratio
ISRCTN	International Standard Randomised Controlled Trial Number
LCTU	Liverpool Cancer Trials Unit
LREC	Local Research Ethics Committee
MACRO	Data Capture & Management Software
MCID	Minimal Clinically Important Difference
MCRN CTU	Medicines for Children Clinical Trials Unit
MDT	Multidisciplinary Team
MHRA	Medicines and Health Products Regulatory Agency
MREC	Multi-centre Research Ethics Committee
NDII	Neck Dissection Impairment Index
NHS	National Health Service
NPSA	National Patient Safety Agency
NWSTC	North West Surgical Trials Centre
PI	Principal Investigator
PIS	Patient Information Sheet
R&D	Research & Development
RNA	Ribonucleic Acid
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SAP	Statistical Analysis Plan
SOC	Standard of Care
SPC	Summary of product characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TAME	Acute Toxicity, Adverse Late Effects and Mortality Risk Generated by a Treatment Programme
TARDIS	Treatment Allocation Randomisation System
TMG	Trial Monitoring Group

TSC	Trial Steering Committee
UAR	Unexpected Adverse Reaction
UKCRN	United Kingdom Clinical Research Network
VAS	Visual Analogue Scale

1 PROTOCOL SUMMARY

Title:	**Determining the Effectiveness of Fibrin Sealants in Reducing Complications in Patients Undergoing Lateral Neck Dissection: A randomised external pilot trial**
Phase:	Randomised External Pilot Trial
Sample Size:	A minimum of 50 patients (UK)
Main Inclusion Criteria:	• Patients due to undergo lateral neck dissection • Neck dissection to include a minimum of 3 levels • Patients who have capacity to consent
Main Exclusion Criteria:	• Age < 18 years • Bilateral neck dissection • Presence of a vascular pedicle for reconstruction • Pregnancy or breast feeding • Known hypersensitivity reaction to Aprotinin • Previous exposure to Fibrin Sealant within 6 months • Known allergy to dairy products
Number of Sites:	Aintree University Hospital, Liverpool UK Queen Victoria Hospital, East Grinstead UK
Study Duration:	12 Months
Description of Intervention:	Application of Artiss fibrin sealant (Baxter Healthcare LTD) to the surgical wound. Up to 2ml driven by medical air at 1.5 bar, minimum 10 cm away from wound prior to closure.
Objectives:	The main objectives of this study are to assess if a future phase III trial is feasible and to ensure the individual aspects of the trial design work well together. The key objectives of this randomised external pilot study are to assess the following points: • Whether patients can be recruited and retained at a rate of approximately 4 patients per month across the 2 centres. • Determining the effectiveness of the blinding strategy using blinding indices. • Ensuring the administrative processes of randomisation and data management work well within the study. • Assess adherence to the conditions of the protocol. • Provide evidence to inform sample size calculation for a future study.

Schematic of Study Design:

2 BACKGROUND INFORMATION

2.1 Introduction

The Problem Being Addressed

Complications after major surgery are a significant cause of morbidity and mortality and have been shown to have a negative impact on long-term quality of life and psychosocial well-being.[1, 2] In surgical oncology, complications can also delay adjuvant treatment (e.g. radiotherapy) which is known to adversely affect survival.[3] Neck dissection is one of the most commonly performed 'major operations' in head and neck surgical oncology and it is estimated, from national audit data, that approximately 7000 major head and neck surgical resections are performed each year in England alone.[4] Significant surgical complications occur in approximately 10 – 20% of patients undergoing neck dissection.[5, 6] Such risks increase to 40% in patients who have had previous chemo-radiotherapy to the area[7] or when operating on higher risk patients of increasing age, with multiple co-morbidities and polypharmacy.[8] Common surgical complications include: haematoma formation, surgical site infection, wound breakdown/dehiscence, and fistula formation. Management of these complications is frequently painful, invasive and may involve returning to theatre. This inevitably delays recovery, which in turn may result in prolonged hospital stay and immobility; both of which are known risk factors for lower respiratory tract infections and venous thromboembolism.

The Patient's Perspective

The direct impact on patients of complications following neck dissections has been borne out by recent and ongoing qualitative research. Currently unpublished doctoral research from colleagues at the University of Liverpool seeking a 'Core Outcome Set' for head and neck cancer has found that 'need for further surgery or invasive treatment' is considered 'very important' in >70% of patients through the Delphi method.[9] This is reinforced by work done at the University of Bristol on a 'Core Information Set' for the broader topic of head and neck surgery that found 'likelihood of wound problems' and 'complications that may require a return to theatre' are both core elements of importance to patients in the consent process.[10] Patients from the 'Aintree Head & Neck Cancer Patient Research Forum' have specifically highlighted their aversion to surgical drains finding them both painful and a significant barrier to mobilisation. Patient opinion is further supported by robust data from a meta-analysis on the use of surgical drains in thyroid surgery that found they increased post-operative pain and infection rates.[11] Clearly drains serve an important role in preventing potentially life threatening complications due to neck swelling, however reduction in the duration of their use, through early safe removal, and in reduction of wound-related complications will clearly translate to significant patient benefit in the immediate post-operative period.

Fibrin Sealants

A recent systematic review and meta-analysis on the use of Fibrin Sealants (FS) in head and neck surgery has found potential clinical advantages to both patients and healthcare organisations through reduction in complications and volume of wound drainage, thereby minimising the retention time of the drains.[12]

FS are commercially available, US Food and Drug Administration (FDA) approved, products that have been investigated broadly across several areas of surgery.[13] FS is applied to the raw surfaces of the surgical wound prior to closure providing an adjunct to haemostasis. The mechanism of action is through replication of the final stages of the clotting cascade through which thrombin cleaves fibrinogen to form a fibrin clot. The subsequent clot effectively seals small vessels and occludes cavity dead space by adhering the wound surfaces, both essential steps in avoiding haematoma formation that may compromise surgical site healing. Results of previous investigations of FS effectiveness in surgery have been variable and have frequently been unduly influenced by poor study design.

The key relevant findings of this systematic review and meta-analysis were:

- There is a paucity of high-quality trials on the use of FS in Head and Neck surgery.
- There was a tendency for FS to reduce drainage volume (mean difference 26.86ml, 95%CI -43.41 to - 10.31, I2 =97%, p=0.001).
- There was a suggestion that FS may reduce 'mean retention time of drains' by 1.24 days (95%CI -3.32 to 0.85, I2 =99%, p=0.25) and 'hospital length of stay' by 2.09 days (95% CI -5.18 to 0.99, I2 =97%, p=0.18) but these were not statistically significant.
- Whilst not reaching statistical significance, FS may be protective against complications compared to standard of care with a relative risk of 0.69 (95% ci 0.35 to 1.38, I2 =0%, p=0.29). The benefit of FS was greater with regards to haematoma/seroma formation (RR 0.49, 95%CI 0.22 to 1.07, I2 =0%, p=0.07).
- Patients at high-risk of complications (e.g. anticoagulation and previous surgery or radiotherapy) were excluded from all studies analysed, leaving the effects of FS in populations most likely to benefit not assessed.
- The role of FS in lateral neck dissection is an area of need for further studies. Only 2 trials have been performed so far that have randomised 78 patients between them.[14, 15] Their inclusion criteria and findings varied greatly and substantial statistical heterogeneity impaired conclusive results in the meta-analysis.

2.2 Rationale

With an understanding of the evidence in combination with clinical experience it is felt that a surgical trial to determine the effectiveness of FS in reducing the rate and severity of complications in patients undergoing lateral neck dissection is warranted. This important clinical question is framed by patient opinion and guided by a clinical desire to reduce morbidity, and indeed it has the potential to translate to patient benefit. However given the difficulties in the delivery of Head and Neck surgical trials,[16] this external pilot study will be used to answer critical questions on how well key components of the proposed study design work together as well as feasibility of the future trial.

2.3 Objectives

The key objectives of this randomised external pilot study are to assess the following points:

I. Whether patients can be recruited and retained at a rate of approximately 4 patients per month across the 2 centres.
II. Determining the effectiveness of the blinding strategy using blinding indices.
III. Ensuring the administrative processes of randomisation, allocation concealment and data management work well within the study.
IV. Assess adherence to the conditions of the protocol.
V. Provide evidence to inform the sample size calculation for the future phase III multicentre randomised trial

2.4 Potential Risks and Benefits

2.4.1 Potential Risks

Each of the following risks has been documented as either potential or theoretical in nature, their occurrence is expected to be highly unlikely should the trial protocol be adhered to. They are detailed in full below.

As Fibrin Sealants are derived from human blood they may contain infectious agents which can cause disease, such as viruses and theoretically, the agent that causes Creutzfeldt-Jakob Disease (CJD) in humans. The manufacturer states that certain measures have been taken to prevent infections. These include: selection of donors,

screening of individual donations for specific markers of infection and the inclusion of effective manufacturing steps for the inactivation/removal of viruses. Despite this, the possibility of transmitting infective agents cannot be totally excluded. The measures taken by the manufacturer are considered to be effective against viruses such as Human Immunodeficiency Virus (HIV), Hepatitis A, B and C. The measures taken may be ineffective against parvovirus B19. Parvovirus B19 infection may be serious for pregnant women as it may cause foetal infection. Pregnant women have therefore been excluded from taking part in this study. There have been no reports of transmission of infectious agents through the application of Fibrin Sealants in the literature. All patients will be informed of this potential risk during the consent process.

Administration of Fibrin Sealants may result in allergic reactions in some patients. The precise frequency of severe life-threatening reactions is unknown as they are incredibly rare. Patients who have a known allergy to Aprotinin (an ingredient of Fibrin Sealants that can cause allergic reactions) will be excluded from taking part in the study. The risk of Aprotinin hypersensitivity is increased in patients who have been exposed to it within 6 months or are allergic to bovine proteins (as the synthetic Aprotinin used in Fibrin Sealant is structurally identical to bovine Aprotinin). Therefore patients who have been exposed to Fibrin Sealant within 6 months prior to recruitment or are allergic to bovine proteins (e.g. dairy products), will be excluded from the study.

Because the Fibrin Sealant is applied to the wound as a spray driven by 'medical grade air', it is possible that the patient may develop an 'air embolism'. There have been 6 reported cases of air embolism following the administration of Fibrin Sealant. It is thought that these cases occurred because either the air pressure was too high or the spray device was held too close to the wound. The manufacturer recommends that the air pressure should be no higher than 1.7 bars and the spray device should be held no closer than 10 centimetres to the wound. These recommendations have been incorporated into the study protocol. Every surgeon that uses Fibrin Sealant on a patient in this study will undergo training by the research team. They will need to demonstrate their understanding of these recommendations by setting up the spray device and entering the correct settings into the machine. They will also need to demonstrate their spraying technique where the distance from the wound will be assessed. Only when they can demonstrate safe use of the Fibrin Sealant will they be accredited to use it on study participants.

Other more minor risks of using Fibrin Sealants include itchiness of the skin (occurs in 2/138 patients), a collection of fluid under the skin (occurs in 1/138 patients) and problems with skin grafts (5/138 patients). The latter risk is not relevant to this study as we will not be using the Fibrin Sealant on skin grafts. Problems with itchiness and fluid under the skin will reported as adverse events/complications and treated on a case-by-case basis.

2.4.2 Known Potential Benefits

There are no known patient benefits however, every effort has been made to minimise inconvenience to study participants by making the research pathway as similar to the normal clinical pathway as possible. As a result the patient has the opportunity to participate in research without a significant burden of extra tests or hospital visits.

3 SELECTION OF CENTRES/CLINICIANS

Each participating centre will be required to offer the following minimum requirements:

1) Centres will either have or be part of a comprehensive Head & Neck Multidisciplinary Team (MDT).
2) Have surgical expertise in the management of Head & Neck Cancer.
3) Have sufficient caseload to recruit 2 patients per month.
4) Demonstrate enthusiasm to participate in the study.
5) Provide information to all supporting staff members involved with the trial or with other aspects of the patient's management.
6) Acknowledge and agree to conform to the administrative and ethical requirements and responsibilities of the study, including signing up to Good Clinical Practice (GCP).

3.1 Centre/Clinician Inclusion Criteria

1) Positive Site Specific Assessment (SSA) by the centre's Research & Development (R&D) Department.
2) Completed Research Site Agreement.
3) Receipt of evidence of completion of points 1) and 2) by NWSTC.
4) Completion and return of 'Signature & Delegation Log' to NWSTC.
5) Personnel on delegation log have attended the proposed site initiation and training days and have been accredited to perform the intervention.
6) Curriculum Vitae (CV) including a record of International Conference for Harmonisation (ICH) of GCP training – Principal Investigator (PI).
7) CV including ICH GCP training – other personnel on the delegation log.
8) Clinical Study Protocol Receipt Form.
9) Patient Information Sheets (PIS) and Informed Consent Form (ICF) on trust letter headed paper.
10) Completion of test SAE reported via web.

3.2 Exclusion Criteria

Those centres that do not fulfil the above inclusion criteria will not be permitted to participate in the trial.

4 TRIAL DESIGN

4.1 Overall Design

Determining the effectiveness of fibrin sealants in reducing complications in patients undergoing lateral neck dissection: a randomised external pilot trial (Acronym: DEFeND). The study design that is being piloted is that of a parallel group superiority trial with patients being randomised in a 1:1 ratio to each arm. The interventional arm will constitute the application of ARTISS (Baxter Healthcare LTD) fibrin sealant to the surgical wound in addition to "standard of care". The control arm will constitute "standard of care" alone (described in more detail in section 7). Both patients and outcome assessors will be blinded to the allocation. An approximate sample size justification of 50 patients (25 in each arm) has been chosen, as this will provide sufficient precision to calculate the sample size required for the future phase III trial. Currently the design of the pilot study mirrors the design of the future phase III trial, however it is expected that refinements will be necessary based on the pilot data. Patients will be stratified according to the hospital they receive their treatment.

4.2 Pilot Study Outcomes

The proposed outcome measures for this study can be divided into those that are specific to the pilot study and those that would potentially inform a future trial to determine the effectiveness of fibrin sealant in neck dissection. As this is a pilot study, no formal assessment of efficacy, cost or safety across treatment arms are made. All analysis shall take the form of summary statistics and graphical summaries. Continuous data shall be presented using medians (inter-quartile ranges) and categorical data shall be presented as frequencies of counts with associated percentages.

The outcomes for the pilot study include:

- Proportion of eligible patients recruited to the study, calculated as the screened:randomisation ratio.
- Reasons for failure to screen potentially eligible patients.
- Recruitment rate measured as the number of patients randomised each month.
- Reasons for failure to randomise.
- Reasons for failure to reveal allocation at a specific time point during surgery.
- Fidelity of the blinding process (both patients and outcome assessors) as detected by blinding indices.
- Accuracy of data recording, summarised by the number of key data items with missing/incomplete data entries.
- Number of patients lost to follow-up.
- Protocol adherence, measured by the number of major/minor protocol deviations observed through the study.
- Determining the minimal clinically important difference (MCID) in clinical endpoints by questioning recruited patients and recruiting clinicians.

4.3 Clinical Endpoints of Future Phase III Trial

Any surgeon who is in theatre after the revealing of allocation is unblinded and must delegate post-operative clinical decisions and reporting of clinical endpoints to an appropriate colleague who is blinded.

- Clavien-Dindo classification of surgical complications (**Appendix A**).
- Twice daily wound drainage volume (ml).
- Assessment of time to drain removal in hours from departure from theatre.
- Assessment of time to being declared 'medically fit for discharge' and actual hospital

discharge in hours from the time of 'end of surgery'.

Patient reported outcomes to be assessed for use in the future phase III study are:

- Neck Dissection Impairment Index (NDII). This is a procedure specific patient reported outcome measure (**Appendix B**).
- Daily patient reported pain score using Visual Analogue Scale (VAS) (**Appendix C**).

5 STUDY POPULATION

The pilot study setting will be Aintree University Hospital and Queen Victoria Hospital. These are both specialist hospitals for the management of Head & Neck Cancer in the UK.

5.1 Inclusion Criteria

- Patients due to undergo lateral neck dissection
- Neck dissection to include a minimum of 3 levels
- Patients who have capacity to consent

5.2 Exclusion Criteria

- Age < 18 years
- Bilateral neck dissection
- Presence of a vascular pedicle for reconstruction
- Pregnancy or breast feeding
- Known hypersensitivity reaction to Aprotinin
- Previous exposure to Fibrin Sealant within 6 months
- Known allergy to dairy products

5.3 Patient Transfer and Withdrawal

By completing the DEFeND consent process, patients are consenting to trial treatment, follow-up and data collection. If voluntary withdrawal occurs, the patient should be asked to allow continuation of scheduled evaluations, complete an end-of-study evaluation, and be given appropriate care under medical supervision until the symptoms of any adverse event resolve or the subject's condition becomes stable.

5.3.1 Patient Transfers

For patients moving from the area, every effort should be made for the patient to be followed-up at another participating trial centre and for this trial centre to take over responsibility for the patient or for follow-up via GP. A copy of the patient CRFs should be provided to the new site. The patient will have to sign a new consent form at the new site, and until this occurs, the patient remains the responsibility of the original centre. The NWSTC should be notified in writing of patient transfers.

5.3.2 Withdrawal from Trial Intervention

Patients may be withdrawn from treatment for any of the following reasons:

1) At their request or at the request of a legal representative.
2) A change in surgical plan after enrolment such that the patient no longer meets the eligibility criteria.
3) The investigators deems further involvement in the study detrimental to the wellbeing of the patient

If a patient wishes to withdraw from trial treatment, centres should nevertheless explain the importance of remaining on trial follow-up, or failing this, of allowing routine follow-up data to be used for trial purposes. Generally, follow-up will continue unless the patient explicitly withdraws consent for follow-up (see section 5.3.3).

5.3.3 Withdrawal from Trial Completely

Patients who withdraw from the trial for other reasons have previously consented to follow-up in the trial. Data up to this time can be included in the trial if anonymised. They may need to reaffirm that they consent to follow-up through usual NHS

mechanisms. If the patient explicitly states their wish not to contribute further data to the study, a withdrawal CRF should be completed.

6 ENROLMENT AND RANDOMISATION

6.1 Screening

Patients eligible for the DEFeND trial will be screened through outpatient clinics and/or Head & Neck MDT. The steps that will be completed on all patients to ensure they meet enrolment criteria include:

- Clinical examination
- Detailed medical history including previous treatment/surgery to the head & neck
- Clinical decision to offer a lateral neck dissection

A pre-screening log of all potential patients should be kept at each site, including individuals who decide not to participate in or are found to be unsuitable for the study.

Screening will be performed upon a patient's possible eligibility for the study as above and must be documented on the NWSTC Web Portal "Screening and Enrolment log". Screening details should be entered into the portal and this will automatically generate a screening number and a confirmation email with these details will be sent to site staff. The screening log can be printed at any time off the Portal to allow for storage in the Investigator Site File.

Step-by-step guides will be issued to research site staff and the process will also be demonstrated during site initiations. All patients will be issued a screening number and, where possible, for patients who are not randomised a reason is recorded. The importance of this is in establishing the screening:randomisation ratio which is a key endpoint of the pilot trial.

6.2 Enrolment/ Baseline

Once the criteria for successful screening are complete, and at that point indicate a patient likely to meet eligibility criteria, the patient may be given information about the trial by means of careful explanation with the help of a PowerPoint presentation, Patient Information Sheets and introduction to the Research Practitioner.

The patient will be told that their lack of participation will not impact on the quality of their care. If they wish to consent they will be told that they may change their mind at any time. After signing the consent form, any necessary additional investigations are carried out prior to randomisation:

- Demographics (height, weight, age, gender, smoking and alcohol status).
- Pre-operative neck pain Visual Analogue Scale (VAS) and Neck Dissection Impairment Index (NDII) questionnaire (**see Appendix B and C**).
- Blood tests including full blood count, clotting screen (INR and APTT), liver function tests
- A pregnancy test (beta-hCG blood test) for women of childbearing age will be offered.

If offered, the pregnancy test needs to be carried out prior to randomisation as it constitutes an eligibility criteria. The other information mentioned above should also be carried out before randomisation as it constitutes important baseline measurements.

Patients will be enrolled onto the study by NWSTC once the following documents have been forwarded by the local investigator or research nurse:

1. Eligibility checklist
2. Enrolment forms
3. Copy of signed Patient Consent Form

When the patient has been enrolled a confirmation email will be sent to the site detailing the patients MACRO ID, site, patient initials, DOB, screening number, proposed date

of surgery, details of consent and a link to the patient in the Treatment Allocation Randomisation System (TARDIS). The investigator will also be sent a link to a bespoke web based application for the DEFeND study. This bespoke application should only be accessed during surgery at the point of wound closure.

6.3 Randomisation

The process of randomisation will be undertaken pre-operatively using the TARDIS software. The allocation will be concealed to everyone including the person performing the randmisation. Once the patient has undergone their neck dissection and immediately prior to the point of wound closure, the theatre team will login to a bespoke wed based application. Once logged in to this application the surgical team will enter data regarding the surgery including start time and surgeons present in theatre. Once this data has been entered the allocation will be revealed. This allocation will be revealed for a period of 30 minutes before being concealed once more.

As part of the blinding strategy, any clinicians who will be assessing study outcomes must leave theatre prior to the revealing of treatment allocation. They must not return until the theatre has been cleared of any evidence of ARTISS usage. The surgeon administering the ARTISS will not be allowed to assess study outcomes for the patient and must delegate this responsibility to a suitable colleague.

To randomise, the research nurse will need to create a patient file on the MACRO database and enter the baseline parameters. Following this the research nurse should follow the link to TARDIS in the enrolment confirmation email. The research nurse will be prompted to confirm eligibility of the patient along with the stratification factor, this will enable randomisation to one of the two treatment arms. As stated before, although the patient has been randomised, their allocation will be concealed. The allocation will be revealed for a 30 minute window in theatre.

Patients will be randomised to either ‘ARTISS’ or ‘Standard of Care’ in a ratio of 1:1. Randomisation lists shall be produced by a statistician at the NWSTC prior to the recruitment of the first patient. Lists shall be produced based on the principle of randomly permuted blocks with random block sizes of 2 and 4. Patients will only be stratified according to the hospital in which they receive their treatment.

Randomisation 24 hours a day (including public holidays) via web

Web site: www.lctu.org.uk/tardis

7 TRIAL TREATMENT/S

7.1 Introduction

Patients will be randomised in a 1:1 ratio between arm A and arm B. Arm A constitutes ARTISS (Baxter Healthcare LTD) in addition to "standard of care". Arm B constitutes "standard of care" only.

7.2 Arm A: Neck dissection with fibrin sealant and standard wound closure

Interventional Arm: Application of ARTISS fibrin sealant to the surgical wound in addition to "Standard of care". "Standard of care" will include the establishment of a dry surgical field after performing the neck dissection using electrocautery &/or surgical ties &/or clips. The wound should then be irrigated with 100ml of Normal Saline and dried. Up to 2ml of ARTISS will be sprayed into the wound adhering to the manufacturer's instructions and surgical protocol steps as defined below.

7.2.1 Formulation, Packaging, Labelling, Storage and Stability

ARTISS is a Fibrin Sealant (FS) manufactured by Baxter Healthcare LTD. Further details regarding this product can be found in the manufacturer's 'product information sheet' in **Appendix D**. For the purposes of this study we will be using the 2ml pre-filled double chamber syringe preparation. ARTISS is licenced for use in the hospital setting and by surgeons trained in its application. Baxter Healthcare LTD describes the therapeutic indications of ARTISS as "a tissue glue to adhere/seal subcutaneous tissue in plastic, reconstructive and burn surgery, as a replacement or an adjunct to sutures or staples. In addition, ARTISS is indicated as an adjunct to haemostasis on subcutaneous tissue surfaces." Baxter Healthcare LTD describes the **contraindications** of ARTISS as:

a) Treatment of massive and brisk arterial and venous bleeding
b) Intravascular application
c) Hypersensitivity to the active substances or to any of the excipients

ARTISS has a shelf life of 2 years and should be stored and transported in a frozen state at < -20^{o}C. The syringe must be kept in the outer container in order to protect from light. Unopened pouches, thawed at room temperature, may be stored for up to 14 days at controlled room temperature (not exceeding +25^{o}C). It is important not refreeze or refrigerate after thawing.

7.2.2 Preparation, Dosage and Administration of Study Treatment/s

Preparation

The inner bag and its contents are sterile unless the integrity of the outside package is compromised. It is recommended to thaw and warm the two sealant components using a sterile water bath at a temperature of 33 – 37°C. The water bath must not exceed a temperature of 37°C. When using a sterile water bath for thawing and warming, the pre-filled double chamber syringe assembly should be removed from the aluminum-coated plastic bags). The protective syringe cap should not be removed until thawing is complete and the joining piece is ready to be attached. Do not use ARTISS unless it is completely thawed and warmed (liquid consistency).

There are several methods of thawing the ARTISS, some of which take over 1 hour. Given that the patient's allocation will be revealed intra-operatively at the time point immediately prior to wound closure, this study will utilise the "Quick Thawing" technique. Quick thawing is done by removing the ARTISS from the aluminium-coated

plastic bags and placing it in a sterile water bath at 33°C to a maximum of 37°C. It is recommended to use an infrared thermometer to check the water temperature prior to placing the ARTISS syringe in the water bath. The prefilled syringe is kept in the water bath for 5 minutes ensuring the contents are completely immersed. It is important to note that ARTISS cannot be thawed in your hands or in a microwave. After 'Quick Thawing' ARTISS may be stored at 33 – 37°C for a maximum of 4 hours. A flow chart summarizing the "Quick Thaw" technique can be found in **Appendix E**.

The Sealer Protein and the Thrombin Solutions should be clear or slightly opalescent. Do not use solutions that are cloudy or have deposits. Thawed products should be inspected visually for particulate matter and discoloration prior to administration or any variation in physical appearance. In the event of either being observed, the solution should be discarded. The thawed Sealer Protein Solution should be a slightly viscous liquid. If the solution has the consistency of a solidified gel, it must be assumed to have denatured (e.g. due to an interruption of the cold storage chain or by overheating during warming). In this case, ARTISS must not be used.

The next stage is to set up the EASYSPRAY pressure regulator device. Ensure there is a charged 9V battery and connect it to an IV pole or trolley using the clamps on the back of the device. Use a suitable connection tube to connect the EASYSPRAY device to medical air. Set the spray pressure to 1.5 bar.

Firmly attach the spray head to the nozzle of the double-chamber syringe containing the thawed ARTISS. Fasten the 'pull strap' to the double-chamber syringe to assure the spray head is tightly secured. Fit the EASYSPRAY connection tube to the luer-lock connector on the underside of the spray head. Attach the clip on the end of the sensor line to the syringe plunger (pressing this clip emits air through the spray set). The ARTISS is now ready for use. A copy of the quick reference guide for setting up the EASYSPRAY pressure regulator device published by Baxter Healthcare LTD can be found in **Appendix F**.

Administration

The administration of ARTISS requires at least 3 people including a scrub practitioner, assistant and surgeon. While the ARTISS is being thawed the surgeon should irrigate the wound with 100ml of Normal Saline, dry the wound with gauze swabs, secure the surgical drain and place several resorbable parachute sutures across the platysma layer. These sutures should be loosely clipped and not tied to ensure good access to the wound. The drain should be held temporarily outside of the wound to ensure the perforations are not occluded by the ARTISS. The prepared spray set should not be held any closer than 10 cm to the wound to avoid the risk of air embolism. Once the application of ARTISS has commenced the surgeon has 60 seconds to administer up to 2ml and manipulate the skin flaps into position prior to polymerisation. It is therefore important to strictly adhere to the time using a stopwatch during the application of ARTISS. The assistant should retract any structures (e.g. sternocleidomastoid muscle) to ensure the surgeon can reach these sheltered areas and apply the ARTISS evenly in a thin layer across the entirety of the wound. It is not absolutely necessary to use the full 2ml, it is more important to apply the ARTISS in a thin layer avoiding pooling and large droplet formation. Once the ARTISS has been applied the drain and skin flaps repositioned and even pressure applied to the wound (using a large rolled up gauze swab) while the surgeon ties off all of the parachute sutures. It is very important that the surgeon does not lift the skin edges up while tying the sutures as this may break any adhesive bond created by the sealant. The surgical vacuum drain should then be activated and the assistant should maintain pressure on the neck for a full 3 minutes. After 3 minutes clips/staples are used to close the skin edges. When spraying the ARTISS, changes in blood pressure, pulse, oxygen saturation and end tidal CO_2 should be monitored because of the possibility of air embolism. A flow chart summarising this surgical protocol can be found in **Appendix G**.

Disposal
Any unused product or waste material should be disposed of in accordance with local requirements.

7.2.3 Dose Modifications

A maximum of 2ml of ARTISS can be applied. It is at the surgeon's discretion how much of the 2ml is applied. It is important that the ARTISS is applied in an even and thin layer avoiding pooling and droplet formation.

7.2.4 Accountability Procedures for Study Treatment/s

Baxter Healthcare LTD has agreed to support the study in terms of ensuring adequate supplies of ARTISS and the associated equipment. If there any faults with the equipment Baxter Healthcare LTD will either repair or replace the equipment in keeping with their standard customer service procedures.

7.2.5 Assessment of Compliance with Study Treatment/s

Only surgeons who have received training and have been accredited will be permitted to use ARTISS within this trial. NWSTC will cross-reference the names of the surgeons on the operation note with the delegation log. Compliance will be granted if at least one member of the operating team present during the administration of ARTISS has received training.

7.3 Arm B: Neck dissection with standard wound closure

Arm B is the control arm and constitutes "standard of care" alone. This will include the establishment of a dry surgical field after performing the neck dissection using electrocautery &/or surgical ties &/or clips. Patients will have a surgical drain placed and the wound closed in the usual manner.

7.4 Unblinding

It is unlikely that this trial will require unblinding as the ARTISS is administered only once in the theatre environment. The surgeon applying the ARTISS will not be blinded. The patient, surgeons assessing outcomes, ward nurses and research nurses will be blinded. The main clinical endpoints of interest (Clavien-Dindo, removal of drain, fitness for discharge) require the assessment of a surgeon. Therefore operating surgeons (who are unblinded) need to delegate these assessments to suitable blinded colleagues. Details of potential risks/complications associated with ARTISS are provided in section 2.4.1.

A severe hypersensitivity reaction, air embolism or transmission of an infective agent constitute a serious adverse event. If they occur, severe hypersensitivity and air embolism would be anticipated to occur during or immediately after administration in the theatre setting. Staff caring for the patient at this time will not be blinded so there will not be a delay in diagnosis and emergency management. Fortunately these adverse events are incredibly rare, however if they did happened, the patient, outcome assessors and nursing staff would be unblinded only if the information is required for the ongoing medical management of the condition.

In the event that the patient is diagnosed with an infectious disease that was not diagnosed pre-operatively, they will be unblinded. Based on the 'Serious Hazards of Transfusion' 2016 annual report, the following infectious diseases are known to have been transmitted via blood products in the UK:

1. Hepatitis A, B, C or E
2. Human Immunodeficiency Virus (HIV)
3. Parvovirus (B19)
4. Cytomegalovirus (CMV)

5. Human T-cell Lymphotropic Virus (HTLV) types I and II
6. Malaria
7. Variant Creutzfeldt-Jakob Disease (vCJD) or any other prion disease

If the patient is newly diagnosed with any of the above infectious diseases, they will be unblinded and immediately referred to the appropriate medical specialists for treatment.

7.5 Concomitant Medications/Treatments

There are no restrictions on concomitant medications/treatments.

7.5.1 Data on Concomitant Medication

Only data on concomitant anticoagulant and anti-platelet medication will be collected.

7.6 Overdoses

No case of overdose has been reported.

7.7 Co-enrolment Guidelines

Patients who are currently participating in another clinical trial of an investigational medicinal product (CTIMP) will not be recruited to this study.

Patients who meet the eligibility criteria and are participating in a subsequent study which is not a CTIMP, may be approached and recruited provided there are no consequences to the scientific validity of either study. Co-enrolment remains at the discretion of the Principal/Chief Investigators for the respective trials.

8 ASSESSMENTS AND PROCEDURES

8.1 Schedule of Trial Procedures

Participants will be involved in the study for 6 weeks from the date of surgery. Post-operative assessments, including daily in-patient and follow-up visits, must be conducted by a blinded member of the trial team. The randomising surgeon MUST NOT conduct any of the post-operative assessments.

							Follow-Up Schedule				
Procedures		Head & Neck Clinic/MDT	Screening	Pre-operative Assessment	Baseline*	Day of Surgery (Day 0)	Daily In-patient Assessment	Follow-up 1 (Day 7 – 14)	Follow-up Unscheduled	Follow-up 2 (Day 28 – 42)	Premature Discontinuation
Identify potential participant		X	X	X							
Approach potential participant to discuss study		X	X	X							
Medical history		X	X	X	X						
Physical examination		X	X	X	X						
Assessment of eligibility criteria		X	X	X							
Review of concomitant anticoagulant medications		X	X	X	X	X	X	X	X	X	X
Review of previous treatment to ipsilateral neck		X	X	X	X						
Demographic assessment		X	X	X	X						
Signed consent form				X	X						
Randomisation					X						
Assessment of patient reported outcome measures	Neck pain (VAS)				X		X	X	X	X	X
	Neck Dissection Impairment Index (NDII)				X					X	X
Surgical Protocol	Neck dissection surgery					X					
	Allocation revealed at point of wound closure					X					
	Prepare and administer ARTISS (interventional arm only)					X					
Assessment of Clinical Outcome Measures	Assessment of AEs (Clavien-Dindo)					X	X	X	X	X	X
	Twice Daily Wound Drainage Volume (ml)						X				
	Wound Drain Removal						X				
	Hospital Discharge						X				
Assessment of Pilot Study Outcomes	Assessment of Blinding Strategy									X	X
	Assessment of Minimal Clinically Important Difference									X	X
Laboratory Tests	Full Blood Count**	X	X	X	X						

							Follow-Up Schedule				
Procedures		Head & Neck Clinic/MDT	Screening	Pre-operative Assessment	Baseline*	Day of Surgery (Day 0)	Daily In-patient Assessment	Follow-up 1 (Day 7 – 14)	Follow-up Unscheduled	Follow-up 2 (Day 28 – 42)	Premature Discontinuation
	INR & APTT	X	X	X	X						
	Pregnancy test (women of childbearing age)	X	X	X	X						
	Microbiology Swab from Neck Wound & Oral Cavity					X	X	X	X	X	
	Histological Lymph Node Yield									X	

Figure 1. Schedule of DEFeND enrolment, interventions and assessments (SPIRIT)
(X) – As indicated/appropriate.
*At baseline, all procedures should be done before study intervention.
**Full Blood Count must include Hb concentration, platelet count and white cell count

8.2 Procedures for assessing Efficacy

A central review process will be undertaken to assess the neck dissection specimen which should include 3 or more levels of the neck. Lymph node yield will be used as a proxy to assess the extent of surgery.

8.3 Procedures for Assessing Safety

Safety will be assessed through reporting on post-operative complications as described in section 10 and **Appendix A**. All post-operative complications that occur from the time of surgery up to data collection at week 6 will be reported.

8.4 Other Assessments

8.4.1 Quality of Life and Health Economics

Neck Dissection Impairment Index (NDII)
The NDII is a procedure specific Health Related Quality of Life (HRQoL) assessment tool. The tool is validated for use in patients who have undergone selective or modified radical neck dissection.[18] Although the NDII is not validated for use 6 weeks after surgery, there is evidence that the NDII score at this early juncture is representative of longer-term HRQoL.[19] A copy of the NDII questionnaire can be found in **Appendix B.**

Incremental Cost-Effectiveness Ratio (ICER)
The health economic (HE) assessment of using fibrin sealant (ARTISS) will be piloted using the 'incremental cost-effectiveness ratio' (ICER). This will calculate the average incremental cost associated with each surgical complication prevented when compared to 'standard of care' (SOC) treatment without ARTISS. This will be calculated using the following equation:

$$\text{ICER} = \frac{\text{Overall cost of ARTISS arm}}{-} \quad \frac{}{\text{Overall cost of SOC arm}}$$

No. of complications in ARTISS arm – No. of complications in SOC arm

The variation in costs between the treatment arms will be calculated individually for each patient based on their time in the operating theatre (including returns to theatre), their length of stay within each ward type, their number of hospital visits in the immediate post-operative period (both planned and unplanned), and the cost of materials (including those required to administer ARTISS).

8.4.2 Special Assays or Procedures

Microbiology swabs will be taken for the sub-study (see section 8.5). This will include taking a standard hospital microbiology swab from the neck wound and oral cavity. These samples will be taken intra-operatively by the surgeon and by nursing staff on the ward and outpatient department. A member of the Institute of Infection & Global Health, University of Liverpool, will collect these samples.

8.5 Sub-studies

Development of novel biomimetic antimicrobial therapies to mitigate against bacterial wound infections following Head & Neck Cancer surgery.

A promising strategy for the next generation of antimicrobial therapeutics will be to specifically target the bacteria's signalling pathways inhibiting biofilm formation and detachment. Theoretically, by disrupting bacterial signalling pathways, there should be a lower tendency for the bacteria to develop defence responses and resistant mutants. The gene-expression patterns of biofilms differ from planktonic bacteria and deciphering the genetic basis of biofilm formation will allow for an inherent understanding of the formation of these sessile communities and their inherent resistance to antimicrobial agents. Biofilms develop an ordered structure whereby bacteria are embedded in a protective exopolysaccharide matrix. This, along with other factors, can make bacterial biofilms incredibly resistant to treatment. In addition, bacteria within biofilms can form multispecies communities which can further complicate treatment regimens with consequent negative clinical outcomes.

Using clinical samples from infected and non-infected neck wounds, molecular characterisation of microbial communities through sequencing will allow the identification of the different bacterial species within the wounds and through network analysis, identify associations with the risk of poor clinical outcomes and prolonged treatment. Furthermore, as part of this work a model of biofilm dispersal will be developed to understand the risk of infection dissemination and enable testing of the novel therapeutics under infection–relevant conditions. This will provide the underpinning knowledge to rationally design efficacious antimicrobial therapeutics that do not lead to antimicrobial resistance.

This aim will be realised though the following objectives:

- Isolation of and 16S rRNA microbiome sequencing of clinical samples from infected and uninfected head and neck surgery patients.
- Encapsulation of naturally derived antimicrobials in currently utilised, aerosol-applied, fibrin sealants for controlled and sustained release.
- Testing of efficacy of antimicrobial/fibrin capsules on clinical isolates.
- Benchmarking of efficacy of antimicrobial therapeutics on laboratory reference strains vs. clinical isolates.
- Develop biofilm dispersal model.

This sub-study will not impact on the main study. Patients who develop neck infections within this study will require microbiology samples as part of their standard care. The

only additional samples required for this sub-study will be non-invasive samples from the neck wound and oral cavity in the form of standard hospital microbiology swabs.

8.6 Loss to Follow-up

If any of the trial participants are lost to follow up, contact will initially be attempted through the PI at each centre. If the PI at the trial centre is not the participant's usual clinician responsible for their speciality care then follow-up will also be attempted through this clinician. Where all of these attempts are unsuccessful, the patient's GP will be asked to provide follow-up information they may have to the recruiting centre.

All patients, whether lost to follow up or not, will have their data collected at week 6.

8.7 Trial Closure

Investigators will be informed when patient recruitment is to cease.

Trial enrolment may be stopped at a site when the total number of participants for the trial has been obtained.

The trial will close once all the subjects that have been randomised have completed six weeks of post-surgical follow up, all centres have completed and returned all necessary (e)CRF's.

The TSC may stop the trial prematurely. Such premature termination / suspension of the trial will be notified to the MREC as required.

The trial will be considered formally closed when the database is locked.

9 STATISTICAL CONSIDERATIONS

9.1 Introduction

This section contains an overview of all statistical considerations for the DEFeND trial including details on trial design patient randomisation and an overview of the statistical methodology used. Note that a separate Statistical Analysis Plan (SAP) will be produced to give full details of all data analysis in the study.

9.2 Method of Randomisation

Randomisation lists shall be produced by a statistician at the NWSTC prior to the recruitment of the first patient. Patients shall be randomised using a 1:1 ratio. Lists shall be produced based on the principle of randomly permuted blocks with random block sizes of 2 and 4. Patients will only be stratified according to the hospital in which they receive their treatment.

9.3 Outcome Measures

As DEFeND is an external pilot study, trial outcomes are categorised into those which address deliverability and feasibility of a larger study, those which address clinical outcomes of patients in the study and patient reported outcomes which will inform patient perspectives of the study and its interventions.

9.3.1 Pilot Study Outcomes

- Proportion of eligible patients recruited to the study, calculated as the screened to
- randomisation rate.
- Reasons for failure to screen potentially eligible patients.
- Recruitment rate measured as the number of patients randomised each month.
- Reasons for failure to randomise.
- Reasons for failure to reveal allocation at a specific time point during surgery.
- Fidelity of the blinding process (both patients and outcome assessors) as detected by blinding indices.
- Accuracy of data recording, summarised by the number of key data items with missing/incomplete data entries.
- Number of patients lost to follow-up.
- Protocol adherence, measured by the number of major/minor protocol deviations observed through the study.
- Determining the minimal clinically important difference (MCID) in clinical endpoints by questioning recruited patients and recruiting clinicians.

9.3.2 Clinical Endpoints of Future Phase III Trial

- Clavien-Dindo classification of surgical complications (**Appendix A**)
- Daily wound drainage volume (ml)
- Time (hours) for daily wound drainage volume to reach <30ml/24hrs
- Time (hours) to drain removal (as dictated by drainage volume)
- Total wound drainage volume (ml)
- Time (hours) to be declared medically fit for hospital discharge and time (hours) to actual hospital discharge
- Incremental cost-effectiveness ratio

9.3.3 Patient Reported Outcomes

- Neck Dissection Impairment Index (NDII). This is a procedure specific validated patient reported outcome measure (**Appendix B**)

- Daily patient reported pain score using Visual Analogue Scale (VAS) (**Appendix C**)

9.4 Sample Size

As this is a pilot study, no formal power/sample size calculation based on clinical data is given. For this study the two main outcomes of interest are to determine accurate estimates of the rate of recruitment (being the number of patients recruited relative to the number eligible) and to collect sufficient clinical data to accurately estimate a sample size for a future study. It is estimated that over the study period, approximately 50 patients will be recruited at rate of 30%. Based on this, 50 patients (25 in each arm) will produce a standard error of approximately 6.5% and a 95% confidence interval of approximately (17 – 43%) will be obtained. With respect to surgical complication rate, being the clinical outcome of current greatest interest, even if a response rate of 50% is observed then a 95% confidence interval of (0.36, 0.64) will be observed which provides sufficient precision for a future sample size.

9.5 Interim Monitoring and Analyses

Formal interim analyses of the accumulating data will be performed at 6 monthly intervals after the recruitment of the first patient. A formal Independent Data Monitoring and Safety Committee (ISDMC) will not be convened. In keeping with the guidance outlined in the document 'Guideline in Data Monitoring Committees' published by the Committee for Medicinal Products for Human Use, it is thought that an IDSMC is not required. This is because patients will be treated for a very short period of time (single administration during surgery) and Fibrin Sealants are well characterised and already widely used within healthcare. Although there are potential risks to patients, these are incredibly rare and known.

The independent members of the TSC (Chairperson, expert, statistician) will take responsibility for reviewing all interim safety data. The independent members will be asked to give advice on whether the accumulated data from the trial, together with results from other relevant trials, justifies continuing recruitment of further patients or further follow-up. Given this is a pilot/feasibility study, it is anticipated that the TSC will only recommend termination on grounds of safety.

9.6 Statistical Analysis

9.6.1 Patient Groups

The primary analysis will be carried out on the full analysis set which will be depend on the intention to treat principle retaining patients in their initially randomised groups irrespective of any protocol violations

9.6.2 Missing Data

Missing data are expected to be small and final analyses are planned to be carried out on a complete case basis. If substantial missing data (>10%) are observed in either a study outcome or key prognostic covariate then multiple imputation using chained equations will be applied.

9.6.3 Levels of Significance

There are no formal comparison of treatment groups and therefore no levels of significance against which hypotheses should be tests. As a guide however, all reported results will be reported using nominal 95% confidence intervals.

9.6.4 Analysis of study outcomes

As this is an external pilot study, all data analyses shall take the form of descriptive statistics. Continuous data shall be summarised as medians with associated inter-

quartile ranges and categorical data shall be summarised as frequencies of counts and associated percentages.

In terms of clinical outcomes, aside from descriptive statistics then informal comparisons between allocated groups will be made using difference in means for continuous covariates and difference in rated for categorical covariates.

9.6.5 Analysis of study toxicity

Adverse events (AEs) and serious adverse events (SAEs) shall be defined using CTC (Version 4) definitions. All AEs and SAEs shall be compared across groups using the TAME guidelines. Furthermore, the worst AE/SAE for each type for each patients shall also be retained and compared across treatment groups using a stratified Chi-Square test.

10 SAFETY

10.1 Terms and Definitions

The following definitions have been adapted from European Directive 2001/20/EC and ICH GCP E6

Adverse Event (AE)
Any untoward medical occurrence (i.e. any unfavourable or unintended sign, symptom or disease) in a research participant to whom a surgical/clinical intervention has been administered, including occurrences which are not necessarily caused by or related to that intervention. **Surgical complications and adverse reactions to ARTISS fibrin sealant will be the only events reported to assess safety**.

Surgical Complication
Any deviation from the ideal postoperative course that is not inherent in the procedure and does not comprise a failure to cure (disease or condition that remains unchanged after surgery).[20]

Unexpected Adverse Reaction (UAR)
An adverse reaction the nature and severity of which is not consistent with the information about ARTISS set out in the summary of product characteristics. All UARs will be reported.

Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR)
Any adverse event or adverse reaction is classified as serious if it:

1) results in death
2) is life-threatening* (subject at immediate risk of death)
3) requires in-patient hospitalisation or prolongation of existing hospitalisation**
4) results in persistent or significant disability or incapacity, or
5) consists of a congenital anomaly or birth defect
6) Important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above should also be considered serious.

*'life-threatening' in the definition of 'serious' refers to an event in which the patient 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.
Hospitalisation is defined as an inpatient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. **Hospitalisations for a pre-existing condition, including elective procedures that have not worsened, do not constitute an SAE.

10.2 Notes on Adverse Event Inclusions and Exclusions

10.2.1 Include

- Associated symptoms and events that are related to the trial surgery and/or use of ARTISS fibrin sealant that are Clavien Dindo grade IV or above (see **Appendix A**).
- An exacerbation of a pre-existing illness/condition that is deemed to be related to the trial surgery and/or use of ARTISS fibrin sealant.
- An increase in frequency or intensity of a pre-existing episodic event/condition that is deemed to be related to the trial surgery and/or use of ARTISS fibrin sealant.
- A condition (even though it may have been present prior to the start of the trial) detected after the trial surgery and/or use of ARTISS fibrin sealant.

- Continuous persistent disease or symptoms present at baseline that worsens following the trial surgery and/or use of ARTISS fibrin sealant.

10.2.2 Do Not Include

- Events including signs, symptoms and disease that are not deemed a complication of the trial surgery as per the definition above.
- Generalised signs and symptoms of having undergone major head and neck surgery e.g. lethargy, difficulty with speech and/or swallow.
- Associated symptoms and events that are related to the trial surgery and/or use of ARTISS fibrin sealant that are Clavien Dindo grade IIIb or below (see **Appendix A**).
- Extended hospital stay due to a delay in planned surgery.
- In-patient hospitalisation or prolongation of existing hospitalisation due to post-operative complications that are grade IIIb or below (see **Appendix A**).
- Medical or surgical procedures - the condition which leads to the procedure is the SAE.
- Pre-existing disease or conditions present before surgery that do not worsen.
- An exacerbation of a pre-existing illness/condition that is not deemed to be related to the trial surgery and/or use of ARTISS fibrin sealant.
- An increase in frequency or intensity of a pre-existing episodic event/condition that is not deemed to be related to the trial surgery and/or use of ARTISS fibrin sealant.
- Situations where an untoward medical occurrence has occurred e.g. cosmetic elective surgery.
- The disease being treated or associated symptoms/signs unless more severe than expected for the patient's condition.
- Injury or accidents.
- Abnormal laboratory results.

10.2.3 Reporting of Pregnancy

Pregnancy is listed as an exclusion criterion for entry to the DEFeND trial.

In the event of a patient becoming pregnant after recruitment to the trial, this fact **should be reported as soon as possible to the C.I through NWSTC** (as if an SAE). The guiding principles in this event are:-

1) If the patient has not yet received treatment, or completed treatment, the patient may be withdrawn from the trial.
2) Once treatment is complete, i.e. the patient is in follow-up phase, it may well be possible to retain the patient to the conclusion of the trial.
3) A decision will be made in the best interests of the patient between the treating clinician and the C.I. as to retention in the trial and any continuing cancer therapy.

10.3 Notes Severity / Grading of Adverse Events (Surgical Complications)

The assignment of the severity/grading should be made by a blinded surgeon who has been delegated this responsibility by the operating surgeon. Regardless of the classification of an AE as serious or not, its severity must be assessed according to medical criteria alone using the Clavien-Dindo Classification of Surgical Complications as detailed in **Tables 1 and 2** in **Appendix A**.[20] **Table 1** describes the original Clavien-Dindo classification whereas **Table 2** provides an interpretation of the Clavien-Dindo classification for some common/established complications after Head & Neck Surgery relevant to this trial.

10.4 Relationship to Trial Treatment

The assignment of causality should be made by a blinded surgeon who has been delegated this responsibility by the operating surgeon using the definitions in Table 3.

Causality should be assigned to the following:

1. Anaesthetic
2. Generality of surgery (including surgical airway, primary tumour resection)
3. Neck dissection surgery
4. Use of ARTISS fibrin sealant

If any doubt about the causality exists the local investigator should inform the study coordination centre who will notify the Chief Investigators. In the case of discrepant views on causality between the investigator and others, the Research Ethics Committee (REC) will be informed of both points of view.

Table 3: Definitions of Causality

Relationship	Description
None	There is no evidence of any causal relationship. N.B. An alternative cause for the AE should be given
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial intervention). There is another reasonable explanation for the event (e.g. the participant's clinical condition, other concomitant treatment).
Possibly	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial intervention). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant treatments).
Probably	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.
Highly Probable	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.

10.5 Expectedness

Expectedness will be assessed against the following:

1. Neck dissection surgery
2. Use of ARTISS fibrin sealant

Post-operative complications related to either neck dissection or use of ARTISS fibrin sealant that are Clavien-Dindo grade IIIb or below are **expected** for the DEFeND trial.

Post-operative complications related to either neck dissection or use of ARTISS fibrin sealant that are Clavien-Dindo grade IV or above are **unexpected** for the DEFeND trial.

An AE (surgical complication) where the causal relationship to the study procedure (neck dissection and/or use of ARTISS fibrin sealant) is assessed by the investigator as "possible", "probable", "highly probable", is graded as serious and unexpected (SUSAR) is subject to expedited reporting to the Research Ethics Committee (REC). This is the responsibility of NWSTC.

10.6 Reference Safety Information

The Reference Safety Information (RSI) to be used for this trial is as follows:

Appendix D: ARTISS Summary Product Information Sheet (section 4.8)

10.7 Follow-up After Adverse Events

All adverse events should be followed until satisfactory resolution or until the investigator responsible for the care of the participant deems the event to be chronic or the patient to be stable.

When reporting SAEs and SUSARs the investigator responsible for the care of the participant should apply the following criteria to provide information relating to event outcomes: resolved; resolved with sequelae (specifying with additional narrative); not resolved/ongoing; ongoing at final follow-up; fatal or unknown.

10.8 Reporting Procedures

All adverse events should be reported from the point of consent until 6 weeks after surgery. Depending on the nature of the event the reporting procedures below should be followed. Any questions concerning adverse event reporting should be directed to the NWSTC in the first instance.

10.7.1 Non serious ARs/AEs

All non-serious expected and unexpected complications of surgery should be reported from the day of surgery at each post-operative study visit and throughout the follow up phase. All complications should be reported on the appropriate CRF and graded using the Clavien-Dindo Classification of Surgical Complications.

10.7.2 Serious ARs/AEs/SUSARs

All complications related to the neck dissection surgery and/or use of ARTISS fibrin sealant that are Clavien-Dindo grade IV or above must be reported as SARs, SAEs and SUSARs. They should be reported within 24 hours of the local site becoming aware of the event up to 6 weeks post-surgery. SARs, SAEs and SUSARs may be reported past 6 weeks if deemed appropriate to do so by the local investigator (e.g. the complication is considered to be related to the trial surgery). The SAE form asks for the nature of event, date of onset, severity, corrective therapies given, outcome and causality. The responsible investigator should sign the causality of the event. Additional information should be sent within 5 days if the complication has not resolved at the time of reporting.

All complications related to the neck dissection surgery and/or use of ARTISS fibrin sealant that are Clavien-Dindo grade IIIb or below that meet the definition of serious are exempt from SAE reporting. Such events should only be reported in the relevant section of the CRF.

Clarification on the Clavien-Dindo grading of common/established complications following major head and neck surgery is provided in Table 2 within Appendix A.

The NWSTC will notify the main REC of all SUSARs occurring during the study according to the following timelines; fatal and life-threatening within 7 days of notification and non-life threatening within 15 days. All investigators will be informed of all SUSARs occurring throughout the study. Local investigators should report any SUSARs and /or SAEs as required by their Local Research Ethics Committee and/or Research & and Development Office.

10.9 Responsibilities – Investigator

The Investigator is responsible for reporting all AEs that are observed or reported during the study, regardless of their relationship to study product.
All SAEs must be reported immediately by the investigator to the NWSTC on an SAE form unless the SAE is specified in the protocol, IB or SPC as not requiring immediate

reporting. All other adverse events should be reported on the regular progress/follow-up reports.

Minimum information required for reporting:

- Study identifier
- Study centre
- Patient number
- A description of the event
- Date of onset
- Current status
- Whether study treatment was discontinued
- The reason why the event is classified as serious
- Investigator assessment of the association between the event and study treatment

i. The SAE form should be completed by the responsible investigator i.e. the consultant named on the 'signature list and delegation of responsibilities log' who is responsible for the patient's care. The investigator should assess the SAE for the likelihood that that it is a response to an investigational medicine. In the absence of the responsible investigator the form should be completed and signed by a designated member of the site trial team and faxed to the NWSTC immediately. The responsible investigator should check the SAE form, make changes as appropriate, sign and then re-fax to the NWSTC as soon as possible. The initial report shall be followed by detailed, written reports.
ii. Send the SAE form by fax (within 24 hours or next working day) to the NWSTC.

Fax Number: 0151 794 8930/8931

iii. The responsible investigator must **notify** their local ethics committee (LREC) and R&D department of the event (as per standard local procedure).
iv. In the case of an SAE the subject must be followed-up until clinical recovery is complete and laboratory results have returned to normal, or until the event has stabilised. Follow-up may continue after completion of protocol treatment if necessary.
v. Follow-up information is noted on another SAE form by ticking the box marked 'follow-up' and faxing to the NWSTC as information becomes available. Extra, annotated information and/or copies of test results may be provided separately.
vi. The patient **must** be identified by trial number, date of birth and initials only. The patient's name **should not** be used on any correspondence.

10.9.1 Maintenance of Blinding

Systems for SUSAR and SAR reporting should, as far as possible, maintain blinding of individual clinicians and of trials staff involved in the day-to-day running of the trial. Unblinding clinicians may be unavoidable if the information is necessary for the medical management of particular patients. The safety of patients in the trial always takes priority. In each report, seriousness, causality and expectedness should be evaluated for all of the trial treatments unless criteria have been fulfilled (section 7.4) and unblinding has taken place.
Cases that are considered serious, unexpected and possibly, probably or almost certainly related to one of the trial therapies (i.e. possible SUSARs) would have to be unblinded at the clinical trials unit prior to reporting to the regulator and re-evaluated for expectedness in light of the administered treatment.

10.10 Responsibilities – LCTU

The NWSTC, part of LCTU, is undertaking duties delegated by the trial sponsor/, University of Liverpool, and is responsible for the reporting of SUSARs and other SARs to the Research Ethics Committee as follows:

- SUSARs which are fatal or life-threatening must be reported not later than 7 days after the NWSTC is first aware of the reaction. Any additional relevant information must be reported within a further 8 days.
- SUSARs that are not fatal or life-threatening must be reported within 15 days of the NWSTC first becoming aware of the reaction.
- A list of all SARs (expected and unexpected) must be reported annually.

It is recommended that the following safety issues should also be reported in an expedited fashion

VI. An increase in the rate of occurrence or a qualitative change of an expected serious adverse reaction, which is judged to be clinically important;

VII. Post-study SUSARs that occur after the patient has completed a clinical trial and are notified by the investigator to the sponsor;

VIII. New events related to the conduct of the trial or the development of the IMPs and likely to affect the safety of the subjects, such as:

- A serious adverse event which could be associated with the trial procedures and which could modify the conduct of the trial;
- A significant hazard to the subject population, such as lack of efficacy of an IMP used for the treatment of a life-threatening disease;
- A major safety finding from a newly completed animal study (such as carcinogenicity).
- Any anticipated end or temporary halt of a trial for safety reasons and conducted with the same IMP in another country by the same sponsor;

IX. Recommendations of the independent members of Trial Steering Committee, if any, where relevant for the safety of the subjects.

Staff at the NWSTC will liaise with the designated Clinical Co-ordinator who will evaluate all SAEs received for seriousness, expectedness and causality. Investigator reports of suspected SARs will be reviewed immediately and those that are SUSARs identified and reported to regulatory authorities and REC. The causality assessment given by the Local Investigator at the hospital cannot be overruled and in the case of disagreement, both opinions will be provided with the report.

The NWSTC will also send an annual progress report to the Research Ethics Committee which will include all safety information.

Patient safety incidents that take place in the course of research should be reported to the National Patient Safety Agency (NPSA) by each participating NHS Trust in accordance with local reporting procedures.

11 ETHICAL CONSIDERATIONS

11.1 Ethical Considerations

Ethical review of the study is a legal requirement to safeguard the rights, dignity and welfare of people participating in research. Amendments made to the study after a favourable ethical and regulatory opinion will be submitted and approved prior to implementation. The requirement for ethical and regulatory authority approvals applies to all participating countries. Each participating PI will be named on the original ethics application form or on a subsequent substantial amendment. Written evidence of favourable NHS capacity and capability must be made available to the NWSTC prior to randomisation of subjects at site.

Specifically for the DEFeND trial:

1) There will be no involvement of patients who are children or deemed to lack capacity. There are no additional hospital visits required.
2) Consent will be sought after a full explanation of the trial including potential risks and benefits. Consent will not be taken on the same day as their surgery.
3) The only additional investigation will be a wound swab. This is an entirely painless and non-invasive procedure with no associated risks.
4) There will be no use of placebo.
5) No patient will be denied any additional treatment.

11.2 Ethical Approval

The trial protocol has received the favourable opinion of the <<Name>> Multi-centre Research Ethics Committee (MREC) but all participating sites must undergo site specific assessment of capacity and capability. A copy of all site approval documents and a copy of the PIS and ICF on local headed paper should be forwarded to NWSTC before patients are entered. The NWSTC should receive a confirmation of capacity and capability for each new centre via the site's R&D department

11.3 Informed Consent Process

Informed consent is a process initiated prior to an individual agreeing to participate in a trial and continues throughout the individual's participation. Informed consent is required for all patients participating in NWSTC coordinated trials. In obtaining and documenting informed consent, the investigator should comply with applicable regulatory requirements and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki.

Discussion of objectives, risks and inconveniences of the trial and the conditions under which it is to be conducted are to be provided to patients by staff with appropriate experience. An appropriate Patient Information and Consent forms, describing in detail the trial interventions/products, trial procedures and risks will be approved by an independent ethical committee (IEC) and the patient will be asked to read and review the document. Upon reviewing the document, the investigator will explain the research study to the patient and answer any questions that may arise. A contact point where further information about the trial may be obtained will be provided

After being given adequate time to consider the information, the patient will be asked to sign the informed consent document. A copy of the informed consent document will be given to the patient representative for their records and a copy placed in the medical records, with the original retained in the Investigator Site File.

The patient may withdraw from the trial at any time by revoking the informed consent. The rights and welfare of the patients will be protected by emphasising to them that the

quality of medical care will not be adversely affected if they decline to participate in this study.

11.4 Study Discontinuation

The chief investigator can prematurely close this trial after consultation with the TSC. The local ethics committee will be informed. Reasons for trial termination include:

1. The incidence or severity of SAE's/morbidity in this trial indicates a potential health hazard caused by the study treatment.
2. External evidence demanding trial termination.

12 REGULATORY APPROVAL

This trial does not require regulatory approval as the MRHA do not consider DEFeND to be a clinical trial of an investigational medicinal product (CTIMP).

13 TRIAL MONITORING

Site monitoring is conducted to ensure protection of patients participating in the trial, trial procedures, laboratory, trial intervention administration, and data collection processes are of high quality and meet sponsor and, when appropriate, regulatory requirements. Provide a description of how site monitoring will be conducted. A monitoring plan based on the risk assessment and in line with NWSTC Monitoring SOPs should be developed to describe who will conduct the monitoring, at what frequency monitoring will be done, and what level of detail monitoring will be conducted.

13.1 Risk Assessment

In accordance with the NWSTC Standard Operating Procedure a risk assessment will be completed in partnership with the following:

- Trial Sponsor
- Chief Investigator
- Trial Coordinator
- Trial Statistician

In conducting the risk assessment, the contributors will consider potential patient, organisational and trial hazards, the likelihood of their occurrence and resulting impact should they occur.

The outcome of the risk assessment will be assigned according to the following categories:

1. Type A: no higher than that of standard medical care
2. Type B: somewhat higher than that of standard medical care
3. Type C: markedly higher than that of standard medical care

This trial is a Non-CTIMP and the risk categories described above for CTIMPs (type A, B or C) have been applied to the DEFeND trial.

As this is a surgical intervention trial comparing ‘ARTISS’ to ‘no ARTISS’, with no changes to the clinical procedure itself, this study is classed as Type A and thus will be of low risk.

13.2 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies) (ICH E6, 1.51).

Original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects’ diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy and laboratory departments involved in the clinical trial (ICH E6, 1.52):62.

In order to resolve possible discrepancies between information appearing in the (e)CRF and any other patient related documents, it is important to know what constitutes the source document and therefore the source data for all information in the (e)CRF. Data recorded in the (e)CRF should be consistent and verifiable with source data in source documents *other* than the (e)CRF (e.g. medical record, laboratory reports and nurses" notes). Each participating site should maintain appropriate medical and research records for this trial, in compliance with ICH E6 GCP, section 4.9 and regulatory and institutional requirements for the protection of confidentiality of subjects.

For data where no prior record exists and which are recorded directly in the (e)CRF (e.g. inclusion/exclusion criteria, adverse events and Quality of life questionnaires), the (e)CRF will be considered the **source document**, unless otherwise indicated by the investigator.

In addition to the above, date (s) of conducting informed consent including date of provision of patient information, trial screening number, trial number, study treatment and the fact that the patient is participating in a clinical trial should be added to the patients' medical record contemporaneously.

13.3 Data Capture Methods

All trial data will be captured using electronic Case Report Forms (eCRFs), transcribed to a MACRO Database. This database is designed and maintained by the NWSTC. The eCRF is the primary data collection instrument for the study. All data requested on the eCRF must be recorded and all missing data must be explained.

All eCRFs are entered directly into a MACRO database that can be accessed via a secure webpage by research site staff and the relevant staff at NWSTC. The client application is secured with a unique username/password combination allocated to each delegated member of the research team. When data is entered into an eCRF it is electronically stamped with the date, time and the person who entered it. If data is changed on an eCRF, it is electronically stamped with the change and will be accompanied with the date, time, person and a reason for making the change or correction. The previous value is recorded in an audit trail for each data item.

Each eCRF contains specific validation checks on the data being entered. If any values are outside what is expected, or data is missing, this is flagged up and will be raised as a discrepancy on the main database system. Regular reports will be generated to identify discrepancies in the data, and allow for follow up. Comprehensive guidelines for eCRF data entry will be provided to all staff who have been delegated the responsibility for data collection. Where the site is unable to upload data using the eCRF, e.g. internet unavailability, a backup paper CRF will be available to use and accessed from the NWSTC portal. In such cases the research staff will retrospectively enter the data onto the trial MACRO database following the visit.

13.4 Monitoring at North West Surgical Trials Centre

Data stored at NWSTC will be checked for missing or unusual values (range checks) and checked for consistency within patients over time. If any such problems are identified, they will be queried with the responsible site.

NWSTC will periodically send reminders for any overdue and missing data.

13.5 Clinical Site Monitoring

13.5.1 Direct access to data

In order to perform their role effectively, monitors and persons involved in Quality Assurance and Inspection will need direct access to primary subject data, e.g. patient records, laboratory reports, appointment books, etc. Because this affects the participant's confidentiality, this fact is included on the Patient Information Sheet and Informed Consent Form.

13.5.2 Confidentiality

Personal data recorded on all documents will be regarded as strictly confidential and will be handled and stored in accordance with the Data Protection Act 1998.

Participants will always be identified using only their unique trial identification number on the Case Report Forms and correspondence between the NWSTC and the participating site. Participants' will give their explicit consent for the NWSTC to be sent a copy of their consent form. This will be used to perform central monitoring of the consent process.
The Investigator must maintain documents not for submission to the NWSTC (e.g. Patient Identification Logs) in strict confidence. In the case of specific issues and/or queries from the regulatory authorities, it will be necessary to have access to the complete trial records, provided that patient confidentiality is protected.

The NWSTC will maintain the confidentiality of all participant data and will not disclose information by which participants may be identified to any third party. Representatives of the NWSTC and sponsor may be required to have access to participant's notes for quality assurance purposes but participants should be reassured that their confidentiality will be respected at all times.

13.5.3 Quality Assurance and Quality Control of Data

Systems of quality assurance, including all elements described in this protocol have been/will be implemented within relevant institutions with responsibility for this trial. Standard Operating Procedures (SOPs) are implemented to ensure that clinical trials are conducted in compliance with regulatory requirements and Good Clinical Practice. Quality control is applied to each stage of data handling to ensure that data are accurate, reliable and processed correctly.

The DEFeND trial investigational sites and all data (including sources) and documentation must be available for GCP audit and inspection by competent authorities (national and foreign) or IEC. Such audits/inspections may take place at any site where trial related activity is taking place, the Sponsor's site(s), NWSTC or at any investigator's site.

As the main outcome of interest is surgical complications, graded according to the Clavien-Dindo classification, there is potential variation in how the severity of complication may be reported in the CRF. To ensure that the CRF accurately represents the clinical case notes, a blinded member of the research team will

regularly verify the source data and correlate the NHS case notes with the CRFs to ensure accuracy of data reporting.

The site staff should assist in all aspects of audit/inspection and be fully cognisant of the NWSTC communication strategy for multicentre trials. This includes management system for the Green light process, conforming to the total Quality Management System currently operating within the NWSTC.

13.6 Records Retention

The investigator at each investigational site must make arrangements to store the essential trial documents, (as defined in Essential Documents for the Conduct of a Clinical Trial (ICH E6, Guideline for Good Clinical Practice)) including the Investigator Trial File, until the Sponsor informs the investigator that the documents are no longer to be retained. In addition, the investigator is responsible for archiving of all relevant source documents so that the trial data can be compared against source data after completion of the trial (e.g. in case of inspection from authorities).

The investigator is required to ensure the continued storage of the documents, even if the investigator, for example, leaves the hospital or retires before the end of required storage period. Delegation must be documented in writing. The NWSTC undertakes to store originally completed (e)CRFs and separate copies of the above documents for the same period, except for source documents pertaining to the individual investigational site, which are kept by the investigator only.

Essential documents should be retained for at least 5 years after the completion of the trial. These documents should be retained for a longer period however if required by applicable regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the NWSTC to inform the investigator/institution as to when these documents no longer need to be retained.

At the point where it is decided that the trial documentation is no longer required; the Investigator will be responsible for the destruction of all site trial specific documentation and the Sponsor/NWSTC will be responsible for the destruction of all trial related materials retained by the Sponsor/NWSTC.

Verification of appropriate informed consent will be enabled by the provision of copies of participants' signed informed consent forms being supplied to the NWSTC by recruiting centres. This requires that name data will be transferred to the NWSTC, which is explained in the PIS. The NWSTC will preserve the confidentiality of participants taking part in the study and the University of Liverpool is a Data Controller registered with the Information Commissioners Office.

14 INDEMNITY

DEFeND is sponsored by the University of Liverpool (sole sponsor) and co-ordinated by the NWSTC in the University of Liverpool. The University of Liverpool does not hold insurance against claims for compensation for injury caused by participation in a clinical trial and they cannot offer any indemnity. As this is an investigator-initiated study, The Association of the British Pharmaceutical Industry (ABPI) guidelines for patient compensation by the pharmaceutical industry do not apply. However, in terms of liability, NHS Trust and Non-Trust Hospitals have a duty of care to patients treated, whether or not the patient is taking part in a clinical trial, and they are legally liable for the negligent acts and omission of their employees. Compensation is therefore available in the event of clinical negligence being proven.

Clinical negligence is defined as:
"A breach of duty of care by members of the health care professions employed by NHS bodies or by others consequent on decisions or judgments made by members of those professions acting in their professional capacity in the course of their employment, and which are admitted as negligent by the employer or are determined as such through the legal process".

15 FINANCIAL ARRANGEMENTS

DEFeND is a non-commercial, investigator-initiated and investigator-led trial. Patients recruited to the study may be reimbursed a maximum of £25 for travel costs incurred due to any extra hospital visits required specifically for the study. The trial is funded by the National Institute for Health Research, Research Doctoral Research Fellowship programme, consequently having automatic endorsement from the UK Clinical Research Network (UKCRN). This organisation will be responsible for providing local investigators with the necessary research infrastructure.

16 TRIAL OVERSIGHT COMMITTEES

16.1 Trial Management Group (TMG)

The composition of the TMG is as follows.

Chief Investigator
Other lead investigators (clinical and non-clinical)
Trial statistician
Speciality Trainees
Trial Coordinator
Data Manager

The role of the TMG is to monitor all day-to-day aspects of the conduct and progress of the trial, ensure the trial protocol is adhered to and take appropriate action to safeguard participants and the quality of the trial itself.

The TMG will meet approximately 3 times a year.

The TMG will provide a recommendations to the TSC concerning any aspect of the trial.

A smaller TMG sub-group comprising of the Chief Investigator, Doctoral Research Fellow, Trial statistician and Trial Co-ordinator will meet on approximately a monthly basis to discuss trial management and progress.

16.2 Trial Steering Committee (TSC)

The composition of the TSC is as follows. Membership details are available from the Trial Coordinator.

Independent chairperson expert in the field of Head & Neck Surgery
Independent expert in the field of Head & Neck Surgery,
Independent statistician,
Principal Investigator (other than the CI)
Patient representative
Chief Investigator
Speciality Trainees
Trial Statistician
Trial Coordinator.

The role of the TSC is to provide overall supervision for the trial and provide advice through its independent chairperson. The full role and responsibilities are stipulated within its Charter.

As no formal Independent Data and Safety Monitoring Committee (IDSMC) will be convened, all interim safety data will be reviewed by the independent members of the TSC (chairperson, expert and statistician). The ultimate decision for the continuation of the trial lies with the TSC.

The frequency of TSC meetings will be decided at the initial meeting. It is expected that they will occur at 6 monthly intervals, with the first meeting to be held prior to the recruitment of the first participant.

16.3 Independent Data and Safety Monitoring Committee (IDSMC)

No formal Independent Data and Safety Monitoring Committee (IDSMC) will be convened for this study. In keeping with the guidance outlined in the document 'Guideline in Data Monitoring Committees' published by the Committee for Medicinal Products for Human Use in 2005, it is thought that an IDSMC is not required. This is because patients will be treated for a very short period of time (single administration during surgery) and Fibrin Sealants are well characterised and already widely used within healthcare. Although there are potential risks to patients, these are incredibly rare and known.

The independent members of the Trial Steering Committee (Chairperson, expert, statistician) will take responsibility for reviewing all interim safety data. The independent members will be asked to give advice on whether the accumulated data from the trial, together with results from other relevant trials, justifies continuing recruitment of further patients or further follow-up. Given this is a pilot/feasibility study, it is anticipated that the TSC will only recommend termination on grounds of safety.

17 PUBLICATION

The results from different centres will be analysed together and published as soon as possible. Individual Clinicians must undertake not to submit any part of their individual data for publication without the prior consent of the Trial Management Group.

The Trial Management Group will form the basis of the Writing Committee and advise on the nature of publications. The Uniform Requirements for Manuscripts Submitted to Biomedical Journals (http://www.icmje.org/) will be respected. All publications shall include a list of participants, and if there are named authors, these should include the trial's Chief Investigator(s), Statistician(s) and Trial Manager(s) involved at least. If there are no named authors (i.e. group authorship) then a writing committee will be identified that would usually include these people, at least. The ISRCTN allocated to this trial should be attached to any publications resulting from this trial.

The members of the TSC and should be listed with their affiliations in the Acknowledgements/Appendix of the main publication.

18 PROTOCOL AMENDMENTS

18.1 Version 1.0 (12/Feb/2018)

Original Pre-approved version.

19 REFERENCES

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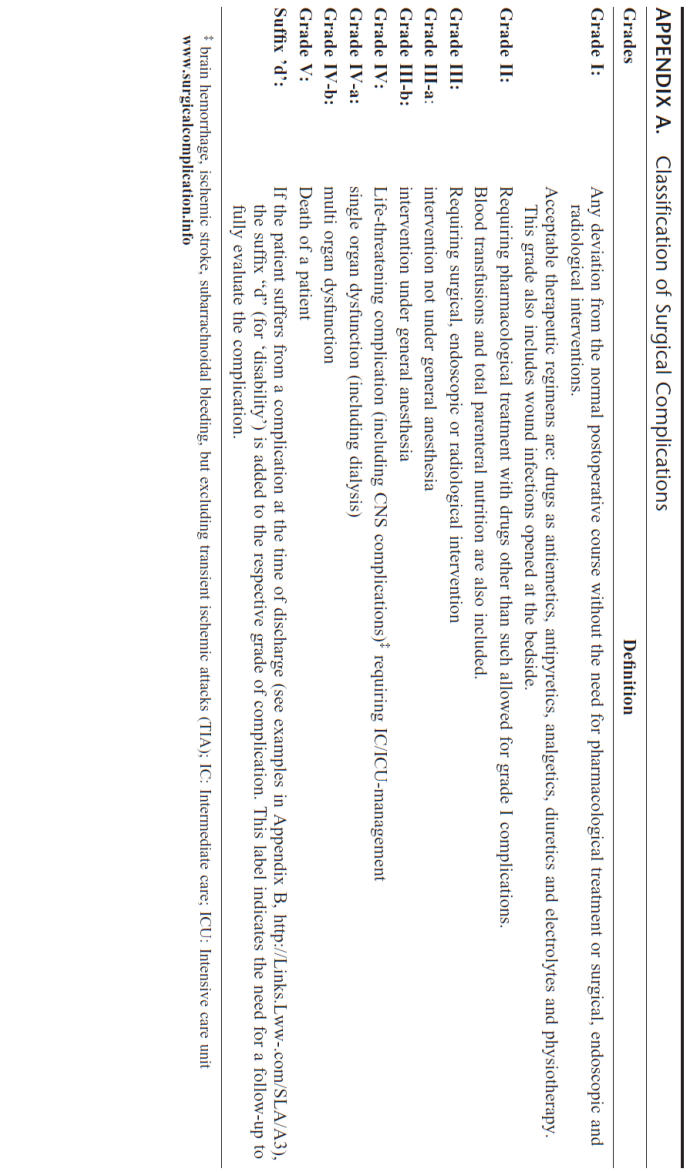
20 APPENDICES

Appendix A: Clavien-Dindo Classification of Surgical Complications



APPENDIX A. Classification of Surgical Complications

Grades	Definition
Grade I:	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions. Acceptable therapeutic regimens are: drugs as antiemetics, antipyretics, analgetics, diuretics and electrolytes and physiotherapy. This grade also includes wound infections opened at the bedside.
Grade II:	Requiring pharmacological treatment with drugs other than such allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included.
Grade III:	Requiring surgical, endoscopic or radiological intervention
Grade III-a:	intervention not under general anesthesia
Grade III-b:	intervention under general anesthesia
Grade IV:	Life-threatening complication (including CNS complications)‡ requiring IC/ICU-management
Grade IV-a:	single organ dysfunction (including dialysis)
Grade IV-b:	multi organ dysfunction
Grade V:	Death of a patient
Suffix 'd':	If the patient suffers from a complication at the time of discharge (see examples in Appendix B, http://Links.Lww-com/SLA/A3), the suffix "d" (for 'disability') is added to the respective grade of complication. This label indicates the need for a follow-up to fully evaluate the complication.

‡ brain hemorrhage, ischemic stroke, subarachnoidal bleeding, but excluding transient ischemic attacks (TIA); IC: Intermediate care; ICU: Intensive care unit

www.surgicalcomplication.info

Table 1. Clavien-Dindo classification of surgical complications.[20]

Post-operative Complication	Description of Severity	Clavien-Dindo Grade
Neck Wound Infection	Localised and superficial to platysma e.g. stitch abscess	**I**
	Spreading cellulitis or superficial wound infection with no underlying collection treated with antibiotics	**II**
	Collection deep to platysma requiring drainage (not under GA)	**IIIa**
	Collection deep to platysma requiring drainage (under GA)	**IIIb**
	Large collection with organ and/or life threatening sequelae (i.e. airway obstruction, severe sepsis, septic shock)	**IV** (**a** or **b** depending on organ dysfunction)
Other Surgical Site Infection	Localised infection requiring topical or non-invasive treatment	**I**
	Infection requiring treatment with antibiotics only	**II**
	Collection requiring drainage (not under GA)	**IIIa**
	Collection requiring drainage (under GA)	**IIIb**
	Large collection with organ and/or life threatening sequelae (i.e. airway obstruction, severe sepsis, septic shock)	**IV** (**a** or **b** depending on organ dysfunction
Bleeding/Haematoma	Haematoma not requiring drainage or suitable for simple aspiration with a needle (not radiologically guided)	**I**
	Need for blood transfusion	**II**
	Requiring drainage (not under GA). Includes radiologically guided aspiration/drainage	**IIIa**
	Requiring drainage or return to theatre for haemostasis (under GA)	**IIIb**
	Haematoma/haemorrhage sufficiently large to obstruct airway or cause hypovolaemic shock	**IV** (**a** or **b** depending on organ dysfunction)

Chyle Leak	Low output leak (<500ml/24hrs) suitable for low fat diet and compression only	**I**
	Requirement for pharmacological management including Total Parenteral Nutrition	**II**
	Radiologically guided occlusion	**IIIa**
	Return to theatre for procedure under GA	**IIIb**
	Evidence of end organ dysfunction	**IV** (**a** or **b** depending on organ dysfunction)
Wound Breakdown	Superficial skin dehiscence (platysma layer intact) managed with dressings	**I**
	Small fistula managed by an enteral tube or parenteral nutrition only	**II**
	Deep dehiscence (through platysma layer) or fistula managed with procedure not under GA	**IIIa**
	Deep dehiscence (through platysma layer) or fistula managed with procedure under GA	**IIIb**
	Evidence of end organ dysfunction	**IV** (**a** or **b** depending on organ dysfunction)
Seroma/sialocele	Small collection not requiring drainage or suitable for aspiration with a needle (not radiologically guided)	**I**
	Salivary fistula managed medically (e.g. anticholinergic)	**II**
	Requiring drainage (not under GA). Includes radiologically guided aspiration/drainage	**IIIa**
	Requiring re-exploration and/or drainage (under GA)	**IIIb**
	Large collection obstructing airway	**IVa**
Hypersensitivity	Mild reaction not requiring treatment	**I**
	Mild/moderate/severe reaction treated with	**II**

	medication (e.g. antihistamine and/or steroid and/or adrenaline)	
	Anaphylactic shock	**IV** (**a** or **b** depending on organ dysfunction)
Air embolism	By definition clinically evident air embolism results in cardiorespiratory dysfunction	**IVb**
Pneumothorax/Haemothorax	Small pneumothorax managed without a chest drain	**I**
	Pneumothorax/Haemothorax without respiratory failure requiring chest drain	**IIIa**
	Evidence of respiratory failure or any other organ dysfunction	**IV** (**a** or **b** depending on organ dysfunction)
Pulmonary Embolism	Small PE without evidence of respiratory failure managed with anticoagulation only	**II**
	Evidence of respiratory failure or any other organ dysfunction	**IV** (**a** or **b** depending on organ dysfunction)
Deep Vein Thrombosis	Managed with anticoagulation only	**II**
	Need for endovascular intervention including filters not under GA	**IIIa**
	Need for endovascular intervention or surgical thrombectomy under GA	**IIIb**
Lower Respiratory Tract Infection (including aspiration)	Managed with physiotherapy only	**I**
	Managed with antibiotics	**II**
	Evidence of respiratory failure or any other organ dysfunction	**IV** (**a** or **b** depending on organ dysfunction)

Table 2. Table clarifying the Clavien-Dindo grading according to the severity of some common/established complications following neck dissection or use of ARTISS Fibrin Sealant.

Appendix B: Neck Dissection Impairment Index (NDII)

Arch Otolaryngol Head Neck Surg. 2002;128(1):44-49. doi:10.1001/archotol.128.1.44

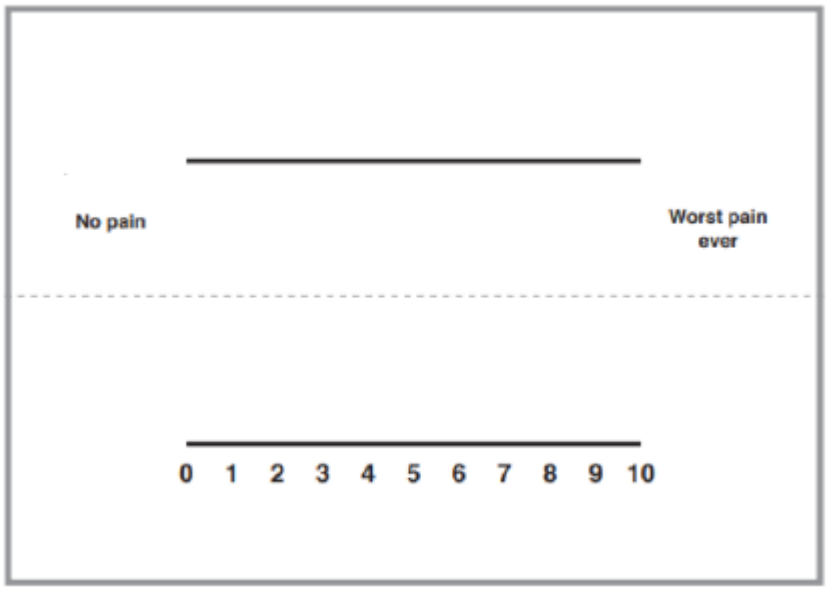
As a result of the cancer **TREATMENT OF YOUR NECK**, how much have you been bothered by the following over the past **4 WEEKS**?

1. Are you bothered by neck or shoulder **pain or discomfort**?
2. Are you bothered by neck or shoulder **stiffness**?
3. Are you bothered by difficulty with **self-care** activities because of your neck or shoulder (for example, combing hair, dressing, bathing, etc)?
4. Have you been limited in your ability to **lift light** objects because of your shoulder or neck?
5. Have you been limited in your ability to **lift heavy** objects because of your shoulder or neck?
6. Have you been limited in your ability to **reach above** for objects because of your shoulder or neck (for example, from shelves, tables, or counters)?
7. Are you bothered by your **overall activity level** because of your shoulder or neck?
8. Has the treatment of you neck affected your participation in **social activities**?
9. Have you been limited in your ability to do **leisure or recreational** activities because of your neck or shoulder?
10. Have you been limited in your ability to do **work** (including **work** at home) because of your neck or shoulder?

Figure Legend:

Ten-item validated Neck Dissection Impairment Index questions. Respondents answered "not at all," "a little bit," "a moderate amount," "quite a bit," or "a lot." Standardization for score of 100: [(raw score − 10)/40] × 100.

Appendix C: Pain Visual Analogue Scale (VAS)



Appendix D: ARTISS Product Information Sheets

ARTISS Solutions for Sealant

Summary of Product Characteristics Updated 18-Nov-2015 | Baxter Healthcare Ltd

1. Name of the medicinal product

ARTISS Solutions for Sealant

Deep frozen

2. Qualitative and quantitative composition

Component 1:

Sealer Protein Solution

Human Fibrinogen (as clottable protein)	91 mg[1]/ml
Aprotinin (synthetic)	3000 KIU[2]/ml

Component 2:

Thrombin Solution

Human Thrombin	4 IU[3]/ml
Calcium Chloride	40 µmol/ml

1 prefilled double chamber syringe which contains Sealer Protein Solution (with Aprotinin), deep frozen <1 ml><2 ml><5 ml>, in one chamber and Thrombin Solution (with Calcium Chloride), deep frozen<1 ml><2 ml><5 ml>, in the other chamber results in <2 ml><4 ml><10 ml> total volume of product ready for use.

After mixing	1 ml	2 ml	4 ml	10 ml
Component 1: Sealer protein solution				
Human Fibrinogen (as clottable protein)	45.5 mg	91 mg	182 mg	455 mg
Aprotinin (synthetic)	1,500 KIU	3,000 KIU	6,000 KIU	15,000 KIU
Component 2: Thrombin Solution				
Human Thrombin	2 IU	4 IU	8 IU	20 IU
Calcium Chloride	20 µmol	40 µmol	80 µmol	200 µmol

ARTISS contains Human Factor XIII co-purified with Human Fibrinogen in a range of 0.6 – 5 IU/ml.

For the full list of excipients, see section 6.1.

[1] Contained in a total protein concentration of 96 - 125 mg/ml

[2] 1 EPU (European Pharmacopoeia Unit) corresponds to 1800 KIU (Kallidinogenase Inactivator Unit)

[3] Thrombin activity is calculated using the current WHO International Standard for Thrombin.

3. Pharmaceutical form

Solutions for Sealant

Deep frozen

Colourless to pale yellow and clear to slightly turbid solutions.

Component 1, Sealer Protein Solution: pH 6.5 – 8.0

Component 2, Thrombin Solution: pH 6.0 – 8.0

4. Clinical particulars

4.1 Therapeutic indications

ARTISS is indicated as a tissue glue to adhere/seal subcutaneous tissue in plastic, reconstructive and burn surgery, as a replacement or an adjunct to sutures or staples (see 5.1). In addition, ARTISS is indicated as an adjunct to hemostasis on subcutaneous tissue surfaces.

4.2 Posology and method of administration

ARTISS is intended for hospital use only. The use of ARTISS is restricted to experienced surgeons who have been trained in the use of ARTISS.

Posology

The amount of ARTISS to be applied and the frequency of application should always be oriented towards the underlying clinical needs of the patient.

The dose to be applied is governed by variables including, but not limited to, the type of surgical intervention, the size of the area and the mode of intended application, and the number of applications.

Application of the product must be individualized by the treating physician. In clinical trials, the individual dosages have typically ranged from 0.2-12 ml. For some procedures (e.g. the sealing of large burned surfaces), larger volumes may be required.

The initial amount of the product to be applied at a chosen anatomic site or target surface area should be sufficient to entirely cover the intended application area. The application can be repeated, if necessary, to any small areas that may have not been previously treated. However, avoid reapplication of ARTISS to a pre-existing polymerized ARTISS layer as ARTISS will not adhere to a polymerized layer.

It is recommended that the initial application covers the entire intended application area.

As a guideline for the gluing of surfaces, 1 pack of ARTISS 2 ml (i.e., 1 ml Sealer Protein Solution plus 1 ml Thrombin Solution) will be sufficient for an area of at least 10 cm^2.

The skin graft should be attached to the wound bed immediately after ARTISS has been applied. The surgeon has up to 60 seconds to manipulate and position the graft prior to polymerization. After the flap or graft has been positioned, hold in the desired position by gentle compression for at least 3 minutes to ensure ARTISS sets properly and the graft or flap adheres firmly to the underlying tissue.

The required amount of ARTISS depends on the size of the surface to be covered. The approximate surface areas covered by each pack size of ARTISS by spray application are:

Approximate area requiring tissue adherence	Required pack size of ARTISS

100 cm^2	2 ml
200 cm^2	4 ml
500 cm^2	10 ml

To avoid the formation of excess granulation tissue and to ensure gradual absorption of the solidified fibrin sealant, only a thin layer of the mixed Sealer Protein - Thrombin Solution should be applied.

ARTISS has not been administered to patients > 65 years old in clinical trials.

Paediatric Population

Currently available data are described in section 5.1 but no recommendation on a posology can be made.

Method of administration

For epilesional (topical) use. Do not inject.

For subcutaneous use only. ARTISS is not recommended for laparoscopic surgery.

In order to ensure optimal safe use of ARTISS it should be sprayed using a pressure regulator device that delivers a maximum pressure of up to 2.0 bar (28.5 psi).

Prior to applying ARTISS the surface area of the wound needs to be dried by standard techniques (e.g. intermittent application of compresses, swabs, use of suction devices). Do not use pressurized air or gas for drying the site.

ARTISS must be sprayed only onto application sites that are visible.

ARTISS should only be reconstituted and administered according to the instructions and with the devices recommended for this product (see section 6.6).

For spray application, see sections 4.4 and 6.6 for specific recommendations on the required pressure and distance from tissue per surgical procedure and length of applicator tips.

4.3 Contraindications

ARTISS is not indicated to replace skin sutures intended to close surgical wounds.

ARTISS alone is not indicated for the treatment of massive and brisk arterial or venous bleeding.

ARTISS must never be applied intravascularly.

ARTISS is contraindicated in the case of hypersensitivity to the active substances or to any of the excipients (see also section 4.4. Special Warnings).

4.4 Special warnings and precautions for use

For epilesional use only. Do not apply intravascularly. Life threatening thromboembolic complications may occur if the preparation is applied intravascularly. Soft tissue injection of ARTISS carries the risk of local tissue damage.

Caution must be used when applying fibrin sealant using pressurized air or gas.

• Any application of pressurized air or gas is associated with a potential risk of air or gas embolism, tissue rupture, or gas entrapment with compression, which may be life-threatening or fatal.

• **Apply ARTISS as a thin layer. Excessive clot thickness may negatively interfere with the product´s efficacy and the wound healing process.**

• **Life-threatening/fatal air or gas embolism has occurred with the use of spray devices employing a pressure regulator to administer fibrin sealants. This event appears to be related to the use of the spray device at higher than recommended pressures and/or in close proximity to the tissue surface. The risk appears to be higher when fibrin sealants are sprayed with air, as compared to CO_2 and therefore cannot be excluded with ARTISS when sprayed in open wound surgery.**

• **When applying ARTISS using a spray device, be sure to use a pressure within the pressure range recommended by the spray device manufacturer (see table in section 6.6 for pressures and distances).**

• **ARTISS spray application should only be used if it is possible to accurately judge the spray distance as recommended by the manufacturer. Do not spray closer than the recommended distances.**

• **When spraying ARTISS, changes in blood pressure, pulse, oxygen saturation and end tidal CO_2 should be monitored because of the possibility of occurrence of air or gas embolism (also see section 4.2).**

• ARTISS must not be used with the Easy Spray / Spray Set system in enclosed body areas.

• Only use application devices CE marked for the administration of ARTISS.

ARTISS is not indicated for hemostasis and sealing in situations where a fast clotting of the sealant is required. Especially in cardiovascular procedures in which sealing of vascular anastomoses is intended ARTISS should not be used.

ARTISS is not indicated for use in neurosurgery and as a suture support for gastrointestinal anastomoses or vascular anastomoses as no data are available to support these indications.

Before administration of ARTISS care is to be taken that parts of the body outside the designated application area are sufficiently protected/covered to prevent tissue adhesion at undesired sites.

Oxycellulose-containing preparations may reduce the efficacy of ARTISS and should not be used as carrier materials (see Section 6.2).

As with any protein-containing product, allergic type hypersensitivity reactions are possible. Signs of hypersensitivity reactions may include hives, generalized urticaria, tightness of the chest, wheezing, hypotension, and anaphylaxis. If these symptoms occur, the administration must be discontinued immediately.

ARTISS contains aprotinin. Even in case of strict local application, there is a risk of anaphylactic reaction linked to the presence of aprotinin. The risk seems to be higher in cases where there was previous exposure, even if it was well tolerated. Therefore any use of aprotinin or aprotinin containing products should be recorded in the patients' records.

As synthetic aprotinin is structurally identical to bovine aprotinin the use of ARTISS in patients with allergies to bovine proteins should be carefully evaluated.

In the event of anaphylactic/anaphylactoid or severe hypersensitivity reactions, administration is to be discontinued. If possible, remove any applied, polymerized product from the surgical site. Adequate medical treatment and provisions should be available for immediate use in the event of an anaphylactic reaction. State-of-the-art emergency measures are to be taken. In case of shock, standard medical treatment for shock should be implemented.

Standard measures to prevent infections resulting from the use of medicinal products prepared from human blood or plasma include selection of donors, screening of individual

donations and plasma pools for specific markers of infection and the inclusion of effective manufacturing steps for the inactivation/removal of viruses. Despite this, when medicinal products prepared from human blood or plasma are administered, the possibility of transmitting infective agents cannot be totally excluded. This also applies to unknown or emerging viruses or other pathogens.

The measures taken are considered effective for enveloped viruses such as human immunodeficiency virus (HIV), hepatitis B virus (HBV), and hepatitis C virus (HCV), and for the non-enveloped hepatitis A virus (HAV).

The measures taken may be of limited value against non-enveloped viruses such as parvovirus B19. Parvovirus B19 infection may be serious for pregnant women (fetal infection) and for individuals with immunodeficiency or increased erythropoiesis (e.g., hemolytic anemia).

It is strongly recommended that every time that ARTISS is administered to the patient, the name and batch number of the product are recorded in order to maintain a link between the patient and the batch of the product.

4.5 Interaction with other medicinal products and other forms of interaction

No formal interaction studies have been performed.

Similar to comparable products or thrombin solutions, the product is denatured after exposure to solutions containing alcohol, iodine or heavy metals (e.g. antiseptic solutions). Such substances should be removed to the greatest possible extent before applying the product.

See section 4,4 or 6.2 for substances that can interfere with the product's performance.

4.6 Fertility, pregnancy and lactation

The safety of fibrin sealants/haemostatics for use in human pregnancy or breastfeeding has not been established in controlled clinical trials. Animal studies have also not been performed.

Therefore, the product should be administered to pregnant and lactating women only if clearly needed.

See section 4.4 for information on Parvovirus B19 infection.

The effects of ARTISS on fertility have not been established.

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

Intravascular injection could lead to thromboembolic events and disseminated intravascular coagulation (DIC) and there is also a risk of anaphylactic reactions (see section 4.4).

Hypersensitivity or allergic reactions (which may include angioedema, burning and stinging at the application site, bradycardia, bronchospasm, chills, dyspnoea, flushing, generalized urticaria, headache, hives, hypotension, lethargy, nausea, pruritus, restlessness, tachycardia, tightness of the chest, tingling, vomiting, wheezing) may occur in rare cases in patients treated with fibrin sealants/hemostatics.

In isolated cases, these reactions have progressed to severe anaphylaxis. Such reactions may especially be seen if the preparation is applied repeatedly, or administered to patients known to be hypersensitive to aprotinin (see section 4.4) or any other constituents of the product.

Even if a first treatment with ARTISS was well tolerated, a subsequent administration of ARTISS or systemic administration of aprotinin may result in severe anaphylactic reactions.

Antibodies against components of fibrin sealant may rarely occur.

For safety with respect to transmissible agents, see section 4.4.

Life threatening/fatal air or gas embolism when using devices with pressurized air or gas occurred; this event appears to be related to an inappropriate use of the spray device (e.g. at higher than recommended pressures and in close proximity of the tissue surface).

Adverse reactions summarized in the table below were reported from clinical studies of ARTISS and from post-marketing experience with Baxter Fibrin Sealants (marked with a [p] in the adverse event table). Known frequencies of these adverse reactions are based on a controlled clinical study in 138 patients where skin grafts were fixed to excised burn wounds using ARTISS. None of the events observed in the clinical study were classified as serious.

The ADRs and their frequencies are summarized below:

Common (≥1/100 to <1/10)

Uncommon (≥1/1000 to <1/100)

Not known (cannot be estimated from the available data)

Table 1

Adverse Reactions

System organ class (SOC)	**Preferred MedDRA Term**	**Frequency**
Skin and subcutaneous tissue disorders	Dermal cyst	uncommon
	Pruritus	common
Injury, poisoning and procedural complications	Skin graft failure	common
Vascular disorders	Air embolism[p] due to an inappropriate use of the spray device (see section 4.4)	not known

[p] Adverse events observed in post-marketing experience with Baxter Fibrin Sealants.

Class Reactions

Other adverse reactions associated with products of the fibrin sealant/hemostatic class include: Hypersensitivity reactions which could manifest as application site irritation, chest discomfort, chills, headache, lethargy, restlessness and vomiting. Further class reactions are: Anaphylactic reaction, bradycardia, tachycardia, hypotension, haematoma, dyspnoea, nausea, urticaria, flushing, impaired healing, oedema, pyrexia and seroma.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard.

4.9 Overdose

No case of overdose has been reported.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: local hemostatics, ATC code: B02BC; tissue adhesives, ATC code: V03A K

ARTISS can replace sutures or staples when used for fixation of skin grafts to burned or otherwise injured wound areas. ARTISS can be used as an adjunct to sutures or staples to adhere and seal skin flaps in cases where sutures/staples are expected to yield unsatisfactory results with respect to postoperative hematoma or seroma formation.

The fibrin adhesion system initiates the last phase of physiological blood coagulation. Conversion of fibrinogen into fibrin occurs by the splitting of fibrinogen into fibrin monomers and fibrinopeptides. The fibrin monomers aggregate and form a fibrin clot. Factor XIIIa, which is activated from factor XIII by thrombin, crosslinks fibrin. Calcium ions are required for the conversion of fibrinogen and the crosslinkage of fibrin.

As wound healing progresses, increased fibrinolytic activity is induced by plasmin, and decomposition of fibrin to fibrin degradation products is initiated. Proteolytic degradation of fibrin is inhibited by anti-fibrinolytics. Aprotinin is present in ARTISS (frozen) as an antifibrinolytic to prevent premature degradation of the clot.

For efficacy, *in vivo* studies in an animal model closely imitating the situation in patients were used. ARTISS (frozen and lyophilized presentations) demonstrated efficacy regarding sealing autologous split skin grafts and mesh grafts.

ARTISS (frozen) was investigated for fixation of split thickness sheet skin grafts in burn patients in a prospective, randomised, controlled, multicenter clinical study. In each of the 138 patients, two comparable test sites were identified. In one test site the skin graft was fixed with ARTISS in the other test site the graft was fixed with staples (control). ARTISS proved to be non-inferior to staples with respect to the primary efficacy endpoint, complete wound closure at Day 28 was evaluated by a blinded evaluator panel from photographs. This was achieved in 55/127 patients (43.3%) treated with ARTISS (frozen) and 47/127 patients (37%) treated with staples.

With respect to secondary endpoints, ARTISS showed a significantly lower incidence and size of hematoma/seroma on Day 1 ($p < 0.0001$ for incidence as well as size). Incidence and area of engraftment on Day 5 and wound closure on Day 14, as well as area of wound closure on Day 28 were not different. ARTISS was also superior to staples with respect to patient satisfaction ($p < 0.0001$) and patients experienced significantly less anxiety about pain with ARTISS than with staples ($p < 0.0001$). Moreover, ARTISS was significantly superior to staples with respect to the investigator's assessment of quality of graft adherence, preference of fixation method and satisfaction with graft fixation, overall quality of healing and overall rate of healing ($p < 0.0001$).

Thirty-seven (37) pediatric patients aged 1.1 to 18 years were evaluated in this trial.

Eighteen (18) of these patients were 6 years old or younger.

Dosage used in clinical trials was the same for pediatric and adult patients.

5.2 Pharmacokinetic properties

ARTISS is intended for epilesional use only. Intravascular administration is contraindicated. As a consequence, intravascular pharmacokinetic studies were not performed in man.

Pharmacokinetic studies in different species of laboratory animals were not conducted.

Fibrin sealants/hemostatics are metabolized in the same way as endogenous fibrin by fibrinolysis and phagocytosis.

5.3 Preclinical safety data

No preclinical safety data are available for ARTISS (thrombin 4 IU/ml). Toxicity studies were done with Fibrin Sealants containing thrombin 500 IU/ml, as representative for products containing thrombin 4 IU/ml. Single-dose toxicity studies in rats and rabbits indicated no acute toxicity of Fibrin Sealant VH S/D (500 IU/ml). Fibrin Sealant VH S/D (500 IU/ml) also proved well tolerated in wound healing models in rats and rabbits, and in in vitro human fibroblast cultures.

6. Pharmaceutical particulars

6.1 List of excipients

Component 1: Sealer Protein Solution

Human Albumin Solution

L-Histidine

Niacinamide

Polysorbate 80 (Tween 80)

Sodium Citrate Dihydrate

Water for Injections

Component 2: Thrombin Solution

Human Albumin Solution

Sodium Chloride

Water for Injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products. Oxycellulose-containing preparations may reduce the efficacy of ARTISS and should not be used as carrier materials.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store and transport frozen (at ≤ -20°C).

Keep the syringe in the outer carton in order to protect from light.

Unopened pouches, thawed at room temperature, may be stored for up to 14 days at controlled room temperature (not exceeding +25°C). Do not refreeze or refrigerate after thawing.

6.5 Nature and contents of container

1 ml, 2 ml, or 5 ml of sealer protein solution and 1, 2 or 5 ml of Thrombin Solution in a single-use double-chamber syringe (polypropylene) with a tip-cap in a bag , and one device set with one double syringe plunger, 2 joining pieces and 4 application cannulae.

Pack size of 1 (1 x 1 ml + 1 ml, 1 x 2 ml + 2 ml, 1 x 5 ml + 5 ml)

Both Sealer Protein Solution and Thrombin Solution are contained in a single-use double-chamber syringe made of polypropylene.

Not all pack sizes may be marketed.

Other accessories for application of the product can be obtained from BAXTER.

6.6 Special precautions for disposal and other handling

General

To prevent ARTISS from adhering to gloves and instruments, wet these with sodium chloride solution before contact.

As a guideline for the gluing of surfaces, 1 pack of ARTISS 2 ml (i.e., 1 ml Sealer Protein Solution plus 1 ml Thrombin Solution) will be sufficient for an area of at least 10 cm^2.

The required dose of ARTISS depends on the size of the surface to be covered.

Handling and Preparation

The inner bag and its contents are sterile unless the integrity of the outside package is compromised.

It is recommended to thaw and warm the two sealant components using a sterile water bath at a temperature of 33 – 37°C. The water bath must not exceed a temperature of 37°C. (In order to control the specified temperature range, the water temperature should be monitored using a thermometer and the water should be changed as necessary. When using a sterile water bath for thawing and warming, the pre-filled double chamber syringe assembly should be removed from the aluminum-coated plastic bags.)

The protective syringe cap should not be removed until thawing is complete and the joining piece is ready to be attached. Do not use ARTISS unless it is completely thawed and warmed (liquid consistency).

Thaw pre-filled syringes using one of the following options:

1. Room Temperature Thawing (not exceeding +25°C):

The product can be thawed at room temperature. Times given in Table 1 are minimum times for thawing at room temperature. The maximum time the product can be kept (in both aluminum-coated plastic bags) at room temperature is 14 days.

When thawing at room temperature, the product must be additionally warmed to 33°C – 37°C in an incubator just before use. Respective warming times in the incubator are also given in Table 1.

Table 1: Thawing times at Room Temperature (= RT) followed by additional warming, prior to use, in an Incubator at 33°C to a maximum of 37°C

Pack Size	Thawing Times at Room Temperature (Product in aluminum-coated plastic bags)		Warming Times at 33-37°C in Incubator after Thawing at RT (Product in aluminum-coated plastic bags)
2 ml	60 minutes	+	15 minutes

4 ml	110 minutes	+	25 minutes
10 ml	160 minutes	+	35 minutes

Once ARTISS has been warmed up to 33 – 37°C the product may be stored for up to 4 hours.

2. Quick Thawing:

Table 2: Thawing and Warming Times with Sterile Water Bath at 33°C to a maximum of 37°C

Transfer plunger and the inner pouch to the sterile field, remove prefilled syringe from inner pouch and place directly into sterile water bath. Ensure the contents of the prefilled syringe are completely immersed in water.

Pack Size	Thawing and Warming Times (Product removed from aluminum-coated plastic bags)
2 ml	5 minutes
4 ml	5 minutes
10 ml	12 minutes

A third alternative is to thaw the product off the sterile field using a non-sterile water bath.

Maintain the prefilled syringe in both pouches and place into a water bath off the sterile field for an appropriate time (see Table 3). Ensure the pouches remain submerged throughout thawing. Remove from the water bath after thawing, dry external pouch and transfer inner pouch with prefilled syringe and plunger to the sterile field.

Table 3: Thawing and Warming times off the Sterile Field with Non-Sterile Water Bath at 33°C to a maximum of 37°C

Pack Size	Thawing and Warming Times (Product in aluminum-coated plastic bags)
2 ml	30 minutes
4 ml	40 minutes
10 ml	80 minutes

Alternatively, the sealant components may be thawed and warmed in an incubator between 33°C and 37°C. The thawing and warming times in the incubator are indicated in Table 4 below. The times refer to product in the aluminum-coated plastic bags.

Table 4: Thawing and Warming Times in Incubator at 33°C to a maximum of 37°C

Pack Size	Thawing and Warming Times in Incubator (Product in aluminum-coated plastic bags)
2 ml	40 minutes
4 ml	85 minutes

10 ml	105 minutes

Note: Do not thaw by holding product in your hands.

Do not microwave.

After thawing do not refrigerate or refreeze.

After Quick Thawing (i.e. thawing at a temperature of 33 – 37°C) ARTISS may be stored at 33 – 37°C for a maximum of 4 hours.

To facilitate optimal blending of the two solutions, the two sealant components must be warmed to 33 – 37°C immediately before use. (The temperature of 37°C must, however, not be exceeded!)

The Sealer Protein and the Thrombin Solutions should be clear or slightly opalescent. Do not use solutions that are cloudy or have deposits. Thawed products should be inspected visually for particulate matter and discoloration prior to administration or any variation in physical appearance. In the event of either being observed, discard the solution.

The thawed Sealer Protein Solution should be a slightly viscous liquid. If the solution has the consistency of a solidified gel, it must be assumed to have become denatured (e.g., due to an interruption of the cold storage chain or by overheating during warming). In this case, ARTISS must not be used.

Unopened pouches, thawed at room temperature, may be stored for up to 14 days at controlled room temperature (not exceeding +25°C). If not used within 14 days after thawing, ARTISS has to be discarded.

The protective syringe cap should not be removed until thawing is complete and the joining piece is ready to be attached. Do not use ARTISS unless it is completely thawed and warmed (liquid consistency).

For further preparation instructions please refer to the responsible nurse or medical doctor.

ADMINISTRATION

For application, the double-chamber syringe with the Sealer Protein Solution and the Thrombin Solution has to be connected to a joining piece and an application cannula as provided in the accompanying set of devices. The common plunger of the double-chamber syringe ensures that equal volumes are fed through the joining piece before being mixed in the application cannula and ejected.

Operating Instructions

- Connect the nozzles of the double-chamber syringe to the joining piece ensuring that they are firmly fixed. Secure the joining piece by fastening the tether strap to the double-chamber syringe. If the tether strap tears, use the spare joining piece. If none is available, further use is still possible but tightness of the connection needs to be ensured to prevent any risk of leaking.

- Fit an application cannula onto the joining piece.

- Do not expel the air remaining inside the joining piece or application cannula until you start actual application as the aperture of the cannula may clog otherwise.

- Immediately before application expel and discard the first several drops from the application cannula to ensure adequately mixed product

- Apply the mixed Sealer Protein - Thrombin Solution onto the recipient surface or surfaces of the parts to be sealed.

If application of the fibrin sealant components is interrupted, clogging may occur in the cannula. Replace the application cannula with a new one only immediately before application is resumed. If the apertures of the joining piece are clogged, use the spare joining piece provided in the package.

Application is also possible with other accessories supplied by BAXTER that are particularly suited for, e.g. minimally invasive surgery, application to large or difficult-to-access areas. When using these application devices, strictly follow the Instructions for Use of the devices.

Spray application

When applying ARTISS using a spray device be sure to use a pressure and a distance from tissue within the ranges recommended by the manufacturer as follows:

Recommended pressure, distance and devices for spray application of ARTISS					
	Spray set to be used	Applicator tips to be used	Pressure regulator to be used	Recommended distance from target tissue	Recommended spray pressure
Open wound surgery of subcutaneous tissue	Tisseel / Artiss Spray Set	n.a.	EasySpray	10 – 15 cm	1.5-2.0 bar (21.5-28.5 psi)
	Tisseel / Artiss Spray Set 10 pack	n.a.	EasySpray		

When spraying the ARTISS, changes in blood pressure, pulse, oxygen saturation and end tidal CO_2 should be monitored because of the possibility of occurrence of air or gas embolism (see sections 4.2 and 4.4).

Disposal

Any unused product or waste material should be disposed of in accordance with local requirements.

7. Marketing authorisation holder

Baxter Healthcare Ltd

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Thetford

Norfolk

IP24 3SE

United Kingdom

8. Marketing authorisation number(s)

PL00116/0634

9. Date of first authorisation/renewal of the authorisation

11/03/2009

10. Date of revision of the text

06/11/15

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Appendix E: Flow Chart of "Quick Thaw" Technique

DEFeND

Preparation using "Quick Thaw" technique in a sterile water bath

Please remember that any **clinicians who will be assessing study outcomes for the patient must leave theatre prior to randomisation** and not return until the theatre has been cleared of any evidence of ARTISS usage. Thank you.

1 A bottle of sterile water is warmed and poured into a sterile kidney dish on the scrub practitioner's trolley. The temperature of the water is checked using an infrared thermometer. The **water bath must be between 33 – 37°C. It must not exceed 37°C.**

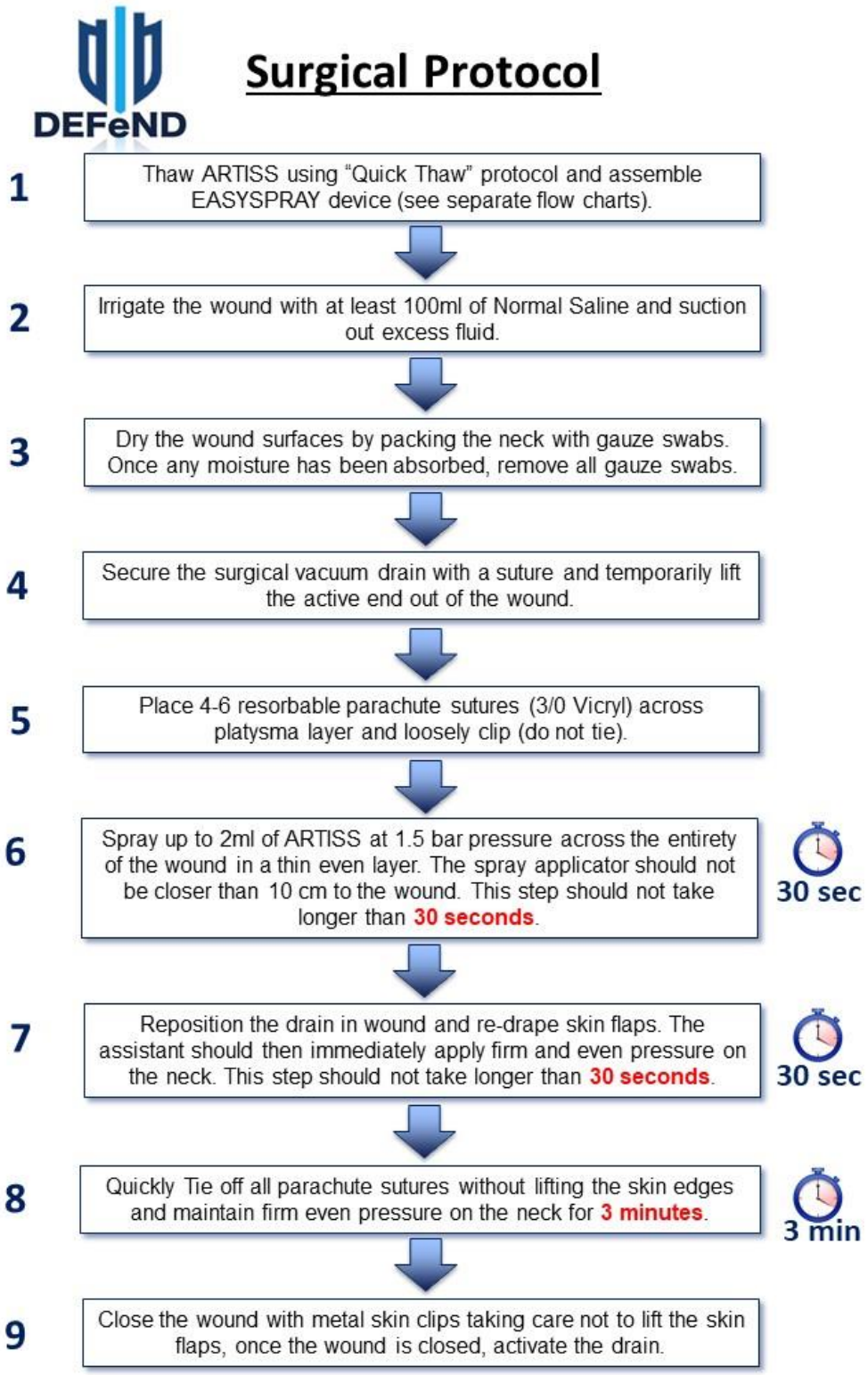
2 Scrub practitioner removes pre-filled syringe of ARTISS from aluminium-coated plastic bag in a sterile fashion. The protective syringe cap is not removed until thawing is complete.

3 The pre-filled syringe is placed in a sterile water bath at 33 - 37°C for **5 minutes** ensuring it is completely immersed.

4 Once thawed for 5 minutes inspect the contents of the syringe to ensure the solutions are clear and slightly opalescent. Any air bubbles must move freely within the soulutions. **Discard the syringe if the solutions are discoloured, contain particulate matter or solidified.**

Appendix F: "EASYSPRAY" Quick Reference Guide

Appendix G: Flow Chart of Surgical Protocol



Appendix H: Participating Sites

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