Trial Title: Randomised trial of Suction for Primary Pneumothorax Early Resolution

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2. LAY SUMMARY

Aim

We aim to understand whether using suction to treat people in hospital with a lung collapse is safe and can shorten the time people need to have a chest tube in place.

Background

A pneumothorax occurs when air gets into the space between the lung and the chest wall, usually through a small hole in the lung. This causes the lung to collapse, and can occur "spontaneously", meaning without an injury to the chest. Primary spontaneous pneumothorax (PSP) occurs in younger patients without known lung disease. Most patients with PSP need to have a tube (or drain) inserted into the chest to remove the air between the lung and chest wall. This allows the lung to re-inflate. The tube is attached to a bottle with water in it, creating an underwater seal, and air bubbles out through the water.

Although some patients with PSP can be treated at home (either by not draining the chest, or with a home drainage device), at least 50% of patients stay in hospital waiting for the lung to re-inflate for 4 to 8 days. In these patients, it is possible to provide suction (negative pressure) to the drain with the aim of expanding the lung more quickly and reducing time in hospital. However, we do not know if using suction is helpful, or if it has risks. There have been no large studies conducted to prove whether suction is effective in reducing treatment time. The current guidelines provide conflicting advice on the routine use of suction, but despite this, doctors often use it. We want to address this question directly. Reducing treatment time is important because interviews and questionnaires conducted with patients who have had a pneumothorax have told us that their top priorities are: 1) To reduce the amount of time that they have a chest tube, and 2) To reduce the length of their hospital stay. In addition, treating these patients in hospital costs the NHS around £7.2m per year, so reducing time in hospital safely will be cost saving for the NHS.

Design and methods

We will recruit 450 patients from 36 centres around the UK over 3 years. We have chosen sites that recruited well to our last big pneumothorax study, and these sites have already expressed an interest in the proposed study. Patients will be randomly assigned to either have suction applied to their chest tube or treated with usual care (no suction) as per current guidelines.

Patient and public involvement

We conducted a survey of twelve patients to find out what was most important to them, and designed this trial based on the results. The survey showed that patients wanted a treatment that reduced the length of treatment and hence time in hospital. A representative from our patient group who previously had a PSP is a co-applicant who will sit on the trial steering committee and represent our Patient Advisory Group.

Dissemination

If we find treating lung collapse with suction is safe, effective and acceptable to patients, this will lead to changes in management. Results will be written up in scientific journals, presented at conferences and we will work with mainstream and social media groups to let doctors know the findings. We expect our research will be reflected in national guidelines. Our patient groups will help us decide the best ways to let patients know about the results. These will include newsletters, social and traditional media and through lung disease charities.

3. SYNOPSIS

Trial Title	**Randomised trial of Suction for Primary Pneumothorax Early Resolution**		
Internal ref. no. (or short title)	**RASPER**		
Trial registration	TBC.		
Sponsor	University of Oxford Research Governance, Ethics and Assurance Boundary Brook House Churchill Drive Headington Oxford, OX3 7GB		
Funder	National Institute for Health Research (NIHR) Evaluation, Trials and Studies Coordinating Centre University of Southampton, Alpha House, Enterprise Road Southampton SO16 7NS Email: netsmonitoring@nihr.ac.uk		
Clinical Phase	3		
Trial Design	Multi-centre open-label RCT (with multicentre internal pilot phase over 12 months) This study will assess the superiority of suction vs standard care with respect to hospital stay.		
Trial Participants	Patients with primary spontaneous pneumothorax (PSP) requiring chest drain in hospital on Day 1 post initial treatment		
Sample Size	450		
Planned Trial Period	48-month project: Set-up (6 months); pilot recruitment (12 months); further recruitment (23 months); patient follow-up (6 months, (1 month only for those participants randomised in the last 3 months of the trial), study close-down analysis and reporting (6 months).		
	Objectives	Outcome Measures	Timepoint(s)
Primary	To test whether use of suction is superior to standard care	Total treatment duration, defined as time from randomisation to completion of pleural treatment (including surgery, if required)	Completion of treatment (discharge home from hospital with no drain in place)
Secondary	1. To estimate the difference between groups with respect to a range of patient-reported and clinical	1a. In-patient surgical rates 1b. Length of hospital stay over first the 30 days post randomisation (including readmissions)	1a. Completion of treatment 1b. 30 days post-randomisation 1c. Baseline, daily until completion of treatment,

	secondary outcomes up to 6 months 2. To estimate the cost-effectiveness of suction compared to standard management 3. To determine the risk profile of suction use compared with standard care	1c. Pain and breathless scores (100mm Visual Analogue Scale (VAS)) 1d. EQ5D 1e. Rate of recurrence of pneumothorax 2. Incremental cost per QALY gained 3a. Complication rates 3b. Overall number in-patient pleural procedures 3c. Adverse events related to the use of suction	and at follow-14 days after the completion of treatment and 30 days post-randomisation) 1d. Baseline, Completion of treatment, 30 days and 6 months post randomisation 1e. 6 months post randomisation 2. Randomisation to 6 months 3a-c. Completion of treatment
Intervention(s)	Suction: The chest drain will be connected to digital suction on Day 1 of treatment. Suction will be incrementally increased over the next 2-4 hours following a trial specific procedure (e.g. initially, -1.0kPa (-10cm H_20, or -7.5mmHg), increasing to -1.5kPa and -2.0kPa as tolerated) with specific criteria for reducing suction (pain, complications).		
Comparator	Usual care: The chest drain will be managed as per BTS guidelines (1), without the use of suction (i.e. connected to an underwater seal bottle) unless clinically indicated for safety reasons.		

4. ABBREVIATIONS

AE	Adverse event
CI	Chief Investigator
CRF	Case Report Form
DMC	Data Monitoring Committee
EQ5D	Euroqol-5 Dimensions 5-levels
GCP	Good Clinical Practice
GP	General Practitioner
HRA	Health Research Authority
HRG	Human Resource Group (codes)
ICF	Informed Consent Form
NHS	National Health Service
ORTU	Oxford Respiratory Trials Unit
PCCTU	Primary Care Clinical Trials Unit
PI	Principal Investigator
PIL	Participant/ Patient Information Leaflet
PSP	Primary Spontaneous Pneumothorax
QALYs	Quality Adjusted Life-Years
R&D	NHS Trust R&D Department
REC	Research Ethics Committee
RGEA	Research Governance, Ethics and Assurance
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
TMF	Trial Master File

5. BACKGROUND AND RATIONALE

Pneumothorax is defined as air in the pleural space (between lung and chest wall). When it occurs without trauma, and in patients with no underlying lung disease, it is referred to as Primary Spontaneous Pneumothorax (PSP), and it is due to a spontaneous hole occurring in the lung. PSP patients are young with no medical comorbidities, and there are 3,000 admissions/year in the UK(2-4).

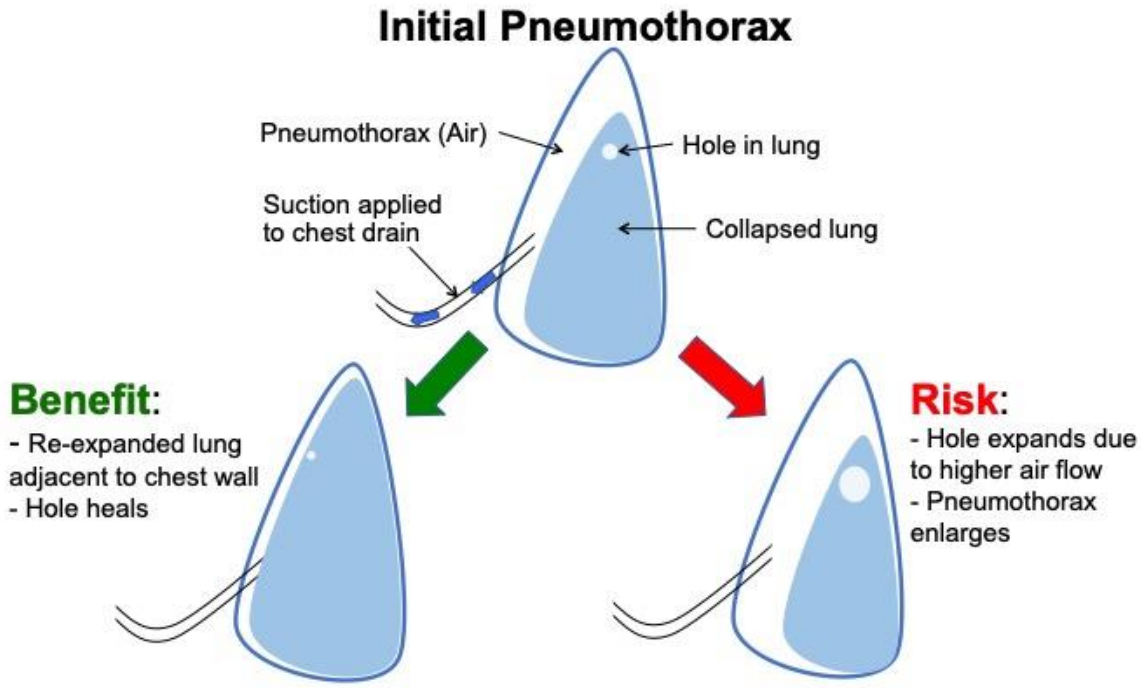
Standard care involves short-term drainage (aspiration), which is effective in up to 50% of cases, allowing discharge on the same day. In those that fail aspiration, a chest drain is inserted, and the patient is admitted to hospital. Recently, an ambulatory strategy has been shown by our group to be effective in PSP, and a further study demonstrates the potential of conservative treatment in patients with large PSP(5).

However, this has not been adopted in the UK (see survey results below) and at least 50% of patients still require treatment and admission to hospital. The median hospital stay of patients admitted is 4-8 days(6-11).

Once admitted to hospital with a chest drain, management of on-going pneumothorax remains contentious. The rationale behind the use of suction (the application of negative pressure to the pleural space via the chest tube) is that the lung will expand more quickly and potentially heal more quickly once the lung is re-expanded and in contact with the parietal pleura. However, suction is not without risk, as it may precipitate injury to the lung (by too rapidly expanding the lung(12), or may result in delayed healing of the pneumothorax if the application of suction maintains flow through the hole in the lung.

The use of suction is thus controversial, highly variable in current practice and has potential risks and benefits (See **Figure 1**).

Figure 1: The potential benefits and risks of the application of suction



Why is this important?

Importance to patients

We have conducted PPI activities (face-to-face discussions with 3 patients, and 12 completed online surveys), to establish priorities of care for patients, which were (in order):

1. Reduction in treatment duration (60%)
2. Reduction of time in hospital (60%)
3. Reducing number of additional procedures (45%)

The use of suction has the potential to influence all of the above patient prioritised outcomes.

Reducing variation in practice

Our survey of physicians demonstrates significant variability in the use of suction(13). We postulate that this is the result of a poor evidence base, which results in suboptimal and variable care, and uncertainty for both patients and healthcare professionals.

Economic benefit

Inpatient hospital stay for PSP is estimated to cost the NHS £7.2m per annum (3,000 patients per year, mean hospital stay of 6 days, assuming £400 per day (14)). The use of suction may reduce treatment duration and hence be cost saving for NHS and for society's productivity.

We therefore propose a study to evaluate whether suction in admitted patients with PSP is safe and effective for outcomes important to patients and the NHS.

Evidence explaining why this research is needed now

Systematic Review

Searches on Pubmed and Medline (for "Pneumothora*" AND "suction) revealed 653 abstracts of which 3 were relevant: Two studies compared suction to standard care (15, 16) and reported no difference, but both were underpowered for the primary outcomes (Reed's recruited 29 of their 120 target). Therefore, a type II error cannot be excluded. Moreover, these studies included either secondary(15) or iatrogenic pneumothoraces (16) and not just PSP. The other RCT (Jablonski (17)) enrolled 60 patients but compared two different forms of suction (digital suction to wall-suction), rather than suction to standard care. Thus, there has never been a robust suction vs no suction trial in PSP.

Current guidelines

Two major guidelines provide conflicting advice, resulting in variability in practice. These are detailed below:

1) The British Thoracic Society (BTS) guidelines 2010 do not recommend the routine use of suction(18).

2) NICE guidelines 2017 (19) on use of digital suction recommend its use post thoracic surgery (based on 5 good quality RCTs), but also in (non post-surgical) pneumothorax. This recommendation was based on the small study by Jablonski(17), which did not compare suction to standard care.

Current suction practice in the UK

Current UK practice is variable: we conducted a survey of 102 UK physicians specifically designed to inform this application (13), which demonstrated only 1% of clinicians use suction immediately for pneumothorax treatment, 64% use suction if the lung is not re-expanded after 2 days, 10% use suction after 4 days, 11% never use suction, and 14% use suction after surgical referral or complications.

Digital Suction

Despite the NICE guidance, digital suction is not widely used in UK practice for PSP. A survey of pleural specialists demonstrated only 25% of expert centres in the UK have access to or use digital suction for PSP. Given the lack of an adequately powered RCT comparing suction to no-suction in PSP and the variability in current practice, testing the key hypothesis that early suction can reduce treatment duration is of vital importance.

6. OBJECTIVES AND OUTCOME MEASURES

	Objectives	Outcome Measures	Timepoint(s)
Primary	To test whether use of suction is superior to standard care	Total treatment duration, defined as time from randomisation to completion of treatment (including surgery, if required)	Completion of treatment (discharge home from hospital with no drain in place)
Secondary	1. To estimate the difference between groups with respect to a range of patient-reported and clinical secondary outcomes up to 6 months	1a. In-patient surgical rates 1b. Length of hospital stay over first the 30 days (including readmissions) 1c. Pain and breathless scores (100mm Visual Analogue Scale (VAS)) 1d. EQ5D 1e. Rate of recurrence of pneumothorax	1a. Completion of treatment 1b. 30 days post-randomisation 1c. Baseline, daily until completion of treatment, and at follow-up (2 weeks after the completion of treatment and 30 days post-randomisation) 1d. Baseline, Completion of treatment, 30 days and 6 months post randomisation 1e. 6 months post randomisation 2. Randomisation to 6 months
	2. To estimate the cost-effectiveness of suction compared to standard management	2. Incremental cost per QALY gained	
	3. To determine the risk profile of suction use compared with standard care	3a. Complication rates 3b. Overall number in-patient pleural procedures 3c. Adverse events related to the use of suction	3a-c. Completion of treatment

7. STUDY DESIGN

Design & Setting

Multi-centre open-label RCT with multicentre internal pilot phase over 12 months. This study will assess the superiority of suction vs standard care with respect to total treatment duration.

Patients with primary spontaneous pneumothorax (PSP) requiring chest drainage in hospital will be enrolled from 36 UK centres, including our established pneumothorax network(20). Patients will be screened from respiratory and general medical wards. Data will be collected from routinely recorded

clinical data (heart rate, blood pressure etc), and patient-completed questions on pain and breathlessness scores and overall health (EQ5D).
Patients will be reviewed daily whilst in hospital and then at three subsequent follow-up visits up to 6 months post-enrolment, which can be undertaken via telephone or in person.

Internal Pilot phase 1 (12 months)

An initial internal pilot (phase 1) will be undertaken to monitor 1) recruitment rates; 2) adherence to the allocated treatment (to assess any bias/lack of equipoise); 3) rates of completion of the primary outcome (see Table 1). Phase 1 will begin when at least 6 sites have been activated.

Table 1: Criteria for progression from internal pilot (phase 1) to main trial (phase 2):

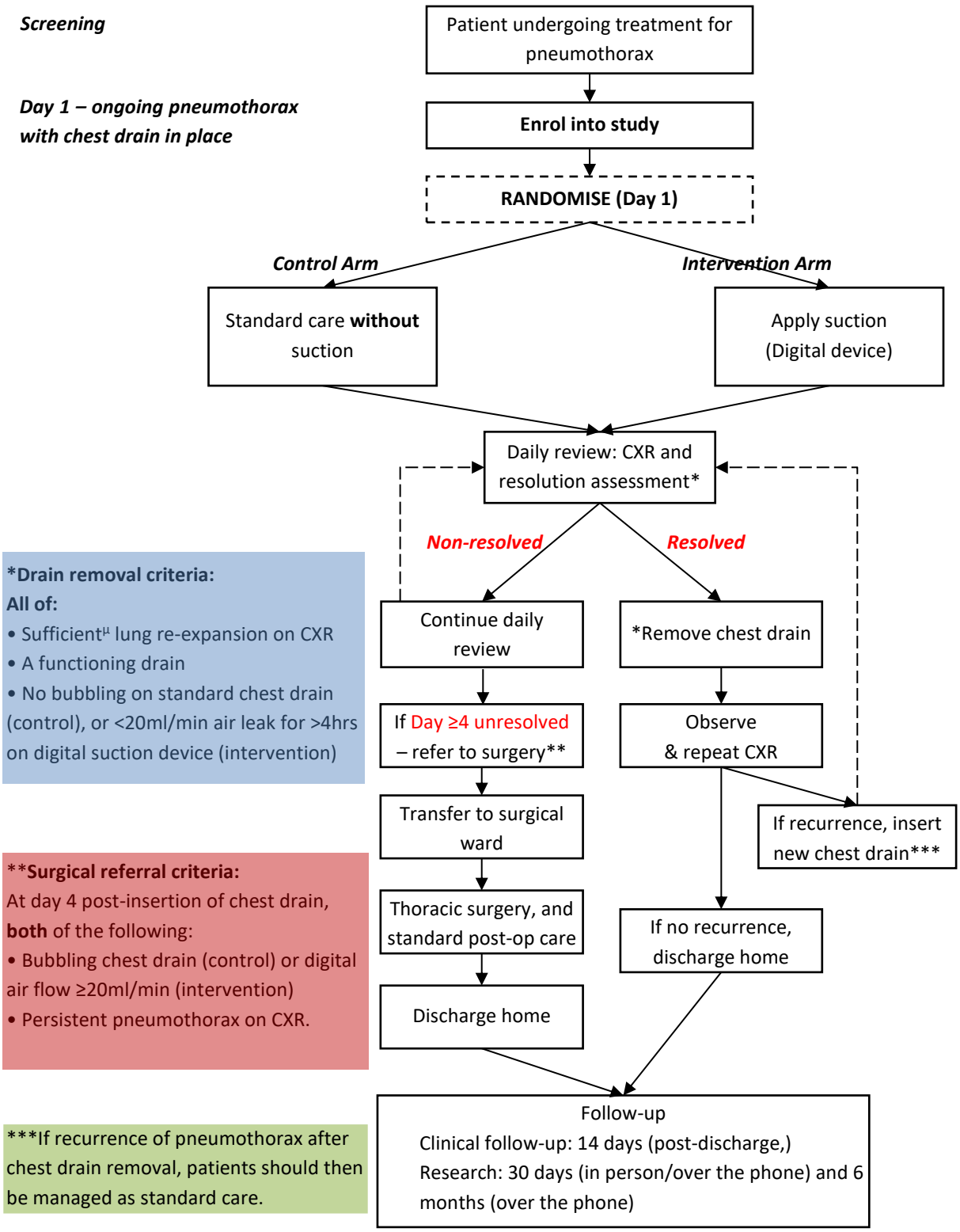
	Green	Amber	Red
Number centres opened	>14	10-14	<10
Number randomised/centre/month	≥0.45	0.3-0.44	<0.3
Adherence to allocated intervention group	95-100%	90-94%	<90%
Completion of primary outcome	98-100%	80-97%	<80%
Attrition rate*	≤4%	4-5%	>5%

* Up to 30 days

If all criteria are green, we will proceed to a full trial with the same protocol; if one or more criteria are amber, we will propose adaptions to address the short fall; if one or more criteria are red, we will discuss with the TSC whether the full trial is feasible.

Main phase 2 (23 months): At least 36 sites recruiting the remaining 370 participants over 23 months.

Figure 2: Trial flowchart



μ:"Sufficient lung re-expansion" is defined as complete or almost complete re-expansion (only a very small (<1cm) rim of air apically) on CXR.

8. PARTICIPANT IDENTIFICATION

8.1. Study Participants

Participants with primary spontaneous pneumothorax (PSP) requiring chest drain who are being treated in hospital.

8.2. Inclusion Criteria

- Participants with primary spontaneous pneumothorax (PSP) (either first or recurrent episode)
- Male and female 16* to 50 years old (consistent with guidelines(18)
- Pneumothorax requiring chest drain in hospital (ideally within 24 hours of drain insertion, but up to 72 hours))
- Willing and able to give written consent
- Access to electronic device for questionnaire completion.

**Common law presumes that young people aged between 16 and 18 are usually competent to give consent to treatment and consent from those with parental responsibility is not legally necessary. Eligible young persons believed to be competent by the PI or delegate should be approached about the study. The involvement of parents in decision-making should be encouraged unless the young person objects.*

8.3. Exclusion Criteria

The participant may not enter the trial if ANY of the following apply:

- Known or suspected underlying lung disease**. This does not include the presence of blebs / bullae on CT chest in the absence of another specific respiratory diagnosis
- Inability to consent or comply with trial requirements
- Any other significant disease or disorder which, in the opinion of the Investigator, may either put the participants at risk because of participation in the study, or may influence the result of the trial, or the participant's ability to participate in the study.

**"Childhood asthma" is not considered an exclusion criterion. Patients with a diagnosis of asthma in childhood/young adulthood who do not require the use of a regular "preventer" inhaler (i.e. inhaler containing a steroid or long-acting beta-agonist), and only occasionally use a "reliever" inhaler (short-acting beta-agonist) and have never been hospitalised due to asthma remain eligible for participation in this study.

9. PROTOCOL PROCEDURES

9.1. Recruitment

Research sites

Research sites will be selected through the research and pleural research networks.

Participants

Patients will be identified by screening new admissions to general medical and respiratory wards.

9.2. Screening and Eligibility Assessment

Patients will be screened for eligibility as per criteria listed above (8.1 and 8.2). No screening procedures are required prior to informed consent.

Patients should ideally be enrolled within 24 hours of chest drain insertion but may be enrolled up to 72 hours to allow for out of hours/weekend admissions. Timing of chest drain insertion will be documented on the Completion of Treatment CRF.

The Clinical Trial Co-ordinator based at ORTU will be on call for advice and to assist with enrolment during office hours locally (Oxford). At trial set-up, training will be provided for research teams, senior respiratory and medical staff (if requested) at each site with regards to the trial protocol and familiarity with the use of digital suction devices to allow recruitment to occur outside office hours.

9.3. Informed Consent

Once an eligible patient is identified and agrees to participate in the study, the patient must personally sign and date the latest approved version of the Informed Consent form before any trial specific procedures are performed.

Written and verbal versions of the Patient Information Leaflet and Informed Consent will be presented to the patients detailing no less than: the exact nature of the trial; what it will involve for the patients; the implications and constraints of the protocol; the known side effects and any risks involved in taking part. It will be clearly stated that the patient is free to withdraw from the trial at any time for any reason without prejudice to future care, without affecting their legal rights and with no obligation to give the reason for withdrawal. Sufficient time for consideration by the patient will be given prior to consent, but there is no minimal time of consideration required, given the nature of this study.

Written Informed Consent will then be obtained by means of patient dated signature and dated signature of the person who presented and obtained the Informed Consent. The person who obtained the consent must be suitably qualified and experienced and have been authorised to do so by the Chief/Principal Investigator. A copy of the signed Informed Consent will be given to the patient and a copy will be placed in their medical notes. The original signed form will be retained at the trial site.

9.4. Randomisation

Patients will be randomised 1:1 to either suction or standard care, via centralised web-based randomisation system (Sortition), with stratification by centre and initial size of pneumothorax (≥4cm vs <4cm).

If sites are unable to randomise online, they will be able to contact ORTU to randomise online on their behalf. A paper-based emergency randomisation procedure will be held by the Chief Investigator (or delegate) if the online system is unavailable.

Randomisation will occur immediately, by PI or delegate, after informed consent is given.

9.5. Blinding and code-breaking

As this study is open label due to pragmatic constraints, consideration has been given to ensure lack of bias for the primary outcome. We will here utilise objective, robust and precisely measurable parameters, which inform the key outcome decisions: time of drain removal and the need for surgery will be based on objective decision-making criteria (see below). No blind breaking procedures are therefore required.

9.6. Description of study intervention(s), comparators and study procedures (clinical)

9.6.1. Description of study intervention(s)

Intervention group: Suction

The chest drain will be connected to digital suction on as soon as possible post randomisation. To ensure consistency across sites, suction will be provided by a digital suction device, not specific to a single manufacturer, depending on local experience. If centres do not have digital suction devices, these (and consumables) will be provided for use in the trial, along with training for research and clinical staff. This training initially will be provided by Rocket Medical UK representatives and the central research team (CI and delegates). Ongoing training will be facilitated by Rocket representatives, central trial coordinator in collaboration with local PIs.

Suction will be incrementally increased as per a trial specific procedure: starting at -1.0kPa (-10cm H_20, -7.5mmHg), increasing to -1.5kPa and then -2.0kPa as tolerated, every 2-4 hours). Suction should be reduced on the basis of specific criteria (pain, complications). Adherence will be documented on daily clinical review CRFs.

No single device will be required or promoted as part of the study, to maintain pragmatic delivery in centres, and to test the treatment intention of digitally delivered suction, rather than a specific device.

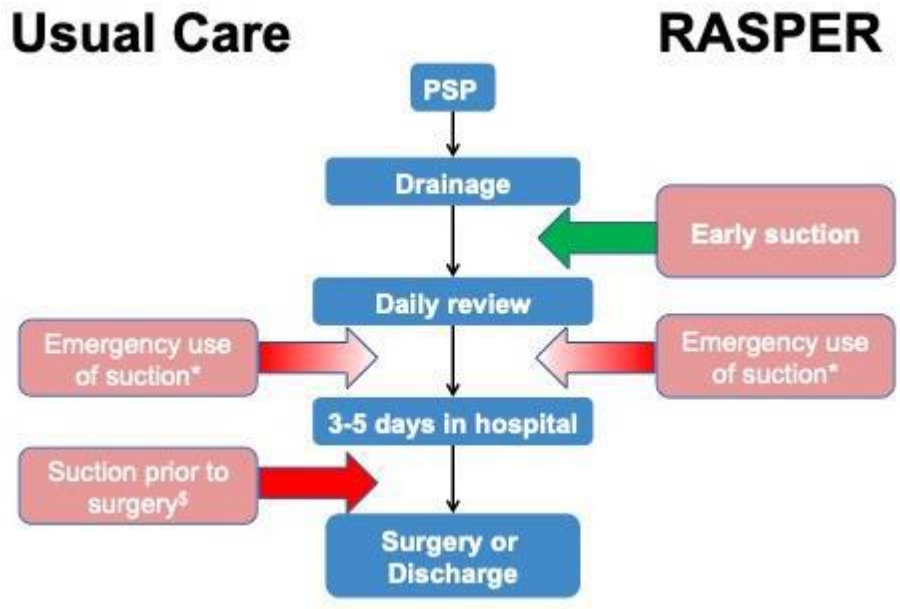
9.6.2. Description of comparator(s)

Comparator: Usual care

The chest drain will be managed as per BTS guidelines(1), without the use of suction (i.e. connected to an underwater seal bottle) unless suction is clinically indicated for safety reasons. Suction is used in some cases of PSP where the air leak is too large to be drained by the in-situ chest drain – in this situation (i.e. bubbling chest tube by worsening patient parameters and physiology), suction is indicated, and will be permitted for safety reasons at any point in this study, and carefully documented. Internal audit data suggests that <2% of the population will required such use of suction, but this design ensures safety across the study.

If suction is applied to patients in the usual care arm, this will be recorded in the CRF, but patients will not be required to withdraw from the study and nor does this constitute a protocol deviation.

Figure 3 demonstrates how suction is applied in usual care and in the proposed study.



*Emergency suction can be used in where the air leak is too large to be drained by the in situ chest drain e.g. enlarging pneumothorax (and worsening patient parameters) or worsening subcutaneous emphysema. $At the request of thoracic surgical team."

9.6.3. Description of study procedure(s)

Figure 4 – Study procedures

Procedures		**Visits: Daily in hospital, plus 3 follow-up^**				
	In hospital			**Follow-up**		
	Baseline (Enrolment)	**Daily review to discharge**	**Discharge/ Completion of Treatment**	**14 days (+/- 3 days)***	**30 days (+ up to 7 days) ^**	**6 months (+/- 2 weeks)^**
Informed consent	X					
Demographics	X					
Medical history	X				X	
Randomisation	X					
Application of suction (intervention group)	X					
Pain and breathlessness (VAS) score	X	X	X	X	X	X
Health status (EQ5D)	X		X	X	X	X
Adverse event assessments		X				
Recording complications		X				
CXR		X				
Removal of drain (if criteria met)		X				
Referral for surgery (if criteria met – from day 4 onwards)		X				
Record number of pleural procedures			X			
Follow-up: Recurrence of pneumothorax, reattendance to hospital and other healthcare usage				X	X	X
Number of days off work			X	X	X	

* 14 day clinical follow-up post-discharge from hospital (+/- 3 days) in person/phone

^ 30 day (+ up to 7 days) person/phone and 6 month (+/- 2 weeks) post-randomisation follow-ups can occur by telephone

Chest drain removal criteria

All participants will be reviewed daily by clinical staff to document the criteria below. Drain removal will only occur when **all** of the following are met:

1. Sufficient$^{\mu}$ lung re-expansion on CXR
2. A functioning drain
3. No bubbling on standard chest drain (control arm), or air leak <20ml/min for >4hrs using digital suction device (intervention arm)

μ: "Sufficient lung re-expansion" is defined as complete or almost complete re-expansion (only a very small (<1cm) rim of air apically) on CXR.

Surgical Referral / Failure of Medical Treatment

25% of patients with PSP will not respond to initial (chest drain +/- suction) treatment and require surgical intervention as in-patients(20). During site set up, the RASPER study should be discussed with local thoracic team to make them aware of the potential to be referred patients with or without the prior use of suction.

Objective criteria for referral to thoracic surgery are the following (as per BTS guidelines(18)) which will be documented on the eCRF:

1. On or after Day 4 post-chest drain insertion
2. Persistent air leak as evidenced by bubbling chest drain (control) or digital air flow >20ml/min (intervention) AND/OR
3. Persistent pneumothorax on CXR$^{\mu}$

Respiratory PIs will refer patients for surgery informing surgical colleagues that there is a persistent pneumothorax and air leak, and that the patient is in the RASPER study. Patients referred for surgery will be assessed by the local thoracic surgical team. For pragmatic reasons, surgeons cannot be blinded as to the use of suction, but patients should be managed as per usual local practice, regardless of the prior use to suction or not. The criteria for acceptance or refusal for surgery will be documented. As per current clinical practice, if the pneumothorax resolves whilst waiting for surgery, the drain can be withdrawn (as per objective criteria above) and the patient discharged in either arm.

Urgent Surgery

In the unlikely event of a serious complication from drain insertion (e.g. haemorrhage) or physiological instability from pneumothorax despite a functioning drain and suction, referral to thoracic surgery may occur at any point in the trial process and in either arm for safety reasons. This will be managed according to normal clinical pathways and requirements and documented in the CRF.

9.7. Baseline Assessments

Baseline characteristics collected:

- Demographics (sex, age, height, weight, ethnicity)
- Past medical history, including previous pneumothoraces
- Family history
- Drug history
- Clinical observations
- Smoking history (tobacco and marijuana)

- Quality of life (EQ5D)
- Pain and breathlessness scores on 100mm Visual Analogue Scale (VAS)

9.8. During hospital stay

The patient will be reviewed daily whilst in hospital and at Completion of Treatment (discharge home from hospital with no drain in place). Data will be collected as per Figure 4.

9.9. Subsequent Visits

Short term

Follow-up at 14 days (+/- 3 days) post-completion of treatment (as per guidelines(18)) and 30 days (+ up to 7days) post-randomisation, in person or by telephone, will collect data as per Figure 4. VAS and EQ5D will be completed online by the patient via a link to the online database.

Long term (recurrence)

The 6-month (+/- 2 weeks) follow up will occur by phone. This methodology will avoid the need for long-term follow-up in this patient group who frequently do not attend. To ensure delivery of the study within the time window and to keep costs down, we will adopt a strategy where those recruited in the last 3 months of recruitment are followed up at 30 days only (for the primary outcome and major secondary outcomes) but not followed up to 6 months.

9.10. Sample Handling

No samples will be taken specifically for this study.

9.11. Early Discontinuation/Withdrawal of Participants

During the course of the trial a participant may choose to withdraw early from the trial treatment at any time. This may happen for a number of reasons, including but not limited to:

- The occurrence of what the participant perceives as an intolerable AE
- Inability to comply with trial procedures
- Participant decision

Participants may choose to stop treatment and/or study assessments but may remain on study follow-up.

Participants may also withdraw their consent, meaning that they wish to withdraw from the study completely. Participants will have the following two options for withdrawal:

1) Participants may withdraw from active follow-up and further communication but allow the trial team to continue to access their medical records and any relevant hospital data that is recorded as part of routine standard of care, i.e., demographics, clinical parameters, radiology, blood results and evidence of pneumothorax recurrence on subsequent hospital visits.

2) Participants can withdraw from the study but permit data obtained up until the point of withdrawal to be retained for use in the study analysis. No further data will be collected after withdrawal.

The type of withdrawal and reason for withdrawal will be recorded in the CRF.

If the participant is withdrawn due to an adverse event, the Investigator may arrange for follow-up visits or telephone calls until the adverse event has resolved or stabilised.

9.12. Definition of End of Study

The end of trial is the point at which all the data has been entered, queries resolved and data lock complete.

10. SAFETY REPORTING

The safety-reporting window for this trial begins at time of randomisation and **ends 48 hours after completion of treatment** (i.e. 48 hours post all drain removals).

Definition of Serious Adverse Events

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 a serious adverse event when, based upon appropriate medical judgement, the event may jeopardise the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.

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.

Foreseeable

The following are considered to be foreseeable events associated with usual care (chest drain insertion for pneumothorax) and the proposed trial interventions for this trial:

- Pain
- Minor haemorrhage (i.e. not requiring any specific intervention such as surgery or blood transfusion)
- Subcutaneous emphysema
- Pleural infection
- Unintentional removal ("falling out")

- Recurrence of pneumothorax/worsening of on-going pneumothorax (if no evidence it fully resolved)
- Re-expansion pulmonary oedema
- Any further (non-emergency) pleural procedure required including thoracic surgery for pneumothorax

The foreseeable events listed above, even if deemed to be serious, are not required to be reported as SAEs, but should be recorded in the CRFs.

10.1. Reporting Procedures for Serious Adverse Events

Any SAE considered **not related** to the study intervention by the local investigator does not require expedited reporting but will be recorded on the appropriate CRF and marked as 'serious but not reportable' and uploaded to the database as soon as practicable.

SAEs that are considered **possibly, probably or definitely related** to the study intervention (i.e. the procedure conducted for the study) will be reported on the relevant reporting form (PM124-A Serious Adverse Event Report Form (non-CTIMPs)) and emailed to ORTU within 24 hours of the local site team becoming aware of the event. ORTU will perform an initial check of the report, request any additional information, ensure it is reviewed by a nominated Medical Reviewer.

Related SAEs that occur in the standard care arm will be documented in the CRF and reviewed periodically by the DSMC but will not require further review or expectedness assessment.

For SARs occurring in the interventional arm, the ORTU Medical Reviewer will assess expectedness against the table of foreseeable events. The event will also be reviewed at the next DSMC meeting. Additional and further requested information (follow-up or corrections to the original case) will be detailed on a new SAE Report Form and scanned/emailed to ORTU.

The safety-reporting window for this trial begins at time of randomisation and **ends 48 hours after completion of treatment** (i.e. 48 hours post all drain removals).

During the defined reporting period, a serious adverse event (SAE) occurring to a participant should be reported to the REC that gave a favourable opinion of the study where in the opinion of the Chief Investigator (or delegate) the event was 'related' (resulted from administration of any of the research procedures) and 'unexpected' in relation to those procedures. Reports of related and unexpected SAEs should be submitted within 15 working days of the Chief Investigator becoming aware of the event, using the HRA report of serious adverse event form (see HRA website)).

11. STATISTICS AND ANALYSIS

11.1. Statistical Analysis Plan (SAP)

The study results will be reported in accordance with the CONSORT 2010 statements and a full detailed statistical analysis plan will be prepared by a statistician, independent of this trial, before the first unblinding of data.

11.2. Description of the Statistical Methods

Baseline variables will be presented by randomised group using frequencies (with percentages) for binary and categorical variables and means (and standard deviations) or medians (with lower and upper quartiles) for continuous variables. There will be no tests of statistical significance nor confidence intervals for differences between groups on any baseline variables.

The primary estimand is the mean difference in the primary outcome (total duration of treatment) for all randomised participants, as defined by protocol eligibility criteria, regardless of what intervention they actually received or compliance of intervention. Duration of treatment in previous studies has shown to be skewed. For this reason, we will explore the appropriate method to analyse the primary outcome. For example, a regression model will be fitted to the data with total duration of treatment adjusting for stratification variables (centre and size of pneumothorax) to assess any violation of assumptions. If assumptions are satisfied, then treatment group will be added to the regression model to assess the treatment effect. If the assumptions of the linear regression are violated an alternative method will be used, such as quantile regression adjusting for stratification variables. In this case the median treatment duration for each arm with interquartile range (IQR), the adjusted difference and 95% confidence interval (CI) will be reported.

For secondary outcomes collected at repeated time (e.g. 30 days and 6 months), a linear mixed effect model will be used for continuous outcomes and generalized linear mixed effect model for binary outcomes. The model will include a random intercept for each participant to account for the repeated measures on the same participant and an interaction term for the treatment by time interaction to allow the treatment effect to differ at each time point. Safety outcomes will be compared using Fisher's Exact or Chi-square tests. Pre-specified subgroup analyses of the primary outcome will be explored by size of pneumothorax, first or recurrent episode, and smoking status.

Missing data will be reported, with reasons where available, and the missing data mechanism explored. We will carry out additional sensitivity analyses, adjusting for covariates that are related to the missingness and, where appropriate, using imputation methods, such as multiple imputation for missing data.

11.3. Sample Size Determination

Data from 107 patients in the usual care arm of the RAMPP trial informs the sample size calculation(20). In patients who required admission to hospital with a chest drain in situ at day 1 (59/107, 55.1%), median duration of treatment was 6.0 days (IQR 3.0-11.0, mean 7.2, SD 4.7) (20).

The superiority margin for a reduction in length of in hospital treatment was chosen as 1.5 days (from a mean of 7.2 days) based upon a survey of expert clinicians. This difference was deemed to be clinically meaningful and would alter current practice (i.e. demonstration of this improvement in treatment duration would promote the routine use of suction in PSP). Thus, the expected mean in the intervention group is 5.7 and in the control group is 7.2 (common SD of 4.7). Using an adjustment to account for use of Wilcoxon–Mann–Whitney for non-parametric data, an alpha of 0.05 and power of 90%, the required sample size is 436 patients randomised 1:1. Assuming a 3% data attrition rate(18), a total of 450 patients will be recruited.

11.4. Analysis populations

All primary and secondary outcomes will be carried out on an intention to treat basis (i.e. patients will be analysed according to their randomised treatment arm, irrespective of what treatment they received).

11.5. Decision points

A blinded interim review (not comparative analysis) of the primary outcome (hospital stay) will be undertaken after approximately 50% patients have been recruited to assess the assumptions made in the sample size calculation (and preventing the need for p-value adjustment in the final analysis). This analysis will be reviewed by the DMC who will make recommendations regarding any necessary changes to the sample size required. No correction of the significance level of the final analysis is planned on this single non-comparative assessment of early event rate by the DMC.

11.6. Stopping rules

No formal stopping rules, other than conventional stopping rules in case of a DMC guided safety signal, are planned.

11.7. The Level of Statistical Significance

The results from the trial will be presented as comparative summary statistics (odds ratios, difference in medians or means) with 95% confidence intervals. All tests will be done at a 5% two-sided significance level. The study results will be reported in accordance with the CONSORT 2010 statements and a full detailed statistical analysis plan will be prepared by a statistician, independent of this trial, before the first unblinding of data.

11.8. Procedure for Accounting for Missing, Unused, and Spurious Data.

Missing data will be reported, with reasons where available, and the missing data mechanism explored. Missing primary outcome data will be presented by randomised group and baseline characteristics associated with missing data will be explored. Logistic regression models will be used to determine which baseline variables are associated with missing outcome data, and a sensitivity analysis, adjusting for covariates related to missingness will be carried out. Where appropriate, imputation methods such as multiple imputation for missing data may be considered.

11.9. Procedures for Reporting any Deviation(s) from the Original Statistical Plan

Any deviations from the statistical analysis plan will be clearly described and justified in the statistical analysis report.

11.10. Health Economics Analysis

The study results will be reported in accordance with the CHEERS statements(27) and a health economics analysis plan (HEAP) will be prepared by a health economist, before the completion of the data.

Data collection

Generic health-related quality of life (HRQoL)

HRQoL will be measured using the Euroqol-5 Dimensions 5-levels (EQ-5D-5L) questionnaire. The EQ-5D-5L will be administered at baseline, completion of treatment, 30-days and 6 months post-randomisation. The 30-day and 6-month follow-up will be undertaken by telephone. Responses will be converted into utilities following NICE's latest recommendation, Currently NICE recommended using a mapping function between EQ-5D-5L and EQ-5D-3L tariffs estimated from a representative sample of the UK population (28).

Quality Adjusted Life Years

In order to keep the trial as pragmatic as possible, avoid overburdening patients with multiple questionnaires over a long-period of follow-up and in a bid to keep missing information to a minimum, EQ-5D information will not be collected past 30 days after randomisation. This decision has been justified by finding from the RAMPP trial which concerned similar population as the current study. For example, despite best efforts to minimise missing data at follow-up, only 48% (109/227) completed an EQ-5D questionnaire at 12-months. At this follow-up, 83% reported utility values higher than 0.8, 62% (67/109) reported being in perfect health with utility value being 1.

Therefore, we will extrapolate 30-day EQ-5D utility in RASPER to utilities at 6 months follow up using data from the RAMPP trial, which sampled patients from the same population as RASPER. For this, we will model the association between 30-day and 6-month EQ-5D utility in RAMPP, adjusting for age, gender and history of pneumothorax.

Survival information collected from the trial will be combined with EQ-5D utilities to generate Quality Adjusted Life-Years (QALYs), the outcome measure preferred by the National Institute for Health and Clinical Excellence (NICE) (29).

Healthcare resource use and costs. The perspective adopted in the economic analysis will be that of the National Health Service (NHS). For this perspective we will include the costs associated with the following healthcare resource use categories from randomisation to 30 days and 6-month follow-up:

- Initial procedures for the treatment of spontaneous pneumothorax (including, aspiration, and /or standard chest tube insertion)
- Application of digital suction
- Initial length of stay following spontaneous pneumothorax
- Subsequent procedures for pneumothorax (including thoracic surgery)
- Subsequent stays in hospital or day cases due to any reason
- Accident and emergency (A&E) visits
- Secondary outpatient care visits

Given that costs due to primary and community care visits accounted for less than 2% (£70/£4,115) of total NHS costs in RAMPP, and with no indication these will likely vary between the two treatment groups in RASPER, information on primary and community visits will not be collected.

Costs of performing the initial and subsequent procedures to treat pneumothorax will be obtained from the micro-costing of procedures undertaken in RAMPP. All other resource use will be obtained from local centres via follow-up CRF. We will obtain Health Resource Group (HRG) codes for each contact using the latest NHS Digital HRG4+ Reference Cost Grouper. HRGs will then be mapped to NHS Reference costs, to

obtain the costs of each contact. To avoid double counting the costs of procedures for pneumothorax, we will remove the procedure codes for hospitalisations with a code for treatment of pneumothorax. In sensitivity analyses, costs will be assessed using NHS reference costs only.

Wider economic costs.

In RAMPP, over the 12-month follow-up, each patient reported an average of 24 (95% CI: 17 to 32) days off work, with half of these days lost in the first month of follow-up. In RASPER, a short questionnaire will be provided on the total number of days off work lost at 30 days post randomisation. As with utility, we will extrapolate 30-day days off work in RASPER to 6 months using data from the RAMPP trial. Days off work will be valued using Office for National Statistics data on mean daily earnings in the UK.

Cost-effectiveness analysis. The perspective adopted in the economic evaluation will be that of the NHS, therefore productivity losses will not be included in the base case analysis. However, in a sensitivity analysis we will assess the impact of including these costs on the cost-effectiveness results.

An economic evaluation adherent to guidelines for good economic evaluation practice will be undertaken integral to the main trial (30, 31). A within-trial cost-utility analysis will explore the incremental cost per QALY gained by early use of digital suction when compared to usual care with no use of suction. Cost and effect results will be reported as means with standard deviations, with mean differences between the two patient groups reported alongside 95% confidence intervals (95% CI). Missing data will be imputed using recommended multiple imputation methods Royston (32) with results from this analysis being presented as an additional sensitivity analysis. Incremental cost-effectiveness will be calculated by dividing the difference in costs by the difference in effects. Uncertainty around the incremental cost-effectiveness ratio will be explored using non-parametric bootstrapping briggs (33). Base case analysis will focus on the time duration of 30 days after randomization. Exploratory analysis will include the time duration to 6 months after randomization for long term effects.

12. DATA MANAGEMENT

The data management aspects of the study are summarised here with details fully described in the Data Management Plan.

12.1. Source Data

Trial site staff will collect data from direct patient questioning and patient records. Data will then be entered onto eCRFs (a secure, validated, GCP-compliant electronic data management system). VAS and EQ5D data will be submitted on patients' own devices via a secure web platform into a GCP-compliant electronic data management system. All staff performing data entry at site will be appropriately trained prior to access being granted. Study staff's access to all systems is controlled by individual user accounts, and a full audit trail is kept of all modifications made to data. The study databases will be hosted on a University of Oxford server. The database will be backed up at least daily.

Standard Operating Procedures (SOPs) will be followed to ensure quality control. The processes for validation of study data will be detailed in the data management plan, and other associated documents. The Chief Investigator and/or Principal Investigator will facilitate access to study records for the purpose

of monitoring, audits, and regulatory inspections. Patients' consent to this will be sought at the time of enrolment into the study.

The participants will be identified by a unique trial specific number and/or code in any database. Participant identifiable details (name and telephone number) will be stored locally in password protected files, accessed only by nominated research staff, to facilitate contact with participants at the non-face-to-face follow-up visit.

12.2. Access to Data

Direct access will be granted to authorised representatives from the Sponsor and host institution for monitoring and/or audit of the study to ensure compliance with regulations.

12.3. Data Recording and Record Keeping

All trial data will be entered onto eCRFs in a web-based database by trained site staff. Installation Qualification, Operational Qualification, Upgrade Qualification and Performance Qualification are performed. The clinical database will be designed and tested in this environment prior to recruitment and will include custom data validation rules embedded to enhance data quality management.

The participants will be identified by a unique trial specific number and/or code in any database. The name and any other identifying detail will NOT be included in any trial data electronic file.

The data entered onto the database and will be regularly monitored for quality and queries will be sent to sites as part of data management activities. Final data cleaning will happen after last patient's last visit with confirmation of completion from sites.

A first data export will be shared with the trial statistician(s) for the planned interim analysis (see section 11.5) and prior to database lock for an opportunity to raise queries and a final dataset export will be planned after database lock. This data will be sent in a pre-agreed format using secure FTP (OxFile or similar).

Data will be retained in accordance with ORTU and PCCTU SOP's/local procedures, through an archiving service as outlined in section 19, and will be retained in accordance with regulatory requirements for a minimum of 5 years after termination of the trial. After publication, anonymised data will be shared upon responsible request to the CI from researchers with bone fida research proposals (e.g. for a systematic review).

13. QUALITY ASSURANCE PROCEDURES

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

13.1. Risk assessment

The trial will be conducted in accordance with the current approved protocol, GCP, relevant regulations and standard operating procedures. A risk assessment and monitoring plan will be prepared before the

study opens and will be reviewed as necessary over the course of the trial to reflect significant changes to the protocol or outcomes of monitoring activities.

13.2. Study monitoring

Monitoring will be performed if required, according to the trial specific Risk Assessment and Monitoring Plan. Data will be evaluated for compliance with the protocol and accuracy in relation to source documents as these are defined in the trial Risk Assessment and Monitoring Plan.

13.3. Study Committees

Trial Management Group (TMG)

The trial will be led by the Chief Investigator (RH) and collaborator (NR) and the Oxford Respiratory Trials Unit (ORTU) in collaboration with the Primary Care Clinical Trials Unit (PCCTU), which is part of Oxford Primary Care and Vaccines Collaborative Clinical Trials Unit (UKCRC registered trials unit). A central Trial Management Group (TMG) will oversee the day-today co-ordination and progress of the trial, managing any key issues and tasks to be addressed. A regular meeting will occur every month throughout the trial involving key team members.

Trial Steering Committee (TSC)

A TSC will be convened to keep oversight of the trial. A charter will be written explaining the role of the TSC and each of its members. All members are required to sign a declaration of their participation. The charter will define how often the committee will meet during the study.

Data Monitoring Committee (DMC)

An independent DMC will be established to assess safety signals over the course of the trial, with the expectation of meeting at least 6 monthly, and as needed in response to safety concerns from the TSC. The aims of this committee review 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

14. PROTOCOL DEVIATIONS

A study related deviation is a departure from the ethically approved study protocol or other study document or process (e.g. consent process or administration of study intervention) or from Good Clinical Practice (GCP) or any applicable regulatory requirements. Any deviations from the protocol will be documented in a protocol deviation form and filed in the study master file.

A standard operating procedure should be in place describing the procedure for identifying non-compliances, escalation to the central team and assessment of whether a non-compliance /deviation may be a potential Serious Breach.

15. SERIOUS BREACHES

A "serious breach" is a breach of the protocol or of the conditions or principles of Good Clinical Practice which is likely to affect to a significant degree –

(a) the safety or physical or mental integrity of the trial subjects; or

(b) the scientific value of the research.

If a serious breach is suspected the Sponsor must be contacted within 1 working day. In collaboration with the C.I., the serious breach will be reviewed by the Sponsor and, if appropriate, the Sponsor will report it to the approving REC committee and the relevant NHS host organisation within seven calendar days.

16. ETHICAL AND REGULATORY CONSIDERATIONS

16.1. Declaration of Helsinki

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

16.2. Guidelines for Good Clinical Practice

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

16.3. Approvals

Following Sponsor approval, the protocol, consent form, participant information sheet will be submitted to an appropriate Research Ethics Committee (REC), and host institutions for written approval.

The Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

16.4. Co-enrolment

Patients may be co-enrolled into other pneumothorax trials that do not impact the intervention or primary outcome in this study, at the discretion of the local PI.

16.5. Other Ethical Considerations

There are no other general or trial-specific ethical considerations.

16.6. Reporting

The CI shall submit once a year throughout the study, or on request, an Annual Progress report to the REC Committee, HRA (where required) host organisation, Sponsor and funder (where required). In addition, an End of Study notification and final report will be submitted to the same parties.

16.7. Transparency in Research

Prior to the recruitment of the first participant, the trial will have been registered on a publicly accessible database.

Where the trial has been registered on multiple public platforms, the trial information will be kept up to date during the trial, and the CI or their delegate will upload results to all those public registries within 12 months of the end of the trial declaration

16.8. Participant Confidentiality

The study will comply with the UK General Data Protection Regulation (GDPR) and Data Protection Act 2018, which require data to be de-identified as soon as it is practical to do so. The processing of the personal data of participants will be minimised by making use of a unique participant study number only on all study documents and any electronic database(s), except for the CRF, where participant initials may be added. All documents will be stored securely and only accessible by study staff and authorised personnel. The study staff will safeguard the privacy of participants' personal data.

16.9. Expenses and Benefits

Reasonable travel expenses for any visits additional to normal care will be reimbursed on production of receipts, or a mileage allowance provided as appropriate.

17. FINANCE AND INSURANCE

17.1. Funding

Funding has been awarded by the NIHR HTA (ref 133787).

17.2. Insurance

The University has a specialist insurance policy in place which would operate in the event of any participant suffering harm as a result of their involvement in the research (Newline Underwriting Management Ltd, at Lloyd's of London). NHS indemnity operates in respect of the clinical treatment that is provided.

17.3. Contractual arrangements

Appropriate contractual arrangements will be put in place with all third parties.

18. PUBLICATION POLICY

The preparation of a manuscript for rapid publication will be a priority for and sole responsibility of the Trial Management Group, under the overall supervision of the Chief Investigator. The Trial Management

Group will also take responsibility for reviewing drafts of any manuscripts, abstracts, press releases and other publications arising from this study. It is anticipated that an initial report would be completed within six months of the study's closure. The Trial Management Group will approve a definitive manuscript detailing the final overall results of the study. Raw data from the study will be made accessible to the public on request once the study has been completed and final results been published.

All publications will include a list of investigators, and named authors will include the study's Chief Investigator, Key Investigator, Statistician and Trial Manager as a minimum. Authors will be determined in accordance with ICMJE guidelines and other contributors to the study will be acknowledged. Authors will acknowledge that the study has been funded by the NIHR and sponsored by the University of Oxford, UK.

19. DEVELOPMENT OF A NEW PRODUCT/ PROCESS OR THE GENERATION OF INTELLECTUAL PROPERTY

Not applicable.

19. ARCHIVING

All trial documentation held within the eTMF will be archived in accordance with ORTU SOP's at Restore Datacare. Recruiting sites will be responsible for their own archiving of site documentation.

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21. APPENDIX A: AMENDMENT HISTORY

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

List details of all protocol amendments here whenever a new version of the protocol is produced.

Protocol amendments must be submitted to the Sponsor for approval prior to submission to the REC committee and HRA (where required).