Royal Brompton & Harefield NHS
NHS Foundation Trust

A randomised, controlled trial of the use of a dedicated ballooned intercostal drain

Short Study Title/Acronym: BASIC

REC Reference: 17/SC/0607
IRAS ID: 217496

CHIEF INVESTIGATOR:
Dr Samuel Kemp
Consultant Respiratory Physician
Royal Brompton Hospital
Fulham Road
London
SW3 6NP

Phone: 020 7351 8021
Email: s.kemp@rbht.nhs.uk
Fax: 020 7349 7771

SPONSOR REPRESENTATIVE:
Mr Patrik Pettersson
Royal Brompton and Harefield NHS Foundation Trust (RB&HFT)
Royal Brompton Hospital (RBH)
Research Office
Chelsea Wing, Level 2
Sydney Street
London SW3 6NP

Phone: 020 7352 8121 ext. 8736
Email: p.pettersson@rbht.nhs.uk
Fax: 020 8725 0794

Signature Page

The Chief Investigator (CI) and the Research Office have discussed and agreed this study protocol. The investigators agree to perform the investigations outlined in this study protocol and to abide by this protocol except in the case of medical emergency that will be notified to the Research Office.

The Investigator agrees to conduct the trial in compliance with the study protocol and/or any subsequent amendments approved by the main REC and the Research Office, the Data Protection Act (1998), the Trust Information Governance Policy (or other local equivalent), the UK Policy Framework for Health and Social Care Research, the Trials Unit SOPs, and any other applicable regulatory requirements.

This protocol has been written in accordance with the Sponsor's guidance for writing non-CTIMP protocols.

Chief Investigator (CI)		
Dr Samuel Kemp Consultant Respiratory Physician		
Royal Brompton and Harefield NHS Foundation Trust (RB&HFT)	Signature	Date
Key Investigators (if different from CI)		
Dr Najib Rahman Consultant Respiratory Physician		
Oxford Centre for Respiratory Medicine	Signature	Date
Sponsor Representative		
Mr Patrik Pettersson Non-Commercial Research Manager		
Royal Brompton and Harefield NHS Foundation Trust (RB&HFT)	Signature	Date

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1. LIST OF ABBREVIATIONS

AE	Adverse Event
AR	Adverse Reaction
ASR	Annual Safety Report
CI	Chief Investigator
CRF	Case Report Form
GCP	Good Clinical Practice
HRA	Health Research Authority
ICF	Informed Consent Form
ICT	Intercostal Tube
ISF	Investigator Site File
MPE	Malignant Pleural Effusion
PI	Principal Investigator
PIS	Participant Information Sheet
RCT	Randomised Control Trial
REC	Research Ethics Committee
PSP	Primary Spontaneous Pneumothorax
SAR	Serious Adverse Reaction
SAE	Serious Adverse Event
SOG	Safety Oversight Group
SOP	Standard Operating Procedure
SSA	Site Specific Assessment
TMG	Trial Management Group
TSI	Trial Specific Instruction
TSC	Trial Steering Committee
UACDR	Unintentional/Accidental Chest Drain Displacement Rate
VAS	Visual Analogue Score

2. STUDY PERSONNEL AND FACILITIES

Chief Investigator (CI): Dr. Samuel Kemp
Department of Respiratory Medicine
Royal Brompton Hospital
Fulham Road
London
SW3 6NP
E-mail: s.kemp@rbht.nhs.uk
Phone: 020 7351 8021
Fax: 020 7349 7771

Key Investigator and ORTU Director: Prof. Najib Rahman
Oxford Respiratory Trials Unit
Churchill Hospital
Headington
Oxford
OX3 7LE
E-mail: najib.rahman@ndm.ox.ac.uk
Phone: 01865 225256
Fax: 01865 857109

For general queries, supply of trial documentation, safety reporting and collection of data, please contact:

Study Coordinator: **Dr. Rachel Mercer**
Oxford Respiratory Trials Unit
Churchill Hospital
Headington
Oxford
OX3 7LE
E-mail: Rachel.mercer@nhs.net
Phone: 01865 226767

Clinical Queries: Clinical queries should be directed to the Principal Investigator at the appropriate site.

3. STUDY SYNOPSIS

Full study title:	A randomised, controlled trial of the use of a dedicated ballooned intercostal drain
Short study title:	BASIC
Chief Investigator:	Dr Samuel Kemp
Medical condition/disease under investigation:	Pleural disease requiring intercostal tube (ICT) drainage, including primary spontaneous pneumothorax (PSP), secondary pneumothorax, malignant pleural effusion (MPE), and non-malignant pleural effusion.
Study duration:	18 months
Clinical phase:	III
Device Name:	Ballooned intercostal drain
Manufacturer Name:	Rocket Medical
Principal intended use:	Drainage of the pleural cavity
Primary Objective:	To compare the unintentional / accidental chest drain displacement rate (UACDR) between standard care and a balloon intercostal drain of the same size.
Secondary Objective:	1. To assess the difference in patient reported pain scores, using a visual analogue scale 2. To assess the frequency of complications such as balloon rupture or drain blockage and any other complications (such as surgical emphysema, nerve damage, intercostal injuries, etc). 3. To assess difference in the length of hospital stay in both arms. 4. To assess the total number of subsequent pleural procedures (including surgical procedures) in the 30 days after drain removal. 5. To assess the number of days which the patient has any chest drain in situ in the 30 days after drain removal. 6. Assess the number of radiological investigations performed due to issues with any chest drain in situ during the patient's hospital admission. 7. To record the consequences of drain displacement such as failure to complete treatment, delayed discharge the need for subsequent pleural procedures or the need for further medical or surgical care.
Study population:	Patients requiring intercostal tube drainage of the pleural cavity.
Methodology:	Randomised controlled trial
Eligibility criteria:	***Inclusion criteria:*** 1. Age 18 years or over 2. Able to give written informed consent

	3. Requiring intercostal tube drainage for clinical reasons
	Exclusion criteria: 1. Inability to provide written informed consent 2. Requiring a large bore drain according to local PI or delegated person's clinical judgement. 3. Frank haemothorax (requiring a large bore chest drain in view of the local PI or delegated person) 4. Pleural space (known prior to intervention) to be too small to place either standard or interventional drain according to local PI or delegated person. 5. Drain planned to be in situ for less than 24 hours. 6. Any contraindication to chest drain insertion (such as uncorrected clotting abnormality) 7. Any patient in acute pain or with an emergency presentation where consideration of the study would inappropriately delay patient care.
Study treatment:	
This trial aims to test the benefits of using a dedicated ballooned intercostal drain in patients requiring in-patient drainage of the pleural cavity.	

4. INTRODUCTION

4.1 BACKGROUND

Intercostal tube drainage of pleural air or fluid is an essential tool in the management of respiratory patients. A common complication of drain insertion is accidental removal of the drain, usually as a result of inadequate securing techniques, with rates of up to 21% quoted in the literature for drains inserted for any condition [1-3]. This study only enrolled patients with malignant pleural effusions so this rate may be higher than in patients with a wider selection of pathologies. The 2015 British Thoracic Society Audit of Pleural Procedures found a 9.2% drain fall out rate, but this was with a range of drain sizes (3). Drain displacement often results in the need for further pleural procedures (including drain re-siting), with associated additional risk to the patient and an increase in health care costs. One suggested method to reduce premature drain removal is to use intercostal drains with ballooned tips, much like Foley bladder catheters. These would provide a relatively atraumatic physical obstruction to the thoracostomy site, whilst being easy to use as stitching or extensive taping may not be required. There is published evidence for the use of non-dedicated ballooned drainage devices for the removal of pleural fluid (5), and data from a pilot study has demonstrated the safety and feasibility of a dedicated ballooned intercostal tube (being prepared for publication). Pain can be a significant issue with intercostal tubes, and occasionally warrants drain removal. The potential reduction in stitching and taping required to ensure the drain remains in the pleural space may reduce the overall discomfort of intercostal tube drainage.

We propose a randomised, controlled trial of a dedicated ballooned intercostal drain (the 'interventional drain') to investigate whether a reduction in accidental early

drain removal can be achieved. Pain scores will also be assessed during this trial to ensure that pleural irritation is not prohibitive, and a cost-effectiveness analysis undertaken.

4.2 PRE-CLINICAL DATA/CLINICAL DATA

Data from a pilot study performed at King's Mill Hospital, Sutton-in-Ashfield, demonstrated a fall-out rate of 5% when the interventional drain was used however in this one patient, it is unclear if the balloon was fully inflated within the pleural space (paper being prepared for publication). This compares favourably with rates in the literature when a standard non-ballooned drain is used.

4.3 STUDY RATIONALE AND RISK/BENEFIT ANALYSIS

The use of a ballooned ICT has the potential to reduce the accidental fall-out rate, improving the care of patients with pleural disease. Potential risks include increased pain, tissues necrosis and traumatic removal of the ICT and balloon, although none of this occurred using the interventional drain in a pilot study of 20 patients. Pain from pleural irritation did not seem to be an additional problem in that small study.

4.4 MANAGEMENT OF POTENTIAL STUDY RISKS

No specific risks related to this study have been identified, although the potential for pleural irritation, incorrect positioning at the time of balloon inflation and tissue necrosis still remains. The patient pathway is identical to usual clinical care, and the interventional drain is CE marked and available for use in clinical practice.
The investigators are not aware of any reported problems or excess adverse events from the use of the interventional drain, and the CI has used the interventional drain without incident.

5. STUDY OBJECTIVES

5.1 PRIMARY OBJECTIVE

To compare the unintentional / accidental chest drain displacement rate (UACDR) between standard care and a balloon intercostal drain of the same size.

Before a decision is made clinically to remove / reposition the drain, the chest drain:

- Falls out of the pleural cavity completely
- Is displaced such that side drainage holes are clinically no longer in the pleural cavity (for example, flushes resulting in water on the skin / dressings), as judged by the local PI or delegated person.
- Is withdrawn any amount such that the displacement stopped the drain from functioning adequately.
- Is withdrawn by a significant amount according to the local PI or delegated person

- Is confirmed to be displaced by any radiological investigation such as chest X-ray, CT or ultrasound.

Clinical decisions to reposition drains / withdraw drains when treatment is completed will be according to agreed upon trial specific instruction, and documented on the CRFs.

5.2 SECONDARY OBJECTIVES

1. To assess the difference in patient reported pain scores, using a visual analogue scale
2. To assess the frequency of complications such as balloon rupture or drain blockage and any other complications (such as surgical emphysema, nerve damage, intercostal injuries, etc).
3. To assess difference in the length of hospital stay in both arms.
4. To assess the total number of subsequent pleural procedures (including surgical procedures) in the 30 days after drain removal.
5. To assess the number of days which the patient has any chest drain in situ in the 30 days after drain removal.
6. Assess the number of radiological investigations performed due to issues with any chest drain in situ during the patient's hospital admission.
7. To record the consequences of drain displacement such as failure to complete treatment, delayed discharge the need for subsequent pleural procedures or the need for further medical or surgical care.

6. DESIGN

6.1 OVERALL DESIGN

This is a prospective, randomised, interventional clinical study to compare the rate of unintentional / accidental chest drain displacement rate (UACDR) between standard care and a ballooned intercostal tube. Patients undergoing ICT of either pleural effusion or pneumothorax as an in-patient as deemed necessary by the managing physician will be randomised on a 1:1 basis to undergo intercostal tube drainage with either a standard intercostal drain or the interventional drain.

Randomisation will occur via web-based programme and occur with minimisation for the following:

- Recruitment Centre
- Primary indication:
    - Pneumothorax
    - MPE
    - Infection
    - Other

6.2 STUDY INTERVENTION AND RATIONALE

6.2.1 Control arm

Subjects randomised to the control arm will have a standard Seldinger-type non-ballooned intercostal drain inserted at the earliest opportunity as per standard hospital protocols using local anaesthetic, ultrasound guidance (where appropriate) and conscious sedation (where appropriate). Details of the procedure will be recorded on the CRFs, including use of imaging and level of operator. The drain will be 12F drain as this is reflective of clinical practice. The drain size of the control arm will be the same as the size of the trial drain.

The standard drain will aim to be inserted to match the depth of insertion needed for the interventional drain (as per the trial specific instructions). It must also be stitched in place (single standard chest drain holding suture) and secured using bespoke drain holding dressing which will be standardized across the entire study.

All other aspects of their treatment will be identical to usual clinical care, including chest drain checks and fluid drainage strategies, with trial specific instructions available to all sites for each disease area.

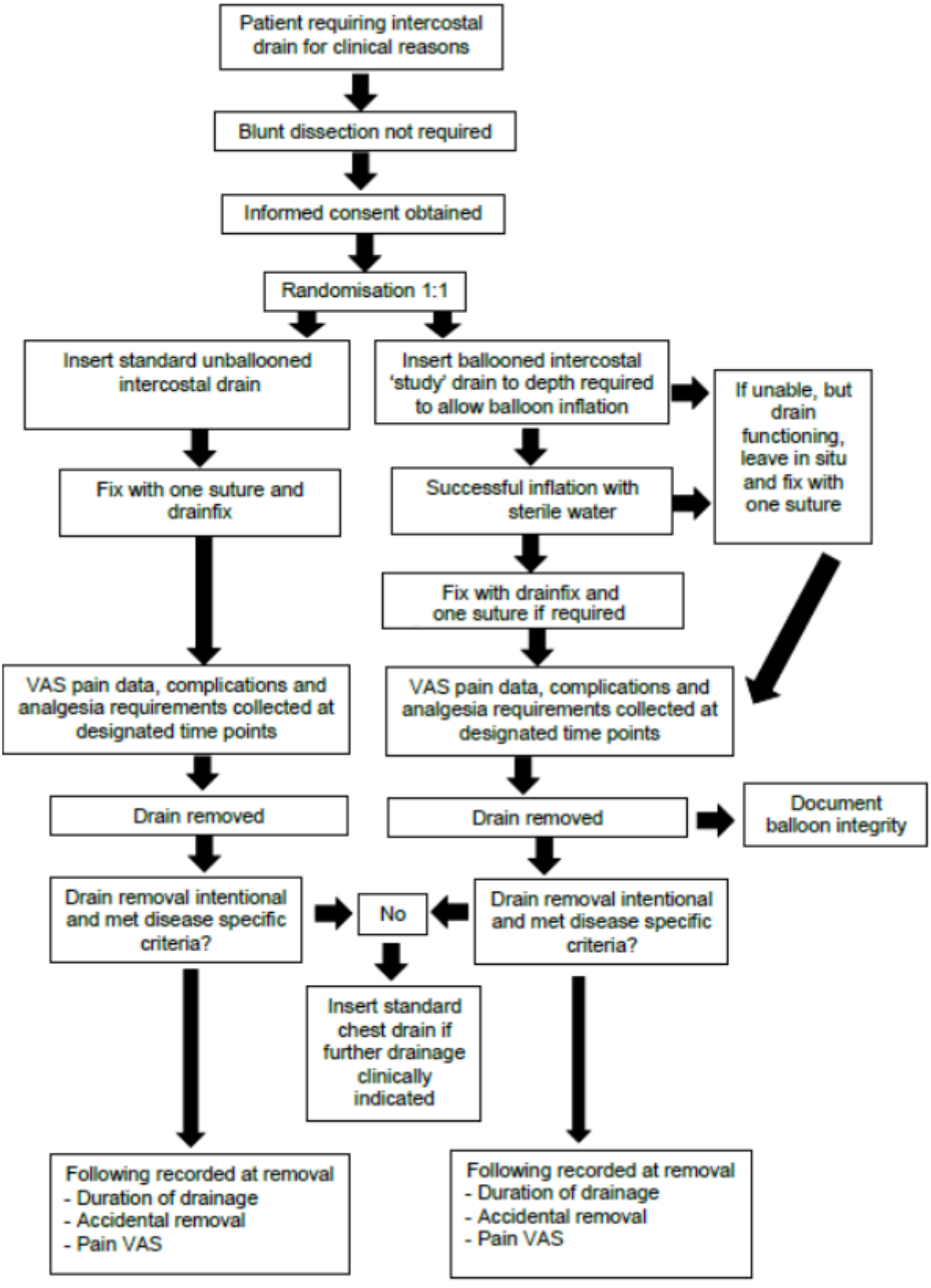
6.2.2 Interventional arm

Subjects randomised to the treatment arm will have the interventional drain inserted at the earliest opportunity as per standard hospital protocols using local anaesthetic, ultrasound guidance (where appropriate) and conscious sedation (where appropriate). Details of the procedure will be recorded on the CRFs, including use of imaging and level of operator.

The drain will be secured using bespoke drain holding dressings which will be standardized across the entire study and the same as for the standard drains. All other aspects of treatment will be identical to usual clinical care, including chest drain checks and fluid drainage strategies, with trial specific protocols available to all sites for each disease area. The operator will be permitted to use a holding suture at their discretion in the interventional arm.

Should any drain in the study become displaced and required re-siting, a standard non-ballooned intercostal drain will be inserted, with size determined by clinical need as assessed by the clinical team. The timing of further drain insertion and drainage time will be recorded (on the discharge CRF).

6.3 SCHEMATIC OF TRIAL DESIGN



7. ELIGIBILITY CRITERIA

7.1 INCLUSION CRITERIA

1. Patients aged 18 years or over
2. Patients able to give written informed consent
3. Patients requiring intercostal tube drainage for clinical reasons

Examples of clinical reasons include:

a. Drainage of malignant pleural effusion (with or without a view to pleurodesis)
b. Drainage of pneumothorax (primary or secondary)
c. Drainage of pleural infection (prior to any surgical intervention)
d. Drainage of any effusion not in the above diagnostic categories

The most likely or suspected clinical diagnosis should be recorded for randomisation to allow for appropriate minimisation but a final diagnosis will be recorded on the 30 day CRF to allow for more accurate data capture.

A number of conditions are to be included in this pragmatic study of drain management in order to ensure external validity of any trial result, and to provide a wide base for recruitment. In call cases, **it is a requirement that the drain is clinically intended to remain in situ for at least 24 hours** (but a subsequent decision to remove within 24 hours, due to clinical reasons, is acceptable). The requirement above is to ensure that patients being treated for "short term" drainage are NOT included in this study.

7.2 EXCLUSION CRITERIA

1. Inability to provide written informed consent
2. Requiring a large bore drain according to local PI or delegated person's clinical judgement.
3. Frank haemothorax (requiring a large bore chest drain in view of the local PI or delegated person)
4. Pleural space (known prior to intervention) to be too small to place either standard or interventional drain according to local PI or delegated person.
5. Drain planned to be in situ for less than 24 hours.
6. Any contraindication to chest drain insertion (such as uncorrected clotting abnormality)
7. Any patient in acute pain or with an emergency presentation where consideration of the study would inappropriately delay patient care.

Haemothorax is defined as a pleural fluid haemoglobin of greater than half of the serum haemoglobin value.

If a participant is found to have a frank haemothorax or the pleural space is not big

enough to insert adrain, during or after the procedure, the patient does not need to be withdrawn and the CRFs should be completed as fully as possible rather than submitting a protocol deviation.

7.3 DISCONTINUATION/WITHDRAWAL OF PARTICIPANTS AND STOPPING RULES

Patients are free to withdraw their consent to participate in the trial at any time. Drainage of the pleural cavity represents usual clinical care, and is not trial-specific, and therefore any drain inserted would only be removed for clinical reasons, unless specifically requested by the patient after thorough discussion with the team responsible for their usual clinical care. If a patient does withdraw their consent to participate, they can request one of the three methods below.

No further contact – means that the research team no longer contacts the patient directly, but still has their permission to use information, samples and to obtain further information from health records.

No further access – means that the research team no longer contacts the patient or obtains information from their health records, but still has permission to use the information and samples already collected.

No further use – means that the research team no longer contacts the patient or obtains further information, aims to destroy all samples already collected (though tracing previously distributed samples may not always be possible), does not use either data or samples for further analyses, but is not able to remove data from analyses already carried out. Data already entered on to the database cannot be deleted, but will be excluded from analysis.

The reason for withdrawal, if known, will be recorded in the CRF. If the participant is withdrawn due to an adverse event, the investigator will arrange for visits or telephone calls to collect follow-up information on the adverse event until the adverse event has resolved or stabilised.

They will still receive the safety follow-up telephone call at 1 month (see section 10.4) unless they expressly request for this not to happen.

If a participant's is randomised and it becomes apparent a chest drain is no longer required the participant should be withdrawn from the study. However if an attempt is made at inserting a chest drain and it fails the participant should remain in the study.

The investigators reserve the right to postpone recruitment or to terminate the trial early if new information comes to light that renders the trial futile (for example new

clinical data), or there is an apparent safety issue with the interventional drain or any other aspect of the study.

8. SUBJECT/PATIENT RECRUITMENT PROCESS

Patient recruitment at a site will only commence once the trial team has ensured that the following approval/essential documents are in place:

1. REC approval,
2. HRA Approval
3. Final sponsorship,
4. Local Site Delegation of Duties and Signature Log is completed.

All sites participating in the trial will also be asked to provide a copy of the following:

1. Signed Clinical Trial Site Agreement (CTSA) if applicable
2. Confirmation of capacity and capability (if applicable).

All subjects who wish to enter the study will be fully screened and consented by the Chief Investigator (CI), or one of the qualified clinicians involved in the study as the local PI or delegated person.

Participants will be recruited from patients who are scheduled to undergo intercostal tube drainage as an in-patient at participating centres. All subjects who wish to enter the study will be fully screened and consented by the Chief Investigator (CI), one of the qualified clinicians involved in the study as the Principal Investigator (PI), or by a delegated person as documented in the study delegation log.

9. STUDY PROCEDURES

9.1 INFORMED CONSENT

Informed consent will be obtained by the Chief Investigator (CI), Principle Investigator (PI) and/or a nominated deputy as recorded on Sponsor's Delegation of Responsibilities Log. All individuals taking informed consent will have received consent training.

Consent to enter this study will be obtained after a full account has been provided of its nature, purpose, risks, burdens and potential benefits, and the patient has had the opportunity to deliberate. The patient will be allowed to specify the time they wish to spend deliberating, usually up to 24 hours.

Periods shorter than 24 hours will be permitted if the patient feels that further deliberation will not lead to a change in their decision, and provided the person seeking consent is satisfied that the patient has fully retained, understood and deliberated on the information given. This provision has been made with the support of our patient advisory group. Patients in severe acute pain will not be approached and all patients will be allowed at least 1 hour to consider whether they would be happy to participate.

Likewise, periods longer than 24 hours will be permitted should the patient request this. The Investigator or designee will explain that the patients are under no obligation to enter the trial and that they can withdraw at any time during the trial, without having to give a reason.

A copy of the signed Informed Consent Form (ICF) along with a copy of the most recent approved Patient Information Sheet (PIS) will be given to the study participant. The original signed consent form will be retained at the study site (one filed in the medical notes and one filed in the Investigator Site File (ISF)) A copy of the consent form will also be given to the patient.

If new safety information results in significant changes to the risk–benefit assessment, the consent form will be reviewed and updated if necessary. All subjects, including those already being treated, will be informed of the new information, given a copy of the revised consent form and asked to re-consent if they choose to continue in the study.

9.2 RANDOMISATION PROCEDURE

Once a patient has been identified for the trial and has signed the informed consent form, baseline details as listed in section 10.2 will be entered into a dedicated web-based programme accessible at all sites, and patients will be allocated 1:1 to either usual care (a standard 12F ICT) or to the interventional drain, minimised by sites and disease areas (MPE/infection/pneumothorax/other).

10.STUDY ASSESSMENTS

10.1 SCREENING ASSESSMENTS

All patients requiring intercostal drainage for clinical reasons will be offered entry into the study, unless, in the view of the treating physician, large bore drain is required. No other screening assessments will be required, other than the ability to sign the informed consent form.

10.2 BASELINE ASSESSMENTS

No changes to usual clinical care occur as part of the trial, and no additional baseline assessments will be made. The following baseline data will, however, be collected:

- Primary diagnosis requiring intercostal drain
- Laterality of pleural disease requiring intervention
- Co-morbidities
- Previous thoracic intervention(s).
- Age
- Sex
- Body habitus

10.3 TREATMENT PROCEDURE

Patients who have provided signed informed consent will then proceed to the study protocol. Patients will be randomised to undergo either standard ICT insertion (usual clinical care) or insertion of the interventional drain.

Standard clinical policies and procedures at each participating centre will be followed for chest drain insertion, and no additional procedures or tests will be required for those randomised to the interventional drain.

The procedure will be performed under local anaesthesia with standard monitoring according to local protocol.

Data collected at the time of insertion will include:

- Laterality
- Site of drain insertion (using visual scale)
- Volume and strength of local anaesthetic used
- Analgesia administered
- Use of ultrasound at time of drain insertion and findings thereof including depth from skin to pleura.
- Number of centimeters to which drain was inserted
- Size of drain

10.4 SUBSEQUENT ASSESSMENTS

All subsequent care will be as per best clinical care for all patients in both arms of the study. The only additional assessments over and above usual care will be the collection of pain scores. Pain will be rated by the patients on a visual analogue scale (VAS).

Patients will be asked to draw a line perpendicular to a 10cm long horizontal line, where the left hand end relates to no pain at all, and the right to the worst pain imaginable. This score will be recorded twice daily by the patient in a VAS booklet, until drain removal or day 5 post insertion, whichever is sooner.

Data collected whilst the original drain is in situ will include:

- Analgesia used
- Additional stitches needed

- Any complications
- VAS scores (To be filled in by the patient twice daily)

Data collected at the time of drain removal will include
- Date of drain displacement or intentional removal
- Clinical decision re drain removal (disease specific criteria)
- Number of centimeters at the skin at the time of removal
- Balloon integrity at the time of removal? (Intervention arm)

Data collected at the time of discharge will include:
- Number of further pleural procedures needed
- Any further complications since drain removal

Data will be collected at 30 days (+/- 7 days) post drain removal (either in clinic or via safety follow-up telephone call). If the patient is being contacted by telephone, their medical records will be reviewed prior to contacting to ensure that contact is appropriate. The patient will then be asked some screening questions when contacted to ensure that capacity has been retained and that it is appropriate to continue with the follow up call. The data collected from the patient and their medical notes will include:
- Complications
- Final diagnosis
- Further pleural interventions
- Total number of days any chest drain was in situ, including the original drain.

Final diagnosis will be confirmed on meeting one of the criteria below:

Malignant pleural effusion diagnosis is made by one of the following:
- Histological or cytological diagnosis of pleural malignancy **OR**
- pleural effusion in the context of histologically proven cancer elsewhere

Pleural infection diagnosis is made by one of the following:
- Pleural fluid pH of ≤7.2 in the context of infection **OR**
- Pleural fluid glucose ≤3.4 in the context of infection **OR**
- Strong clinical suspicion of pleural infection provided by clinical or radiological information **OR**
- Frank pus in the pleural space or positive microbiology from pleural fluid samples

Pneumothorax is defined as air in the pleural space.

Other causes include parapneumonic effusions, hydropneumothorax, transudative effusions, reactive effusions, effusion of unknown aetiology and these data will be collected on the appropriate CRFs.

The final point of data collection will be 30 days (+/- 7 days) after the original chest drain was removed. If the patient is still an inpatient at this point both the discharge CRF and follow up CRF should be completed at this point. If it is not possible to

contact the patient the 30 day CRF should be completed using the medical notes and any other available information.

All data will be anonymised and stored according to ORTU standard operating procedures.

10.5 SUMMARY CHART OF STUDY ASSESSMENTS

	Insertion	*Day 0-5*	*Removal*	*Discharge*
Pain score	✓	✓	✓	
Drain re-sited?		✓	✓	
- *If so, when and why?*				
Complications?	✓	✓	✓	✓
Further pleural procedures			✓	✓
Balloon intact?				✓
Total days drain in situ				✓
Total hospital stay				✓

11. METHODS

11.1 LABORATORY PROCEDURES

No samples will be taken, and no laboratory procedures will be undertaken other than those required as part of usual clinical care.

11.2 RADIOLOGY OR ANY OTHER PROCEDURE(S)

No additional radiology procedures are undertaken as part of this trial but data will be collected from radiological investigations conducted as part of clinical care.

11.3 TECHNIQUES AND INTERVENTIONS

11.3.1 Description of interventional drain

The Rocket ballooned drain is similar in design to standard small bore intercostal drains, except for the addition of an inflatable balloon between 8cm and 10cm from the drain tip (figure 1) which is inflated using sterile water *via* a separate inflation channel running within the wall of the drain (figure 2). Although the balloon is capable of accommodating a greater volume of fluid, it is recommended that 5mls of

fluid be used for inflation. This will minimise the risk of balloon rupture or tissue injury whilst providing ample volume to prevent the balloon from regressing through the thoracostomy site. Detailed drawings can be found in appendix 2.

Figure 1: Picture showing position of balloon

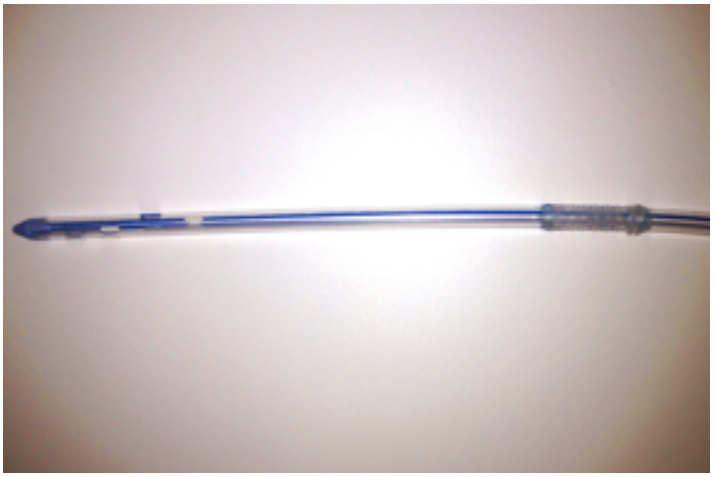
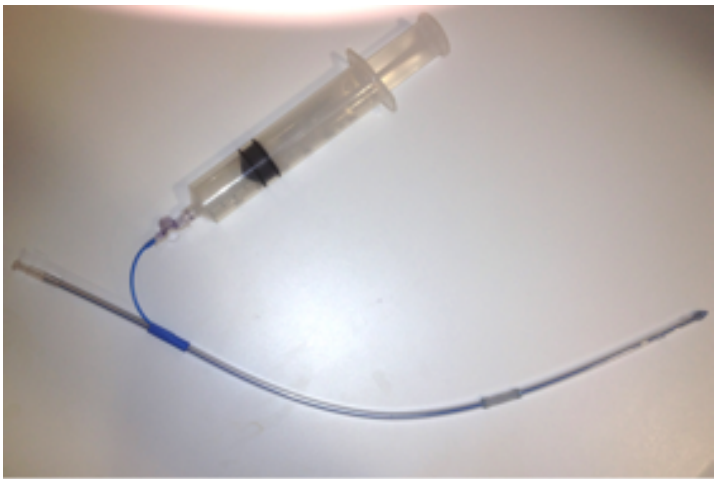


Figure 2: Picture showing syringe attached to balloon inflation channel



11.4 DEFINITION OF THE END OF TRIAL

The end of the trial is defined as the Last Patient Last Visit (LPLV), that is when the final patient has completed their 30 day (+/- 7 days) post drain removal safety telephone call or completed a 30 day review (+/- 7 days), if routinely being seen in clinic.

12. SAFETY REPORTING

12.1 DEFINITIONS

Adverse Event (AE)	Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.
Adverse Reaction (AR)	An untoward and unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant. The phrase "response to an investigational medicinal product" means that a causal relationship between a trial medication and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out. All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the trial medication qualify as adverse reactions.
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: • results in death • is life-threatening • requires inpatient hospitalisation or prolongation of existing hospitalisation • results in persistent or significant disability/incapacity • consists of a congenital anomaly or birth defect. Other 'important medical events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences. NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
Serious Adverse Reaction (SAR)	An adverse event that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to one of the trial treatments, based on the information provided.

Suspected Unexpected Serious Adverse Reaction (SUSAR)	A serious adverse reaction, the nature and severity of which is not consistent with the information about the medicinal product in question set out: • in the case of a product with a marketing authorisation, in the summary of product characteristics (SmPC) for that product • in the case of any other investigational medicinal product, in the investigator's brochure (IB) relating to the trial in question.

NB: to avoid confusion or misunderstanding of the difference between the terms "serious" and "severe", the following note of clarification is provided: "Severe" is often used to describe intensity of a specific event, which may be of relatively minor medical significance. "Seriousness" is the regulatory definition supplied above.
Any pregnancy occurring during the clinical trial and the outcome of the pregnancy should be recorded and followed up for congenital abnormality or birth defect, at which point it would fall within the definition of "serious".
The relationship of each adverse event to the trial medication must be determined by a medically qualified individual according to the following definitions:

Unrelated – Where an event is not considered to be related to the IMP / intervention

Possibly Related – although a relationship to the IMP / intervention cannot be completely ruled out, the nature of the event, the underlying disease, concomitant medication or temporal relationship make other explanations possible.

Probably Related – the temporal relationship and absence of a more likely explanation suggest the event could be related to the IMP / intervention

Definitely Related – the known effects of the IMP, its therapeutic class or based on challenge testing suggests that the IMP / intervention is the most likely cause.

Foreseeable Events

A large proportion of patients in this study are likely to have life limiting diseases. Patients with malignant pleural effusions who have been hospitalized have a 30 day mortality of 15% (6) and those with pleural infection have a 20% 3 month mortality. In this study, therefore, using the conventional timelines for adverse event reporting is not appropriate.

Disease related expected SAEs include: re-admission, death, and disease progression as judged by the local PI (or delegated person if the PI is unavailable). These will be recorded on the CRFs as expected adverse events but not subject to the timelines for SAE reporting.

Drain related expected AEs include: pain, infection, bleeding, organ puncture, hypoxia, persistent air leak, surgical emphysema, hypotension and prolonged length

of stay due to drain removal/displacement. All drain related adverse events as judged by the local PI (or delegated person if the PI is unavailable) will be captured on the CRFs up to 30 days after initial drain removal. At the 30 day telephone / clinical follow up point, CRFs will be used to record any further defined adverse events. Only those which are directly attributable to drain insertion / use / removal will be recorded at this point.

Unexpected adverse events are those not on the list above that in the investigators view is directly attributable to the chest drain. If these are serious (i.e. Serious and Unexpected Adverse Event), these events will be subject to expedited reporting to the sponsor as per SUSAR guidelines.

12.2 Recording Adverse Events (AEs)

All drain related Adverse Events will be recorded in the hospital notes and Case Report Form (CRF). Only AEs felt to be directly attributable to the chest drain should be recorded. All expected AEs will be collected on the CRFs so separate AE forms do not need to be completed. Unexpected AEs will be reported in the normal manner.

If the Investigator suspects that the disease has progressed faster due to the administration of the study treatment/procedure, then he/she will report this as an unexpected adverse event to Oxford Respiratory Trials Unit who will refer to the Sponsor and the main REC, if appropriate, as detailed in Section 12.3.

12.3 Reporting SAEs

Only related, unexpected SAEs occurring as judged by the local PI (or delegated person if the PI is unavailable) will be reported up to 30 days after initial drain removal. These should be reported on the ORTU reporting form to ORTU within 24 hours of the Site Study Team becoming aware of the event at respiratorytrialsunit@ouh.nhs.uk ORTU will perform an initial check of the report, and ensure the SAE is reviewed by the Medical Reviewer (including expectedness assessment), if appropriate the sponsor and the main REC will also be notified. The SAE will also be reviewed at the next ORTU Safety Oversight Group meeting. Additional and further requested information (follow-up or corrections to the original case) will be detailed on a new SAE Report Form and reported to ORTU.

12.4 The type and duration of the follow-up of subjects after SAEs

All SAEs will be treated as per clinical need, and follow-up will be arranged with the relevant PI in the out-patient department to monitor progress from adverse events if felt necessary on discharge. Adverse events will be recorded on the CRFs up to and including the 30 day month safety follow-up telephone call/clinic review.

12.5 Pregnancy

There is no requirement for special measures for pregnant patients undergoing intercostal tube drainage in normal clinical practice. Therefore, pregnant patients will be offered the opportunity to participate in this trial. Intercostal tube drainage does not confer any significant risk to the foetus, and is not teratogenic.

12.6 ANNUAL PROGRESS REPORTS (APRS)

The Chief Investigator will prepare the APR for the study. It will be reviewed by the RO and sent to the main REC by the CI within 30 days of the anniversary date on which the favourable opinion was given by the main REC, and annually until the trial is declared ended.

12.7 REPORTING URGENT SAFETY MEASURES

The Sponsor and/or the Investigator may take appropriate urgent safety measures in order to protect the subjects of a clinical study against any immediate hazard to their health or safety. If safety measures are taken, the main REC approval is not required before the measure is taken.

The Investigator will immediately and in any event no later than 3 days from the date the measures are taken, give written notice to the main REC and the study Sponsor of the measures taken and the circumstances giving rise to those measures.

In order to prevent any delays in the reporting timelines the Sponsor has delegated this responsibility to the CI/PI. Therefore the CI/PI must report any urgent safety measures to the main REC directly, and in parallel to Oxford Respiratory Trials Unit and the Sponsor. The REC coordinator will acknowledge receipt of urgent safety measures within 30 days.

All urgent safety measures reported by PIs from participating sites will also be forwarded to the relevant local REC.

13. DATA MANAGEMENT AND QUALITY ASSURANCE

13.1 CONFIDENTIALITY

All data will be handled in accordance with the Data Protection Act 1998, NHS Caldecott Principles, the UK Policy Framework for Health and Social Care Research, and the condition of the main REC approval.

The Case Report Forms (CRFs) will not bear the subject's name or other personal identifiable data. The subject's initials, and trial Identification Number (ID), will be used for identification.

13.2 DATA COLLECTION TOOL

Case Report Forms (CRF) will be appropriately designed and reviewed by the trial management group. The study will utilise a secure web-based, trial data management system designed for remote electronic data capture. Details of data security arrangements will be given in the Data Management Plan.

It is the Investigator's responsibility to ensure the accuracy of all data entered and recorded in the CRFs. The Delegation of Responsibilities Log will identify all trial personnel responsible for data collection, entry, handling and managing the database.

13.3 DATA HANDLING AND ANALYSIS

At the time of the 30 day telephone call or clinic review, the investigator making that call will aim to ensure a complete dataset has been entered on the CRFs by reviewing the patient's medical notes and the electronic patient record (EPR) system, and consulting with the histopathology team where necessary.

13.4 ARCHIVING ARRANGEMENTS

The key study documents (including the Trial Master File (TMF)) will be kept for a minimum of five years. The CI is responsible for the secure archiving of trial documents. Trial data will also be archived electronically and securely for a minimum of five years.

The approved repository for longer retention of local materials for studies that involve RB&HFT patients will be stored in accordance with the current SOP. The study documentation will be prepared for archiving by the research team in line with the Research Office Archiving SOP and the transfer will be arranged by the Research Office.

14. STATISTICAL DESIGN

14.1 SAMPLE SIZE AND RECRUITMENT

Based on data from previous studies of drain fall-out rates with standard ICTs and data from the pilot study of ballooned drains, 66 recruited subjects will be required in each arm of the trial on the basis of the following assumptions:

Binary data (drain displaced; drain not displaced)
Power: 0.8
Level of significance: 0.05
Fall-out rate in pilot study: 5%
Fall-out rate in previous studies: 21%

Estimated sample size calculation: 66 in each arm

Calculation based on the formula:

$n = f(\alpha/2, \beta) \times [p_1 \times (100 - p_1) + p_2 \times (100 - p_2)] / (p_2 - p_1)^2$

where p1 and p2 are the percent 'success' in the control and experimental group respectively and $f(\alpha, \beta) = [\Phi^{-1}(\alpha) + \Phi^{-1}(\beta)]^2$. Φ^{-1} is the cumulative distribution function of a standardised normal deviate.

Allowing for a ~2% withdrawal rate (which is realistic as this is a short term study only), the estimated combined sample size for the study is 136 subjects.

It is estimated that recruitment will take up to 18 months, aiming for approximately 1 patient per site per month.

At 50% recruitment the assumption that 21% of non-balloon drains would displace was reviewed by the TSC. However after reviewing the data this was found to be 12%. Since this was lower than expected the trial was likely to be underpowered, and therefore the sample size was increased to allow the same relative reduction in displacement to be detected. The initial sample size calculation aimed to detect a reduction from 21% to 5%, a relative reduction of 21-5/21 = 76%. To detect the same relative reduction the displacement rate in the balloon arm would be assumed to be 12*(1-0.76) = 2.88%. This was rounded to 3% (i.e. more conservative and therefore a slightly higher sample size). The new sample size required to detect a reduction in displacement rates from 12% to 3%, and allowing for a 2% withdrawal rate, was 267.

14.2 ENDPOINTS

14.2.1 Primary endpoints

To compare the unintentional / accidental chest drain displacement rate (UACDR) between standard care and a balloon intercostal drain of the same size.

Before a decision is made clinically to remove / reposition the drain, the chest drain:

- Falls out of the pleural cavity completely
- Is displaced such that side drainage holes are clinically no longer in the pleural cavity (for example, flushes resulting in water on the skin / dressings), as judged by the local PI or delegated person.
- Is withdrawn any amount such that the displacement stopped the drain from functioning adequately.
- Is withdrawn by a significant amount according to the local PI or delegated person
- Is confirmed to be displaced by any radiological investigation such as chest X-ray, CT or ultrasound.

14.2.2 Secondary endpoints

1. To assess the difference in patient reported pain scores, using a visual analogue scale.

- assessed by simple measurement of the distance of the line drawn by the patient from the left hand end of the VAS.2. To assess the frequency complications such as balloon rupture, drain blockage or other drain related complications

- Assess balloon rupture in the interventional arm only, by inflation of the balloon with fluid after removal (accidental or intentional) from the pleural space.
- Assessed by review of medical notes or patient review whilst the original chest drain is in situ

3. To assess the difference in the length of hospital stay

- Record the number of days, after insertion of the initial study drain, that the patient was discharged (Including day of drain insertion and date of discharge)

4. To assess the total number of pleural procedures (including surgical procedures) in the 30 days after the initial study drain was removed

- Record the number of pleural procedures undertaken in the 30 days after the initial study drain was removed

5. To assess the number of days which the patient has any chest drain in situ in the 30 days after the initial drain removal

- Record the number of days the patient had a chest drain in situ in the 30 days after the initial study drain was removed after the initial study drain was removed

6. To record the total number of radiological investigations performed from the time of drain insertion until the 30 day follow up has been completed

- Assessed by review of medical notes radiology systems.

7. To record the consequences of drain displacement such as failed treatment, delayed discharge the need for subsequent pleural procedures or the need for further medical or surgical care

- Assessed by review of medical notes and/or patient review.

14.3 STATISTICAL ANALYSIS PLAN

Analysis of baseline characteristics will include:

Age	Sex	Co-morbidity
Laterality	Drain size	Presence of fluid loculation
Body Habitus	Diagnosis	Previous pleural interventions

All statistical analysis will be managed according to a detailed statistical analysis plan which will be written and signed off by the trial management group prior to recruitment completion, data lock or any meaningful analysis of the data. In brief terms, primary and secondary outcomes will be compared between treatment arms, and include time to event analysis (i.e. including tube dwell time in the analysis) where appropriate.

14.3.1 Primary endpoint analysis

The primary end point for the trial is difference in the UACDR between control and interventional arms and will be analysed as part of a detailed statistical analysis plan, to include time to event analysis as above. The analysis will be performed on an intention to treat basis.

14.3.2 Secondary endpoint analysis

Secondary endpoints will be analysed as part of a detailed statistical analysis plan which will be written and signed off by the trial management group prior to recruitment completion, data lock or any meaningful analysis of the data.

14.4 RANDOMISATION

Patients will be randomised using a centralised, web-based service. Patients will be allocated 1:1 to either usual care (a standard 12F ICT) or to the interventional drain. Patients will be minimised by sites and disease areas (Pneumothorax/MPE/Infection/Other).

14.5 OTHER STATISTICAL CONSIDERATIONS

Intention to treat will be undertaken in order to account for patients who are randomised but then do not have an intercostal tube sited for any reason. The reason for non-insertion will be documented in the clinical notes.

15.COMMITTEES INVOLVED IN THE STUDY

15.1 TRIAL MANAGEMENT GROUP (TMG)

The members of this group will be defined separately. The role of this group is to monitor all aspects of the conduct and progress of the trial, ensure that the protocol is adhered to and take appropriate action to safeguard participants and the quality of the trial itself.

15.2 Safety Oversight Group

The Oxford Respiratory Trials Unit (ORTU) Safety Oversight Group will conduct a review of all SAEs for the trial reported during the reporting period and cumulatively. The ORTU Safety Oversight Group requires at least three clinicians to attend each meeting (this may include the Chief Investigator). The Group will provide advice to the TSC and may correspond directly with the Sponsor if potential safety concerns are raised. The aims of this committee include:

- To pick up any trends, such as increases in un/expected events, and take appropriate action
- To seek additional advice or information from investigators where required
- To evaluate the risk of the trial continuing and take appropriate action where necessary

The content and timings of the ORTU Safety Oversight Group will be detailed in a Safety Oversight Group Charter, which will be agreed with the members.

15.3 MONITORING AND AUDITING

The study may be monitored or audited in accordance with the current approved protocol, GCP, relevant regulations and Trial Unit standard operating procedures.

Study monitoring and/or audit will be discussed with the CI before arrangements are made to conduct the visit.

16. DIRECT ACCESS TO SOURCE DATA

The Investigator(s)/institution(s) will permit trial-related monitoring, audits, REC review, and regulatory inspection(s), providing direct access to source data/documents. Trial participants are informed of this during the informed consent discussion. Participants will consent to provide access to their medical notes.

17. ETHICS AND REGULATORY REQUIREMENTS

The Sponsor will ensure that the trial protocol, Patient Information Sheet (PIS), Informed Consent Form (ICF), and submitted supporting documents have been approved by the main Research Ethics Committee (REC) and the Health Research Authority (HRA), prior to any patient recruitment taking place. The protocol and all agreed substantial protocol amendments, will be documented and submitted for ethical approval prior to implementation.

It is the responsibility of the PI at each site to ensure that all subsequent amendments gain the necessary local Trust approval. This does not affect the individual clinician's responsibility to take immediate action if thought necessary to protect the health and interest of individual patients.
Within 90 days after the end of the trial, the CI and Sponsor will ensure that the main REC is notified that the trial has finished. If the trial is terminated prematurely, those reports will be made within 15 days after the end of the trial.

The CI will supply a final summary report of the clinical trial to the main REC and the Sponsor in parallel within one year after the end of the trial.

18. FINANCE

There are no costs above those of usual clinical care. The interventional drains will be provided free of charge by Rocket Medical, and therefore the trial is anticipated to present an overall cost saving.

Support for the trial is provided by an endowment to RBHFT as part of The Royal Brompton and Harefield Charitable Trust. Clinical trial materials and some consumables are provided by Rocket Medical who have no part in data acquisition, analysis or publication.

19. INSURANCE AND INDEMNITY

NHS bodies are liable for clinical negligence and other negligent harm to individuals covered by their duty of care. NHS Institutions employing researchers are liable for negligent harm caused by the design of studies they initiate. The provision of such indemnity for negligent harm should be stated to the participant.

20. PUBLICATION POLICY

Data ownership rights will lie with the institution.

21. STATEMENT OF COMPLIANCE

The trial will be conducted in compliance with the protocol, TSI, Trials Unit Standard Operating Procedures (SOPs), GCP and the applicable regulatory requirement(s).

The study conduct shall comply with all relevant laws of the EU if directly applicable or of direct effect and all relevant laws and statutes of the UK country in which the study site is located including but not limited to, the Human Rights Act 1998, the Data Protection Act 1998, the Medicines Act 1968, and with all relevant guidance relating to medicines and clinical studies from time to time in force including, but not limited to, the ICH GCP**,** the World Medical Association Declaration of Helsinki entitled 'Ethical Principles for Medical Research Involving Human Subjects' (2008 Version), the UK Policy Framework for Health and Social Care Research.

This study will be conducted in compliance with the protocol approved by the main REC and according to RGF standards. No deviation from the protocol will be implemented without the prior review and approval of the Sponsor and the main REC except where it may be necessary to eliminate an immediate hazard to a research subject. In such case, the deviation will be reported to the Sponsor and the main REC as soon as possible.

22. LIST OF PROTOCOL APPENDICES

Appendix 1 Summary Chart of Study Assessments
Appendix 2 Interventionaldrain design diagrams
Appendix 3 ORTU Safety Reporting Process

23. REFERENCES

1. Davies HE, Merchant S, McGown A. A study of the complications of small bore 'Seldinger' intercostal chest drains. Respirology (Carlton, Vic). 2008;13(4):603-7.
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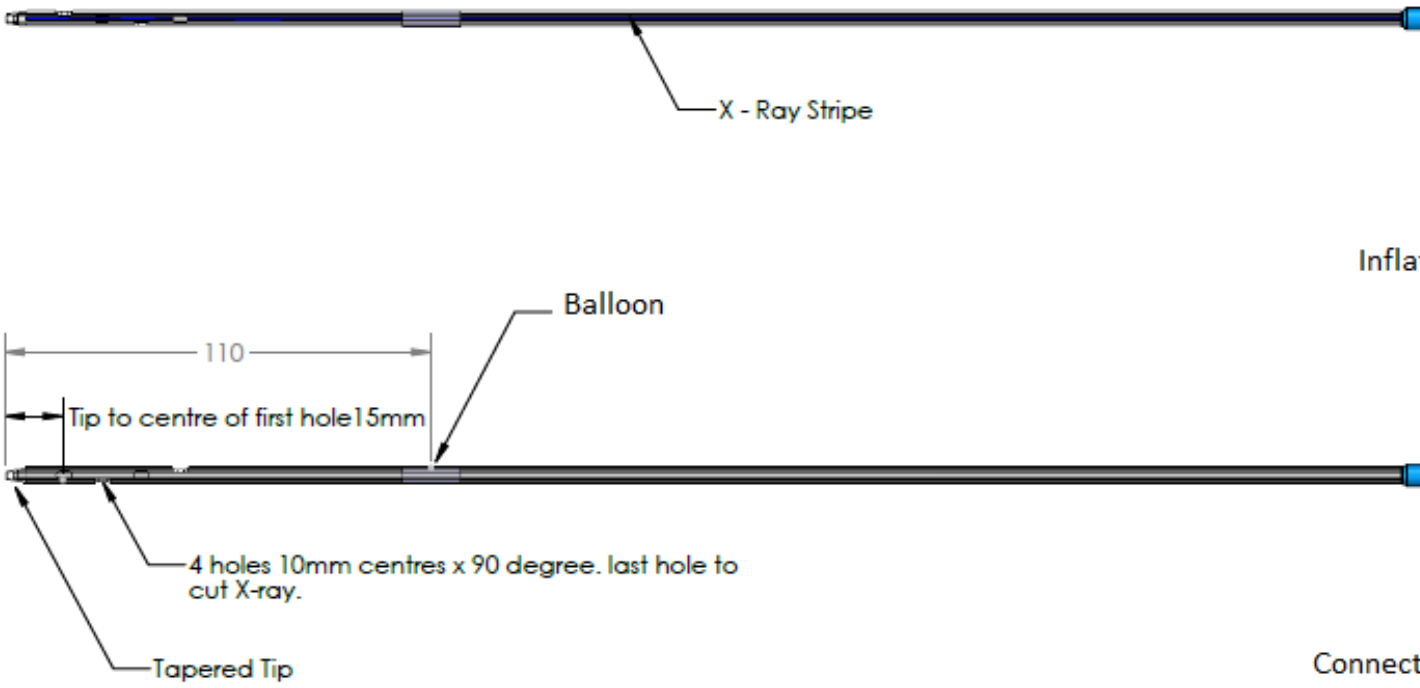
3. Hooper CE, Welham SA, Maskell NA. Pleural procedures and patient safety: a national BTS audit of practice. Thorax. 2015;70(2):189-91.
4. Rahman NM, Pepperell J, Rehal S, Saba T, Tang A, Ali N, et al. Effect of Opioids vs NSAIDs and Larger vs Smaller Chest Tube Size on Pain Control and Pleurodesis Efficacy Among Patients With Malignant Pleural Effusion: The TIME1 Randomized Clinical Trial. Jama. 2015;314(24):2641-53.
5. Ben-Nun A, Best LA. A simple method of using a Foley catheter to drain pleural effusion. Surgery today. 2008;38(8):769-70.
6. Kookoolis AS, Puchalski JT, Murphy TE, Araujo KLB, Pisani MA. Mortality of Hospitalized Patients with Pleural Effusions. Journal of pulmonary & respiratory medicine. 2014;4(3):184.

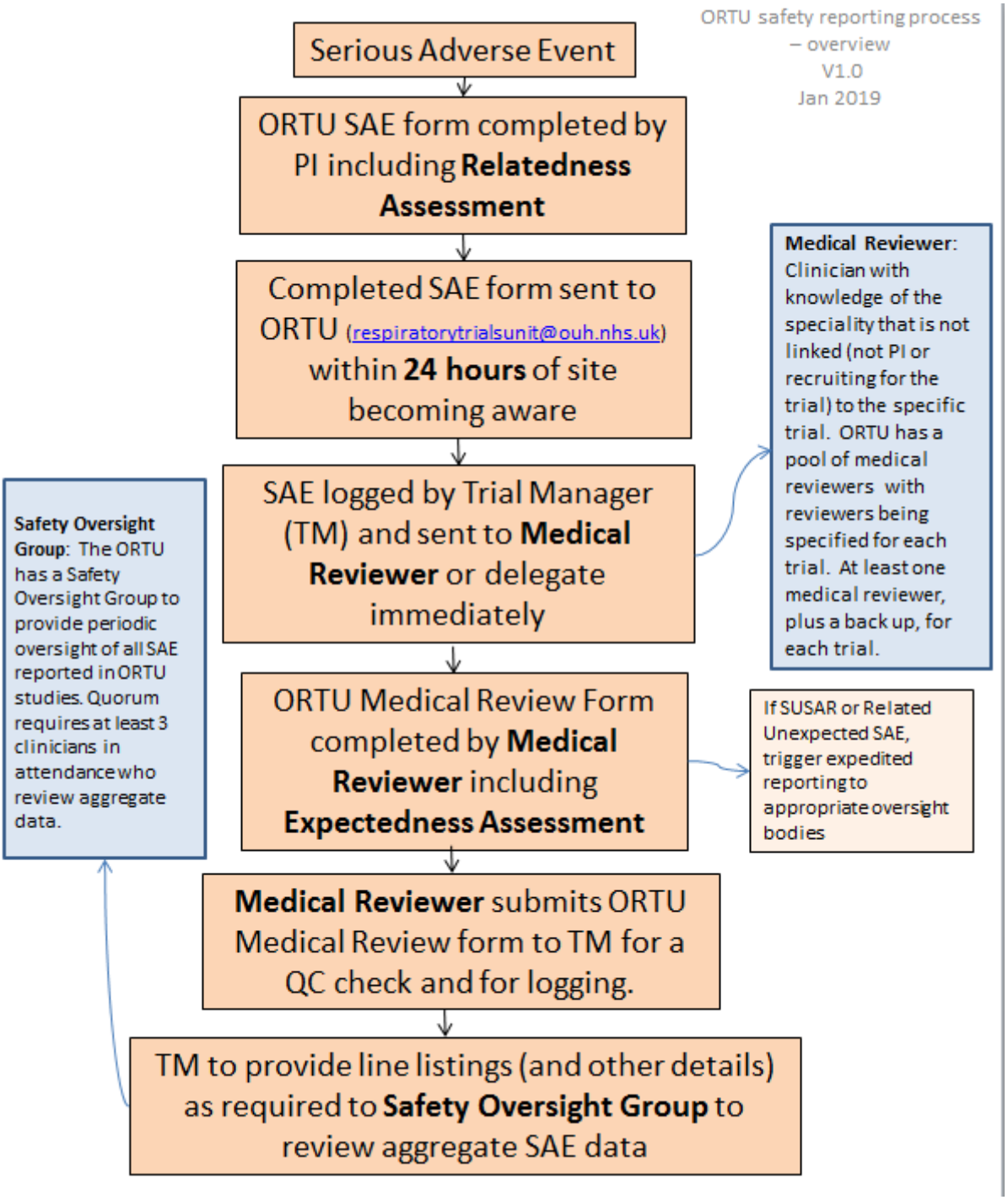
Appendix 1: Summary Chart of Study Assessments

Study Procedures	Screening	Baseline	During treatment:			
			Insertion	Day 0 - 5	Day 5 onwards	Drain removal
Informed consent	X			X		
Inclusion/exclusion criteria	X					
Medical history/co-morbidities		X				
Demographics		X				
Documentation of primary diagnosis		X				
Documentation of site and laterality		X				
Randomisation		X				
Drain insertion			X			
Documentation of drain fixation			X			
Documentation of USS use and findings			X			
Pain VAS			X	X	X	X
Documentation of complications			X	X	X	X
Documentation of re-siting				X	X	X
Record of further pleural procedures						X
Check of balloon integrity						X
Telephone call						

Appendix 2: Study Drain Design Diagrams



Appendix 3: ORTU Safety Reporting Process


ORTU safety reporting process – overview
V1.0
Jan 2019
Serious Adverse Event
ORTU SAE form completed by PI including **Relatedness Assessment**
Completed SAE form sent to ORTU (respiratorytrialsunit@ouh.nhs.uk) within **24 hours** of site becoming aware
SAE logged by Trial Manager (TM) and sent to **Medical Reviewer** or delegate immediately
Medical Reviewer: Clinician with knowledge of the speciality that is not linked (not PI or recruiting for the trial) to the specific trial. ORTU has a pool of medical reviewers with reviewers being specified for each trial. At least one medical reviewer, plus a back up, for each trial.
ORTU Medical Review Form completed by **Medical Reviewer** including **Expectedness Assessment**
If SUSAR or Related Unexpected SAE, trigger expedited reporting to appropriate oversight bodies
Safety Oversight Group: The ORTU has a Safety Oversight Group to provide periodic oversight of all SAE reported in ORTU studies. Quorum requires at least 3 clinicians in attendance who review aggregate data.
Medical Reviewer submits ORTU Medical Review form to TM for a QC check and for logging.
TM to provide line listings (and other details) as required to **Safety Oversight Group** to review aggregate SAE data