ACTion Trial

Short Title: **A**spiration versus **C**hest **T**ube drainage for Pleural Infect**ion** trial

Full Title: Comparing therapeutic thoracentesis to chest tube drainage for pleural infection: a feasibility trial.

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This protocol describes the ACTion trial and provides information about procedures for entering participants. Every care was taken in drafting this protocol, but corrections or amendments may be necessary in the future. Any amendments 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 and general queries should be directed to the Sub Investigator (Dr David Arnold) via 0117 414 8041 or the Clinical research team on 0117 414 8114.

Sponsor

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

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Funding

This trial is being funded by the National Institute for Health Research (NIHR) via a Doctoral Research Grant to the Sub Investigator who is hosted by the University of Bristol.

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Clinical Phase	Feasibility Study	
Trial Design	Randomised Control Trial	
Trial Participants	Patients presenting with pleural infection to North Bristol NHS Trust	
Planned Sample Size	30	
Treatment duration	Not specified	
Follow up duration	3 months	
Planned Trial Period	30 months	
	Objectives	Outcome Measures
Primary	To assess the feasibility of a full-scale randomised trial of ambulatory management in pleural infection.	Randomisation rates, assessed by the proportion of the total number of patients who are eligible for trial entry who are randomised.
Inclusion Criteria	Clinical presentation consistent with pleural infection and fulfilling at least one of the following criteria; • Purulent pleural fluid • Pleural fluid pH ≤ 7.2 • Pleural fluid glucose ≤ 3.4 mmol/L • Pleural fluid lactate dehydrogenase (LDH) > 1000 IU/L • Pleural fluid gram stain and/or culture positive for bacteria • Large effusion occupying >50% of hemithorax	
Exclusion Criteria	Any one of the following; • Severe septations/locations on ultrasound (assessed using a validated scoring system) • Ongoing sepsis requiring support beyond basic fluid resuscitation • Uncorrectable coagulopathy • Unable to consent for study • Previous pneumonectomy, recent thoracic surgery or indwelling pleural catheter on side of pleural infection • Age < 18 years • Lives alone with no access to a telephone.	

2. BACKGROUND

2.1. Current management of pleural infection

Pleural infection is a frequently occurring clinical condition with 15,000 new cases in the UK every year(1). Incidence is rising in all age groups but is increasingly common in children, the elderly and the immunocompromised(2).

Pleural infection encompasses a spectrum of disease ranging from 'simple' parapneumonic effusions through complicated fibro-purulent collections to frank pus (commonly referred to as empyema). There is little debate that prompt pleural fluid drainage and antibiotics are required for adequate resolution of infection(1, 3, 4). In the UK, patients are usually admitted to hospital for chest tube placement and intravenous antibiotics. A proportion of pleural infection will require intrapleural fibrinolytics to reduce fluid viscosity and breakdown septations(5). Around 5% require referral to thoracic surgeons for surgical management of their pleural infection(1).

The average hospital length of stay (LOS) in trials of pleural infection was 13 days(5, 6). This is places a significant burden on patients, their families, and the health service. Given that a significant proportion of these patients are clinically stable once the initial infective process has been controlled, there may be an opportunity for earlier discharge and improved patient experience. However, the current management of pleural infection dictates the insertion of a chest tube for fluid drainage. These can only be managed in hospital, cause discomfort and reduced ambulation. Numerous studies have shown that reduced ambulation has a significant impact on recovery and rehabilitation(7).

This research is based on the concept that pleural infection management is unnecessarily hospital centric. As incidence rises, so will the number of hospital bed days required to manage patients conventionally. Ambulatory strategies for pleural fluid drainage have been successful in reducing hospital stay in malignancy. Conversely, the initial management of pleural infection (chest tube insertion) has not altered in decades. The findings of this fellowship have the potential to improve the care of patients and improve resource utilisation within the NHS.

2.2. Alternatives to chest tube insertion in pleural infection

Therapeutic thoracentesis (TT) is an alternative to chest tube insertion that confers some distinct advantages. TT involves the insertion of a smaller temporary catheter into the infected pleural space under ultrasound guidance. The space is then aspirated to dryness and the catheter removed(8). Not only is the patient able to mobilise after, TT is a simple procedure (a core competency for all acute medical trainees), reduces the risk of site infection, and can be better directed at multi-loculated effusions. In addition, TT removes the risk of accidental chest tube displacement, which affects up to 30% of cases(9). However, there is a potential requirement for repeated procedures on patients, with cumulative exposure to procedural complications. It is also uncertain whether continuous drainage via a standard chest tube offers additional benefit, in terms of time to resolution, compared with repeated TT.

There are no randomised trials comparing TT to chest tube drainage in pleural infection. There are several retrospective case series documenting its safe use in European centres. Storm et al published a retrospective study comparing the outcomes of 94 patients with pleural empyema(10). Over a 5-year period, 51 patients were treated with TT compared to 43 patients treated with chest tube. Although the hospital LOS was longer than more recent studies (potentially due to more serious infection at baseline and/or differing medical practices), it was considerably shorter in the TT group (2.3 versus 5 weeks). Given the retrospective nature of the study and potential for selection bias, it is impossible to infer superiority of the TT strategy, but it appears to be a safe approach. A more recent case series from France retrospectively analysed patients who had been managed with TT(11). From 79 patients only 3 (4%) required subsequent thoracic surgery. Complication rates were low, and managed conservatively in all.

The only prospective study of TT in pleural infection was carried out in a paediatric population with ‘severe empyema’(12). Shoseyov and colleagues performed a non-randomised study comparing TT to chest tube, by virtue of differing practices between three regional hospitals. TT was carried out on alternate days until clinical or radiographic resolution. They found no significant difference between groups in terms of LOS, duration of fever or fluid drained. It demonstrated that TT was safe, even in a paediatric population with severe pleural infection. Recent review articles have confirmed the limited evidence base and the need for a randomised trial(8, 13).

2.3. The safety of ambulatory management

Any attempt to alter the management of pleural infection should account for the spectrum of presentations and outcomes between patients. The RAPID score is a validated prognostic scoring system based on the two largest randomised trials of pleural infection(14). Using 5 demographic and biochemical indicators it can identify those at highest risk of mortality at diagnosis. In the 'low-risk' group (which was also the most numerous within the cohorts) mortality was 1.4% at 3 months, compared to 43.8% in the 'high-risk' group. Despite this, the median length of stay for the 'low' and 'medium' risk groups remained 7 and 10 days respectively. It is these low/medium risk patients for whom an ambulatory approach to pleural fluid drainage may be beneficial. Those patients with a higher RAPID score may also be suitable for therapeutic aspiration to manage their pleural infection but careful consideration should be paid to these patients when considering hospital discharge.

2.4. Rationale for current study

Previous case series literature has demonstrated that therapeutic thoracentesis (TT) is a safe approach in the management of pleural infection. The potential benefit of using TT in this condition is to ambulate patients earlier, which may aid recovery and reduce hospital length of stay. The potential benefit of conventional chest tube is the continuous drainage of infected fluid which may speed resolution over TT. A randomised trial is required to access whether TT reduces length of stay without adversely affecting patient outcomes. Given this is the first study of its kind, a feasibility trial is needed to access the practicality and acceptability of randomisation to patients and healthcare professionals.

2.4. Patient and Public Involvement

The ACTion trial has been designed with patient and public involvement as well as embedded qualitative research methodology. On 20/10/17, a disease specific PPI meeting was organised at North Bristol NHS trust (NBT). The 6 participants had been previously admitted to hospital and undergone chest tube drainage. The premise of the ACTion trial was explained with the aid of a draft lay summary and trial flow chart. The participants supported, in principal, an intervention that might reduce hospital stay from pleural infection. Although recognizing the need for a feasibility study, the group was clear that the design should attempt to replicate a full-scale trial in order to gain maximum information. We reviewed the recruitment process, and participants raised several points that might improve the participant experience and the recruitment rate simultaneously. Two

participants kindly gave further comments on the readability and accessibility of the lay summary which improved it considerably.

We discussed the practicalities of embedding qualitative research within the feasibility trial to help design a future trial and explore the impact of pleural infection on patients. An interview topic guide was created collaboratively and has been incorporated into the study protocol. Two further PPI discussions were undertaken in Jan & Feb 2018 with two participants who had been recently hospitalised with pleural infection. These conversations focused on whether the intervention itself (therapeutic thoracentesis) would be acceptable to patients diagnosed with pleural infection. These participants echoed the feeling of the formal PPI group with further emphasis on ensuring patient safety when making decisions about hospital discharge. They felt that the possibility of additional pleural procedures would not put off the majority of patients if it reduced the need for chest tube insertion.

2.5. Assessment and management of risk

Pleural infection has the potential to be a serious and potentially fatal condition. Recent longitudinal data has shown the mortality in all cases is around 5% when managed conventionally. Patients at higher risk of mortality or adverse events could be anticipated using a recently developed prognostication tool called the RAPID score. This study will collect the data needed to perform a RAPID score and it will form part of the consideration for hospital discharge and early follow up. Subsequent morbidity from pleural infection is poorly understood, even following standard care.

Therapeutic thoracentesis is a frequently performed intervention in the management of pleural fluid. It is a relatively straightforward procedure and is part of the mandatory curriculum for UK core medical trainees. The case series data for TT in pleura infection is limited to 165 patients across 3 non-comparative studies but these have not shown adverse outcomes compared to normal practice.

Within the ACTion trial participant safety will be guaranteed by regular clinical and radiological review. Participants will have radiological assessment using ultrasound and chest radiograph at baseline (Day 1), Day 3 and Day 7 as a minimum. Whilst an inpatient, participants will have daily review from a physician and their clinical and radiological status will dictate the requirement for further procedures, intrapleural fibrinolytics or surgical referral. Once a participant is felt to be well enough to be discharged from hospital, their current clinical status will dictate the requirement for outpatient follow up. It is anticipated that some patients may require more intensive outpatient

follow up initially. All patients will be reviewed in pleural outpatient clinic at 3 months as part of standard care.

A trial steering committee (TSC) will meet on 3 separate occasions throughout the trial period (3, 6, 12 months). There will be a PPI representative on the TSC, and the role of the committee is to ensure concordance with the protocol and to ensure it remains safe and patient centred.

2.6. External review of research

This project is funded by a personal NIHR Doctoral Research Fellowship grant (to Dr David Arnold). As such the scientific and statistical validity have been externally peer-reviewed by representatives from the NIHR. In addition, Dr David Arnold attended a 20-person interview panel (including 2 lay members) where the proposal was scrutinised and found to be of scientific merit to justify funding.

2.7. Lay summary

When people get chest infections, fluid can sometimes build up around the lung. This is called a pleural effusion. In about 1 in 10 cases, the fluid itself becomes infected, this is called pleural infection. Pleural infection is usually treated by removing the infected fluid, and using antibiotics to mop up the left-over infection. The most common method to remove the fluid is to insert a chest tube (about 6mm across) through the chest wall, to allow fluid to drain into a collection bottle. This tube stays in until all the fluid has come out, which is usually between 3-5 days, although it can be much longer. The drain can be sore, and prevents people moving around normally. Patients need to stay in hospital whilst the drain is in position. The average hospital stay for pleural infection is 13 days, placing a significant burden on patients, their families, and the health service.

An alternative to chest tube drainage is a procedure called therapeutic thoracentesis (TT). This involves inserting a smaller (3mm) tube into the fluid and drawing off as much as possible, over 20 minutes or so, before removing the tube. This can be repeated if the fluid builds up again. This method allows patients to move around freely between procedures and even be managed out of hospital. However, we do not know whether TT might mean it takes longer for the infection to fully clear. Although some hospitals in Europe use TT for pleural infection, no studies have ever directly compared chest tubes to TT.

The ACTion trial is a feasibility (test) trial to assess whether a full-scale trial would be possible, safe and acceptable for patients. Before starting, we will involve patients who have had pleural infection to get their input on improving the trial design and processes.

In the trial, information will be collected on all patients who are admitted to Southmead hospital with pleural infection. Provided they don't have a particularly complicated pleural infection they will be invited to participate. Thirty participants will be randomly allocated to have either chest tube or TT. Information on hospital stay and quality of life will be collected. However, the main outcome will be whether a full-scale trial would be possible (were participants willing to take part). We will also be interviewing patients and health professionals who took part to get their opinions on the trial processes and possible improvements.

3. STUDY DESIGN

3.1. Trial Type

The ACTion trial is an open-label, randomised, feasibility study aiming to assess the feasibility of a full-scale randomised trial of therapeutic thoracentesis versus chest tube in pleural infection. Once patients are diagnosed with pleural infection, based on well recognised diagnostic criteria, they are allocated to chest tube (standard care) or therapeutic thoracentesis for pleural fluid drainage. Both interventions are routinely performed for other causes of pleural effusions. Therefore, the ACTion trial will be classified as a non-CTIMP for the purposes of regulatory approvals and adverse event reporting.

A subset of patients will be invited to participate in semi-structured interviews to qualitatively assess the acceptability of a full-scale trial.

3.2. Target population

The target population for this feasibility study are patients who have been diagnosed with pleural infection requiring drainage at North Bristol NHS Trust, based on well recognised criteria (see Inclusion Criteria).

The study will aim to randomise 30 patients (in a 1:1 ratio) to receive either chest tube or therapeutic thoracentesis.

3.3. Study Outcome Measures

Primary outcome

The primary outcome of the ACTion trial is to assess the feasibility of a randomised trial of chest tube versus thoracentesis in pleural infection. This will be assessed by proportion of the total number of patients who are eligible for trial entry that accept randomisation. The primary outcome will be defined as successful if ≥50% of eligible patients are willing to be randomised.

Secondary outcome measures:

- Number of pleural procedures required before resolution of infection
- Requirement of intrapleural fibrinolytics
- Hospital Length of Stay (days) and readmission rates within 30 days
- The impact of the RAPID score on success of the trial intervention
- Number of patients requiring surgical intervention
- All-cause mortality, as measured by the number of patients alive at days 30 and 90.

- Validity of lung function testing at 90 days (measured as % predicted of forced volume vital capacity).
- Patient-reported outcomes measures (PROMS), including health related quality of life (HRQoL)-using the EQ-5D-5L questionnaire and Visual Analog Score (VAS) for chest pain and shortness of breath.
- Total costs of interventions, measured by the difference in costs between the treatment arms
- Difference in pleural thickening on chest radiograph at 90 days compared to baseline.

Justification of secondary outcome measures

- All exploratory outcomes measures have been chosen as they are clinically relevant and present valid options for the primary outcome measure for a subsequent full-scale trial.
- The number of procedures required is important information for designing a future trial.
- Hospital length of stay (LOS) is important, given the often-protracted periods patients stay in hospital with standard care.
- Another significant outcome measure used in the management of pleural infection is the number of patients who go on to require surgery and mortality rates.
- The impact of this intervention on HRQoL is an important patient outcome, and forms the basis for health economic analysis.
- The costs of a more ambulatory strategy would need assessing in monetary terms in a full-scale trial. Within this feasibility study the accessibility and usability of this data will be reviewed by health economic advisers.

Exploratory outcome measures

- Patient experiences of the trial process using semi-structured interview.

Justification of exploratory outcome measures

- Semi-structured interviews will focus on the acceptability of a full scale trial to patients and healthcare professionals as well as gathering valuable information on the patient experience of pleural infection.

4. PARTICIPANT ELIGIBILITY CRITERIA

4.1. Inclusion criteria

Clinical presentation consistent with pleural infection with an effusion that, in the view of the treating physician, requires a chest tube as it fulfils at least one of the following criteria;

- Purulent pleural fluid
- Pleural fluid pH ≤ 7.2
- Pleural fluid glucose ≤ 3.4 mmol/L
- Pleural fluid lactate dehydrogenase (LDH) > 1000 IU/L
- Pleural fluid gram stain and/or culture positive for bacteria
- Large effusion occupying >50% of hemithorax

4.2. Exclusion criteria *(any one of the following)*

- Severe septations/locations on ultrasound (assessed using a validated scoring system)
- Ongoing sepsis requiring support beyond basic fluid resuscitation
- Uncorrectable coagulopathy
- Unable to consent for study
- Previous pneumonectomy, recent thoracic surgery or indwelling pleural catheter on side of pleural infection
- Age < 18 years
- Lives alone with no access to a telephone.

4.3. Withdrawal criteria

Participants have a right to withdraw from the trial at any point. The participant does not have to justify the reasons for their withdrawal and it will not affect their ongoing or future care. If the participant is happy to give reasons for their withdrawal these should be recorded and clarified where possible. This information is important for the current and any subsequent trials of this intervention. At the discretion of the Chief Investigator, patients may be withdrawn if it is felt to be in their best interests to do so.

Available data from patients withdrawn after randomisation will be included in the intention to treat analyses unless the patient has withdrawn permission for use of this data.

4.4. Co-enrolment Guidelines

Patients may only undergo randomisation as part of the ACTion 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. Patients may be enrolled in observational trials or interventional trials not related to pleural infection following discussion between the research teams to ensure compatibility between protocols, as well as with the patient to ensure they are happy with involvement in multiple trials.

5. RECRUITMENT, RANDOMISATION AND TREATMENT

5.1. Pre-Screening Procedure

Participants will be screened from normal care. Patients with pleural infection are generally diagnosed as inpatients, with a minority also diagnosed in respiratory outpatients and a hospital admission planned from there.

Patients may only be enrolled in the ACTion trial once the diagnosis of pleural infection is confirmed. Once the diagnosis is made, and therefore the patient meets the study inclusion criteria, a screening assessment will be performed by a clinical member of the trial team (see below). If this highlights that the patient fulfils any exclusion criteria (see Page 12) then this data is captured but the patient is not approached for trial enrolment. If the patient meets the inclusion criteria but has one or more exclusion criteria this is defined as a “pre-screen failure”. The patient continues normal clinical care, which would normally involve inpatient admission for chest tube.

5.2. Screening procedure

If a patient meets the inclusion criteria and has no exclusion criteria at pre-screening, then they are approached by a doctor from the trial team to discuss the ACTion trial and given a trial information sheet. Due to the urgent need for treatment in pleural infection, trial consent should take place on the same day as baseline assessment and randomisation. Given the urgency it would be acceptable to discuss the ACTion trial (with the aid of the trial information sheet) with patients with a strong clinical suspicion of pleural infection prior to definite diagnosis (through pleural fluid sampling). This would give patients more time to consider entry into the trial if they subsequently met the inclusion criteria.

Patients who are eligible for the ACTion trial but, after discussion and reading the trial information sheet, decline entry into the study are defined as “screen failures”. Despite no longer participating in the ACTion trial selected patients who decline entry may be invited to take part in semi-structured interviews to discuss their initial concepts of the trial.

5.3. Baseline assessment

Patients who are willing to enrol in the trial have baseline assessment performed by a clinical member of the team. This will involve a collection of the following data onto a paper CRF:

- Patient demographics
- Past Medical History
- Details of current pleural infection (community or hospital acquired)
- Results from a standardised thoracic ultrasound (presence of loculations)
- Results from PA chest radiograph (specifically size of effusion)
- Results of recent blood tests
- RAPID score
- EQ-5D quality of life questionnaire, VAS for chest pain and shortness of breath

5.4. Randomisation

Following consent and baseline assessment, randomisation will be performed by a member of the trial team using a secure web-based system (REDCap). Participants will be randomised in a 1:1 ration to either the control (chest tube) or interventional (therapeutic thoracentesis) arm of the study. Randomisation will be randomly generated by the REDCap software to reduce selection bias. Randomisation will be stratified by size of the effusion on chest radiograph (>50% or <50% using visual estimation of the chest radiograph).

5.5. Blinding

It is impractical to conceal treatments from either patients or healthcare professionals. Therefore, the ACTion trial will be conducted unblinded.

5.6. Post randomisation

Control arm

Patients allocated to the control arm will have a chest tube inserted as per standard care. There should be minimal delay between randomisation and intervention in keeping with usual care for urgent pleural drainage.

The size of this tube is at the discretion of the treating physician and inserted using Seldinger technique after bedside ultrasound marking (as per local guidelines). The chest tube is attached to an underwater seal and drained according to the discretion of the treating physician.

Following insertion, any samples of pleural fluid that are required for clinical purposes should be taken from the chest tube e.g. microbiological analysis.

A post procedure chest radiograph should be performed after chest tube insertion.

Intervention arm

Patients who are allocated to the intervention arm will have therapeutic thoracentesis. Again, there should be minimal delay between randomisation and drainage. Separate procedural consent must be taken as per hospital policy. Drainage will be performed using a 6 or 8F French therapeutic thoracentesis kit using bedside ultrasound marking

Initially the effusion should be drained to dryness or until the patient develops symptoms associated with trapped lung (coughing or chest pain). Catheter blockages can be managed with a small volume flush of 10-100ml of normal saline (as would be done for chest tubes).

Following thoracentesis, samples of pleural fluid that are required for clinical purposes should be taken e.g. microbiological analysis.

A post procedure chest radiograph should be performed after each therapeutic thoracentesis.

5.7. Post procedure inpatient period

All patients

Whilst in hospital, all patients will have a clinical review on every working day. As a minimum a chest radiograph will be performed on Day 3 (+/- 1 day) and Day 7 (+/- 1 day), with additional as deemed necessary by the treating physician.

Blood tests should be performed on at least alternate days until day 7, and then at least weekly if the patient remains in hospital.

Thoracic ultrasounds should be performed on day 2 (the day after the first procedure), and then on days 3 (+/- 1 day) and 7 (+/- 1 day), with additional performed as deemed necessary by the treating physician.

Discharge from hospital is ultimately at the discretion of the treating physician. Numerous factors form the basis of this decision to the extent it becomes impossible to protocolise. It is assumed that

as part of good clinical care all aspects of a patient's condition will be assessed before discharge, including clinical status, outpatient follow up and social set up

Control groups

The timing for chest tube removal in the control group is at the discretion of the treating physician. If the chest tube is removed, the patient should have a chest radiograph afterwards.

Interventional group

There may be a requirement for patients to have further therapeutic aspirations if there is reaccumulation of infected pleural fluid. This is an anticipate drawback of this approach and will be explained to the patients as part of the randomisation process. The need for a timing of further procedures will be decided by the treating physician. It is advised they consider the following before making a decision

- clinical/biochemical factors (such as rising CRP/WBC, or fevers).
- Chest radiograph appearances suggesting persisting collections
- Pleural ultrasound appearances suggesting persisting collections as well as the amenability of these collections to drainage

5.8. Post procedure outpatient period

As dictated above patients will only be discharged if the treating clinician feels they are well enough and will be safe as an outpatient.

Patients in the control arm are likely only to be discharged if their pleural infection has resolved and chest tube has been removed. Patients in the interventional arm, given the nature of the drainage method, have the potential to be discharged before the pleural infection has completely resolved.

The treating physician will have the ability to ask patients from either arm of the study to return early outpatient clinics for repeat blood tests, clinical and radiological review, and even pleural procedures and intravenous antibiotics. It is likely that this service will be utilised more frequently for patients in the interventional arm. As an important part of the ACTion trial's health economic analysis, data will be collected from all patients about the requirement for outpatient hospital visits, primary care attendances, district nurse and social care visits, as burden on informal carers in their home.

5.9. Use of antibiotics

The choice (including type, route and course) of antibiotics is at the discretion of the treating physician. North Bristol NHS Trust has a policy covering empirical antibiotic choice in pleural infection. Professor Alasdair MacGowan (NBT Microbiology Consultant) is advising on this trial so if there are patients where different regimens are required, we will seek his advice.

5.10. Use of intrapleural therapies

Normal saline flushes have been used in previous case series of therapeutic thoracentesis in pleural infection. In addition, the PIT trial demonstrated that intrapleural flushes of 500ml three times a daily was effective at reducing the need for thoracic surgery (15). Within the ACTion cohort, intrapleural flushes of up to 500ml of sterile normal saline can be used twice daily (at the discretion of the treating physician), provided it is aspirated within the same pleural procedure or the chest tube is on continuous drainage to prevent accumulation of fluid. This will prevent catheter blockage and can assist in the clearance of infected pleural fluid from the pleural space.

Intrapleural fibrinolytics are used to breakdown septations that can develop within infected pleural fluid collections. Within the ACTion cohort they can be used, in either treatment arm, at the discretion of the treating physician. Within the control arm this will follow a well standardised local protocol. Within the intervention arm, if a patient is deemed to need fibrinolytics these can be administered via the therapeutic thoracentesis catheter or via a chest tube depending on the view of the treating physician.

In all trial patients, the use of intrapleural fibrinolytics should be considered in the following circumstances:

- Persistent or rising inflammatory markers (WBCs or CRP) or ongoing fevers despite 48hours of intravenous antibiotics and fluid drainage.

- Radiological evidence of ongoing fluid collection radiologically with no fluid output from the chest tube (control arm) and no clear site for further therapeutic thoracentesis (interventional arm)

The requirement for intrapleural fibrinolytics should be recorded as a trial outcome measure.

5.11. Referral for thoracic surgery

A referral to thoracic surgery is occasionally required to resolve pleural infection. This is often seen as an indicator of failure of medical management, so is important data to collect. The timing and indications for a referral is up to the treating physician.

The requirement for referral for surgery and surgical procedure performed will be recorded as a trial outcome measure.

5.12. Trial follow up visits

Trial follow up visits are exclusive of the "post procedure outpatients visits" documented above. Participants will be asked to return on days 30 (+/- 3days) and 90 (+/- 7days) after trial enrolment. At both these follow ups they will be asked to complete a HRQoL questionnaire with VAS.

At day 30 they may be asked to participate in a semi-structured interview (see below)

At day 90, as part of standard care, patients will have a clinical assessment, blood tests, chest radiograph, pleural ultrasound scan and pulmonary function tests. They will also be asked to complete the EQ-5D questionnaire. These data will be recorded on the trial database.

Patients who are unable to attend their trial follow up will be contacted by phone and as much trial data collected as is possible. Additionally, the EQ-5D questionnaire and VAS will be sent to them via post for completion and return to the trial co-ordinating centre.

Patients who are inpatients in North Bristol NHS Trust, at either Day 30 or 90, will be assessed whilst in hospital and have trial data collected as appropriate.

6. BIOLOGICAL SAMPLES, IMAGING, QUESTIONNAIRES AND INTERVIEWS

6.1. Biological samples

Blood

All of blood tests performed during the ACTion trial are part of the standard care of patients with pleural empyema. These samples will be processed at North Bristol NHS Trust via normal laboratory processes. There will be no requirement for storage of blood samples for research purposes.

These tests will include full blood count, urea and electrolytes, C-reactive protein, and liver function tests taken on at least alternate days for the first 7 days.

Pleural fluid

As part of the diagnosis of pleural empyema a diagnostic pleural aspiration is performed, which will, by definition, occur before enrolment in the ACTion trial. The results from this procedure will be recorded on the trial database and is expected to include pleural fluid protein, lactate dehydrogenase (LDH), glucose, pH, cytological assessment and standard microbiology (culture and microscopy). If any of the above standard pleural fluid investigations were not requested, they can be performed on this pleural fluid collected during therapeutic thoracentesis or chest tube insertion as per standard care. The will be no requirement for storage of pleural fluid for research purposes.

6.2. Imaging

Thoracic Ultrasound

All pleural ultrasounds will be performed as part of standard care. The scan results from the baseline assessment, third (+/- 1 day) and seventh (+/- 1 day) days should be recorded on the electronic trial database. Additionally, the results prior to any pleural procedure that are additional to the above should be recorded as they form part of the reasoning for additional pleural procedures. A pleural ultrasound should also be performed and recorded at the trial follow-ups (Day 30 and 90).

Scans should be performed by those with at least Royal College of Radiologists Level One accreditation (or equivalent).

Chest radiography

All chest radiographs performed during the ACTion trial are part of standard care. Images should ideally be performed as P-A. Whilst an inpatient, chest radiographs should be performed on Day 3 and Day 7, with additional as deemed necessary by the treating physician. They will also be performed after every pleural procedure as part of standard care (including chest tube removal), as well as on trial follow-ups (Day 30 and 90). Given the intervention arm may result in patients having additional pleural procedures there may be an increased number of chest radiographs required in this group. However, the exact number of additional pleural procedures is difficult to predict and forms part of the trial outcomes.

The size of effusion on chest radiograph will be reported by a clinical member of the research team and recorded in the online database.

6.3. Health related quality of life questionnaires

All patients will be asked to fill in an EQ-5D questionnaire and a VAS scoresheet for chest pain and breathlessness. These assessments will take place at baseline (Day 1), Day 3 (+/- 1 day), Day 7 (+/- 1 day) and at the trial follow ups (day 30 and 90).

EQ-5D

The EQ-5D is a 5 domain (paper-based or electronic) questionnaire which gives an overall assessment of an individual's quality of life at a particular timepoint. There are 5 questions and it is envisaged this should take between 1-2 minutes to complete.

VAS score

The ACTion trial is using a VAS score instrument to record patients reported chest pain and shortness of breath. The patient will be asked to mark on a line scale their assessment of their symptoms at that time. This should take around 30 seconds per scale.

6.4. Semi-Structured Interviews

An important aspect of a feasibility study is the participant experience of the trial processes, interventions and follow up. A selection of patient who were eligible for the ACTion trial (both those who accepted randomisation and those who did not) will be invited to semi-structured interviews. A

selection of healthcare professionals who were responsible for the clinical care of participants in the ACTion trial will be invited towards the end of the recruitment period.

Patient interviews

Patients will be given the interview specific PIS at the same time as they are given the ACTion trial specific PIS (near the time of diagnosis of their pleural infection). The interviews will take place 1 month after trial recruitment. This time period will ensure they are recovered from their condition without reducing recall.

Participants will be invited to have face-to-face or telephone interviews with Dr David Arnold. The interview will be conducted at a time and place convenient for the patient (e.g. home, clinic or hospital). Interviewees will be asked to provide written informed consent prior to the interview commencing, including consent to be audio-recorded and for anonymised quotes to be used in the final report and any peer-reviewed literature.

Declining entry into the ACTion trial will not preclude a patient from being invited to interview, as the views of patients who declined randomisation will be particularly valuable.

The following interview topic guide was developed in collaboration with a pleural disease PPI group (26/10/17). The following areas were felt to be of significant importance;

- The patient experience of pleural infection.
- What were the participant's experiences of having a chest tube or thoracentesis.
- Experience and acceptability of the outpatient follow-up.
- Suggested improvements to trial processes or documents (consent, information sheet, etc).
- Reasons for declining participation in the trial (if applicable).

A sample size of 20 patient who were eligible for enrolment in the ACTion trial has been felt to be adequate to reach data saturation, such that no new data is emerging by the time of completion. The final number interviewed may be different if the Sub-Investigator and qualitative supervisor (Dr Andrew Moore) feel that data saturation has/hasn't been reached.

Healthcare professional interviews

Ten healthcare professionals who were significantly involved with the care of trial participants will be invited to interview near the end of the recruitment period. They will be provided with a specific PIS and given at least 24 hours to consider taking part. The consent process will be similar to the patient interviews with written informed consent required prior to the interview commencing, including consent to be audio-recorded and for anonymised quotes to be used in the final report and any peer-reviewed literature.

The interview topic guide will focus on the following areas

- The experience of using TT to manage pleural infection.
- Suggested improvements to the trial processes to optimise participant recruitment and retention.
- Understanding physician equipoise e.g. are there any patients with pleural infection that physicians would not be willing to randomise to a trial of this type?

As with the patient interviews the samples size (n=10) has been felt to be adequate to reach data saturation, such that no new data is emerging by the time of completion. The final number interviewed may be different if the Sub-Investigator and qualitative supervisor (Dr Andrew Moore) feel that data saturation has/hasn't been reached.

All interviews

All interviews will be digitally audio-recorded, transcribed verbatim, and anonymised before being uploaded to NVivo data management software.

7. STATISTICAL ANALYSIS

7.1. Sample Size

As a feasibility study, sample sizes have not been formally calculated. The Pleural Irrigation Trial (PIT) was a single centre randomised pilot study based at Southmead hospital (before it merged with another large hospital in 2014). Over 2 years, 38 patients were recruited from 47 eligible patients with pleural infection (80% randomisation rate). This was achieved with more stringent inclusion criteria and a smaller medical take than the proposed trial. For this trial, we suggest that 30 patients randomised (15 in each arm) would be achievable given the timeframe (15 months). Internal audit over the last 4 months has identified 13 patients who would have been eligible for trial entry. Two patients identified by this audit have kindly agreed to act as members of a disease-specific PPI group for subsequent participation in the trial design and management.

This is an application for an extension to the current trial was made in January 2021 in order to maximise recruitment. Prior to the COVID-19 pandemic this trial was recruiting to time and target. The COVID-19 pandemic meant the trial closed for a period from March to June 2020. In addition, social distancing has significantly affected rates of invasive pneumococcal disease which is the main driver of rates of pneumococcal transmission. As a result, trial recruitment significantly slowed. An application to extend the duration of the trial by 12 months was granted (IF APPLICABLE) on xx.xx.xxxx.

7.2. Primary Outcome Analysis

Primary outcome is feasibility, specifically the acceptability of the trial intervention to patients. This will be assessed by proportion of the total number of patients who are eligible for trial entry that accept randomisation. The primary outcome will be defined as successful if ≥50% of eligible patients are subsequently randomised.

7.3. Secondary Endpoint Analysis

Quantitative analysis will focus on obtaining estimates and measures of variation of key unknowns required for the design of a full-scale RCT of TT versus conventional chest tube in pleural infection. We need the following information in order to design an adequately powered trial;

- Descriptive statistics for rates of recruitment, randomisation, attrition, data completion (including differences between the intervention and controls).
- Descriptive statistics for the proposed secondary outcomes (including hospital LOS, number of procedures, readmission rates and surgical referrals), and common adverse clinical events (such as persistent fever, or abnormal blood chemistry and radiography).
- The costs of an ambulatory strategy will need assessing in monetary terms and data on social and NHS costs will be collected here and reviewed by health economic advisors as to their adequacy for use or to identify required amendments for a subsequent full trial.

7.4. Analysis of Semi-structured Interviews

Interview data will be analysed using Thematic Analysis. Audio-recordings will be listened to and transcripts read and re-read for familiarisation, then open coded to develop an initial code list. A subset of interviews will be independently double-coded by a member of the supervisory team with qualitative expertise (Dr Andrew Moore) and code-lists compared, refined and re-applied to the dataset.

Codes will then be grouped into categories, and data explored to identify connections and to develop a descriptive account of the dataset. The analysis will focus on the acceptability of trial processes to patients and physicians, individual and group equipoise, and the patient experience of pleural infection and treatment.

7.5. Interim Analysis

No formal interim analysis for the primary outcome (feasibility) is planned. However, given this is the first randomised trial of this intervention in pleural infection, the Trial Steering Committee will be asked to review the trial's progress after ten patients have been successfully randomised in order to assess for safety and trial issues.

8. ADVERSE EVENTS

8.1. Definitions

Adverse Event (AE)

An untoward medical occurrence in a patient or clinical trial subject, administered the intervention and which does not necessarily have a causal relationship with this treatment.

Adverse Reaction

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

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.

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 Sub Investigator or Chief Investigator in the first instance.

All adverse events/reactions

All AE/AR should be recorded on the dedicated CRF 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. The CRF will detail the date/time of the event and any actions

Serious adverse events/reactions

Any events that meets the criteria for an SAE should be discussed with the Sub Investigator or Chief Investigator. SAEs and SARs should be reported to the sponsor within 24 hours of the Sub Investigator or Chief Investigator becoming aware of the event, using the separate Sponsor-specific SAE.

Events which are serious, causally related to a trial procedure (in the opinion of the C.I), 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.

8.3. 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 David.arnold@nbt.nhs.uk

For any queries related to SAEs, please contact Tel: 0117 414 8041 (Mon to Fri 08.00 – 16.00)

8.4. 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.

8.5. 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)
- Subcutaneous infection related to therapeutic thoracentesis or drain insertion, (unless unresponsive to antibiotic therapy)
- Chest drain falling out, becoming dislodged or becoming blocked
- Further pleural procedures required to drain ongoing fluid collection in either control or intervention group
- Pneumothorax or evidence of non-expandable lung following chest drain insertion or therapeutic thoracentesis (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 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 topic guide to be asked during the semi-structured interview component of the study. All the above will also be approved by the Sponsor.

9.3. Risks and Anticipated Benefits for Participants & Society

Despite the ACTion 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 therapeutic thoracentesis and chest tube insertion are considered routine procedures in the management of patients with pleural effusions. Several case series exist documenting the safe and effective use of therapeutic thoracentesis to manage pleural infections in adult and paediatric populations.

The primary potential benefit to those being randomised to the intervention arm in this study is a reduced duration of in-hospital treatment. Should the ACTion trial prove feasible this would lead to a larger fully powered trial. A full-scale trial has the potential to improve the care of patients with pleural infection, as well as better resource allocation within the NHS.

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

Approval from the local NHS Trust (North Bristol NHS Trust) is required prior to recruitment.

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

9.6. Investigator Responsibilities

This is a single site feasibility trial. The Sub Investigator (Dr David Arnold) within North Bristol NHS trust 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 participants. The Sub Investigator will also be required to allow access to study documentation or source data, on the request, for monitoring visits and audits performed by the Sponsor or any regulatory authority.

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, 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.

For those patients who are approached to have a semi-structured interview, a written 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 ACTion trial, 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.

9.8. Confidentiality

The Chief Investigator (Professor Nick Maskell), Sub Investigator (Dr David Arnold), and Sponsor (North Bristol NHS Trust) 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.

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 (e.g. travel for early follow up appointments or semi-structured interviews).

10. DATA MANAGEMENT

10.1. Data Recording, Storage and Access

Accurate and contemporaneous source data will be kept for all trial participants. This will typically comprise the standard demographic information, past medical history, results from haematological biochemical, microbiological and radiological investigations.

All data will be stored securely in line with the Data Protection Act and the principles of the GCP. Electronic data will be stored on encrypted and password-protected severs. Physical records will be stored securely in the Clinical Research Centre (CRC) within North Bristol NHS Trust, with access limited to members of research teams only.

The trial database will be built using the REDCap database management software. Trial data will be captured using case report forms (eCRF), which will be completed by the trial team. The trial database will only be accessible to named personnel within the trial team using the password-protected REDCap website.

The semi-structed interview data will be audio-recorded using a specified voice recorder. 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 and anonymised. 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. All data transfer and storage will be performed in line with the rules stipulated by the Data Protection Act (2018) by the University of Bristol.

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. Missing data will be minimised 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.

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. 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

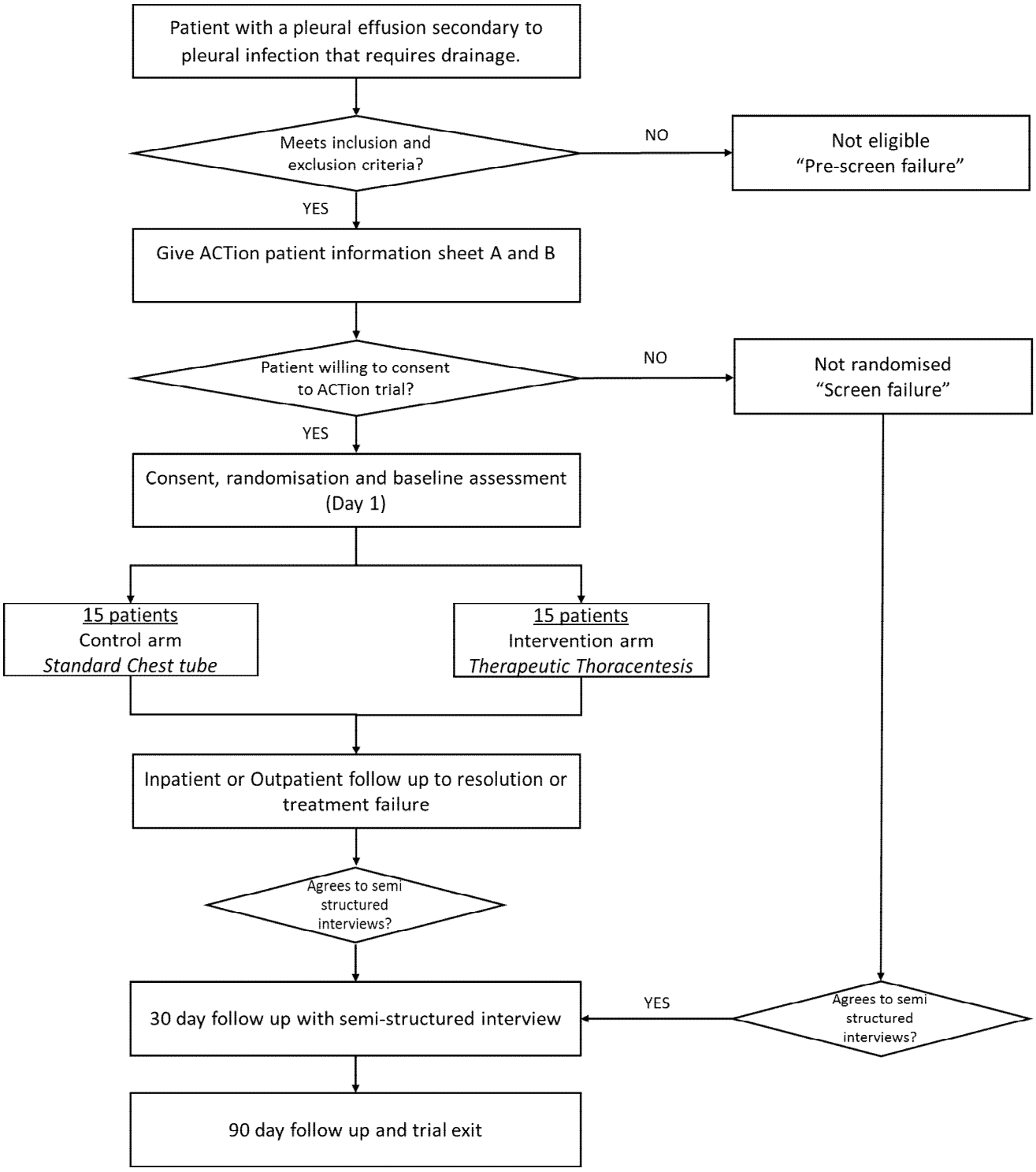
11.1. Trial management group (TMG)

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 Sub Investigator, Chief Investigator, 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.

APPENDIX 1; ACTION TRIAL FLOWCHART



APPENDIX 2; TRIAL INTERVENTION SUMMARY TABLE

Timepoint	Events	Duration	Activities
Pre-enrolment	Screening and pre-screening	10 mins	Complete screening log for all patients with pleural infection Provide patient information sheet A where applicable (ACTion trial) Provide patient information sheet B (semi-structured interview)
Enrolment	Trial consent	30 mins	Complete consent form A (Trial consent)
Baseline assessment	Baseline assessment	60 mins	Baseline CRF HRQoL questionnaire and VAS 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 REDCap randomisation system and input required information Inform patient and necessary staff of treatment allocation
Intervention arm	Therapeutic thoracentesis	60 mins	Appropriate procedural consent Therapeutic thoracentesis using Rocket aspiration kit- aspirate largest collection of fluid to dryness or until symptoms of trapped lung. Chest radiograph within 12 hours of procedure end
Control arm	Chest tube insertion	60 mins	Appropriate procedural consent Seldinger chest tube (12 or 18F) Chest radiograph within 12 hours of procedure end
Inpatient period	Inpatient assessments	30 mins each	At least alternate day bloods until day 7 post randomisation Thoracic ultrasound on days 3 and 7 (if working days) Chest radiograph on days 3 and 7 (if working days) and after pleural procedures including chest tube removal Clinical assessments as part of standard care HRQoL questionnaire and VAS on days 3 and 7 days (if working days) then every 7 days till discharge
Discharge from admitting hospital	Discharge assessment	30 mins	Discharge CRF including HRQoL questionnaire and VAS Arrange date for semi-structured interview if applicable

Early outpatient assessments	Outpatient assessment	60 mins	Bloods if not performed within 48 hours Clinical assessment Thoracic ultrasound Repeat therapeutic thoracentesis if necessary Consideration for cessation of outpatient assessments or re-admission to hospital
Day 30 post randomisation (+/- 5 days)	Semi-structured interviews	60 mins	HRQoL questionnaire and VAS Complete consent form for semi-structured interviews (Consent form B) Semi-structured interview (patient's home, clinic or hospital)
Day 90 post randomisation	3- month follow up	30 mins	Day 90 post randomisation CRF Clinical assessment Bloods Thoracic ultrasound Chest radiograph Pulmonary function tests HRQoL questionnaire and VAS

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