Study Title: **I**nitial **M**anagement of **P**leural infection: Aspiration vs **C**hest **T**ube (IMPACT) trial

Internal Reference Number / Short title: IMPACT trial

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Sponsor: North Bristol NHS Trust, Southmead Hospital, Bristol, BS10 5NB

Funder: National Institute for Health and Care Research

Chief Investigator Signature: D Arnold David Arnold 18/12/2025

Statistician Signature:

No conflicts of interest. M Shanyinde Milensu Shanyinde 18/12/2025

Confidentiality Statement

This document contains confidential information that must not be disclosed to anyone other than the Sponsor, the Investigator Team, HRA, host organisation, and members of the Research Ethics Committee, unless authorised to do so.

Trial Title: Initial Management of Pleural infection: Aspiration vs Chest Tube (IMPACT) trial
Protocol Date and Version No: insert

Protocol signature page

The undersigned has read and understood the trial protocol detailed above and agrees to conduct the trial in compliance with the protocol.

Principal Investigator (Please print name)	**Signature**	**Site name or ID number**	**Date**

Following any amendments to the protocol, this page must be updated with the new protocol version number and date and re-signed by the site PI.

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1. KEY CONTACTS

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Committees	Study Management Group Study Steering Committee Details of all committees can be found in the committee charters separate from the protocol

2. LAY SUMMARY

When people get chest infections, fluid can sometimes build up around the lung. In about 1 in 10 cases, this “pleural fluid” itself becomes infected and needs drainage. This is called pleural infection. Pleural infection is a serious condition, affecting over 10,000 people per year in the UK. The condition can affect anyone but is more likely to affect those who are elderly or have a weakened immune system. These groups are also the most harmed by long stays in hospital.

The current practice to remove the fluid is to insert a chest tube (about 6mm across) between the ribs, to allow fluid to drain into a collection bottle. This tube stays in place until all the fluid has come out, which usually takes between 3-5 days, but it can take 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. As important as draining the fluid is treating the infection with antibiotics, but there is uncertainty about how well antibiotics work in the infected fluid and how best to give them (through the vein or as tablets).

These uncertainties have meant that, unlike for other lung infections, the length of time patients stay in hospital is over a fortnight. These long hospital stays place a burden on the patient, their family, and the NHS. Patients are also given long courses of antibiotics through the vein (intravenous antibiotics), a problem for antibiotic resistance. This study aims to reduce the length of time patients with pleural infection need to stay in hospital by answering two linked questions.

Firstly, can we drain the fluid in a better way? Using a less invasive single drainage approach called therapeutic thoracentesis for the infected fluid might allow patients to be more mobile. We will carry out a study of 172 participants with pleural infection in 12 different hospitals. Patients who consent to the study will be randomly assigned to have their fluid drained using a chest tube or therapeutic thoracentesis. This trial (called the IMPACT trial) will show whether this approach can safely reduce the number of days patients need to stay in hospital.

Secondly, can we improve antibiotic treatment for pleural infection? We will collect samples of pleural fluid from the patients taking part in the IMPACT trial and antibiotic levels within that fluid will be measured. We will test if how we drain the fluid affects the antibiotic levels. If so, this will encourage doctors to use shorter intravenous courses, removing another barrier to earlier hospital discharge.

3. SYNOPSIS

Study Title	**I**nitial **M**anagement of **P**leural infection: Aspiration vs **C**hest **T**ube (IMPACT) trial
Internal ref. no. / short title	IMPACT trial
Study registration	ISRCTN: TBC
Sponsor	North Bristol NHS Trust, Southmead Hospital, Bristol, BS10 5NB
Funder	National Institute for Health and Care Research (NIHR) Efficacy and Mechanism Evaluation (EME) Programme
Study Design	Randomised controlled trial with embedded mechanistic study
Study Participants	Adult patients hospitalised with pleural infection
Sample Size	172 participants (86 per arm)
Planned Study Period	Total length of study- 60 months Recruitment period- 30 months Patient follow-up- 90 days

Planned Recruitment period	01Jul2025-31Dec2027		
	Objectives	Outcome Measures	Timepoint(s)
Primary	Does initial treatment with therapeutic thoracentesis reduce hospital length of stay compared to insertion of a chest tube (standard care)	Length of initial hospital stay in days	Day 90
Secondary	To investigate if the initial treatment with therapeutic thoracentesis changes:		
	Proportion of patients readmitted to hospital within 30 days following discharge	Readmission rates	Day 90
	Total duration of intravenous antibiotic use	Days of intravenous antibiotics	Day 90
	Number of pleural procedures performed by 90-day follow-up	Total number of pleural procedures	Day 90
	Number of additional pleural treatments performed fibrinolytics or thoracic surgery	Details of additional pleural treatments required from medical notes	Day 90
	Patient reported health related quality of life (HRQoL)	EQ-5D and VAS for chest pain and breathlessness	Day 7 and Day 90.
	Pleural thickening at Day 90 (measured on chest radiograph and ultrasound)	Pleural thickening on chest radiograph	Day 90
	Mortality	Mortality	Day 90
Mechanistic Research Question Objectives			
Primary	Assess current dosing and delivery of antimicrobial therapy for pleural infection.	Antibiotic concentrations of pleural fluid and serum compared to minimum inhibitory concentrations of causative organisms	Baseline
Secondary	Investigate if antibiotic PK/PD within the pleural space are:		

			Baseline
	Related to treatment failure i.e. need for fibrinolytics/thoracic surgery	Antibiotic concentrations in pleural fluid	
	Impacted by the method chosen to drain the pleural fluid (TT vs chest tube)	Antibiotic concentrations in pleural fluid	
	Impacted by route of antibiotic (oral versus intravenous)	In-vitro modelling of pleural infection	
	Adequate to provide bacterial pathogen clearance.	In-vitro modelling of pleural infection	
Intervention(s)	Patients who are allocated to the intervention arm will have therapeutic thoracentesis with the aim of draining the fluid to dryness.		
Comparator	Patients allocated to the control arm will have a chest tube inserted, and admitted to hospital if not already an inpatient, as per standard care.		

4. ABBREVIATIONS

Define all unusual or 'technical' terms related to the project. Add or delete as appropriate to your study. Maintain alphabetical order for ease of reference.

CI	Chief Investigator
CRF	Case Report Form
GCP	Good Clinical Practice
HRA	Health Research Authority
ICF	Informed Consent Form
IVDU	Intravenous Drug Users
NHS	National Health Service
RES	Research Ethics Service
PI	Principal Investigator
PIL	Participant/ Patient Information Leaflet
R&D	NHS Trust R&D Department
REC	Research Ethics Committee
SOP	Standard Operating Procedure
TT	Therapeutic Thoracentesis

5. BACKGROUND AND RATIONALE

Epidemiology

Parapneumonic pleural effusions develop in up to 50% of patients with pneumonia. The majority will resolve with antibiotic treatment of the underlying infection. However, 10% will progress to pleural infection where the pleural fluid itself becomes infected requiring drainage. There are around 10,000 new cases of pleural infection in the UK every year [1]. Previous epidemiological work demonstrates that incidence is rising and disproportionately affects those with excessive alcohol use, intravenous drug users (IVDUs), and the elderly [2, 3].

Current medical management

Once a decision has been made to drain the infected fluid, patients are admitted to hospital for chest tube placement, which is inserted under ultrasound guidance, stitched in place and attached to a drainage bottle on the floor, an approach that has not altered in decades. This approach is supported by national and international guidelines [4, 5] but has no randomised trials comparing it to more conservative approaches. The drain can be painful and prevents people moving around normally. Numerous studies have shown that reduced ambulation has a significant impact on recovery and rehabilitation[6]. Patients need to be managed on specialist respiratory wards in hospital whilst the chest tube is in position. A proportion (5-20%) will subsequently require a rescue therapy such as intrapleural fibrinolytics or surgery [7].

Defaulting to the insertion of a chest tube means patients cannot be ambulated easily and cannot be discharged home. The average UK hospital length of stay (LOS) in observational studies of pleural infection is over 14 days [2, 8, 9], placing a significant burden on patients, their families, and the health service. As 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. As incidence continues to rise, so will the number of hospital bed days required to manage patients conventionally, currently estimated at over 140,000 NHS bed days annually [10]. This not only has a significant impact on patients and their families it is also very expensive. A recent study estimated that the cost of pleural infection in the USA alone was over $1.1billion with the majority of cost driven by extended hospital admissions [11].

An alternative to chest tube insertion in pleural infection- Therapeutic Thoracentesis

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 [12]. The patient is able to mobilise after, reduces the requirement for high level respiratory nurse care, 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 [13]. 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.

Therapeutic Thoracentesis- proof of concept

A search of Medline, EMBASE, EMCARE and CINAHL (01.08.2023) using pre-specified pleural infection search terms [14] identified 6462 records. After screening, 100 full text articles of interventional studies in pleural infection were accessed, of which 4 studies on the topic of TT as the initial management strategy for adults with pleural infection were identified. One retrospective comparative study [15], one randomised controlled trial [16], and two case series [17, 18].

Storm et al published a retrospective study comparing the outcomes of 94 patients with pleural infection in Denmark [15]. Over a 5-year period, 51 patients were treated with TT in a medical ward and compared to 43 patients treated with chest tube who were admitted to a surgical ward. Hospital stay 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.

The Aspiration versus Chest Tube drainage for pleural infectION (ACTion trial) recruited 10 adult patients with pleural infection[16]. The trial met its pre-specified feasibility criteria for patient acceptability (over 90% accepted randomisation) and suggested that patients randomised to TT had a shorter overall mean hospital stay (5 days) compared to the chest tube control group (13 days). Several other findings from the trial demand further exploration in a full-scale study including a reduced intravenous antibiotic use in the intervention group.

Review articles have confirmed the limited evidence base and the need for a full-scale randomised trial [19].

Antibiotics stewardship in pleural infection

Closely intertwined with the method of pleural fluid drainage is providing optimal antibiotic therapy. Physicians treating pleural infection often prescribe long courses of broad-spectrum intravenous antibiotics concerned that as the pleural membrane becomes thickened, and pleural fluid becomes acidic and protein-rich, this might affect antibiotic penetration and binding, and contribute to failure of medical management [29]. Reducing this dependence on long intravenous courses will remove a barrier to earlier hospital discharge and improve antibiotic stewardship [31]. The ability to repeatedly access the infected fluid from the site of infection without performing further invasive procedures is a phenomenon unique to pleural infection. By employing modern pharmacokinetic/pharmacodynamic (PK/PD) principles and tools recommendations on antibiotic choice, route of administration, and mechanisms of resistance can be established. Such PKPD approaches are now widely used in other infective therapeutic areas as well as being central to antimicrobial drug development.

Recent studies using rich PK sampling showed that levels of intravenous antibiotics were, in contrast to expectations, no different to that in blood and well above the minimum inhibitory concentrations (MICs) for causative bacteria [20]. This is the largest study to date of antibiotic PK performed in infected pleural effusions. The findings require validation in external cohorts with differing antibiotic regimens and routes. In addition, a clearer understanding of the relationship between plasma and pleural PK/PD will enable assessment of the impact of intermittent (TT) versus continuous (chest tube) fluid drainage, and how patient/disease factors affect antibiotic PK.

6. OBJECTIVES AND OUTCOME MEASURES

Main clinical efficacy question

For adults who present to hospital with pleural infection, does initial treatment with therapeutic thoracentesis reduce length of initial hospital stay compared to insertion of a chest tube (standard care)?

Other clinical objectives

To investigate if the initial treatment with therapeutic thoracentesis changes:

1. Proportion of patients readmitted to hospital within 30 days following discharge
2. Total duration of intravenous antibiotic use
3. Number of pleural procedures performed by 90-day follow-up
4. Number of rescue therapies performed (fibrinolytics or surgery)
5. Patient reported health related quality of life (HRQoL) measurements at Day 7 and Day 90.
6. Pleural thickening at Day 90 (measured on chest radiograph and ultrasound)
7. Mortality at Day 90

7. STUDY DESIGN

This study is a prospective, multi-centre randomised controlled study with internal pilot and embedded antibiotic pharmacokinetic (PK) study of adult patients hospitalised with pleural infection. Patients are randomised to therapeutic thoracentesis or chest tube insertion as the initial pleural procedure to drain the infected pleural fluid.

Following screening, baseline assessment and randomisation there will be trial visits at Day 7 and Day 90. The focus of these will be the collection of clinical information to inform primary and secondary outcomes.

Whilst patients are having pleural procedures (either with TT or chest tube), pleural fluid and or blood samples may be collected and stored for antibiotic analysis. This will be optional for both study sites and participants

8. PARTICIPANT IDENTIFICATION

8.1. Study Participants

Hospitalised adult patients with a clinical presentation consistent with and fulfilling at least one of the established criteria for pleural infection

8.2. Inclusion Criteria

Inclusion criteria: Hospitalised adult patients with a clinical presentation consistent with pleural infection AND requiring initial pleural fluid drainage based on one of the following parameters:

1. Pleural fluid pH ≤ 7.2
   OR
2. Pleural LDH ≥ 900
   OR
3. Pleural fluid glucose ≤ 4.0 mmol/L (or 72mg/dl)
   OR
4. Pleural septations/loculation on ultrasound
   OR
5. Evidence of pleural infection on CT
   OR
6. Pleural effusion occupying >50% of hemithorax on chest radiograph
   AND

- Age ≥ 16* years
- Participant willing and able to give informed consent for participation in the study and/or personal nominated consultee willing and able to give informed consent for participation on behalf of participant

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

8.3. Exclusion Criteria

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

- Excessive bleeding risk in view of the treating clinician
- Previous pneumonectomy, chest tube/drain, indwelling catheter or recent surgery on side of current pleural infection
- RAPID score (if calculable) >5 (indicating a high risk of mortality within 3 months) [21]
- Enrolment onto another study where the burden on the participant will be too high if they are enrolled onto both. Or if the enrollment onto both would compromise one or both of the study's objectives. To be decided on a case-by-case basis.

9. PROTOCOL PROCEDURES

9.1. Recruitment

Recruiting centres will be selected on the basis of size, geographical location and design of pleural services. ORTU has run several previous studies of pleural infection and sites that recruited well previously will be specifically invited. We will also seek expressions of interest through the NIHR Respiratory Research Delivery Network (RDN) and UK Pleural Society.

Within recruiting sites, participants will be screened from routine 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.

9.2. Screening and Eligibility Assessment

Patients will be screened from hospital admission lists, respiratory referrals and outpatient appointments. Patients meeting the inclusion criteria will be initially approached for the study by the clinical team who will contact the research team if a potential participant is interested in taking part. If a patient meets the study inclusion criteria, a full screening assessment will be performed by a clinical member of the study team. If this highlights that the patient fulfils any exclusion criteria (based on RAPID score, bleeding risk, and past medical history) then this anonymised data is captured on a screening log but the patient is not approached for study enrolment. If the patient meets the inclusion criteria but has one or more exclusion criteria this is defined as a “screen failure”. The patient continues normal clinical care, which would normally involve inpatient admission for chest tube.

Each participant must satisfy all the approved inclusion and exclusion criteria of the protocol. If a patient meets the inclusion criteria and has no exclusion criteria at screening, then they are approached by a member of the study team to discuss the IMPACT trial and given a patient information sheet. As diagnostic pathways differ between hospitals, we do not specify a maximum duration between screening and randomisation. However, due to the urgent need for treatment in pleural infection, randomisation should take place within 24 hours of consent. Given the urgency it would be acceptable to discuss the IMPACT trial (with the aid of the patient information sheet) with patients with a strong clinical suspicion of pleural infection prior to definite diagnosis. This would give patients more time to consider entry into the study if they subsequently met the inclusion criteria.

All eligible patients, whether or not they consented, will be entered onto the study screening log.

9.3. Informed Consent

Patients with capacity to consent to the study

Once an eligible patient (with capacity) has been identified, a member of the clinical team and/or research nurse or appropriately delegated person will present the patient with a full patient information

sheet and written informed consent will then be obtained by means of participant-dated signature and dated signature of the person who presented and obtained the informed consent. The person who obtained the consent must be suitably qualified and experienced and have been authorised to do so by the Chief/Principal Investigator. A copy of the signed informed consent will be given to the participant. The original signed form will be retained at the study site and one copy will be sent to North Bristol Trust where the samples will be stored. Routine clinical interpretation services will be used at locations for participants who require this.

Patients without capacity:

The target population, identified in the emergency setting by the usual care team, poses challenges in terms of information provision and informed consent: patients will potentially be in significant pain/respiratory distress at the time of presentation, may be hypoxic and may have diminished or absent capacity.

If the patient is capable of giving consent but is unable to read and/or sign the consent form, a witness can sign (in the presence of the patient) to confirm that informed consent was provided.

Personal / Nominated Consultee consent (relative/family member/independent treating physician)

Should the patient lack capacity to give consent due to the severity of their medical condition (e.g. acute respiratory failure or the need for immediate ventilation), then consent may be obtained from a relative acting as the patient's legally designated representative.

Where a relative is to act as the legally designated representative is not immediately available, randomisation and consequent treatment will proceed with consent provided by a clinician (independent of the clinician seeking to enrol the patient or involved in the study in any capacity) who will act as the legally designated representative. Any advance directives or statements of wishes by the participant relating to treatment or welfare decisions will be taken into consideration when appointing a consultee. In this event, personal/nominated consultee will complete the personal/nominated consultee declaration form, and this will be documented in the patient's clinical notes. The personal/nominated consultee's details (name and contact No.) will also be documented in the patient's clinical notes.

Those patients who regain capacity during their hospital admission will be contacted by a member of the research team. That member will explain to the patient that they participated in this study after advice had been sought from the legal representative. Members of the research team should inform the participant that they can decide whether to continue participating in the study, this means deciding whether or not to continue the treatment and the associated study procedures. Written confirmation will be sought at that time that the patient is willing for the data and samples already collected to be used in the way set out in the patient information sheet (PIS).

The participant must be given a copy of the Regained Capacity Patient Information Sheet and full Patient Information Sheet. The participant should be given the opportunity to ask questions regarding continued participation and if willing, will be asked to sign a consent form.

If the participant does not want to continue to participate, they will be withdrawn from the study. See section 9.10 for further information regarding withdrawals.

9.4. Randomisation

Participants will be randomised (1:1) to receive either therapeutic thoracentesis (intervention) or chest tube (control). Randomisation will be stratified by size of effusion on chest x-ray (<50% vs >50%) and

presence of septation on ultrasound (present Vs absent). Randomisation will use a secure, internet-based system Sealed Envelope https://www.sealedenvelope.com/, managed by ORTU.

To randomise a participant, the recruiting doctor or appropriately trained and delegated site staff will access the secure online randomisation system and enter brief participant details at point of randomisation. Once the online randomisation process is complete, the computer screen will indicate to the randomiser and site team which treatment arm the participant has been randomised to therapeutic thoracentesis (TT-intervention) or chest tube (standard care).

The online randomisation system will automatically send an email to delegated users confirming the randomisation. Site staff should note in the medical records what treatment the participant was allocated to and which treatment was delivered. Hospital (site/equivalent research) staff should proceed to complete and send a study approved letter to the participant's GP (e.g. via post or secure email), informing the GP that their patient has entered the trial, if the participant has consented to this.

9.5. Blinding and code-breaking

Concealment will be achieved pre-randomisation by completing the eligibility assessment and baseline data collection from all participants before randomisation with a bespoke randomisation system designed by individuals independent from the recruiting team.

Due to the nature of the intervention and usual care treatments, clinicians and participants cannot be blinded, with the further potential need for clinical decisions made by treating clinicians. The primary outcome (LOHS) is an objective measure, calculated from routine data thus reducing potential bias.

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

9.6.1. Description of study intervention(s)

Intervention: Patients who are allocated to the intervention arm will have therapeutic thoracentesis with the aim of draining the fluid to dryness.

9.6.2. Description of comparator(s)

Patients allocated to the control arm will have a chest tube inserted as per standard care.

9.6.3. Description of study procedure(s)

Therapeutic thoracentesis (TT)

Patients who are allocated to the intervention arm will have therapeutic thoracentesis (TT). Again, there should be minimal delay between randomisation and drainage. Separate procedural consent must be taken as per hospital policy. Drainage will be performed as per local policy, using bedside ultrasound guidance. TT is a commonly performed procedure for pleural effusions of other causes. It has a well-established safety profile and is an essential curriculum competency for UK medical trainees.

Initially the effusion should be drained to dryness, this can be repeated once if the fluid builds up again. 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.

Chest tube

Patients allocated to the control arm will have a chest tube inserted as per standard care. Separate procedural consent must be taken as per hospital policy. 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. Patients require hospital admission whilst a chest tube is in-situ.

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.

9.7. Baseline Assessments

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

- Patient demographics
- Comorbidities
- Details of current pleural infection (community or hospital acquired)
- Details of the symptoms the participant has had for the current pleural infection (at enrolment)
- Details of the antibiotic treatment the participant has had for the current pleural infection
- Results from a standardised thoracic ultrasound (specifically grading of loculations)
- Results from PA chest radiograph (specifically size of effusion)
- Recent blood test results as part of usual clinical care including RAPID parameters where available (within 1 week) (see trial specific instructions)
- EQ-5D quality of life questionnaire, VAS for chest pain and shortness of breath
- Sample collection (blood and pleural fluid). See Section 9.9
-

9.8. Subsequent Visits

Participants will have a study follow-up at on Day 7 (+/- 1 day) and Day 90 (+/- 5 days). It is standard care for patients to have outpatient appointment approximately 90 days following admission.

Specifically, data should be collected on:

- Recent blood results including renal function and inflammatory markers (if performed as part of standard care)
- Radiology results from tests performed as part of routine care
- Antibiotic treatment (route and type of antibiotic)
- Details of pleural procedures i.e. what pleural procedures the patients have received and for what duration (this includes number of TTs, chest tube insertions and duration of placement, fibrinolytics used, referral for thoracic surgery, type of surgery performed).
- Cumulative volume of pleural fluid drainage
- Adverse events
- Pain score (100mm VAS) for chest pain and breathlessness
- EQ-5D-5L questionnaires

There may be a requirement for patients to have further pleural procedures, intrapleural fibrinolytics and thoracic surgery to resolve their infection. These will be dictated by the treating physician but a suggested approach for routine management will be provided in a Trial Specific Procedure.

The participant's electronic healthcare record (EHR) will be accessed to assess the primary outcome (hospital length of stay including readmissions). Hospital admissions are accurately recorded on EHR systems. To reduce errors, for example from admissions to external hospital trusts, site staff will cross check with the patient at the 90 day follow-up.

9.9. Sample collection and Handling

Samples for routine clinical care will be collected and stored as per local hospital practice.

Participants randomised in the IMPACT trial will have the option (defined on the consent form) to provide additional research samples. It will not be mandatory for sites/participants to take part in the sample collection aspect of this study.

These research samples will primarily be used for an embedded pharmacokinetic study looking at antibiotic concentrations in the pleural space. This will involve collection of a single baseline blood and or pleural fluid sample. This will involve the collection of a maximum of 5ml of blood (from venepuncture or peripheral cannula) and pleural fluid from chest tube or thoracentesis catheter. Samples will be couriered to the Sponsor site (North Bristol NHS trust) for antibiotic pharmacokinetic analysis.

Excess samples will be held under an appropriate HTA licence or under ethical approval for future use. These samples will be retained indefinitely.

9.10. Early Discontinuation/Withdrawal of Participants

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

- The occurrence of what the participant perceives as an intolerable AE.
- The investigator or treating physician feels that it is in the best interests of the patient
- Inability to comply with study procedures
- Participant decision

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

Participants may also withdraw their consent, meaning that they wish to withdraw from the study completely.

Participants have the right to withdraw from the study at any time without having to give a reason and this will not affect their future care.

a) Withdrawal of a participant from the study should be under the guidance of the principal investigator (in liaison with the ORTU team as appropriate). Withdrawal details will be recorded on the relevant CRF.

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

c) Participants are only withdrawn if they specifically request no further data collection. In the event of participants not wishing to attend visits, or to discontinue treatment, they are not considered withdrawn but this will be within the withdrawal CRF. Should a participant decide to withdraw, all efforts will be made to complete and report the observations as thoroughly as possible.

d) Participants samples obtained up to the point of participant withdrawal will be retained for future use unless the participant requests for samples to be destroyed.

9.11. Definition of End of Study

Study closure will be the point when all samples have been analysed.

9.12. 9.12 SAFETY REPORTING

All AEs/ARs presenting from point of randomisation until point of discharge should be recorded on the dedicated CRF at the earliest opportunity following the study team becoming aware of the event.

The population of patients involved in IMPACT is one in which a high number of adverse events are expected due to the presence of pleural infection, therefore only adverse events meeting the criteria to be a Serious Adverse Event and deemed to be related to the study intervention (TT) will be reported. Given the nature of the patient population, the below list captures events that are anticipated in this population that do not require expedited reporting (even if meeting the criteria of an SAE) but will be captured in CRFs. Any anticipated SAE or SAE considered not related to the presence of pleural infection by the local investigator does not require expedited reporting but will be recorded on the appropriate CRF.

Anticipated 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 study 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))

9.13. Definition of Serious Adverse Events

A serious adverse event is any untoward medical occurrence:

- Results in death
- Is life-threatening
- 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

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

NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

9.14. Reporting Procedures for Serious Adverse Events

The safety reporting period is from randomisation to discharge.
SAEs that are considered (by the site investigator) to be possibly, probably or definitely related to the study intervention and not an anticipated event (listed above) will be reported via (PM124A Serious Adverse Events Form (non-CTIMPs) to ORTU at IMPACT@ndm.ox.ac.uk as soon as possible following the local site team becoming aware of the event.

ORTU will perform an initial check of the report, request any additional information and ensure it is reviewed by a nominated Medical Reviewer. CRF.
ORTU will also inform the sponsor North Bristol NHS Trust as soon as possible.

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

10. STATISTICS AND ANALYSIS

10.1. Statistical Analysis Plan (SAP)

The statistical aspects of the study are summarised here, details will be fully described in the statistical analysis plan (SAP).

10.2. Description of the Statistical Methods

All analyses will be conducted in accordance with CONSORT guidelines, we will record and report participant flow. Descriptive statistics of recruitment, drop-out/withdrawal and completeness of intervention will be reported.

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

The primary estimand relating to time to hospital discharge from randomisation is the hazard ratio (HR), comparing intervention and usual care group.

The numbers and percentages of patients experiencing the event will also be presented by treatment group. Medians and interquartile range of time to hospital discharge will be summarised by randomised group.

A Cox's proportional hazards will be fitted to the data adjusting for stratification factors, severity (RAPID score), size of effusion on chest x-ray and presence of septation on ultrasound (present vs absent). Treatment effect will be presented as adjusted hazard rations (aHRs) and 95% confidence intervals (CIs) and corresponding p-value. If the assumptions of the Cox proportional hazard model are violated, alternative methods such as non-parametric models will be used as appropriate.

Where there are relevant competing risks (e.g. mortality prior to 90 days without experiencing primary endpoint), these will be treated either using a composite approach (e.g. assigning worst possible value for those who die from causes related to pleural infection prior to discharge) or as a form of non-informative censoring if unrelated to the infection, with censoring taken as the time point the competing event occurred. If the competing events are substantial, a Fine and Gray model (ref) or other suitable model will be fitted to the primary endpoint, adjusting for severity (RAPID score) and size of effusion on chest-x-ray and treatment comparisons presented as sub distribution hazard ratios. If the proportional hazards assumptions are violated, suitable non-parametric tests will be used to compare treatment groups in the presence of competing risks.

Patients not experiencing primary outcome event by end of the study will be censored at date of last follow-up. Secondary outcomes will be analysed using generalised linear models. Missing data will be reported with reasons were available and the missing data mechanism will be explored in a sensitivity analysis. Exploratory analysis to determine whether antibiotic use mediates the effect of intervention on length of hospital stay will use modern causal inference methods.

10.3. Sample Size Determination

The sample size for this trial is 172 participants (86 per arm). This is based on the following assumptions and calculations.

1. The median hospital length of stay in the control group is 13 days (IQR 7-23 days). This is based on data from the PILOT study [21], the largest prospective study of pleural infection ever performed in the UK.
2. Patients are followed up for 90 days.
3. Length of stay is compared using a time to event approach (i.e. the event being hospital discharge). This was selected as it accounts for skewness within the data, censoring due to death, censoring due to a length of stay over 90 days.
4. A 40% reduction in hospital length of stay (from 13 to 7.8 days), with a power of 90% and alpha of 0.05.

The justification for a 40% reduction is based on case-control evidence and the previous feasibility trial. A case-control study performed by Storm and colleagues compared chest tube insertion (n=43) to TT (n=51) for proven pleural infection[15]. Despite the patients being well matched at baseline (in terms of age, comorbidities and symptomatology) there was a 54% reduction in hospital stay in the TT group (median 5 weeks vs 2.3 weeks, $p<0.001$). In the ACTion feasibility trial, patients randomised to TT had a 58% reduction in mean length of stay (13.0 days vs 5.4 days, $p=0.04$)[16]. We have taken a more conservative reduction of 40% which would still be a meaningful reduction to patients and the healthcare service.

10.4. Analysis populations

All randomised participants as defined by protocol eligibility criteria, regardless of the interventions they actually received or compliance to the intervention, will be included in the analysis. Participants who withdraw from the study will be included in the analysis until the point at which they withdrew.

Other analysis populations for secondary and safety analysis will be detailed in the SAP.

10.5. Decision points

There will be no planned interim analysis for efficacy and futility.

A pilot phase to assess feasibility in the first 12 months of recruitment when it's estimated that at least 50% of screened eligible patients will be consenting to take part. Estimated that 6 hospital sites will be recruiting and 30 patients randomised.

10.6. Stopping rules

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

10.7. The Level of Statistical Significance

The level of significance will be set at 5% two-sided significance level. There is a single primary outcome, so there will be no adjustment for multiplicity.

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

Missing data in all outcomes will be inspected and reported, with reasons give where available and missing data mechanisms explored across randomised groups.

Factors found to be predictive of missingness will be included as fixed effects in the analysis models as part of a sensitivity analysis of the primary outcome.

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

The final statistical analysis plan will be agreed prior to final data lock and prior to any analyses taking place. Any deviation thereafter will be reported in the final study report.

10.10. Health Economics Analysis

No health economic analysis is planned.

11. DATA MANAGEMENT

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

11.1. Source Data

Source documents are where data are first recorded. These include, but are not limited to, hospital records (from which medical history and previous and concurrent medication may be obtained), clinical and office charts, laboratory and pharmacy records, and medical imaging.

Data required for the conduct and analysis of this study will be collected on Case Report Forms (CRFs). This may be transcribed or summarised from source documents, or may be collected directly in study CRFs. CRF entries will be considered source data if the CRF is the site of the original recording (e.g. there is no previous written or electronic record of data).

11.2. Access to Data

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

11.3. Data Recording and Record Keeping

Data will be entered into a secure, validated, GCP-compliant electronic data management system. All staff performing data entry will be appropriately trained prior to access being granted. Access is controlled by individual user accounts, and a full audit trail is kept of all modifications made to data.

Standard Operating Procedures (SOPs) will be followed to maximise completeness and accuracy of study data. The processes for quality assurance of study data will be detailed in the study monitoring plan, data management plan, and other associated documents.

Participants will only be identified in all study documents and datasets (other than the signed consent form) by a unique study-specific number or code. The name and any other identifying detail will NOT be included in any study data electronic file.

All study documents will be stored securely. Both paper and electronic study data will be retained through an archiving service for a period as described in the Data Management Plan.

12. QUALITY ASSURANCE PROCEDURES

12.1. Risk assessment

The study will be conducted in accordance with the current approved protocol, GCP, relevant regulations and standard operating procedures. A risk assessment and monitoring plan will be prepared before the study opens and will be reviewed as necessary over the course of the study to reflect significant changes to the protocol or outcomes of monitoring activities.

12.2. Study monitoring

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

12.3. Study Committees

Study Management Group

Study Management Group will meet regularly throughout the study to discuss the day to day management of the study, a TMG charter will be written detailing all of the requirements.

Study Steering Committee

The Study Steering Committee will meet on a 6 monthly basis throughout the study to assess the progress of the study. A TSC charter will be written detailing the requirements of this committee and its members. The SSC will also monitor the safety events occurring within the study, they will aim to cover

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

Data Safety Monitoring Committee (DSMC)

An independent Data Safety Monitoring Committee will be established to assess safety signals over the course of the trial, with the expectation of meeting at least annually, and as needed in response to safety concerns from the SSC. Membership, responsibilities, and reporting mechanisms of the DSMC will be formalised in a DSMC charter. The aims of this committee review include:

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

13. PROTOCOL DEVIATIONS

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

The Oxford Respiratory Trials Unit has Standard Operating Procedures for incidents and breaches which will be used throughout.

14. SERIOUS BREACHES

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

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

(b) the scientific value of the research.

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

15. ETHICAL AND REGULATORY CONSIDERATIONS

15.1. Declaration of Helsinki

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

15.2. Guidelines for Good Clinical Practice

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

15.3. Approvals

Following Sponsor approval, the protocol, informed consent form, participant information sheet and any proposed advertising material will be submitted to an appropriate Research Ethics Committee (REC), and HRA (where required) and host institutions for written approval.

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

15.4. Other Ethical Considerations

Eligible participants will be given detailed information and the opportunity to discuss the trial further with a member of the trial team. Participants are generally given 24 hours 'thinking time' thereafter to consider enrolling in a trial. It is recognised that clinical circumstances in this trial are likely to make this impossible. The participants will be asked to consent to trial entry, the collection of information about their care, and collection of subsequent data sheets. All will be appropriately anonymised.

15.5. Reporting

The CI shall submit an End of Study notification and final report will be submitted to Sponsor and funder (where required). Transparency in Research

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

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

15.6. Participant Confidentiality

The study staff will ensure that the participants' anonymity is maintained. The participants will be identified only by a participant ID number on all study documents and any electronic database, with the exception of the CRF, where participant initials may be added. All documents will be stored securely and only accessible by study staff and authorised personnel. The study will comply with the General Data Protection Regulation (UK GDPR) and Data Protection Act 2018.

15.7. Expenses and Benefits

Reasonable travel expenses for any visits additional to normal care will be reimbursed on production of receipts, or a mileage allowance provided as appropriate, this includes the use of taxis to get to outpatient appointments during the study follow-up.

16. FINANCE AND INSURANCE

16.1. Funding

Funding is provided in full by an NIHR MRC-NIHR Efficacy and Mechanism Evaluation (EME) Programme grant.

16.2. Insurance

NHS bodies are legally liable for the negligent acts and omissions of their employees. If you are harmed whilst taking part in a clinical research study as a result of negligence on the part of a member of the study team this liability cover would apply.

Non-negligent harm is not covered by the NHS indemnity scheme. North Bristol NHS Trust, therefore, cannot agree in advance to pay compensation in these circumstances.

In exceptional circumstances an ex-gratia payment may be offered.

16.3. Contractual arrangements

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

17. PUBLICATION POLICY

The Investigators will be involved in reviewing drafts of the manuscripts, abstracts, press releases and any other publications arising from the study. Authors will acknowledge that the study was funded by the NIHR. Authorship will be determined in accordance with the ICMJE guidelines and other contributors will be acknowledged.

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

No specific IP is expected in this trial.

19. ARCHIVING

The eTMF documentation will be archived within ORTU's electronic archiving system. Recruiting sites will be responsible for their own archiving locally.

20. REFERENCES

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3. Chalmers, J.D., A. Singanayagam, M.P. Murray, et al., *Risk factors for complicated parapneumonic effusion and empyema on presentation to hospital with community-acquired pneumonia.* Thorax, 2009. **64**(7): p. 592-7.
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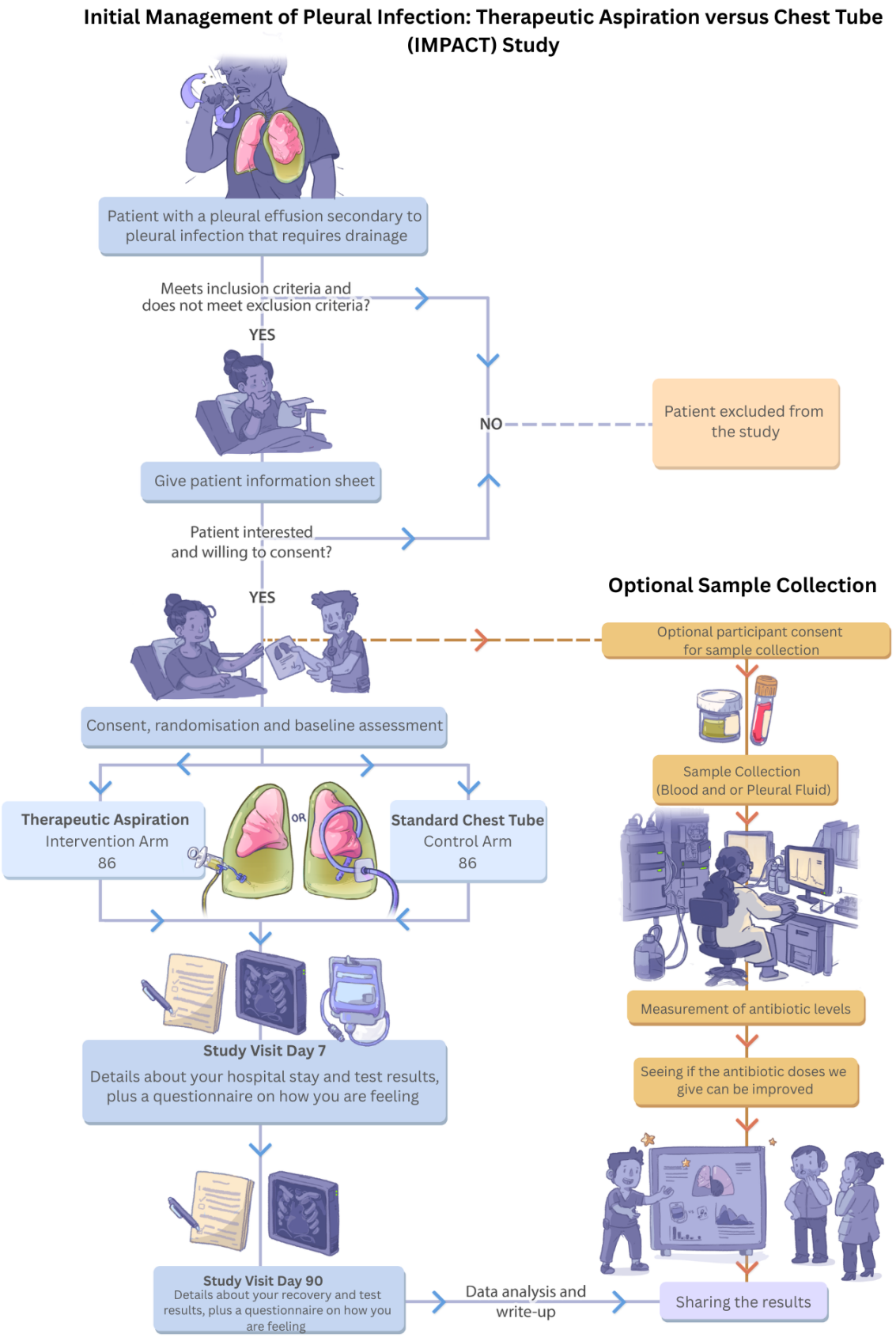
21. APPENDIX A: STUDY FLOW CHART



22. APPENDIX B: SCHEDULE OF STUDY PROCEDURES

Procedures	**Visits**				
	Visit timing Day 0	**Day 0**	**Day 7**		**Day 90**
	Screening	**Baseline**	**Follow-up**		**Follow-up**
Informed consent	X				
Demographics	X				
Eligibility assessment	X				
Randomisation		x			
Medical history		x			
Medication history (specifically antibiotic timing)		x	x		x
Radiology results (chest x-ray and pleural ultrasound)		x	x		x
RAPID score		x			
Laboratory tests		x	x		
Intervention (TT or Chest tube)		x			
Blood and Pleural fluid sample collection		x			
Patient reported outcomes EQ-5D and VAS questionnaires		x	x		x
Adverse event assessments		x	x		x

23. APPENDIX C: AMENDMENT HISTORY

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

List details of all protocol amendments here whenever a new version of the protocol is produced. This is not necessary prior to initial REC / HRA submission.

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

This Document has been Signed with a **secure electronic signature** via E-Sign.

Envelope Details

Title	IMPACT Protocol V2.0
Author	David Smith (david.smith@ndm.ox.ac.uk)
Envelope Created on	Mon, 15 Dec 2025 12:35:34
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Document Details

Title	IMPACT_Protocol_V2.0_07Nov2025_Clean.docx.pdf
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Document Signers Scan/Click the QR Code to view signature information

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Status	**SIGNED** at Thu, 18 Dec 2025 02:00:00 GMT(+0000)
Signature Fingerprint	d72395c4-6939-4253-a28e-9e9ef8cae41d

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Signature Fingerprint	55f133a1-50dc-49cf-a4cf-6668f9b855a6

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Thu, 18 Dec 2025 02:00:00	**David Arnold** Signed the Document (IP: 62.255.13.162)