SPIRIT

Studying Pleuroscopy in Routine Pleural Infection Treatment

Trial Protocol

Protocol version	3.1
Protocol date	6th April 2018
Sponsor	North Bristol NHS Trust
Funder	The Academy of Medical Sciences
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Funder project reference number	SGL015\1002
Sponsor project reference number	3943
IRAS ID number	219173
REC number	17/YH/0074
ISRCTN	ISRCTN98460319

Chief Investigator's signature	

This protocol describes the SPIRIT trial and provides information about procedures for entering participants. Every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to and approved by investigators in the study.

This study will adhere to the principles outlined in the NHS Research Governance Framework for Health and Social Care (2nd edition). It will be conducted in compliance with the protocol, the Data Protection Act and other regulatory requirements as appropriate.

Trial queries

Clinical queries should be directed to the local Principal Investigator or Chief Investigator. For general queries, supply of study documentation, and collection of data, please contact the trial administrator.

Sponsor

North Bristol NHS Trust is the research Sponsor for this trial. For further information regarding the sponsorship conditions, please contact:

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GLOSSARY OF ABBREVIATIONS

AE	Adverse Event
AR	Adverse Reaction
CI	Chief Investigator
CRP	C-Reactive Protein
CT	Computed Tomography
CTIMP	Clinical Trial of an Investigational Medicinal Product
CXR	Chest X-ray
DMC	Data/Safety Monitoring Committee
eCRF	Electronic Case Report Form
F	French
FEV1	Forced Expiratory Volume in 1 Second
f-LAT	Flexible Local Anaesthetic Thoracoscopy
FVC	Forced Vital Capacity
ICH GCP	International Conference for Harmonisation of Good Clinical Practice
ICMJE	International Committee of Medical Journal Editors
LAT	Local Anaesthetic Thoracoscopy (also known as pleuroscopy)
M, C+S	Microscopy, Culture and Sensitivity
NAAT	Nucleic Acid Amplification Techniques
NBT	North Bristol NHS Trust
NHS	National Health Service
P-A	Posterior-Anterior
PI	Principal Investigator
PPI	Patient and Public Involvement
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMG	Trial Management Group
tPA	Tissue Plasminogen Activator
TSC	Trial Steering Committee
TSP	Trial-Specific Procedure document
UK	United Kingdom
USA	United States of America
VAS	Visual Assessment Scale
VATS	Video-Assisted Thoracoscopic Surgery

1. STUDY SUMMARY

TITLE	Studying Pleuroscopy in Routine Pleural Infection Treatment (SPIRIT)		
DESIGN	Open-label, randomised, feasibility study (Non-CTIMP) with embedded qualitative interviews		
AIMS	To assess the feasibility and acceptability of randomising 30 patients to undergo either medical thoracoscopy or standard chest drain insertion for the treatment of pleural infection requiring drainage.		
PRIMARY OUTCOME	The feasibility of screening and enrolling patients into the study, and delivering the trial protocol		
INCLUSION CRITERIA	1. Suspected pleural infection, defined as an effusion (in the appropriate clinical context) with one or more of the following characteristics: a. Fluid pH ≤7.20 or visually contains pus b. Pleural fluid glucose ≤3.4 mmol/L c. Positive bacterial or mycobacterial culture d. Positive gram stain or stain for acid-fast bacilli 2. Clinical team expect to be able to perform a medical thoracoscopy, if allocated, on either the same or the next day as the effusion is diagnosed as requiring drainage 3. Clinical team expect to be able to deliver the post-procedure trial schedule as detailed in the protocol		
EXCLUSION CRITERIA	1. Any contraindication, in the opinion of the trial team or lead clinician, to a. Medical thoracoscopy performed under conscious sedation b. Chest drain insertion c. Patient trial involvement 2. Research team unable to obtain, or patient unable/unwilling to provide, informed consent to trial participation 3. Thoracic imaging demonstrating fluid septation, loculation or position which would render medical thoracoscopy or standard medical management alone inappropriate, in the opinion of the trial team or lead clinician 4. Maximum pleural fluid depth of ≤2cm on thoracic ultrasound 5. Ongoing sepsis requiring haemodynamic support beyond basic fluid resuscitation 6. Previous pneumonectomy or lobectomy on the side of the effusion (or any ipsilateral thoracic surgery within six months) 7. Age <18 8. Pregnancy or lactation 9. Expected survival ≤3 months		
FOLLOW-UP	3 months	**SPONSOR**	North Bristol NHS Trust

CHIEF INVESTIGATOR	Dr Rahul Bhatnagar	**FUNDER**	The Academy of Medical Sciences

2. INTRODUCTION

2.1 BACKGROUND

2.1.1 Pleural infection epidemiology

Pleural infection is common, and can affect patients across a wide range of age groups. Incidence is highest in those who are either particularly old or young, with evidence to suggest that there are more cases year-on-year in children and adolescents, (1-3) perhaps as a result of childhood vaccination programmes altering host susceptibility profiles. (4) The increasing incidence appears to be an international phenomenon, with latest estimates suggesting there are at least 15,000 new cases in the United Kingdom each year, and approximately 80,000 cases in the UK and USA combined. (1) Hospital stays for such patients are often lengthy, with approximately one quarter requiring more than one month as inpatients. (2, 3, 5-7) Pleural infection patients also have a high risk of mortality (10-20%), which worsens in those who are more susceptible. (5, 7-9) Other than the old and young, at-risk populations include those who have chronic lung disease or diabetes; those with poor dentition or a higher-than-usual risk of aspiration; those who are immunosuppressed; or those with a history of drug or alcohol abuse. Chest trauma or medical intervention also predispose to pleural infection. (10, 11)

2.1.2 Pleural infection aetiology

Although primary pleural infection (without any evidence of lung parenchymal involvement) is increasingly recognised as an important condition, (12) the majority of patients will present having suffered a pneumonic illness in the build-up to their presentation. Up to 60% of patients with pneumonia will go on to develop an associated reactive fluid collection (parapneumonic effusion) around the lung, and around 10% of these go on to develop evidence of secondary infection. (13-15) The diagnosis of pleural infection can be made directly, by the demonstration of pus (empyema) or organisms in a pleural sample, or indirectly, when markers of high metabolic activity (such as a low glucose or pH level) are found. Although not entirely specific, indirect these parameters are codified in national guidelines (1) and commonly form the basis of entry criteria to studies recruiting from the pleural infection population.

The pattern of organisms implicated in pleural infection has evolved over the last few decades, with the most significant shift assumed to be associated with the widespread introduction of antibiotics. (13) Gram positive cocci, specifically the Streptococcus anginosus group in adults and Strep pneumoniae in children, are the primary culprits in community-acquired disease, although Gram-negatives (e.g. Haemophilus influenzae) and anaerobes are also found not infrequently. (16) Given this information, the choice of appropriate empirical antibiotics in pleural infection often differs subtly from that required in pneumonia. (1) Modern nucleic acid amplification techniques (NAAT) are beginning to reveal more about the pleural infection microbiome, suggesting a complexity and individuality which is not readily apparent using traditional culture and microscopy. (17) NAAT, however, is not yet in widespread clinical use and thus remains a tool largely reserved for research. The distinction between community-acquired disease and the less common healthcare-associated pleural infection, HAPI, (which accounts for around 15% of cases (12)) is an important one to make in deciding initial treatment. HAPI carries a significantly higher chance of morbidity and mortality and is caused by a different spectrum of bacteria, largely Staphylococci including MRSA, necessitating alternative antibiotic approaches. (12)

2.1.3 Medical management of pleural infection

As mentioned above, the early and rationalised use of empirical antibiotics forms the cornerstone of modern pleural infection management. (1) Patients also tend to be significantly catabolic and pro-thrombotic, and so require increased nutritional support alongside prophylactic anticoagulation during the presentation phase of their illness when they are most likely to be septic. (13) For those who have evidence of anything other than a very small effusion, (18) drainage of their collection is recommended – usually on at least a semi-urgent basis. (1) First line intervention for pleural infection usually involves insertion of an intercostal chest tube, under local anaesthetic, in the ward setting. The choice of drain size (diameter) has been a subject for historical debate. (19) Recent randomised evidence would suggest that wider tubes are more efficacious in some settings (such as malignant pleural effusions), (20) but this has not been supported in subgroup analysis of large pleural infection cohorts, where bigger drains appear only to be as effective as smaller ones, and at the expense of more pain. (7) Guidelines suggest that if a smaller drain is used, it should be flushed routinely to prevent occlusion with debris. (1) Extrapolating from this, pleural irrigation has been shown to improve outcomes in a randomised pilot study, (21) with this practice already considered routine in some European centres.

In some, effective drainage of fluid can be hindered by the presence of "septations" – strands of scar tissue which form a complex network of fluid pockets ("loculations") within the pleural cavity. These patients may require treatment with newer, enzyme-based agents (specifically tissue plasminogen activator and deoxyribonuclease in combination) which are administered intrapleurally, and which have been shown to be efficacious enough to improve clinically-relevant outcomes in randomised trials. (7, 22, 23) This treatment, however, is expensive, laborious and needs to be given over an additional three day period. (7)

Should the approaches described above fail, then patients will often need thoracic surgery to enable debridement of the pleural cavity. Modern pleural infection surgery tends to be done using a minimally-invasive approach (video-assisted thoracoscopic surgery, VATS) and has excellent outcomes. (13) This technique, however, is reserved for those who are sufficiently fit to undergo general anaesthetic, a limitation which excludes many of the more elderly or frail patients who might fail to respond to medical treatment.

2.1.4 Medical thoracoscopy

Local anaesthetic thoracoscopy (LAT) is now an established investigation in pleural effusion. (24) It can be performed safely under conscious sedation, even as a day-case, and usually lasts around 45 minutes. It entails complete drainage and visual examination of the chest cavity using a small fibreoptic camera which is inserted via an intercostal port under local anaesthetic. During this time, there is usually opportunity to perform additional interventions such as parietal pleural biopsies, breakdown of septations, and in the case of suspected malignant disease, talc poudrage. (25) A chest drain is inserted at the end of the procedure to allow the lung to re-expand and to drain any residual fluid, with the size of tube determined by the diameter of the port inserted initially.

Rigid thoracoscopy is the commonest variant and can be performed using either a single- or dual-port approach. The stiffer device has the benefit of allowing larger biopsy size and more control over the whole of the scope, however it is sometimes limited in both the views it can provide and the areas of the chest which can be accessed for sampling. Flexible LAT (f-LAT) is a relatively novel technique which may address some of these issues, albeit at much greater cost and smaller biopsy size. (26, 27)

2.1.5 The role of medical thoracoscopy in pleural infection

In a few isolated centres on the European continent, the use of medical thoracoscopy for pleural infection is relatively common. However, there are currently only four published studies relating to this

practice: None of them are comparative or randomised; describe UK patients; include patient-subjective outcomes; look at rapidity of performing the procedure or duration of stay; or include flexible thoracoscopy. (28-31) A total of 191 patients are reported overall, the bulk coming from a paper by Brutsche et al, who undertook a multicentre retrospective review series of patients from three hospitals in Italy and Switzerland over a 14-year period. A third of this series' cases were performed as a result of failed initial tube drainage and half received post-procedure intrapleural fibrinolytics (albeit without DNase).

Despite their limitations, however, these studies would seem to support the hypothesis that medical thoracoscopy can be performed safely in this population, with complication rates akin to those seen in other thoracoscopy studies. Clinical outcomes were also encouraging, with a combined rate of 90% (172/191) of patients for avoiding surgery.

2.2 RATIONALE FOR CURRENT STUDY

2.2.1 The need for the SPIRIT trial

At the time of writing, UK thoracoscopy services are largely geared towards elective diagnostic procedures, with those who do undertake LAT for therapeutic purposes tending to do so only in the malignant population. In this group, the primary perceived benefit of choosing LAT over standard chest drain insertion is the ability to completely drain the pleural cavity and administer talc in a single procedure. Although logistically more challenging and slightly more demanding for patients, this approach is typically able reduce the number of days spent in hospital such that there is likely to be a significant healthcare cost benefit. Given that patients with pleural infection can have average inpatient stays in excess of those with malignancy, the question of whether a similar reduction can be achieved by using LAT in this population is an important one. If either this, or an improvement in the need for step-up treatment, can be demonstrated then it could be argued that therapeutic medical thoracoscopy would represent a new standard of care for pleural infection in the UK, necessitating a shift in long-term service provision.

The most appropriate way to address the above is with a randomised controlled trial comparing the newer intervention to the current standard. However, before this can be attempted, it must be shown that there is enough flexibility in current set-ups to allow for urgent or semi-urgent thoracoscopy to be performed, as patients cannot be left with untreated pleural infection for extended periods of time. The SPIRIT trial will address this question directly, examining the feasibility of randomising patients to undergo either standard care or rapid medical thoracoscopy. This, along with the collection of basic

outcome and patient experience data, will hopefully allow the design and justification of a larger trial which is fully powered to evaluate those outcomes on a larger scale.

2.2.2 Patient and Public Involvement

The design of the SPIRIT trial incorporates valuable patient-subjective and qualitative components, as described in more detail below. To ensure that these are relevant, and to ensure the trial is run with a participant perspective in mind, the trial questions, the trial protocol, the semi-structured interview questions, and the trial steering committee all have patient involvement.

2.3 LAY SUMMARY

A pleural effusion is a collection of fluid in the space between the lung and the chest wall (the pleural cavity). It commonly occurs as a result of pneumonia and can cause significant breathlessness because the lung becomes compressed. In about 10% of cases, this fluid can itself go on to become infected, which increases the chances of someone becoming unwell enough to need surgery, or even dying. To reduce the chance of this happening, it is vital that the fluid is drained away completely as soon as possible after someone is diagnosed with pleural infection. This is usually done by inserting a small chest tube between the ribs and allowing the fluid to come out over period of about 24 hours. This treatment typically requires many days in hospital but is common and generally low risk.

Medical thoracoscopy is a common technique used to diagnose and drain effusions, although it is not routinely used for pleural infection in the UK as it tends to be reserved for those who are suspected of having cancer. It involves inserting a small camera between the ribs into the fluid and can be done under local anaesthetic. The procedure is very safe, but carries a slightly higher risk of complications than standard chest tube insertion. However, the main benefit of the procedure is that it can allow a patient to spend less time in hospital because the chest is drained completely all at once.

This study, the SPIRIT trial, Is designed to see if a group of UK hospitals are able to safely offer medical thoracoscopy to patients with pleural infection. It will recruit 30 patients from 7 UK hospitals over a year and will randomly allocate half of them to undergo thoracoscopy and half to the standard chest drain. Over 3 months of follow up, we shall also examine how the treatment affects patients themselves, and whether it is effective at reducing patients' time in hospital or their need for surgery.

3. STUDY OBJECTIVES

3.1 PRIMARY RESEARCH QUESTION

Is it feasible and acceptable to randomise 30 patients to undergo either medical thoracoscopy or standard chest tube insertion for the treatment of pleural infection requiring drainage, and to deliver the trial protocol to a UK population of patients?

3.2 SECONDARY RESEARCH QUESTIONS

Regarding those patients who are treated with medical thoracoscopy for pleural infection:

1. Does this approach reduce the time spent in hospital compared to standard treatment?
2. Does this approach affect the need for “step-up” therapy?
3. Does this approach affect lung function over the weeks following treatment?
4. Does this approach affect pleural effusion size or overall complexity, measured radiologically over time?
5. Does this approach affect the microbiological yield in comparison to standard sampling techniques?
6. How does using this approach affect overall costs compared to standard treatment?
7. How does using this approach affect patients’ subjective quality of life?
8. What are patients’ experiences of trial involvement and of the procedures themselves?

4. STUDY DESIGN

4.1 TRIAL TYPE

The SPIRIT trial is an open-label, randomised, feasibility study aiming to gather preliminary information on whether there is a role for medical thoracoscopy in the management of pleural infection requiring chest drainage.

The trial allocates participants to receive one of two treatments which are both freely available and routinely used throughout the NHS. There are no novel devices or investigational medicinal products incorporated in the trial design. As such, SPIRIT will be classified as a non-CTIMP study for the purposes of regulatory approvals and adverse event reporting.

A subset of participants will also be invited to undergo qualitative, semi-structured interviews to better understand their experiences of pleural infection and trial involvement.

4.2 TARGET POPULATION

The target population for the SPIRIT trial are those patients who have been diagnosed with a pleural infection requiring intercostal drainage, and who meet the inclusion and exclusion criteria as described in sections 5.2 and 5.3.

The study will aim to randomise 30 patients (in a 1:1 ratio) to either the control or intervention arm, with up to 10 patients from each undergoing semi-structured interview.

4.3 STUDY OUTCOME MEASURES

4.3.1 Primary outcome

The primary outcome is the feasibility of being able to recruit patients and randomise them to undergo medical thoracoscopy for pleural infection, and of being able to deliver the trial protocol. This will be assessed as follows:

- Pre-randomisation:
    - The total number of pre-screen and screen failures, and the proportions of each compared to the overall number assessed for trial involvement
- Post-randomisation:
    - The total number of allocation failures in both arms of the study

Pre-screen, screen and allocation failures are defined in sections 5.1 and 6.3.3.

4.3.2 Secondary outcomes

- Duration of stay due to pleural infection, as measured by the number of nights in hospital between enrolment and being recorded as medically fit for discharge
- Total inpatient time, as measured by the number of nights in hospital between enrolment and the end of the 90-day post-procedure follow-up period
- Need for step-up therapy, as measured by the difference in proportion of patients requiring intrapleural fibrinolytic therapy or referral for surgical debridement
- All-cause mortality, as measured by the number of patients remaining alive at days 30 and 90 post procedure
- Degree of pleural fluid septation, as measured by the change in bedside thoracic ultrasound septation score from baseline to follow-up days 1, 3, 7, 30 and 90 post procedure
- Pleural effusion size, as measured by the change in radiographic hemithorax opacification from enrolment to discharge, and days 1, 30 and 90 post procedure
- Microbiological yield, as measured by the difference in proportion with positive culture or stain between the control and intervention arms
- Total costs of interventions, as measured by the difference in total cost of treatment for pleural infection (from enrolment to being medically fit for discharge) between two arms
- Quality of life, as measured by the change in EQ-5D subjective health score from baseline to days 30 and 90 post procedure
- Patient experiences, as determined by exploring patients' perceptions and experiences of interventions before and after their procedure through semi-structured interviews

4.4 FUNDING

The SPIRIT trial is supported by a Starter Grant for Clinical Lecturers awarded to the Chief Investigator by the Academy of Medical Sciences.

4.5 TRIAL DESIGN JUSTIFICATION

- As mentioned above, the role of medical thoracoscopy in the management of pleural infection is largely unexplored. Theoretically, this intervention may have a place at any stage, ranging from first fluid drainage through to using it as a tool to try to avoid surgery in those who have failed first-line drainage, or even as an alternative to more invasive VATS procedures in those with persistent non-resolving disease. This study has chosen to focus on the former, and examines whether using medical thoracoscopy as the first intervention in pleural infection is feasible and acceptable. The primary rationale for this is minimising the demand for UK thoracoscopists to undertake procedures outside of their typical experience, which lies in the management of collections which should theoretically respond to standard drainage.
- SPIRIT is a feasibility study as opposed to a pilot study, which means the information it is able to generate will hopefully be used to *inform the design* of a larger study examining the efficacy of LAT in the pleural effusion population, rather than being a smaller but fixed template for such a study.
- The decision to target a relatively selected pleural infection cohort for randomisation has been carefully considered. It would be possible to design the SPIRIT trial to include and randomise all pleural infection patients needing drainage regardless of day or time of presentation, or indeed of 'suitability' for LAT, and then analyse them on an intention-to-treat basis to determine the 'real-world' impact of using LAT in this population. This approach would theoretically minimise selection bias. However, given that very few (if any) UK centres are currently set up to perform urgent thoracoscopy, and not all investigators would be comfortable performing LAT in a completely unselected population, this approach would likely place investigators in the situation of having to consent patients to potentially being randomised to a treatment arm they know they will not be able to deliver. Aside from the ethical issues this may raise, it would likely also lead to a significant number of allocation failures in the LAT arm and would thus blunt the ability to interpret any data based on comparisons with this group.
- The trial will therefore only look to enrol those patients who are felt to be suitable for a LAT, and can also have one performed if that procedure is assigned. However, understanding as complete a picture as possible of the population from which trial participants are drawn is considered vital to the design of any future studies. As such,

robust pre-screening and screening data will be collected alongside those regarding enrolled patients, and this will form part of the analysis and discussion of SPIRIT.

5. PARTICIPANT ENTRY

5.1 PRE-SCREENING AND SCREENING

Potential trial participants will be identified by clinical members of staff at participating recruitment centres, and may be drawn from acute respiratory and general medical services, as well as from ward referral and outpatient pathways. Electronic logs will be kept maintaining details of all patients who are pre-screened and screened, as defined below.

5.1.1 Pre-screening

All patients who have a suspected infected pleural effusion, based on radiological findings and routine clinical assessment by an appropriate specialist, should be entered onto the pre-screening log ("pre-screened" patients). All pre-screened patients should be assessed against the inclusion and exclusion criteria, detailed below. Those who are ineligible for trial entry should have the reasons for this entered on the log, and will be deemed to be "pre-screen failures". Patients may be entered onto the pre-screening log retrospectively, but only if they presented with suspected pleural infection during the trial recruitment period.

5.1.2 Screening

Those who meet the trial inclusion and exclusion criteria should be entered onto the screening log and offered a patient information sheet ("screened patients."). Those patients who do not proceed to trial enrolment should be recorded as "screen failures," with the reason for this documented on the screening log. If a patient deteriorates clinically while they are considering trial entry such that they require urgent chest drainage before they are enrolled, they should also be recorded as a screen failure.

As per the inclusion criteria below, patients must undergo drainage on either the same or next day as they are diagnosed as needing drainage. Therefore, if a patient wishes to consider trial entry overnight, the trial team must be able to perform the allocated procedure on the *same* day as enrolment and randomisation.

5.2 INCLUSION CRITERIA

1. Suspected pleural infection, defined as an effusion (in the appropriate clinical context) with one or more of the following characteristics:

   a. Fluid pH ≤7.20 or visually contains pus
   b. Pleural fluid glucose ≤3.4 mmol/L
   c. Positive bacterial or mycobacterial culture
   d. Positive gram stain or stain for acid-fast bacilli
2. Clinical team expect to be able to perform a medical thoracoscopy, if allocated, on either the same or the next day as the effusion is diagnosed as requiring drainage
3. Clinical team expect to be able to deliver the post-procedure trial schedule as detailed in the protocol

5.3 EXCLUSION CRITERIA

1. Any contraindication, in the opinion of the trial team or lead clinician, to
   a. Medical thoracoscopy performed under conscious sedation
   b. Chest drain insertion
   c. Patient trial involvement
2. Research team unable to obtain, or patient unable/unwilling to provide, informed consent to trial participation
3. Thoracic imaging demonstrating fluid septation, loculation or position which would render medical thoracoscopy or standard medical management alone inappropriate, in the opinion of the trial team or lead clinician
4. Maximum pleural fluid depth of ≤2cm on thoracic ultrasound
5. Ongoing sepsis requiring haemodynamic support beyond basic fluid resuscitation
6. Previous pneumonectomy or lobectomy on the side of the effusion (or any ipsilateral thoracic surgery within six months)
7. Age <18
8. Pregnancy or lactation
9. Expected survival ≤3 months

5.4 WITHDRAWAL CRITERIA

Patients in the trial will have consented to randomisation and trial follow-up. Patients have the right to withdraw from the trial at any point. Withdrawal does not have to be justified and will not affect future or ongoing care. In the event of withdrawal, any details available for the reason(s) should be

recorded, and clarification on the nature of the withdrawal of consent, as outlined below, should be sought. At the discretion of the Principal Investigator, patients may be withdrawn if it is felt to be appropriate or in their best interest to do so. Patients may still be stratified as 'alive' or 'dead' at the end of their follow-up period, unless consent for clinical data use is withdrawn. Available data from patients withdrawn following randomisation will be included intention to treat analyses unless patients withdraw permission for use of this data.

5.5 CO-ENROLMENT GUIDELINES

Patients may only undergo randomisation as part of the SPIRIT trial once. Patients who enrol but are withdrawn before randomisation may be re-enrolled as a new participant.

Patients should not be enrolled if they are participating in another interventional study relating to pleural infection. Participation in other clinical trials will not be limited, however there should be discussion between the relevant teams prior to enrolment to ensure compatibility between protocols, as well as with the patient to ensure they are happy to be involved in multiple studies.

6. RECRUITMENT, RANDOMISATION AND TREATMENT OF PATIENTS

Summaries of patient assessments can be found in Appendices 1 and 2.

6.1 PRE-RANDOMISATION

6.1.1 Consent and enrolment

Following confirmation of eligibility, patients who are willing may have consent taken for trial participation. This should be done by a clinical member of the trial team. Further details on consent are given in section 9.7 below. Patients who have signed the trial consent form are deemed to have been "enrolled". Due to the general need for urgent treatment of pleural infection, trial consent should take place on the same day as baseline assessment and randomisation.

6.1.2 Baseline assessment

The baseline assessment should be performed by a clinical member of the trial team. This will include collection of the following data:

- Patient demographics
- Past medical history
- Details of current pleural infection, including symptoms and treatment
- Standardised thoracic ultrasound scan
- Results of relevant recent radiology
- Results of relevant recent blood tests
- EQ-5D quality of life health questionnaire

Patients who have not had a chest radiograph (ideally P-A) performed within the two days prior to the baseline assessment should have this done before they undergo their allocated procedure.

Patients who have not had relevant clinical blood tests (as defined in section 6.4.1) performed within one day of the baseline assessment should have these done prior to undergoing their allocated procedure.

6.2 RANDOMISATION AND TREATMENT ALLOCATION

6.2.1 Randomisation

Following baseline assessment, randomisation will be performed by a member of the trial team using a web-based system (Sealed Envelope Ltd). Participants will be randomised in a 1:1 ratio to either the control or the intervention arms of the study. The allocation will be determined following minimisation with a random component. The minimisation factors will be:

- Evidence of fluid complexity on thoracic ultrasound – none or mild vs moderate or severe
- Effusion size - ≥50% thorax or <50% thorax using visual estimation on chest radiograph

Concealed randomisation will reduce selection bias. The sequence of random allocations will be generated by computer and will be concealed from all clinical and research personnel.

6.2.2 Treatment allocation

In the control arm, patients will undergo standard chest drain insertion. In the intervention arm, patients will undergo a medical thoracoscopy. Further details for both these procedures can be found in the sections below, and in the trial manual.

6.2.3 Blinding

The SPIRIT trial will be conducted on an “open label” basis. As such, treatment allocation will not be concealed from either participants or trial personnel. No attempt at “sham” procedures will be made.

6.3 POST-RANDOMISATION

6.3.1 Control arm

Patients who are allocated to the control arm should undergo chest drain insertion on either the same or following day as they are *diagnosed as needing drainage*. Separate procedural consent must be taken as per local policy. Thoracic ultrasound guidance (either direct vision or contemporaneous marking) should be used for all such procedures. The chest drain may be inserted using either Seldinger or dissection techniques as per local hospital guidelines. It must be of size 16 French or greater and must be secured using at least one skin suture. The drain should be attached to an underwater seal (or digital equivalent), with the rate of initial fluid removal at the discretion of the inserting physician.

Following insertion, samples of pleural fluid should be taken directly from the drain and sent as per section 6.4.2 below. A post-procedure chest radiograph should be performed within 12 hours of drain insertion.

6.3.2 Intervention arm

Patients who are allocated to the intervention arm should undergo a medical thoracoscopy on either the same or following day as they are *diagnosed as needing drainage*. Separate procedural consent must be taken as per local policy. Patients with a small effusion may have an induced pneumothorax performed prior to their thoracoscopy if necessary. The medical thoracoscopy should be performed as per local hospital guidelines, including using thoracic ultrasound where appropriate. Either a rigid or semi-rigid approach is acceptable, as are either single- or dual-port techniques. Conscious sedation may be used at the discretion of the operator. A sample of the pleural fluid which is drained should be sent as per section 6.4.2 below. During the procedure, the patient should undergo breakdown of accessible septations; parietal pleural biopsies; and intrapleural washout. Further details about these interventions may be found in the trial manual. At the end of the procedure, an appropriately-sized chest drain (minimum gauge 16 French) should be inserted and secured to the skin using at least one suture. The drain should be attached to an underwater seal (or digital equivalent) to allow full evacuation of the pleural cavity.

A post-procedure chest radiograph should be performed within 12 hours of completion of the thoracoscopy.

6.3.3 Allocation failures

The nature of a participant's care is at all times the responsibility of the treating physician. However, on any occasion where treatment differs from that specified in the trial protocol then a protocol deviation form should be completed. In addition, patients who do not undergo their allocated procedure will be recorded as "allocation failures." The full reasons for all allocation failures should be recorded.

In the control arm, an allocation failure will refer to any patient who does not have a chest drain performed within the stipulated time window, or does not have a chest drain insertion performed as allocated.

In the intervention arm, an allocation failure will refer to any patient who does not have a medical thoracoscopy within the stipulated time window. Such patients should, in the first instance, aim to have a 16F gauge (or larger) chest drain performed as per the control arm.

If a patient is unable to undergo their allocated procedure, all subsequent tests and follow-up visits should be timed from the day of randomisation.

6.3.4 Post-procedure inpatient period

Whilst an inpatient post-procedure, a patient's care will essentially follow standard practice. As such, on their first day post-procedure patients should undergo a clinical assessment, as well as a chest radiograph and blood tests (as detailed below). Further clinical assessments should then be made as per standard local clinical practice.

Blood tests should be performed on at least alternate days until day 9, and then at least weekly thereafter if the patient remains in hospital.

Thoracic ultrasounds should be performed on day 1 post procedure, and then on days 3 and 7 post procedure (+/- 1 day), and then every 7 days (+/- 1 day) if the patient remains in hospital.

The results of these, as well as the patient's symptoms (as measured by VAS scores) and clinical observations, will be recorded for trial purposes on days 1, 3 and 7 (+/- 1 day), and then every 7 days (+/- 1 day) until discharge or transfer to another hospital for ongoing care.

On day 7 post procedure (+/- 1 day), the patient should be asked to complete the EQ-5D health questionnaire. If the patient has been discharged, this should be completed at home and returned to the co-ordinating trial unit at Bristol.

The need for and timing of drain removal is at the discretion of the treating physician.

6.3.5 Use of intrapleural enzyme therapy

Intrapleural enzyme therapy, such as tPA and DNase, may be used in trial participants (in either treatment arm) at the discretion of the treating physician. As a guideline, however, the use of these agents should follow standard practice and be reserved for those who are continuing to demonstrate evidence of active pleural infection despite intercostal drainage. In all trial patients, the use of enzyme therapy should be considered in the following circumstances:

- Persistent or rising inflammatory markers on the second day post trial procedure
- Persistent or intermittent fevers on the second day post procedure

- Radiological evidence of ongoing fluid collection with no associated fluid output on the second day post procedure

The need for intrapleural enzyme therapy will be recorded as a trial outcome measure.

6.3.6 Referral for thoracic surgery

For some patients, in the event of the failure of the medical treatments described above, a referral for thoracic surgery (e.g. VATS debridement) may become necessary. As before, the use of this option is at the discretion of the treating physician and may be considered in any patient at any time during their treatment course.

The need for referral for rescue surgery will be recorded as a trial outcome measure.

6.3.7 Discharge

The timing of a patient's discharge remains at the discretion of the treating physician. For the purposes of the trial analysis, both the date when a patient is made medically fit for discharge and the date of their actual discharge will be recorded.

6.3.8 Trial follow-up visits

Trial follow-up visits are intended to match the schedule of routine follow-up for patients with pleural infection. As such, participants will be asked to return for assessment on day 30 post procedure (+/- 3 days) and on day 90 post procedure (+/- 7 days).

As part of standard care at these visits, patients should have a clinical assessment, chest radiograph (if not performed within the 7 days before), thoracic ultrasound, and blood tests as described below. They will also be asked to complete the EQ-5D quality of life questionnaire. The results of these tests will be recorded as part of the trial.

Patients who attend their post-discharge follow-up visit outside of the specified windows may still have their data collected, but these visits should be recorded as protocol violations.

For patients who are unable to attend a post-discharge follow-up visit, attempts should be made to contact them over the telephone in order to complete as much of the trial data collection as possible. Patient-reported data, such as the EQ-5D, may be sent by to the patient by post for completion and return to the trial co-ordinating centre.

For patients who remain in the study but can neither attend a visit nor be contacted over the telephone at the appropriate time, as much information as possible should be gathered from either the patient's hospital notes or through contacting community healthcare services.

6.4 BIOLOGICAL SAMPLES

6.4.1 Blood tests

All blood tests performed during the SPIRIT trial are accepted as being part of the standard care of patients with pleural infection. Samples will be processed at local hospital laboratories. Results from these tests will be recorded at the following time points: at the baseline assessment; on the first day after allocated procedure, and every alternate day after that until discharge; at the day 30 follow-up visit; and at the day 90 follow-up visit.

The results recorded at each time point should cover: full blood count, urea and electrolytes, C-reactive protein, and liver function tests. In addition, results for random serum glucose and lactate dehydrogenase should be recorded at the time of baseline assessment.

6.4.2 Pleural fluid

All pleural fluid tests performed during the SPIRIT trial are accepted as being part of standard care. During their allocated procedure, patients in both the control and the intervention arms should have pleural fluid samples sent to the local microbiology laboratory for culture and microscopy processing. A minimum of 5mls of fluid should be sent in both a sterile, universal container and in blood culture bottles.

6.4.3 Pleural biopsy samples

All pleural biopsy samples taken during the SPIRIT trial are accepted as being part of a standard thoracoscopy procedure. For patients in the intervention arm, at least five parietal pleural biopsy samples should be taken at the time of medical thoracoscopy. These samples should be sent in a sterile container (with or without sterile saline) to the local microbiology laboratory for culture and microscopy processing.

6.4.4 Research samples

Patients will be asked if they are willing to consent to up to 200mls of pleural fluid and up to 3 additional biopsy samples being taken for storage, transport and subsequent biomolecular testing. If taken, these samples should be processed and stored as per the trial manual.

6.5 IMAGING

6.5.1 Thoracic ultrasound

All thoracic ultrasound scans are to be performed as part of standard clinical care. Scan results should be documented during the baseline assessment; on the first, third and seventh days post allocated procedure (and then every seven days (+/- 1 day) after that if the patient remains in hospital); and at the time of the day 30 and day 90 follow-up appointments. The scans on days one and three do not need to be completed if they fall outside of normal working hours, but at least one of these assessments must be completed.

Scans should be performed by those with at least Royal College of Radiologists Level One accreditation (or equivalent), or by those with sufficient experience to be equivalent to this standard.

6.5.2 Chest radiography (x-ray)

All chest radiographs performed during the SPIRIT trial are part of standard care. Images should ideally be performed as P-A and are to be taken at or prior to baseline assessment; within 12 hours of the allocated procedure finishing; on the first day post procedure; after drain removal (but before discharge); and at the day 30 and 90 follow-up visits.

6.6 OTHER TESTS

6.6.1 Quality of life

Patients' serial quality of life will be assessed using the validated EQ-5D-5L (EuroQol Research Foundation). They will be asked to complete the document at baseline; on day 7 (+/- 1 day) post procedure; and at the day 30 and day 90 follow-up visits.

6.7 SEMI-STRUCTURED INTERVIEWS OF PATIENT EXPERIENCES

In order to better understand patient (and carer) subjective experiences of recruitment and randomisation procedures, and thus help determine the trial's acceptability, a subset of participants will

be invited to participate in semi-structured interviews. The sample size for the qualitative study is 20 patients (10 from each treatment arm), as this figure is expected to allow data saturation to be achieved.

All patients will be asked at enrolment whether they are willing to be contacted about taking part in an interview. Those who give their consent will be provided with a more detailed, specific patient information sheet regarding the interviews.

Interviews will take place approximately two weeks (14 days +/- 3 days) post trial procedure. Patients will have the option of interview either by telephone or face-to-face in their own home, whichever they feel is more appropriate. Patients who remain in hospital after two weeks may also be interviewed, but this must be done in an appropriate environment as described in Appendix 4. They will be asked to confirm their consent verbally (in the case of telephone interviews) or in writing if face-to-face. Should an additional party (such as a member of their family or a carer) wish to participate, they will be asked to complete a separate consent form.

Interviews will be semi-structured in nature and will last approximately 60 minutes. Interviews will be audio-recorded, transcribed, anonymised and imported into a qualitative data management software package (NVIVO, QSR International Pty Ltd.)

The interviews will employ a topic guide designed to explore patients' views regarding their illness; the trial recruitment process; and the interventions. This will allow areas for refinement to be identified. The topic guide will be developed with patient and public involvement (PPI). Further details regarding semi-structured interviews and their analysis can be found in Appendix 4.

6.8 END OF TRIAL

The trial will close to recruitment when the thirtieth patient has undergone randomisation and treatment allocation, unless the trial steering committee, regulatory bodies or Sponsor recommend stopping before this point. The trial will end with the final follow-up visit, death or withdrawal of the last patient remaining in the study.

7. STATISTICS AND DATA ANALYSIS

7.1 STATISTICAL ANALYSIS

7.1.1 Sample size

The SPIRIT study is a feasibility study and as such there has been no attempt at formal power or sample size calculation. A recently completed prospective observational study of pleural infection patients requiring drainage (32) would suggest that approximately 150 patients in total would be seen by the selected trial centres over the course of a year. Based on a conservative accrual rate of one of every five patients, a sample size of 30 patients will be used as this is felt to be both sufficient to assess practicability and to suggest the presence of possible between-group differences.

7.1.2 Primary outcome analysis

The primary outcome (feasibility) will be assessed in three parts:

- The ability to recruit to the study will be determined by the proportion of the total number of "pre-screened" patients (those with suspected pleural infection seen during the trial period) who are not eligible for trial entry. The primary outcome will be defined as successful if <2/3 of pleural infection patients are recorded as pre-screen failures. This will be a surrogate for whether the trial's question is applicable to a reasonable proportion of the pleural infection population.
- The ability to randomise patients to the trial interventions will be determined by the proportion of the total number of patients who are offered a patient information sheet (screened patients) who do not proceed to trial enrolment and randomisation. The primary outcome will be defined as successful if <2/3 of those who receive trial information are recorded as screen failures. This will be a surrogate for whether suitable patients are willing to take part in the trial, and whether any delays associated with trial recruitment impact on patient care.
- The ability to deliver the trial protocol will be determined by the proportion of the total number of patients who do not receive their allocated procedure on either the same day as randomisation or the next. The primary outcome will be defined as successful if <50% are recorded as allocation failures in both trial arms, assessed individually. This will be a surrogate for whether the trial centres are able to offer a rapid pleural intervention having committed to doing so.

Trial logs will also be scrutinised for specific reasons which occur regularly for pre-screen, screen, or allocation failures.

7.1.3 Secondary endpoint analysis

Quantitative secondary endpoints will be analysed on both an intention-to-treat and, separately, a per protocol basis. Results will be presented in terms of between-group differences in either means or medians, with associated 95% confidence intervals.

Categorical data will be analysed using the Chi-squared approach (or Fisher's exact test where appropriate). Ordinal data will be analysed using the Mann Whitney U test or an independent sample t-test. Survival (time-to-event) data will be presented in the form of Kaplan-Meier curves and analysed using the Logrank test (with Cox proportional hazards analysis also performed).

The semi-structured interview component of the study will be analysed using a recognised qualitative approach, such as framework analysis, thematic analysis, or a combination of the two.

Analysis of anonymised radiological images will be performed by two clinicians, who will be blind to treatment allocation. Assessment of pleural effusion size will be performed using a recognised and previously published method. (7)

The comparison of treatment costs between randomisation and being medically fit for discharge will be performed from the perspective of the UK National Health Service, with prices of interventions or treatments being referenced from standard resources.

7.1.4 Interim analysis

No formal interim analysis for feasibility is planned. However, the Data/Safety Monitoring Committee will be asked to review the trial's progress after ten patients have been successfully randomised in order to assess for safety.

8. ADVERSE EVENTS

8.1 DEFINITIONS

8.1.1 Adverse Event (AE)

An untoward medical occurrence in a patient or clinical study subject, which does not have a causal relationship with the trial intervention.

8.1.2 Adverse Reaction (AR)

An untoward medical occurrence which has a clear causal relationship between the event and the research procedure

8.1.3 Serious Adverse Event (SAE) / Serious Adverse Reaction (SAR)

Any untoward and unexpected medical occurrence or effect that:

- Results in death
- Is life-threatening – *refers to an event during which the subject 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*
- Requires hospitalisation, or prolongation of existing in-patients' hospitalisation
- Results in persistent or significant disability or incapacity
- Is or results in a congenital anomaly or birth defect

Medical judgement should be exercised in deciding whether an AE or AR is serious in other situations. Important AE/ARs which do not strictly meet the criteria for being serious but which may jeopardise the subject or require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

8.1.4 Suspected Unexpected Serious Adverse Reaction (SUSAR)

Any adverse event which is classed as serious and for which there is evidence of a causal relationship with a research procedure, but where that event is unexpected.

8.2 RECORDING AND REPORTING PROCEDURES

Any questions concerning adverse event reporting should be directed to the trial manager or Chief Investigator in the first instance. A flow chart for adverse event recording and reporting can be found in Appendix 3.

8.2.1 All adverse events/reactions

An AE/AR should be recorded on the dedicated eCRF at the earliest opportunity following the trial team becoming aware of the event. This is most likely to be during the regular follow-up visits.

8.2.2 Serious adverse events/reactions

Any event which meets the criteria for an SAE should be discussed with the local principal investigator in the first instance. SAEs and SARs should be reported to the Sponsor within 24 hours of the local Principal Investigator (or nominee) becoming aware of the event, using the separate Sponsor-specific SAE form. Events listed in the expected events section below do not need to be reported as SAE/SARs, but will still be recorded as having met the criteria for being serious.

Events which are serious, causally related to a trial procedure (in the opinion of the PI), and which are unexpected (i.e. a SUSAR) should be reported to the Sponsor immediately upon the trial team becoming aware of the event. The Sponsor has a duty to undertake and co-ordinate the expedited reporting required following such events, including to the approving REC.

8.2.3 Contact details for reporting SAEs

Sponsor: North Bristol NHS Trust

Email: ResearchSponsor@nbt.nhs.uk

Fax: 0117 414 9329 (mark SAE forms for the attention of Helen Lewis-White)

Please also send email copies to:

RespiratoryResearch@nbt.nhs.uk and Rahul.Bhatnagar@Bristol.ac.uk

For any queries related to SAEs, please contact Tel: 0117 414 8114 (Mon to Fri 08.00 – 16.00)

8.2.4 Following reporting

All reported events should be followed to resolution, with additional reports submitted as necessary. This should occur regardless of whether the patient was withdrawn from the trial as a result of the adverse event, unless the withdrawal request rescinded permission for outcome data to be collected and used.

8.3 EXPECTED ADVERSE EVENTS

The following are considered to be expected in the context of patients suffering with pleural infection and who require an intervention for fluid drainage.

- Chest pain, or discomfort around procedure site (unless not improving or remains unresponsive to analgesia)
- Bleeding associated with trial procedure (unless causing haemodynamic compromise, requiring transfusion, or requiring intervention to achieve haemostasis)
- Surgical emphysema (unless requiring surgical referral or causing airway compromise)
- Subcutaneous infection related to thoracoscopy or drain insertion, (unless unresponsive to antibiotic therapy)
- Chest drain falling out, becoming dislodged or becoming blocked
- Pneumothorax or evidence of non-expandable lung following chest drain insertion or thoracoscopy (unless requiring surgical intervention)
- Hospital admission, elective procedure or surgery, disability, incapacity or death due to underlying or pre-existing condition
- Delay in planned discharge date (unless due to a complication directly related to a trial procedure)
- Readmission to hospital or need for thoracic surgery due to pleural infection or pneumonia
- Hypotension or tachycardia due to sepsis requiring intravenous fluid support alone
- Hypothermia or hyperthermia due to sepsis, within the range ≥34.0°C to ≤39.4°C
- A reaction to an administered medication (unless not described in the current version of the British National Formulary (BNF))

9. REGULATORY ISSUES

9.1 RESEARCH GOVERNANCE

This study will be conducted in accordance with:

- The International conference for harmonisation of good clinical practice (ICH GCP)
- The Research governance framework for health and social care, and
- The Declaration of Helsinki

9.2 ETHICS APPROVAL

A research ethics committee will be review the trial prior to recruitment commencing. The REC will be asked to approve the trial protocol, GP letter, as well as all "public-facing" or "participant-facing" documentation (e.g. patient information sheet, consent forms, or advertising materials). They will also approve the questions to be asked during the semi-structured interview component of the study. All of the above will also be approved by the Sponsor.

9.3 RISKS AND ANTICIPATED BENEFITS FOR PARTICIPANTS & SOCIETY

Despite the SPIRIT trial being an investigation of feasibility, there are not expected to be any significant increased risks to individual participants over those associated with the standard clinical care of pleural infection. Both medical thoracoscopy and chest drain insertion are considered routine procedures in the management of patients with pleural effusions. Moreover, although the use of LAT is relatively rare for those with confirmed pleural infection in the UK, there are sufficient (albeit non-randomised) data to suggest that it may be undertaken safely by those with adequate experience. The primary potential benefit to those being randomised to the intervention arm in this study is a reduced duration of in-hospital treatment. Should this be supported by the trial's results, it will enable a larger study to be performed looking to directly address this question, which may in turn lead to a wider, societal benefit in terms of improving the care pathway of those with pleural infection.

9.4 SPONSOR APPROVAL

All trial documents will be approved by the Sponsor prior to submission to the REC. Any amendments following a favourable ethical opinion, will be approved by the Sponsor prior to submission to REC.

9.5 NHS APPROVAL

For all sites, approval from the local NHS Trust is required prior to recruitment beginning at that location.

Any amendments to the trial documents will be approved by all necessary parties prior to implementation.

9.6 INVESTIGATORS' RESPONSIBILITIES

Local investigators will be required to ensure that local research approvals have been obtained and that any contractual agreements required have been signed off by all parties before recruiting any participant. Investigators will be required to ensure compliance with the protocol and completion of the CRFs. Investigators will be required to allow access to study documentation or source data on request for monitoring visits and audits performed by the Sponsor or any regulatory authorities.

Investigators will be required to read, acknowledge and inform their trial team of any amendments to the trial documents approved by the REC that they receive and ensure that the changes are complied with.

9.7 CONSENT

Consent to trial participation must be sought from each potential participant only after a full explanation has been given and a patient information sheet offered. Due to the relatively acute nature of pleural infection, whereby those requiring chest drainage would normally be expected to undergo their procedure as soon as possible, as well as the likely difficulties which will be associated with having to arrange an urgent medical thoracoscopy in some patients, it is not felt practical to mandate participants have 24 hours or more to consider trial entry. However, it is imperative that all participants be given sufficient time (as determined by the participant themselves) for trial information to be considered and for questions to be asked. Signed participant consent should ideally be obtained, but for those patients who are unable to provide a signature an alternative identifying mark (such as a fingerprint) may be used if witnessed by a third party signatory. The right of the participant to refuse to participate without giving reasons must be respected.

In addition to consent for the study, separate written consent should be taken for the allocated trial intervention in accordance with the recruitment centre's local guidance. For those patients who are approached to have a semi-structured interview, a verbal confirmation of consent should be sought at

the time of questioning. Written consent should also be obtained for any additional party who contributes to the semi-structured interview.

After the participant has entered the study, the treating clinician remains free to give alternative treatment to that specified in the protocol at any stage if he/she feels it is in the participant's best interest, but the reasons for doing so should be recorded. In these cases the participants remain within the study for the purposes of follow-up and data analysis. All participants are free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing further treatment.

If a trial participant loses the capacity to consent during the trial then they will be withdrawn from the trial at that point. Data collected with their consent up until the point they lose capacity may be used.

Details of consent relating to the semi-structured interview component of the trial is covered in Appendix 4 (section A4.7).

9.8 CONFIDENTIALITY

The Chief Investigator, Principal Investigators, and Sponsor will preserve the confidentiality of participants taking part in the study in accordance with the Data Protection Act and any other local requirements. Trial documentation and the study database will be anonymised using a unique identification number, generated during enrolment. Any patient-identifying information will be stored either at the local trial centre or at the main trial co-ordinating centre in Bristol, as long as consent has been gained for the transfer of data between these two locations.

No individual participant will be identified in any publications which may arise from this study.

9.9 INDEMNITY

North Bristol NHS Trust holds standard NHS Hospital Indemnity and insurance cover with NHS Litigation Authority for NHS Trusts in England, which apply to this trial.

9.10 SPONSOR

North Bristol NHS Trust will act as the Sponsor for this trial. Delegated responsibilities will be assigned to the NHS trusts taking part in this trial.

9.11 MONITORING

The study may be subject to inspection and audit by North Bristol NHS Trust (under their remit as sponsor) and other regulatory bodies to ensure adherence to GCP and the NHS Research Governance Framework for Health and Social Care (2nd edition).

9.12 PATIENT EXPENSES

No incentive payment will be made to patients for participation in the trial. However, the study will reimburse (upon production of receipts where appropriate) all reasonable travel expenses incurred by patients for follow-up visits which are outside of standard care.

10. DATA MANAGEMENT

10.1 DATA RECORDING, STORAGE AND ACCESS

10.1.1 Main trial data

Accurate and contemporaneous source data should be kept for all trial participants. This will typically comprise the standard medical records, including results for radiological, microbiological, biochemical and haematological tests. All trial records at all sites will be stored securely in line with the Data Protection Act and the principles of GCP. As such, electronic data will be stored on encrypted and password-protected servers and physical records will be stored in secured and lockable cabinets.

Trial data will be captured using electronic case report forms (eCRF), which are to be completed by local trial teams at recruitment sites. A guide for using the eCRF will be provided to each site. The eCRF will enter data directly onto the trial database, except for VAS scores and quality of life data which will be filled out on paper by patients and transcribed into the database by the trial team. Both the eCRF and the database will be built using Red Pill software (Sealed Envelope Ltd., London) and will be housed remotely on their servers, with regular back-ups taking place. The database will maintain an audit trail of access, data entry, data amendments, and final sign-off.

The eCRF will only be accessible to named personnel at recruitment sites via an encrypted and password-protected web link, with all data entered associated with the participant's unique trial identifier.

The complete trial database will only be routinely accessible to named personnel at the trial co-ordinating site in Bristol. However, each centre will also be able to access trial data previously recorded by that site. No satellite recruitment centre will have access to another site's data.

10.1.2 Semi-structured interview data

Those patients who enter the qualitative component of the study will have their semi-structured interviews audio recorded. These recordings, taken on a password-protected device, will be encrypted at source and then, if necessary, transported immediately to the trial co-ordinating centre in Bristol on an encrypted memory drive or laptop computer. These recordings will then be uploaded and stored on password-protected and encrypted NHS servers which are owned and managed by the Sponsor. During recordings, patients will only be identified by their trial number.

For the purposes of analysis, semi-structured interview recordings will be transcribed. This will be performed by The Transcription Company (Sutton Coldfield, West Midlands,

http://www.thetranscription.co.uk/security-confidentiality-statement/), who are approved by the University of Bristol (who will be advising and assisting with the qualitative component of SPIRIT). All data transfer and storage will be performed in line with the rules stipulated by the Data Protection Act (2000) by the University of Bristol.

10.1.3 Radiological images

Certain images (as specified above) taken during trial participants' periods of care will be requested for review and analysis as part of the trial. Prior to transfer, these images will be stored and managed on recruitment centres' local encrypted NHS servers. When required, they will be sent in an encrypted or anonymised format to equivalent NHS servers at the co-ordinating centre in Bristol. All trial images will be anonymised prior to analysis.

10.2 MISSING DATA AND DATA QUERIES

Data queries will be automatically generated by the trial database at the time of data entry. The database will only be locked (allowing final analysis to begin) once the Trial Steering Committee is satisfied that all data queries have been addressed as completely as possible. Local recruitment sites should look to minimise missing data by maintaining contact with participants (to avoid missed appointments), and by completing eCRFs using notes reviews or telephone contact if necessary (where appropriate consents are in place).

10.3 DATA MONITORING

The trial may be monitored by the Sponsor or other regulatory bodies. For the purposes of audit and compliance monitoring, clinical trial data will be available to delegated members of the local trial teams, as well as to representatives of the Sponsor, relevant regulatory authorities, and the trial co-ordinating team. Participants will consent to their trial data being released for this purpose. Principal Investigators at individual sites will facilitate access to study records for the purposes of monitoring and audit.

10.4 PUBLICATION POLICY

The Trial Management Group will have sole responsibility for the expedient preparation, review and submission of any manuscripts, abstracts, press releases or other publications detailing the trial's

procedures or findings. Individual investigators may not publish data concerning their patients that are directly relevant to the objectives of the study until publication of full study data.

Any publication will include a list of investigators, with authors being determined in line with the ICMJE guidelines, as well as an acknowledgement of roles of the trial Sponsor and Funder(s).

11. STUDY MANAGEMENT

11.1 TRIAL MANAGEMENT GROUP (TMG)

The TMG is responsible for the day-to-day management of the study. It is responsible for all aspects of the trial, including budget management; protocol compliance; and ensuring the immediate safety of trial participants. The TMG will consist of: the Chief Investigator, the trial manager, and the lead trial nurse. The TMG will report to the Trial Steering Committee at regular intervals.

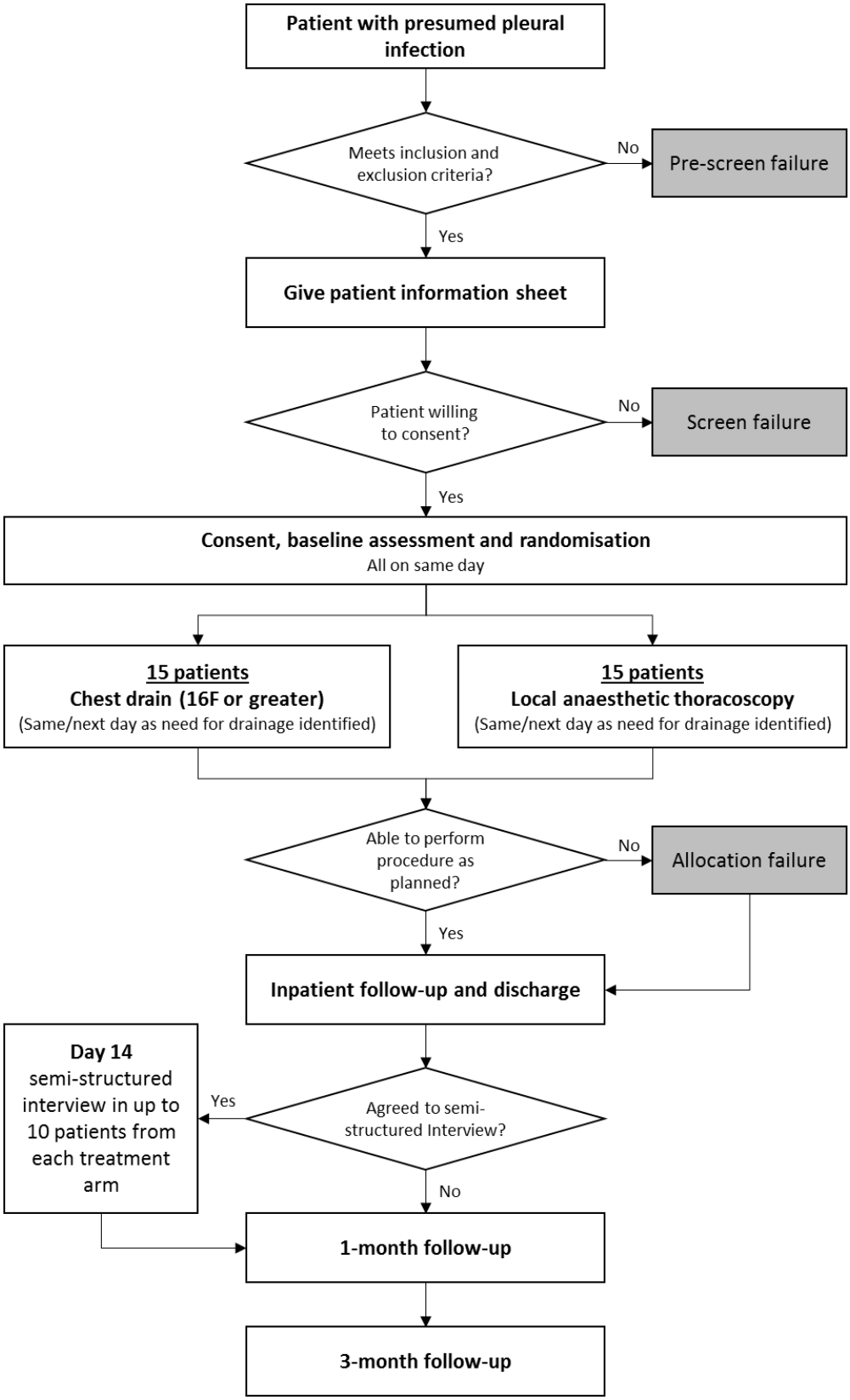
11.2 TRIAL STEERING COMMITTEE (TSC)

The role of the TSC is to provide overall direction and supervision for the trial, as well as to monitor its progress and its adherence to the necessary regulations. It will meet regularly to discuss the trial's progress. It comprises both researchers working on the study and independent physicians, as well as both lay and medical members. The TSC members will include the members of the TMG, along with an independent Chairperson, two key investigators; an independent lay (patient) member; and an independent physician expert.

11.3 DATA/SAFETY MONITORING COMMITTEE (DMC)

The DMC comprises individuals entirely independent from the trial, and will consist of both a medical experts. They will be asked to assess the progress, conduct, and safety of the trial after 15 patients have been enrolled. They will report their recommendations to the Chair of the TSC.

APPENDIX 1 – MAIN TRIAL FLOW CHART



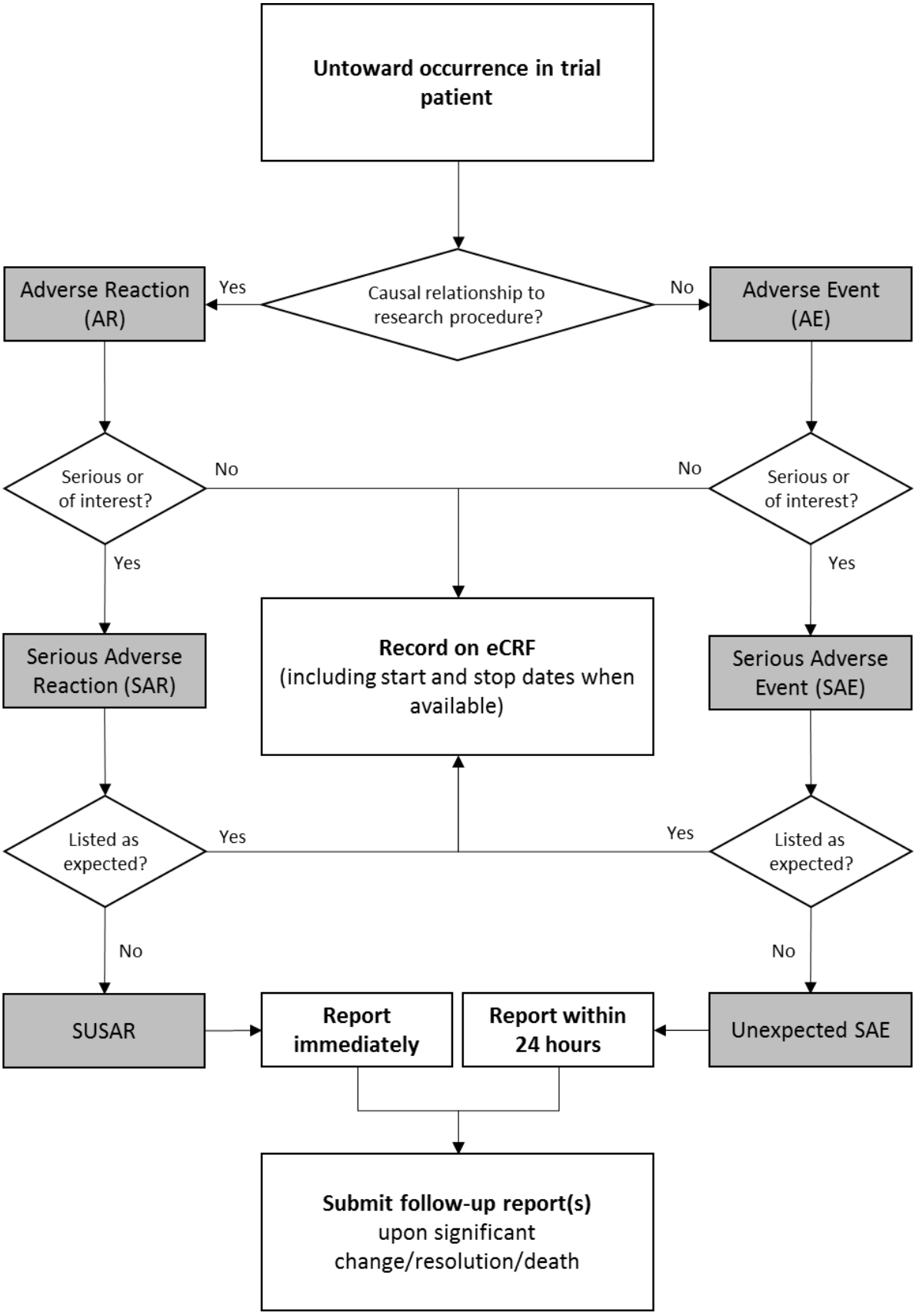
APPENDIX 2 - TRIAL INTERVENTIONS SUMMARY TABLE

Timepoint	Events	Duration	Activities
Pre-enrolment	**Screening and pre-screening**	5 mins	Complete screening log for all patients with suspected pleural infection Provide patient information sheet where applicable
Enrolment	**Trial consent**	30 mins	Complete consent form A Provide patient information sheet B if participant agrees to semi-structured interview
Baseline assessment	**Baseline assessment**	60 mins	Baseline CRF EQ-5D questionnaire Thoracic ultrasound scan Bloods if not performed within previous 24 hours Chest x-ray if not performed within the previous two days
Randomisation	**Randomisation and treatment allocation**	10 mins	Access randomisation system and input required information Inform patient and necessary staff of treatment allocation
Intervention arm	**Medical thoracoscopy on same or next day as need for drainage identified**	90 mins	Appropriate procedural consent LAT (with pleural biopsies, maximal fluid drainage with samples, breakdown of immature septations, and pleural lavage with normal saline) Targeted 16F+ drain placement Fluid samples for M,C+S Chest radiograph within 12 hours of procedure end Research sample processing
Control arm	**Chest drain insertion on same or next day as need for drainage identified**	60 mins	Appropriate procedural consent Blunt dissection or Seldinger chest drain insertion of size ≥16F Fluid samples for M,C+S Chest radiograph within 12 hours of procedure end Research sample processing
Day 1 post procedure	**Post procedure assessment**	30 mins	Bloods Clinical assessment Thoracic ultrasound (if working day) Chest radiograph Day 1 post procedure CRF (including VAS)
Inpatient period	**Inpatient assessments**	30 mins each	At least alternate day bloods until day 9 post intervention (and at least every 7 days thereafter if remains in hospital) Thoracic ultrasound on days 3 (if working day) and 7 post intervention, and at least every 7 days thereafter if remains in hospital Clinical assessments as per local practice Days 3 and 7 post procedure CRFs and then extended stay CRF every 7 days until discharge (inc. VAS) EQ-5D day 7 post procedure Chest radiograph after drain removal (if occurs)
Discharge from admitting hospital	**Discharge assessment**	30 mins	Discharge CRF Arrange date for semi-structured interview if applicable

Timepoint	Events	Duration	Activities
Day 14 post procedure (+/- 3 days)	**Qualitative semi-structured interview**	45 mins	Complete consent form B or C (and consent form D if applicable) Visit patient's home or conduct interview over telephone. (Interview can also be performed on the ward if patient still in hospital)
Day 30 post procedure (+/- 3 days)	**1-month follow-up**	30 mins	Day 30 post procedure CRF (including VAS) Chest radiograph Clinical assessment Bloods Ultrasound scan EQ-5D
Day 90 post procedure (+/- 7 days)	**3-month follow-up**	30 mins	Day 90 post procedure CRF (including VAS) Chest radiograph Clinical assessment Bloods Ultrasound scan EQ-5D

Trial-specific activities highlighted in red; All other activity would be considered routine clinical practice for patients requiring chest drain or follow-up for pleural infection.

APPENDIX 3 - ADVERSE EVENT REPORTING SUMMARY



APPENDIX 4 - SUB-PROTOCOL FOR SEMI-STRUCTURED INTERVIEWS

A4.1 Number of participants

The semi-structured interview component of the SPIRIT trial will consist of a maximum of 10 patients from each trial arm. No further patients will be approached for inclusion once either this target has been reached, or once the main trial closes to recruitment.

A4.2 Pre-screening and screening

At the time of consent for the main SPIRIT trial, patients will be asked if they are willing to be contacted regarding the qualitative component of the study. They will constitute the pre-screened population. Those who indicate their consent to being approached will be provided with a separate patient information leaflet regarding the semi-structured interviews, and will be recorded as having been screened.

A4.3 Selection for interview

Those who have received a patient information sheet will be contacted initially on a consecutive basis. However, specific patients may be approached during the later stages of the study in order to ensure as much balance as possible between those from different trial arms and different trial sites. Only members of the trial team in Bristol will make an approach to a patient regarding interviews.

A4.4 Timing of interviews

Patients who are selected will be contacted approximately 7-10 days after their trial intervention with a view to arranging their interview to take place on the 14th day (+/- 3 days) post intervention. Interviews will be expected to last approximately 45 minutes and will only be arranged for a time which is mutually convenient for both the patient and the researcher.

A4.5 Interview locations

Patients from any trial centre may be asked to participate, but not all need have their interview conducted face-to-face – those who are more geographically remote from the main trial co-ordinating centre (in Bristol) may have their interview by telephone or video call. Participants who remain as inpatients on the 14th day post procedure may still have an interview, but this should be conducted in a quiet area of the ward away from other patients.

A4.6 Interview personnel and patient preparation

Interviews will be conducted by a member of the research team with experience and/or training in conducting semi-structured interviews.

A4.7 Consent (patient and family) and conducting interviews

At the agreed time, the member of the research team performing the interview will either contact the patient over the telephone or will meet them at the pre-arranged location. For face-to-face interviews, the research team member will wear their hospital/university identification badge at all times and will begin by taking separate, interview-specific consent before starting recording. For those having telephone interviews, verbal consent must be taken and recorded on a dedicated form, which will subsequently be copied and sent to the patient for their records.

On occasion, additional parties (such as members of a patient's family) may be present and wish to contribute to an interview. If the patient is in agreement with this, then the additional party or parties should be asked to complete a separate consent form which gives permission for their responses to be used alongside the patient's. They will also receive a copy of this for their records.

Once all necessary consents have been taken, the researcher will begin recording the conversation (having notified the interviewees immediately beforehand).

A4.8 Semi-structured interview questions

Patients should be encouraged to speak freely, but the direction of the conversation should be based upon the following series of questions, which are designed primarily to gauge the trial participant's experiences of the study, their allocated procedure, and the period associated with their illness:

- How did you feel about being approached for the SPIRIT trial?
    - Who approached you?
- Did you have any concerns about taking part in the trial?
- What did you think about the written information you received about the trial?
    - Was it easy to understand?
    - Did it prepare you for taking part in the trial?
    - Can you think of any ways to improve the information you were given?

- When you agreed to participate in the trial, what did you understand about how we decided which treatment to give you?
    - How did you feel about this?
- Did you have any preference for one treatment over another beforehand?
    - How did you feel when you were told which treatment you would have?
    - Did you feel prepared before you had it?
- How did you feel during the procedure and in the days after you had it?
    - Did you experience any problems or complications during the time after your procedure?
- What did you think about the questionnaires you were asked to do as part of the trial?
    - Did you understand them?
    - How did you feel about filling them in?
- What did you think about the tests we asked you to do as part of the trial?
    - Did you feel able to do the tests?
    - Were there any which were particularly difficult?
- Did you need any assistance with any of the tests or questionnaires?
- Is there anything you would change about the questionnaires or tests?
- How did you feel about the time you spent in hospital after your procedure?
    - Could anything have been improved?
- Did you feel ready to go home when the time came?
    - What did you think of the discharge process from the hospital?
- When you got home, did you require any additional help compared to before you were admitted?
- Had you ever heard of pleural infection before being affected by it?
- Is there anything further that you would like to discuss?

A4.9 Ending the interview

Once all of the above questions have been asked and the semi-structured conversation concluded, the researcher should explain to the participant(s) that the end of the interview has been reached. Consent to interview data being used will be re-affirmed verbally before recording finishes.

A4.10 Data handling

As described in section 10.1.2, recordings will be made onto an appropriate device. At the beginning of the recording, the participant will only be identified by their trial number. Upon completion, if necessary, recordings will then be transported immediately to the trial co-ordinating centre in Bristol on an encrypted memory drive or laptop computer. These recordings will then be uploaded and stored on password-protected and encrypted NHS servers which are owned and managed by the Sponsor.

For the purposes of analysis, semi-structured interview recordings will be transcribed. This will be performed by The Transcription Company (Sutton Coldfield, West Midlands, http://www.thetranscription.co.uk/security-confidentiality-statement/), who are approved by the University of Bristol (who will be advising and assisting with the qualitative component of SPIRIT). All data transfer and storage will be performed in line with the rules stipulated by the Data Protection Act (2000) by the University of Bristol.

Any publication which arises from the semi-structured interviews will not contain any identifiable patient data, although quotations may be used if permission for this is given.

A4.11 Researcher lone working

The safety of those conducting interviews away from the main trial centre is of paramount importance. All off-site work will be conducted according to the Sponsor's comprehensive lone working protocols. At a minimum, researchers will ensure the following:

- That at least one person is aware of their destination, and expected arrival and departure times
- That when conducting an interview, all effort will be made to have no obstruction between themselves and a main exit
- That they carry a charged mobile phone at all times during an interview
- That they contact at least one person immediately before and immediately after the interview, and that they have in place a plan to raise an alarm in the event that they are unable to make contact at pre-agreed times

APPENDIX 5 - VISUAL ANALOGUE SCALE

	Date and time of entry	DD	MM	YYYY		TIME

HOW MUCH CHEST PAIN ARE YOU FEELING AT THE MOMENT?

No pain at all — Worst possible pain

FOR OFFICE USE ONLY	Assessor 1 score mm	Signature/Initials	Assessor 2 score mm	Signature/Initials

HOW SHORT OF BREATH ARE YOU FEELING AT THE MOMENT?

Not breathless at all — Worst possible breathlessness

FOR OFFICE USE ONLY	Assessor 1 score mm	Signature/Initials	Assessor 2 score mm	Signature/Initials

APPENDIX 6 - TRIAL AMENDMENTS

First approved protocol			1.0 (15 Feb 2017)		
Amendment number	**Substantial or minor**	**Documents affected**	**Resulting versions (and dates)**	**Amendment prepared by**	**Details of amendment**
1	**Substantial**	• Protocol • Consent A • PIS A	2.0 (12 Jun 2017) 3.0 (12 Jun 2017) 3.0 (12 Jun 2017)	**Rahul Bhatnagar**	• Clarification that a fluid pH of ≤7.2 or the discovery of pus are sufficient for inclusion • Confirmation that fluid and biopsy samples will be taken for storage and biomolecular analysis • Updated expected adverse events section to include medication reactions • Clarified time points for VAS completion • Updated Sponsor details
2	**Substantial**	• Protocol • Consent A	3.0 (10 Feb 2018) 4.0 (10 Feb 2018)	**Rahul Bhatnagar**	• Various grammatical and syntax errors corrected • Clarified wording of inclusion and exclusion criteria • Allowed patients who have had certain types of previous thoracic surgery to be enrolled • Removed inclusion criterion relating to patient willingness to receive information sheet • Clarified that trial data may be sent between SPIRIT sites for analysis purposes • Updated logos • Corrected discrepancy in patient target between main protocol and qualitative sub-protocol • Clarified that patients may be entered onto pre-screen logs retrospectively • Removed need for spirometry from study • Extended trial end date to 31st January 2019
3	**Minor**	• Protocol • PIS A	3.1 (6 Apr 2018) 4.1 (6 Apr 2018)	**Rahul Bhatnagar**	• Updated version numbers • Removed spirometry from PIS A

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