LONGITUDINAL INVESTIGATION OF SECONDARY PNEUMOTHORAX (LISP)

CHIEF INVESTIGATOR & RESEARCH TEAM CONTACT DETAILS

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SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928) and any subsequent amendments of the clinical trial regulations, GCP guidelines, the Sponsor's (and any other relevant) SOPs, and other regulatory requirements as amended.

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

I also confirm that I will make the findings of the trial publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the trial will be given; and that any discrepancies and serious breaches of GCP from the trial as planned in this protocol will be explained.

Chief Investigator:

Signature:

..... Date: ...../...../.....

Name: (please print):

.....

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Contents

LIST OF ABBREVIATIONS

COPD	Chronic obstructive pulmonary disease
CT	Computed tomography
CXR	Chest X-Ray
DAL	Digital air leak
EQ-5D-5L	EuroQol 5D Health Questionnaire
ICD	Intercostal chest drain
NBT	North Bristol NHS Trust
PAL	Persistent air-leak
PIS	Participant information sheet
PPI	Patient and public involvement
PSP	Primary spontaneous pneumothorax
PS	Performance status
SP	Spontaneous pneumothorax
SSP	Secondary spontaneous pneumothorax
VAS	Visual Analogue Scale

TRIAL SUMMARY

Trial title	LONGITUDINAL INVESTIGATION OF SECONDARY PNEUMOTHORAX
Short title	LISP
Trial design	Longitudinal observational study
Trial participants	Population of interest: patients presenting to hospital with secondary spontaneous pneumothorax
Planned recruitment rate	60 patients/year minimum
Planned trial period	1 years
Trial objectives	To determine the characteristics, healthcare burden, management, and outcomes of secondary spontaneous pneumothorax (SSP) in UK over a 1-year period
Inclusion criteria	Emergency attendance to hospital with secondary spontaneous pneumothorax, confirmed by radiology, with SSP defined as: • spontaneous pneumothorax in presence of known or suspected lung disease OR • spontaneous pneumothorax in patient ≥50 years of age and smoking history
Exclusion criteria	Exclusion • age <16 years of age • iatrogenic pneumothorax • traumatic pneumothorax

FUNDING AND SUPPORT:

Funders	Financial and non-financial support given
Rocket Medical plc Imperial Way Watford WD24 4XX Tel: 01923 651 400	Unrestricted research grant and equipment

Role of trial Sponsor and Funder:

The Sponsor and Funders have no role or remit in the trial design, conduct, data analysis and interpretation, manuscript writing or dissemination of results.

Protocol contributors:

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External Peer review

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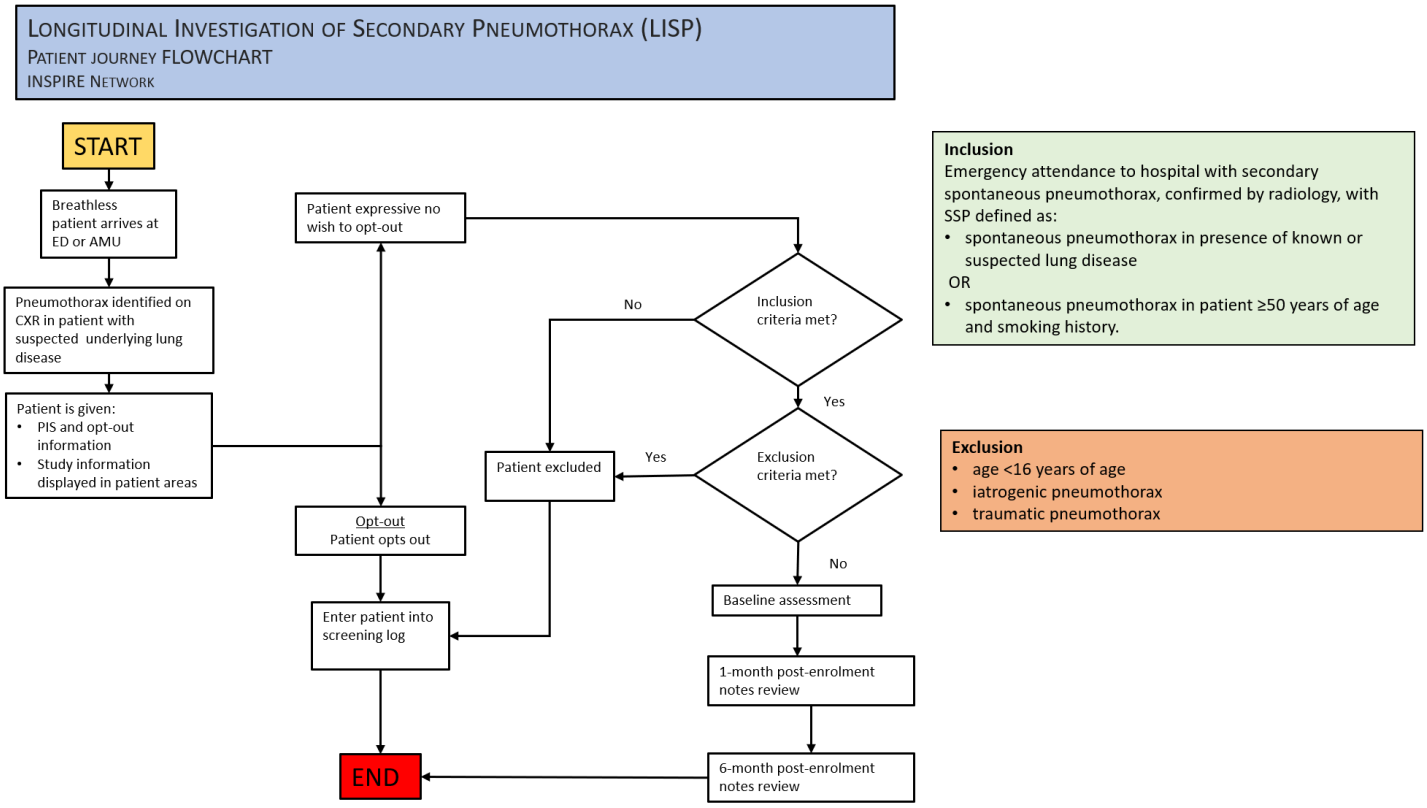
STUDY FLOW CHART



PLAIN ENGLISH SUMMARY

Background

Secondary spontaneous pneumothorax (SSP) is a medical emergency where an abnormal collection of air develops in the space between the lung and the chest wall, causing lung collapse. This occurs in patients with existing lung disease such as Chronic obstructive pulmonary disease (COPD). In the UK, patients with SSP are usually treated by inserting a drain into the chest to remove the air. The drain is stitched in place and left until the air is completely removed. The drain typically remains in place for over a week, leading to long hospital stays. Sometimes these patients need surgery to help stop the air leaking into the lung, but it is also recognised that these patients may not be fit for major surgery.

Unfortunately, we don't have data from UK patients about key consequences of developing a secondary spontaneous pneumothorax. For example, we don't know how long patients stay in hospital, how many go for surgery, and how many develop complications. With this information we can better plan for care, but also look at why some patients stay longer in hospital and why some patients need surgery, whilst others don't.

The aim of this study is to gather information about SSP in an attempt to answer some of these unknown questions. We will recruit patients admitted to hospital with SSP throughout the UK over a period of 1 year. We will collect routine data from the patients' records, such as age, medical history and how long they stay in hospital.

Patient and public involvement

We had discussions with patients and conducted a survey to find out what outcomes were most important to them. Patients told us that length of hospital stay was really important and also that they want treatments that aren't painful. We used this feedback to design this study.

Dissemination

The findings of these study will help us decide on the best care for patients and help us plan for future research projects. We will work with social media groups to let patients and doctors know the findings, write up our results in journals and present at conferences. We will work with key professional societies to incorporate our findings into relevant guidelines.

BACKGROUND

Spontaneous pneumothorax is a common acute medical emergency, where an abnormal collection of air forms in the space between the lung and the chest wall, causing collapse of the lung. It can be subclassified as primary spontaneous pneumothorax (PSP) or secondary spontaneous pneumothorax (SSP) depending on absence or presence of lung disease. PSP occurs in patients typically in young adults, between the ages of 15 and 35 who do not have lung disease. SSP typically occurs in older patients and is secondary to patients' existing chronic lung disease. It can be an acute medical emergency when the lung collapses in the presence of underlying chronic lung disease. Because of their underling lung disease, patients with SSP are typically much more breathlessness and unwell than patients with PSP.

SSP is the commonest cause of spontaneous pneumothorax, with over 3,000 patients per year admitted to hospital with SSP in England and accounts for 60% of all spontaneous pneumothorax (SP). However, the literature base for SSPs is much smaller than that for PSP(1). There is currently a large disconnect between trial and real-world populations; with less than 10% of the randomised studies in SP investigating SSP.

UK specific data on SSP is entirely absent, with even basic data on typical length of stay, underlying aetiology and surgical referral rates having to be extrapolated from international studies out of necessity. Currently, a single centre study from Japan and a French epidemiological study provide the best estimates for length of stay in SSP(2, 3). National databases, such as the Hospital Episode Statistics (HES) database, do not distinguish between PSP and SSP, and do not provide detailed individual patient level data.

British Thoracic Society (BTS) guidelines provide clear advice on different treatment strategies for primary (PSP) and secondary (SSP) spontaneous pneumothorax, but compliance with these guidelines amongst non-respiratory healthcare professionals is reportedly low(8). Additionally, the advice on SSP is based on limited data and there are many outstanding research questions that need answering. There is no current guidance on patient selection for surgical management for persistent air leak (PAL) and recurrence prevention. Patients with SSP are typically felt to be poor surgical candidates, due to poor physiological reserves and comorbidities, but there is a lack of information about which patients would most benefit and which are most are risk. This project would identify the patient characteristics of those accepted for surgery, and their outcomes. Additionally, the management of persistent air leak is extremely problematic in this patient cohort, with no clear evidence on how best to manage. This project would capture current national practice on PAL and the impact this had on air leak duration.

Recurrence rates are felt to be higher in SSP compared to PSP, with historic and poorly evidenced cited rates between 40-50%(5), however there is no robust data to inform on this, or the factors which influence it. This project would give vital insights and help inform practice.

AIMS & OBJECTIVES:

To determine the characteristics, healthcare burden, management, and outcomes of secondary spontaneous pneumothorax (SSP) in UK over a 1-year period

AIMS AND OBJECTIVES:

- To determine characteristics of SSP patients admitted in study period (age, gender, underlying respiratory condition)
- To determine management of SSP in study period (procedures, recurrence prevention, surgery)
- To determine outcomes of SSP admission (length of stay, duration of air leak, mortality)
- To determine factors, including inter-site variability, influencing surgical referral and acceptance rates for air leak and recurrence management
- To determine factors influencing short-term recurrence rates

Research questions which may be addressed as part of the study are listed below.

CLINICAL OUTCOMES

1. What are the demographics of the SSP population in the UK (age, gender, underlying aetiology, previous SSP, lung function)?
2. What are the size and location of pneumothorax on chest x-ray (side, maximum intrapleural distance, hilar intrapleural distance)?
3. How are the patients managed during their inpatient stay (initial management, prolonged air leak management, recurrence prevention interventions, surgical referral, surgical intervention)?
4. What are the patients' length of stay?
5. What are the patients' duration of air leak?
6. What are the patients' mortality rate?
7. What proportion are referred and receive surgery?
8. What are the patients 6-month ipsilateral recurrence rates?
9. What is the expertise available at hospital (presence of onsite thoracic surgical unit, dedicated pleural clinic)?

METHODOLOGY

STUDY DESIGN

LISP is a multi-centre, prospective, longitudinal cohort study of patients diagnosed with SSP.

STUDY POPULATION

Population of interest: patients presenting to hospital with secondary spontaneous pneumothorax.

Inclusion

Emergency attendance to hospital with secondary spontaneous pneumothorax, confirmed by radiology, with SSP defined as:

- spontaneous pneumothorax in presence of known or suspected lung disease OR
- spontaneous pneumothorax in patient ≥50 years of age and smoking history.

Exclusion

- age <16 years of age
- iatrogenic pneumothorax
- traumatic pneumothorax

RECRUITMENT

Recruitment procedure

Research in an emergency setting is always challenging due to high clinical work load and the proportion of eligible patients presenting out of hours. Clinicians have additional levels of clinical demand during night shifts and research teams are often not available to support recruitment. Additionally, patients with SSP will potentially be in significant pain/respiratory distress at the time of presentation and may have diminished capacity. However, it is vital that patients presenting out of hours with SSP are offered the opportunity to participate in this research, and it is also vital to the integrity of the research methodology that these patients are included within a consecutive sample, to ensure the findings are generalizable.

To minimize the risk of recruitment bias in our sample, this study plans to recruit 24 hours a day, 7 days a week, at all sites. To achieve this, there will be extensive departmental awareness of the study raised at each site, and we will use trained clinicians to recruit to the study as part of routine care, in addition to research teams. As such, it is essential that we minimize the administrative burden for these busy clinicians. We have chosen an opt-out consent process to facilitate this, designed to ensure patients are robustly informed and provided with tiered opportunity to ask questions/engage with the research at their preference. This method will minimize the risk of

missing a significant cohort of patients presenting between 2200 and 0800, minimize the burden on clinical staff recruiting during standard working hours, but maximise the generalisability of the research.

This study involves no change in clinical treatment and no additional interventions for participants. It therefore carries no clinical risk. It is also well recognised that patients attending the ED with SSP are in pain and at a time of acute anxiety/distress; often, they require immediate management. As such it will be impractical and potentially distressing to seek fully informed consent in an emergency setting. We will therefore adopt a proportionate approach using an opt-out strategy, as supported by the Health Research Authority (HRA). Participation in LISP will not impact on any part of the patients' routine care and they will be entitled to withdraw from the study at any point, without giving a reason.

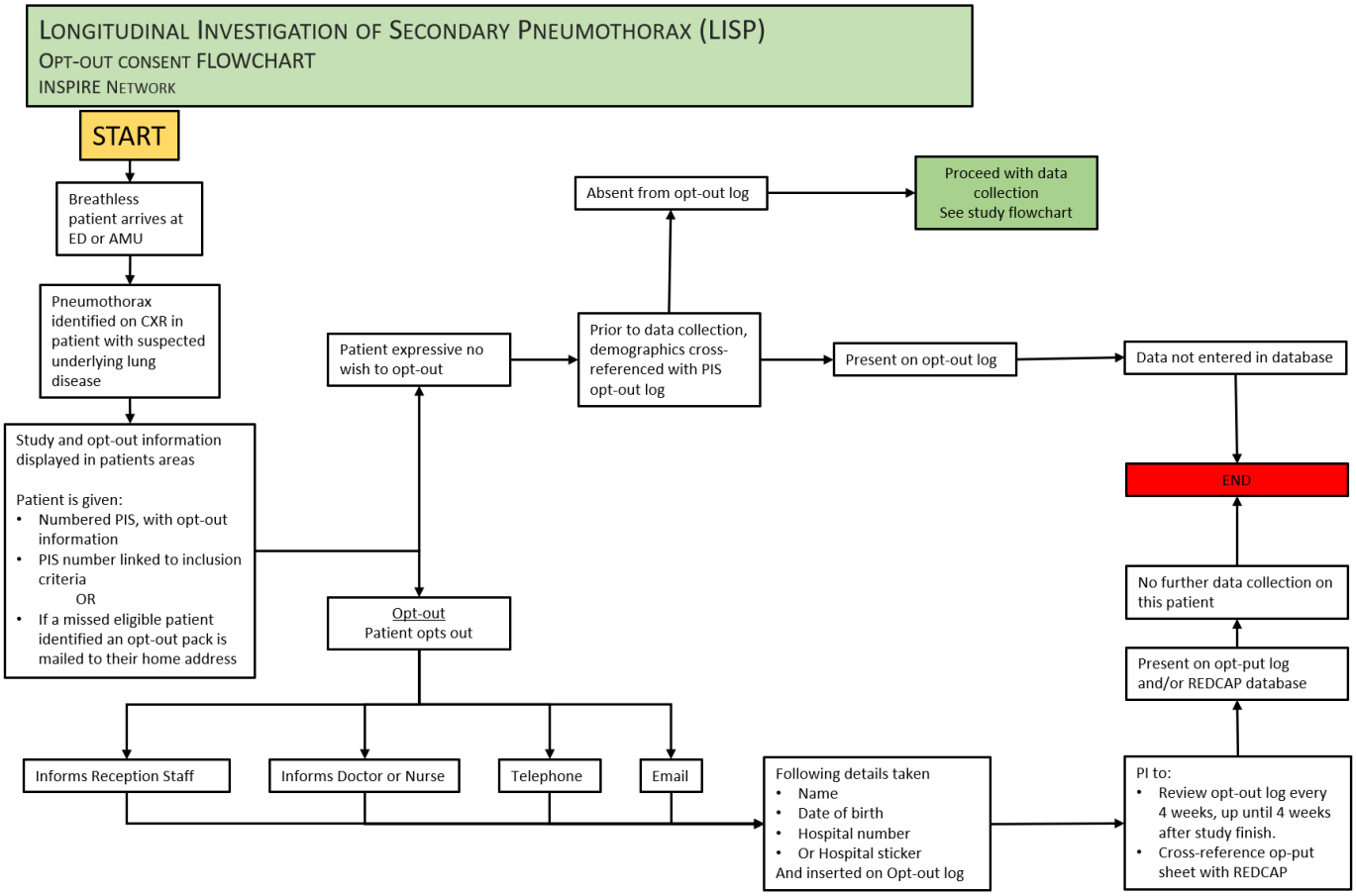


FIGURE 1: OPT-OUT CONSENT FLOW CHART

RECRUITMENT TARGET

A conservative estimate of patients with SSP presenting and identified by research staff at each site is 12 per annum (based on Hi-Spec RCT screening log(6)). Provisional anonymised HES data suggest that this may be a

considerable underestimate, demonstrating a mean of 40.5 SSP presentations/annum at the top 15 NHS Trusts. As SSP typically have substantial inpatient length of stay and are managed by Respiratory team, high identification rates are anticipated. Additionally, the opt-out consent model should maximize data capture. With 20 participating sites, we would expect a minimal of 120 patients over a 6-month period.

The recruitment target is a minimum of 120 patients per year. The LISP will run over a one-year period (recruiting for 6 months with a 6 month follow up period). Given the observational nature of this study, patients will be eligible to co-enrol in other studies if invited.

FOLLOW-UP SCHEDULE

All participants will only undergo assessment at a single time point, at enrolment ("baseline assessment"). This will be performed by a member of the study team and should be done within the first week from enrolment.

Subsequently, study data will be acquired from the medical records at two further time points, at 1-month and 6-months post enrolment. This will be conducted by the local medical research investigator. As this is a trainee-lead project, it is anticipated this will a respiratory trainee.

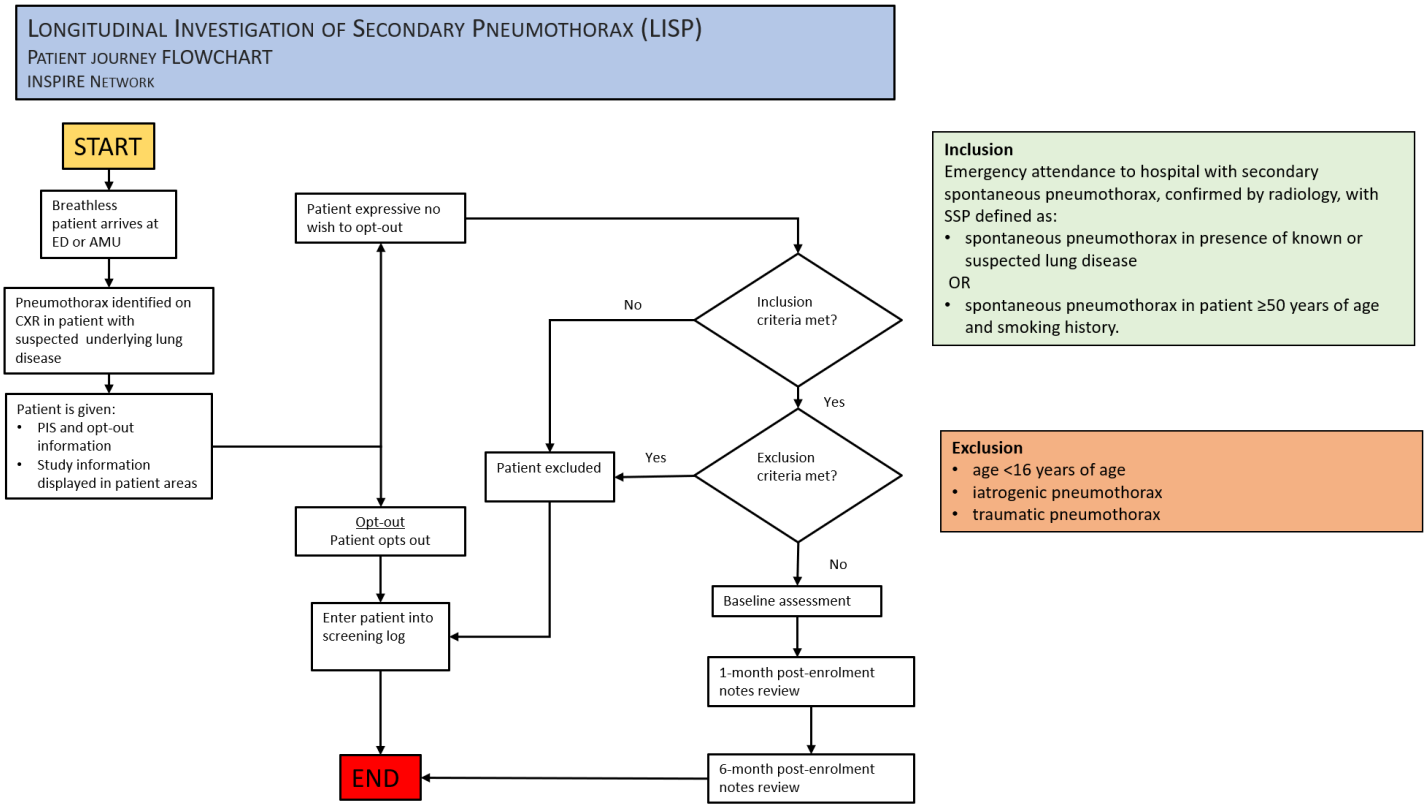


FIGURE 2: PATIENT JOURNEY FLOWCHART

DATA COLLECTION

Baseline assessment

The baseline assessment for all patients will incorporate routinely collected clinical information, such as:

- History and examination by a Respiratory physician, including duration of symptoms, co-morbidities and past medical history, current/recent medications, smoking status including cannabis, clinical frailty score (CFS) and performance status (PS).
- CXR data- size of pneumothorax

1-month post-enrolment (+/- 14 days)

A review of participant's clinical records to collect data on key clinical outcomes, including but not exclusively, the:

- Initial length of stay
- Digital air leak (DAL) measurement (if available)
- Analogue air leak assessment
- Number of type of interventions, including therapeutic aspirations, intercostal chest drains (ICD) insertions, blood batch, ambulatory care and surgical procedures.
- Treatment complication
- Mortality

6 month post-enrolment (+/- 14 days)

A review of participant's clinical records to collect data to identify:

- Initial Length of stay (if exceeded 1 month)
- Ipsilateral recurrence of pneumothorax

STUDY FLOW CHART:

Schedule of assessments:

Description	Investigation	Baseline assessment	4 -week follow up assessment (+/- 7 days)	26-week follow up assessment (+/- 4 weeks)

Clinical review	Patient demographics	X		
	Pneumothorax history	X		
	Patient co-morbidities	X		
	Assessment of PS/CFS	X		
	Medication history	X		
	Number of interventions		X	
	Mortality		X	
	Length of stay		X	X
	Recurrence		X	X
Imaging	CXR	X		
	CT		X*	
Air leak assessment	Analogue air leak assessment (if available)		X	
	Digital air leak assessment (if available)		X*	
***-if clinically available**				

DEFINITION OF END OF TRIAL

All participants will be actively followed up for 6 months after recruitment. The opt-out log will be reviewed 4 weeks after data-collection has finished. The end of the trial as a whole will be after all trial participants have completed follow up, all data queries have been resolved, the database locked and the analysis completed.

DATA HANDLING AND RECORD KEEPING

Data collection tools and source document identification

Source data will all be electronic from NHS Trust computer systems i.e., patients' medical records, laboratory and radiology reports and directly entered onto an eCRF in REDCap.

Data handling and record keeping

Data entry at will use a bespoke study database housed on the University of Bristol server, built using the validated open-source REDCap system and regularly backed up. The study investigator will facilitate data entry into the database via an electronic case report form (eCRF) with the support of the clinical team. Each participant will be allocated an unambiguous subject identification code (trial participant ID).

REDCap includes data validation checks which are inbuilt into the database build and a data query management system to allow management of data quality throughout the trial. The LISP database will be validated as part of the Database Activation process and final data quality checks will be incorporated as part of the Database Lock process.

It is also possible to download the data for all records in this project in a single PDF file that could be printed and retained with the TMF. This file contains the actual page format as you would see it on the data entry page or survey and includes all data for all records for all data collection instruments.

Access to Data, Data Protection and Confidentiality

All data will be stored in line with Good Clinical Practice (GCP) requirements and the General Data Protection Regulation (GDPR).

All study documentation will be kept secure in an access restricted environment and only accessible by LISP study staff and authorised representatives from the Sponsor and regulatory authorities to permit trial-related monitoring, audits and inspection.

Patient data will be kept confidential. On all trial specific documents the patient will be referred to only by the trial participant ID. Only usual care team will have access to identifiable data.

REDCap is password protected with only approved users having access. User access can be restricted to different levels by assigning users with limited permissions based on their role (i.e., data entry only). Interaction with the software automatically creates an access log data trail, ensuring that the access of data can be audited to ensure data protection (e.g. by data point, function or individual user).

Archiving

Once all required downloads have been confirmed with the University of Bristol REDCap team, they will delete the study data from the REDCap project but keep the metadata and put this into archived status. This way, the project can still be brought back to life if needed (by uploading the data from long term storage) but it no longer exists on the REDCap server. Data will be retained as per NBT archiving policy.

STATISTICAL CONSIDERATIONS

Sample size calculation

The prospective descriptive nature of this observational study renders a sample size calculation unnecessary. Our aim is to recruit a minimum of 120 patients over the 6 month study period of the study would allow us to adequately assess the above research questions.

Analyses

Baseline characteristics will be described using descriptive statistics. Patient characteristics and treatment outcomes will be compared by the chi-square test, Fisher's exact test, or *t*-test, as appropriate. Categorical variables will be represented as frequencies and percentages. Continuous variables with standard distribution will be represented as mean values and standard derivations. Predictors of in-hospital mortality, length of stay, duration of air leak, surgical management and recurrence will be identified by multivariate logistic regression analysis. Evaluated parameters will include underling lung disease, FEV1 (≥ or <50%), recurrent pneumothorax (yes/no). Differences will be considered significant at values of $p < 0.05$.

Consent

We will display relevant materials in the appropriate areas of every participating ED and acute medical unit, describing the study and providing assurance that clinical care will not be affected in any way. We will offer individual patient information sheets (PIS) at the point of clinical assessment, with a description of the study and identified point of site contact for every patient enrolled to the study. Staff in the ED will be available at initial clinical assessment and on request, to speak to any participant or their next of kin. All PIS documents will be numbered and linked to the study inclusion checklist. Completion of this checklist will ensure a robust process for ensuring all eligible patients have received the opt-out information. In addition, the PIS will contain links for headache support groups and patient information.

All patients who wish to opt-out will be highlighted on a specific opt-out log. The opt-out log will be cross-referenced with the inclusion checklists and REDCap database at 3 different time points, to ensure that any patient expressing a wish to opt out of the study has been acknowledged and no further data recorded:

1. Prior to initial data entry
2. Retrospectively by the study team at the end of 4 weeks period
3. 4 weeks after data-collection has finished.

Any patients deemed eligible for the study but not present on the opt-out log will be included in the study and data transcribed to case report forms as per study procedures. Sites will be offered a tiered strategy for

further/additional patient information, including a PIS to be mailed to a home address or research nurse contact (face to face if in hospital, or by telephone). Each patient will have a unique study number. The opt-out log will be checked for a final time 4 weeks after data-collection has finished. For patients who choose to opt-out from the study, the only information that will be kept on the opt-log will be their name, date of birth and a corresponding study number. The opt-out log will be cross-referenced with the central REDCAP database using this study number. The opt-out log will only be kept at local site, any only accessible to usual care team.

This approach, targeted to the individual, is considered to constitute active recruitment as per paragraph 21 of the NIHR Clinical Research Network (CRN) recruitment policy document(7)

In addition, this methodology for observational research has been used with ethical approval and CRN portfolio adoption/accrual for multiple ED projects, including the PAT-POPS study, the AHEAD, the HEAD study, and most recently, the SHED study (12-16)

Finance and Insurance

The study has been funded through an unrestricted research grant provided by Rocket Medical.

This is an NHS-sponsored research study. For NHS sponsored research HSG(96)48 reference no. 2 refers. If there is negligent harm during the clinical trial when the NHS body owes a duty of care to the person harmed, NHS Indemnity covers NHS staff, medical academic staff with honorary contracts, and those conducting the trial. NHS Indemnity does not offer no-fault compensation and is unable to agree in advance to pay compensation for non-negligent harm. Ex-gratia payments may be considered in the case of a claim.

Reporting and Dissemination

A plain English summary will be prepared and disseminated with the help of our PPI group, including via social media, and provided to trial participants. We will report our results via a high-impact medical journal and present findings at international respiratory and conferences.

This study is supported by the INSPIRE (INtegrated reSPIratory REsearch) collaborative, a respiratory trainee work which aims to facilitate a collaborative approach to performing clinical research projects and high-quality audits at regional and national scale for the benefit of patients with respiratory disease. The study results will be published on the INSPIRE website and at INSPIRE events.

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