**Study Title: RAPID driven Treatment of Pleural Infection (feasibility study) RAPTOR - f**

**Internal Reference Number / Short title:** RAPTOR -f

**Ethics Ref: 25/WA/0161**

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**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.

**Study Title: RAPID driven Treatment of Pleural Infection (feasibility study) - RAPTOR-f**

**Protocol Date and Version No**: 09/09/2025_V2.0

**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** |
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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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| **Funder(s)** | National Institute for Health and Care Research, Research for Patient Benefit Programme, application number NIHR207229 |
| **Committees** | Study Management Group<br><br>Study Steering Committee |

## 2. LAY SUMMARY

### 2.1. Background

Pleural infection is a common and serious complication of infection in the lung (pneumonia), which results in a collection of fluid between the chest wall and the lung. It affects more than 65,000 patients each year in the United States (US) and the United Kingdom (UK), and in the UK there are 40 new cases per day. The disease is fatal in 20% of people, and patients stay in hospital for an average of 13 days for treatment. The cost of treatment in the NHS is approximately £4000 per patient, equating to £58 million per year.

Standard treatment for pleural infection includes antibiotics and drainage of the fluid through a tube inserted between the ribs (chest drain). When patients do not respond to initial treatment, surgery is sometimes required. Alternatively, medications can be given through the chest drain which clears out the infected material (called Intrapleural Enzyme Therapy or IET). This treatment has been shown to reduce hospital stays and the need for surgery. Surgery is an effective treatment, but it has several side effects and is not an option for very unwell patients and the elderly, where the death rate is 40%.

Being able to predict which patients are most vulnerable to a bad outcome from a pleural infection (i.e. need surgery or die) at the start of treatment would be very valuable. This would help us to identify the sickest patients and offer the best treatment option as early as possible. Our group has developed a simple score (called RAPID) which uses information routinely collected in clinical care. We have proven that RAPID is reliable in identifying those at the highest risk of death and bad outcomes. What we do not know is whether we can use the RAPID score to inform treatment decisions and therefore benefit patients. To prove this, we need to conduct a large study. Before doing this, it is essential that we conduct a smaller pilot study to know such a large study would be possible, and that selecting the best treatment option according to RAPID score is acceptable to patients and doctors.

### 2.2. Study design and methods:

This pilot study will recruit 30 patients who are in hospital with a confirmed pleural infection from 4 UK centres over an 8 to 10 month period. The patients will be randomised (assigned by computer) to the standard treatment pathway or treatment driven by the RAPID risk stratification score. We will follow patients for up to 3 months. We will measure whether this approach to treatment decisions is acceptable to patients and doctors and whether the study answers the key questions. This will help us know if a larger, definitive study is possible.

We will also interview around 12 patients who are willing to be part of the study, and some who decide not to participate to understand what is important to them when treating this disease and their reasons for taking part or not. Additionally, we will interview 6 clinicians to assess their views and the acceptability of the study and to explore any barriers to participation. This will help us understand what should be measured in a larger study to best improve patient care.

We will collect pairs of pleural fluid and blood from all RAPTOR-f participants to measure the biomarkers and assess for microbiology alongside the septations score on the ultrasound scan to evaluate whether rising levels of these biomarkers will predict treatment failure for patients with pleural infection.

The biomarkers include suPAR (Soluble Urokinase Plasminogen Activator Receptor), PAI-1 (Plasminogen-Activator Inhibitor-1), NE (Neutrophil Elastase) and cytokines interleukins (IL) 1 and 2 on both blood and the pleural fluid.

## 3. SYNOPSIS

| | | | |
|---|---|---|---|
| Study Title | **RAPTOR – RAPID driven Treatment of Pleural Infection (feasibility study)** | | |
| Internal ref. no. / short title | **RAPTOR -f** | | |
| Study registration | 25/WA/0161 | | |
| Sponsor | University of Oxford<br>Research Governance, Ethics and Assurance Team<br>1st floor, Boundary Brook House<br>Churchill Drive<br>Headington<br>Oxford OX3 7LQ<br>RGEA.Sponsor@admin.ox.ac.uk<br>Tel: 01865 616480 | | |
| Funder | National Institute for Health and Care Research, Research for Patient Benefit Programme, application number NIHR207229 | | |
| Study Design | Feasibility study | | |
| Study Participants | Adults with confirmed pleural infection requiring admission to hospital with:<br>1. A clinical presentation compatible with pleural infection or infective illness.<br>2. A pleural collection on radiology (CXR, ultrasound or CT) with a chest drain in situ or planned<br>3. Pleural fluid features diagnostic of infection which is either:<br>A. purulent **or**<br>B. gram positive **or**<br>C. culture positive (pleural fluid or biopsy) **or**<br>D. acidic with a pH<7.2 **or**<br>E. low pleural fluid glucose <4.4 mmol/L or 72mg/dL(non-diabetic) or LDH ≥ 900 iu/L **OR**<br>F. (non-fluid criteria) – CT findings suggestive of pleural infection (pleural enhancement) or pleural fluid septations on thoracic ultrasound | | |
| Sample Size | 30 participants randomised (15 in each arm) from 3 to 4 centres | | |
| Planned Study Period | 01/06/2025 – 01/03/2027 | | |
| Planned Recruitment period | 10 months | | |
| | Objectives | Outcome Measures | Timepoint(s) |
| Primary | To assess the feasibility of recruitment, data collection and acceptability of the | 1. 30 patients randomised 1:1 between RAPID driven treatment versus standard treatment. Recruitment and | 1. At recruitment completion |

| | | | |
|---|---|---|---|
| | participants and of Healthcare professionals of randomisation. | retention rate, the proportion of participants screened who consented to be randomised and who consented to be interviewed. Data completeness/availability and participant completion.<br><br>2. To conduct semi-structured interviews with a proportion of the randomised participants and healthcare professionals<br><br>3. The primary outcome will be defined as successful if ≥50% of the eligible patients are willing to be randomised and ≥ 50% of the healthcare provisional and participant agreed to take part into the interviews | <br><br>2. 4 to 6 weeks post hospital discharge<br><br>3. At recruitment completion |
| Secondary | 1. Length of hospital stay strategies.<br><br>2. Mortality rate over 3 months (all cause)<br><br>3. Need for IET<br><br>4. Need for surgery | 1. Review completeness of data regarding the time of the participants staying in hospital over 3 months from randomisation until discharge.<br><br>2. Proportion of participants who died (all cause) over 3 months post randomisation.<br><br>3. Proportion of participants who required IET post randomisation<br><br>4. Proportion of participants who required surgery post randomisation | 1. From time of admission to hospital discharge<br><br>2. Until the end of the study<br><br>3. From time of admission until discharge<br><br>4. From time of admission until discharge |

| | | | |
|---|---|---|---|
| | 5. Medical treatment failure | 5. Proportion of participants who did not respond to medical treatment (pleural fluid drainage + IET) and required surgery post randomisation. | 5. From time of admission until discharge |
| | 6. Need for repeat intervention and admission | 6. Number of participants who need further pleural procedure e.g chest drain insertion or therapeutic thoracocentesis and proportion of the participant who required re admission to hospital. | 6. Until the end of the study |
| | 7. Duration of antibiotics | 7. Review completeness of data regarding the use of antibiotics from start date of antibiotics to date that has been stopped. | 7. From day of starting antibiotics up to 6 weeks post discharge |
| | 8. Time to complete recovery and return to normal function | 8. SF36 measurements | 8. At 4 and 12 weeks post randomisation |
| | 9. Health related quality of life | 9. EQ5D 5l questionnaire | 9. At baseline, 2, 4 and 12 weeks post randomisation |
| | 10. Mean change and standard deviation in breathlessness and pain | 10. Serial measurement of 100mm VAS score for breathlessness and pain | 10. Post randomisation and until discharge from hospital |
| | 11. To assess feasibility of delivering the intervention arm (RAPID driven arm) | 11. Record time of failure of medical treatment to surgery (VATS, thoracotomy) or time from ICD insertion to IET | 11. End of the study |
| | 12. Healthcare utilisation | 12. Number of pleural procedures and days in hospital post randomisation | 12. During hospital stay |

| | | | |
|---|---|---|---|
| | 13. To assess the pattern of computed tomography of the chest (CT chest) in pleural infection e.g., consolidation | 13. Computed tomography of the chest to assess for consolidation | 13. During hospital stay |
| | 14. Radiological changes following treatment | 14. Chest x- Ray to assess for pleural thickening | 14. At 12 weeks post randomisation |
| | 15. To assess if levels of pleural fluid and blood biomarkers (suPAR, PAI-1 , IL 1+2, and NET) will predict treatment failure | 15. The proportion of participants with an elevated level of pleural fluid and blood biomarkers in serial samples taken on day 1 (randomisation day), 3 and 5(post - randomisation) who did not respond to medical treatment. | 15. During hospital stay and while the chest drain in situ (optional). |
| Intervention(s) | In the intervention arm, following randomisation, a baseline RAPID score will be calculated (see Table 1). According to the score, participants will be allocated into two groups, as outlined below. The subsequent treatment will be determined by the calculated RAPID score.<br><br>**Low RAPID score group:**<br>- Admission for drainage – Therapeutic aspirate or short-term chest tube insertion for 24 hours and subsequent tube removal if there are no features of sepsis syndrome or significant residual collections, see predefined treatment failure criteria below.<br>- Early discharge home within 24 to 48 hours of admission if they meet the proposed discharge criteria (see page 26) and they will be provided with a 24/7 contact number for the clinical study fellow if they have any concerns.<br>- Review in clinic within 3days +/- 2 days, if any features of medical treatment failure are present, they will be admitted to hospital and treated as a medium-high risk score group.<br><br>**Medium – high RAPID score group:**<br>- Admission for drainage – Chest tube insertion<br>- Intrapleural instillation of recombinant human deoxyribonuclease (DNAse) 5mg BD (diluted in 30mls sterile water) and Recombinant human tissue plasminogen activator (tPA, Alteplase) 5-10mg BD (diluted in 30mls sterile water) intrapleural immediately after chest drain insertion if deemed safe and no contraindication e.g. no active bleeding or bleeding disorder. | | |

| | |
|---|---|
| | - Surgical referral at time of chest tube insertion for consideration of Video Assisted Thoracoscopic Surgery (VATS) or open surgery. |
| Comparator | Standard care and intergroup comparison in the RAPID driven arm.<br><br>The standard care involves admission to hospital, chest drain insertion and antibiotics as defined by recent British Thoracic Society guidelines 2023(1), if this fails in 3 to 5 days, patients will be referred to a thoracic surgeon for assessment for VATS or open surgery. Alternatively, IET may be considered if it is deemed safe and appropriate. |

## 4. ABBREVIATIONS

| | |
|---|---|
| CI | Chief Investigator |
| CRF | Case Report Form |
| eCRF | Electronic Care Report Form |
| GCP | Good Clinical Practice |
| GP | General Practitioner |
| MIST 1 | Multicentre Intrapleural Sepsis Trail 1 |
| MIST 2 | Multicentre Intrapleural Sepsis Trail 2 |
| MIST 3 | Multicentre Intrapleural Sepsis Trail 3 |
| SSPS | Standard Study Specific Procedures |
| SSC | Study Steering Committee |
| PIS | Participant/ Patient Information Sheet |
| PI | Principal Investigator |
| NHS | National Health Service |
| ICF | Informed Consent Form |
| HRA | Health Research Authority |
| LDH | lactate dehydrogenase (LDH), |
| suPAR | Soluble Urokinase Plasminogen Activator Receptor |
| TP | Total protein |
| PAI-1 | (Plasminogen-Activator Inhibitor-1 |
| NE | Neutrophils Elastase |
| IL 2, 3 | Interleukin 2, 3 |
| CT chest | Computed Tomography of the Chest |
| CXR | Chest X Ray |

| | |
|---|---|
| ICD | Intercostal Chest Drain |
| VATS | Video-Assisted Thoracoscopic Surgery |
| IET | Intrapleural Enzyme Therapy |
| TUS | Thoracic Ultrasound |
| HRA | Health Research Authority |
| HCP | Healthcare Professionals |
| QOL:EQ-5D-5L | Quality of life questionnaire: EuroQol- 5 Dimension |
| SF - 36 | Short Form Survey (SF-36) |
| VAS | Visual Analogue Scale |
| ICF | Informed Consent Form |
| NHS | National Health Service |
| RES | Research Ethics Service |
| PI | Principal Investigator |
| PIS | Participant/ Patient Information sheet |
| R&D | NHS Trust R&D Department |
| REC | Research Ethics Committee |
| RGEA | Research Governance, Ethics and Assurance |
| SOP | Standard Operating Procedure |

## 5. BACKGROUND AND RATIONALE

Pleural infection occurs when fluid gathers between the chest wall and lung and becomes infected, usually as a complication of pneumonia. Pleural infection is a frequently occurring clinical condition with 15,000 new cases in the UK annually (1). Incidence is rising in all age groups but is increasingly common in children, the immunocompromised and the elderly (2–5), who have the worst outcome (6–8). This is a serious disease and continues to be associated with high morbidity and mortality (9,10).

**Impact on patients and health service:**

The mean hospital length of stay (LOS) in pleural infection is 13 days (6,11) which places a significant burden on patients, their families, carers and the health service.

Unfortunately, the clinical outcomes of pleural infection have remained poor over the last two decades with a mortality rate of 20%, increasing up to 40% among elderly populations, and it is noteworthy that, 20% of patients fail initial medical treatment which includes chest tube insertion, antibiotics and intrapleural enzyme therapy and consequently these patients may require surgical operation(6,11–15). Overall, treatment of pleural infection is highly burdensome; 25% of affected individuals require hospital admission for more than a month with a median hospital stay of 12 – 15 days including the most recent data from the UK (6,7,11,13,15,16).

In the United Kingdom, approximately 40 patients are admitted with pleural infection daily. The cost of treating each patient in the National Health Service is approximately £4,000, equating to £58 million annually. This is largely driven by the prolonged hospital stays associated with the condition.

Implementing more efficient and evidence-based care pathways that prioritise the delivery of targeted treatments such as surgery and intrapleural therapy to patients who benefit the most is likely to enhance cost-effectiveness and reduce the length of hospital admissions.

**Current practice of management of pleural infection:**

Standard treatment for pleural infection involves broad-spectrum antibiotics and drainage of the pleural fluid using a tube inserted between the ribs (chest drain) and connected to a drainage bottle, which means that patients have to be admitted to the hospital for the whole course of treatment (while the chest tube in situ), and this cause discomfort and reduced mobility of the patients. Numerous studies have shown that reduced ambulation has a significant impact on recovery and rehabilitation (17). When these initial treatments fail, more aggressive treatment is required (1,18). This includes surgical treatment (Video-Assisted Thoracoscopic Surgery (VATS) or keyhole surgery) (8,19–22). However, surgery is a significant undertaking and carries significant morbidity including perioperative and anaesthetic mortality (23), a high rate of conversation to a larger operation (10-15% thoracotomy (24–26)) and up to 5% of patients suffering long term pain (27,28). An alternative to surgery is the use of enzyme therapy through the chest drain (Intrapleural Enzyme Therapy or IET) which has been proven to improve drainage and reduce hospital stay. However, IET treatment is also associated with side effects including pain and bleeding in around 4% (29).

**Rationale of RAPTOR f study (feasibility clinical study):**

Currently, all patients with pleural infection are treated in an identical way with initial medical treatment (drainage and antibiotics) for a period of 3 to 5 days, and then referral for further treatment (VATS or IET) if they have a poor clinical response (1). Early identification of which patients will have a poor clinical outcome would be highly valuable, as this may enable more aggressive treatment to be given early on to those that need it most, effectively personalising treatment in pleural infection.

A number of predictive factors have been identified in retrospective small-scale studies including radiological features (ultrasound)(15), pleural fluid characteristics (30) and delayed access to surgery (14). However, the only prospectively validated risk prediction model to date has been published by our unit and is called the RAPID score which reliably predicts 3-month mortality in pleural infection from 5 baseline clinical characteristics which are routinely collected in normal care.

The current national treatment guidelines for pleural infection (BTS 2023(1)) suggest the use of the RAPID score early in the treatment of pleural infection but do not specifically mandate its use, nor suggest how the score should alter treatment therefore in this study we are hoping to prove that it's feasible to assign the patient to the right treatment at the right time using RAPID score risk stratification tool.

**Potential benefits of the RAPTOR f study:**

Assuming the feasibility study is successful, and a definitive similar study of RAPID driven treatment is conducted – the potential of these results to directly alter patient management in pleural infection is very significant. The potential areas of benefit to patients, clinicians and the NHS are as follows:

1. Targeting the right treatment to the right patients at the right time and to those that need it most. This includes less invasive and burdensome management (low RAPID score group) where this is not required as they have a better prognosis, and earlier more aggressive treatment (early IET or surgery for moderate to high risk group) to those at the highest risk of death. This is an efficient, targeted and focused resource where it is needed most, allowing fast decisions to be made during the illness.

2. Successful use of the RAPID score to alter treatment will result in fewer interventions including avoidance of unnecessary surgery and reduced time in hospital, and earlier use of the correct intervention in the illness course. This will lead to improved quality of life and less suffering, and earlier recovery with a reduction of carer burden with the potential of earlier return to work and / Or normal function.

3. There is the potential for a significant reduction in healthcare costs by early identification of those at the highest risk of death and prioritising invasive treatment for them, resulting in fewer interventions, shorter hospital stays and potentially shorter courses of antibiotics.

4. Although there is no data as yet to demonstrate this, there is a distinct possibility that using more aggressive treatment in the most unwell group will lead to reductions in the significant mortality rate of pleural infection. This would of course need to be tested in a phase 3 study after a successful feasibility study.

**Patient and public involvement:**

The RAPTOR feasibility study has been designed with patient and public involvement as well as embedded qualitative research methodology. On 20/10/2023, a pleural infection PPI meeting was organised via Zoom meeting at Oxford University Hospitals (OUH) NHS Foundation Trust. The 6 participants had been previously admitted to OUH for treatment of pleural infection including chest drain insertion, antibiotics plus IET or surgery, this group has been selected from 15 patients with pleural infection who have been interviewed following treatment and recovery from pleural infection, the interviews were to explore their views and experience of treatment of pleural infection and impact of their quality of life and career. The premise of the RAPTOR f feasibility study was explained to the PPI group with the aid of a draft lay summary and study flow chart. The participants supported using RAPID score to guide the management of patients with pleural infection particularly those at low risk of dying or deteriorating and this might reduce hospital stay from pleural infection. Although recognising the need for a feasibility study, the group was clear that the design should attempt to replicate a full-scale study 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 joined the group in February and March 2024, and they have similar views regarding reducing the length of the hospital stay.

We discussed the practicalities of embedding qualitative research within the feasibility study to help design a future study and explore the impact of pleural infection on patients.

## 6. OBJECTIVES AND OUTCOME MEASURES

| | Objectives | Outcome Measures |
|---|---|---|
| **Primary** | To assess the feasibility of recruitment, data collection and acceptability of the participants and of healthcare professionals of randomisation of patient with pleural infection to standard care versus RAPID care driven treatment | 1. 30 patients randomised 1:1 between RAPID driven treatment versus standard treatment. Recruitment and retention rate, the proportion of participants screened who consented to be randomised and who consented to be interviewed. Data completeness/availability and participant completion<br><br>2. To conduct semi-structured interviews with a proportion of the randomised participants and healthcare professionals<br><br>3. The primary outcome will be defined as successful if ≥50% of the eligible patients are willing to be randomised and ≥ 50% of the healthcare provisional and participant agreed to take part into the interviews. |
| **Secondary** | 1. Length of hospital stay strategies<br><br>2. Mortality rate over 3 months (all cause)<br><br>3. Need for IET | 1. Review completeness of data regarding the time of the participants staying in hospital over 3 months from randomisation until discharge<br><br>2. Proportion of participants who died (all cause) over 3 months post randomisation<br><br>3. Proportion of participants who required IET post randomisation |

| | | |
|---|---|---|
| | 4. Need for surgery | 4. Proportion of participants who required surgery post randomisation |
| | 5. Medical treatment failure | 5. Proportion of participants who did not respond to medical treatment (pleural fluid drainage + IET) and required surgery post randomisation |
| | 6. Need for repeat intervention and admission | 6. Number of participants who need further pleural procedure e.g chest drain insertion or therapeutic thoracocentesis and proportion of the participant who required re admission to hospital |
| | 7. Duration of antibiotics | 7. Review completeness of data regarding the use of antibiotics from start date of antibiotics to date that has been stopped |
| | 8. Time to complete recovery and return to normal function | 8. SF36 measurements |
| | 9. Health related quality of life | 9. EQ5D 5l questionnaire |
| | 10. Mean change and standard deviation in breathlessness and pain | 10. Serial measurement of 100mm VAS score for breathlessness and pain |
| | 11. To assess feasibility of delivering the intervention arm (RAPID driven arm) | 11. Record time of failure of medical treatment to surgery (VATS, thoracotomy) or time from ICD insertion to IET |

| | | |
|---|---|---|
| | 12. Healthcare utilisation | 12. Number of pleural procedures and days in hospital post randomisation |
| | 13. To assess the pattern of computed tomography of the chest in pleural infection e.g., consolidation | 13. Computed tomography of the chest to assess for consolidation |
| | 14. Radiological changes following treatment | 14. Chest x- Ray to assess for pleural thickening |
| | 15. To assess if levels of pleural fluid and blood biomarkers (suPAR, PAI-1, IL 1+2, and NET) will predict treatment failure | 15. The proportion of participants with an elevated level of pleural fluid and blood biomarkers in serial samples taken on day 1 (randomisation day), 3 and 5 (post - randomisation)who did not respond to medical treatment. |

## 7. Study design

### 7.1. RAPTOR f feasibility design

This is a multi-centre, open-label, randomised two-arm parallel feasibility study. Aiming to assess the feasibility of a full-scale randomised study of RAPID driven treatment of pleural infection versus standard care.

Once participants are diagnosed with pleural infection, based on well-recognised diagnostic criteria in accordance with the evidence-based recent national British Thoracic Society guidelines(BTS 2023)(1), they are allocated to either the standard care group, who receive pleural infection management as per BTS guideline 2023) (1), or the intervention group, who receive treatment which is driven according to the baseline calculated RAPID score (see below).

Participants with suspected pleural infection will be approached initially by the clinical team as in-patients. Enrolment will occur within 24 hours of confirmation of the diagnosis of pleural infection and / or chest drain insertion using standard criteria for the diagnosis of pleural infection as per BTS guidelines (1).

***The RAPID score***

For participants allocated to the RAPID driven treatment arm only, the risk stratification "RAPID score" will be calculated at the time of presentation according to the parameters in Table 1. According to the calculated RAPID score, subsequent treatment will proceed (see below).

| Parameter | Measure | | Score |
|---|---|---|---|
| **Renal** | Serum Urea Level | < 5 mmol/L | **0** |
| | | 5 – 8 mmol/L | **1** |
| | | >8 mmol/L | **2** |
| **Age** | Age | < 50 years | **0** |
| | | 50 – 70 years | **1** |
| | | > 70 years | **2** |
| **Purulence of fluid** | Purulent fluid | | **0** |
| | Non-purulent fluid | | **1** |
| **Infection source** | Community-acquired | | **0** |
| | Hospital-acquired | | **1** |
| **Dietary factors** | Serum albumin level | >27mmol/L | **0** |
| | | <27mmol/L | **1** |
| **Risk categories** | **Low risk** | **Moderate risk** | **High risk** |
| | **0 – 2** | **3-4** | **5 – 7** |

**Table 1**:The RAPID risk–prediction score (7,12)

### 7.2. Embedded Qualitative Interviews design

This involves semi-structured interviews involving (n=12) participants and (n = 6) healthcare professionals (Respiratory or pleural and general or acute medicine physicians). Participants enrolled on the RAPTOR f feasibility study or those declined to participate will be verbally consented for their willingness to participate in in-depth interviews. In addition, up to 6 of the treating healthcare professionals will be interviewed. The interviews will be conducted by a person who will be appropriately trained and delegated. Interviews guide topics for the patient participants and the health care professionals were developed in collaboration with patient and public involvement group. Both patients and healthcare professionals will be consented to the interviews.

## 8. PARTICIPANT IDENTIFICATION

### 8.1. Study Participants

All participants with pleural infection fulfilling the inclusion are eligible for the study. Screening logs will be kept, documenting reasons for non-inclusions. The study will aim to randomise 30 patients (in a 1:1 ratio) to receive either RAPID driven treatment or standard care treatment for pleural infection.

### 8.2. Inclusion Criteria

Adults with confirmed pleural infection requiring admission to hospital with ALL of the following:

1. A clinical presentation compatible with pleural infection or infective illness
2. A pleural collection on radiology (CXR, ultrasound or CT) with a chest drain in situ or planned
3. Pleural fluid features diagnostic of infection which is either:
    A. purulent **or**
    B. gram positive **or**
    C. culture positive (pleural fluid or biopsy) **or**
    D. acidic with a pH<7.2 **or**
    E. low pleural fluid glucose <4.4 mmol/L or 72mg/dL(non-diabetic) or LDH ≥ 900 iu/L **OR**
    F. (non-fluid criteria) – CT findings suggestive of pleural infection (pleural enhancement) or pleural fluid septations on thoracic ultrasound
4. Willing and able to give written informed consent

### 8.3. Exclusion Criteria

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

1. Age less than 18 years
2. Previous pneumonectomy on the infected side
3. Pleural collection not amenable to chest tube drainage
4. Has previously received intra-pleural fibrinolytics and /or DNase for this empyema (ipsilateral and deemed by the clinical team to be the same, ongoing infection)
5. Has a known sensitivity or allergy to DNase or tissue plasminogen activator
6. Participants who are pregnant or lactating
7. Patients with pleural infection and an estimated survival period of less than three months due to an unrelated pathological condition, such as metastatic lung carcinoma.
8. Participant who are unable to give informed consent (lacking capacity)

## 9. PROTOCOL PROCEDURES

The following table illustrates scheduled study related procedures and data collection

| **Procedure** | **Screening** | **Consent Baseline/ Randomisation** | **Inpatient Assessment(s)** | **Follow up visits** | | | |
|---|---|---|---|---|---|---|---|
| | | | | **3 days[1]** | **14 days** | **28 days** | **90 days** |
| | | | | **+/- 2 days** | **+/- 3 days** | **+/- 3 days** | **+/- 3 days** |
| Eligibility assessment | X | X | | | | | |
| Informed consent | X[2] | X[2] | | | | | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Demographics [R] | X | X | | | | | |
| Medical history [R] | X | X | | | | | |
| Clinical assessment [R] | X | X | X | X | X | X | X |
| Concomitant medication [R] | X[3] | X[3] | | | | | |
| Imaging routine – chest x ray [R] | | X | | | X | X | X |
| Imaging routine – Thoracic Ultrasound [R] | | X | X (on days 3±1 and 5±1 post – randomisation ) | X | X | X | |
| Imaging routine – CT chest [R] | X[4] | X[4] | X[4] | | | | |
| Chest drain insertion or therapeutic aspiration in situ or planned [R] | X | X | | | | | |
| Intrapleural enzyme therapy [R] | | | X | | | | |
| Surgery [R] | | | X | | | | |
| Routine clinical bloods [R] | X | X | X | X | X | X | |
| Routine pleural fluid [R] | X | | | | | | |
| Randomisation | | X | | | | | |
| RAPID score | | X[5] | | | | | |
| Research pleural fluid collection and storage | | X[6] | X[6] | | | | |
| Research blood collection and storage | | X[6] | X[6] | | | | |
| Breathlessness and/or pain (VAS) score | | X[7] | | | X[7] | X[7] | X[7] |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| QOL: EQ-5D-5L | | X[8] | | | X[8] | X[8] | X[8] |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Assessment of functional ability (SF36) | | | | | X[9] | X[9] | X[9] |
| Health utilization | | | X | | | | |
| Semi-structured interviews | | | | | | X[10] | |

[R] Indicates procedures or data collection that is part of routine care for all patients. The results of these are required to be collected and documented as part of the RAPTOR - f study, hence are included in this table.

[1] This will be applied to the low RAPID score group, please see the protocol for the details

[2] Informed consent will be taken within the first 24 hours after discussing the study and offering the participant information sheet.

[3] If the participant had any antibiotics prior to admission to the hospital or if they are on anticoagulation or antiplatelet.

[4] CT scan will be conducted as part of the usual care for all participants with pleural infection during the inpatient stay

[5] The RAPID score will be calculated for the intervention group ONLY following randomisation.

[6] The research samples (paired pleural fluid and blood) will be collected on day 1 (randomisation day) 0,3 and 5 post- randomisation (with the first week). This is optional, please see the protocol for the details of the process.

[7] These assessments will take place in person at baseline, 14 days +/- 3, 28 days +/-3 days and remotely in 90 days +/- 3 days, please see protocol.

[8] These will be collected at baseline, day 28 +/-3 days in person and day 90 +/- 3 days (remotely), please see protocol.

[9] These assessments will take place at day 28 +_ 3 days and day 90+_ 3 days, please see protocol.

[10] The interview PIS will be given to the participant when attending the clinic in 2 weeks post-discharge and the interviews will take place between 4 to 6 weeks post-discharge, please see protocol

### 9.1. Recruitment

This feasibility study aims to recruit 30 patients from 3 – 4 UK centres (Oxford, Norfolk and Norwich, Plymouth and Royal Devon and Exeter with well-established pleural centres that will enroll eligible patients over 8 - 10 months. The sites are geographically distributed to ensure the population recruited is diverse and representative of the UK pleural infection population.

### 9.2. Screening and Eligibility Assessment

A member of the clinical team may identify participants with confirmed or suspected pleural infection. Due to the nature of the study, all participants will be in inpatient care at the time and will be offered the opportunity to participate at an early stage of their admission (by definition, within 24 hours of either confirmation of pleural infection or insertion of the chest tube for the treatment of pleural infection). The clinical team will approach potential participants and either the clinical or research team will then provide the participant with the participant information sheet and be available to answer any questions. Participants will be identified through respiratory and general wards or outpatient referrals, clinics, and ambulatory care.

There is no maximum time limit between screening and randomisation. However, due to the nature of the disease, treatment must not be delayed, so participants are likely to have less than 24 hours to consider enrolment following diagnosis of pleural infection with chest drain in situ or had therapeutic aspiration or both are planned.

Day 0 should be considered as the first contact with the research team and a decision on randomisation must be made by the end of day 1. If the participant remains eligible, randomisation is possible.

Pleural fluid samples required to confirm eligibility will be collected as part of clinical care and are not study-specific, therefore prior consent is not required. Research samples will be collected (paired blood and pleural samples) at day 1 (randomisation day), 3 and 5 post- randomisation following optional consent (agreement to collect pleural fluid 100 millilitres and blood 10 millilitres for research purposes). These samples will be transferred to the central site of the study for analysis of biomarkers.

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

### 9.3. Informed Consent

Consent can be obtained **prior** to confirmation of pleural infection in participants who are likely to have a chest drain insertion or therapeutic pleural aspiration. These participants will be randomised once the eligibility criteria have been confirmed.

If pleural infection is ruled out, participants will not be required to continue in the study. The number of patients that have been screened in this manner will be recorded as part of the consort diagram. The participant must personally sign and date the latest approved version of the informed consent form before any study-specific procedures are performed.

Participants will be given the written and verbal versions of the participant information sheet, interview information sheet and informed consent, which will outline the following: the exact nature of the study;

what it will involve for the participant, the implications and limitations of the protocol, the known side effects and any risks associated with participation. The participant will be aware that participation in the study is voluntary, that it is possible to withdraw from the study at any time for any reason, and that no adverse consequences will result from such a withdrawal. In addition, participants will be assured of continuity of care. Their legal rights will remain unaffected, and they will not be obliged to provide a reason for withdrawal. While it is usually a requirement in clinical studies that a participant is offered 24 hours in which to decide whether to take part in a study, given the acute, severe nature of pleural infection and the intervention arm requires a time specific administration of medication to drain the pleural space, a delay of more than a few hours in administering the medication may be detrimental to participant care and delay surgical referral for early surgical assessment and intervention if required. As such, a shortened period of reflection will be offered to participants considering participation in the study, however, investigators will check with potential participants that they understand the study and feel that they have had adequate time to give informed consent. This strategy has been demonstrated to be effective in previous clinical studies of pleural infection. (MIST1, MIST2 and MIST3), (6,11,16) and will be specifically addressed in the ethics application.

Subsequently, the written informed consent of the participant will be obtained utilizing the participant's dated signature and the dated signature of the individual presenting and obtaining the informed consent. The individual responsible for obtaining consent must be suitably qualified and experienced, have been authorised to do so by the Principal Investigator, and have been assigned this responsibility.

The original signed informed consent form will be provided to the participant. A copy will be retained at the study site.

### 9.4. Baseline assessment

Patients who are willing to participate in the study will have a baseline assessment performed by a member of the research team and documented into relevant CRF. The baseline data will be collected while the participant is in hospital and completed before the patient is discharged. This will include a collection of the following data onto an electronic CRF (REDCap) as follows:

1. Confirmation of the inclusion and exclusion criteria
2. Participant demographics
3. Relevant medical history:
    - Co-morbidities (at enrolment) including the presence of chronic renal failure or bleeding disorder
    - Details of the symptoms the participant has had for the current pleural infection (at enrolment) including length of symptoms and nature of the infection (community or hospital acquire infection)
    - Uses of antibiotics before admission to hospital e.g. types and duration
    - Details of the treatment that the participant has had for the current pleural infection (at enrolment i.e. antibiotics, chest drain insertion or therapeutic aspiration)
    - Current medications including antiplatelets and anticoagulants
    - Recent blood test results as part of usual clinical care where available (within 1 week prior to randomization)
4. Details of recent radiology results including CXR, and first TUS to be uploaded (videos and images where available) (within 1 week prior to randomization)

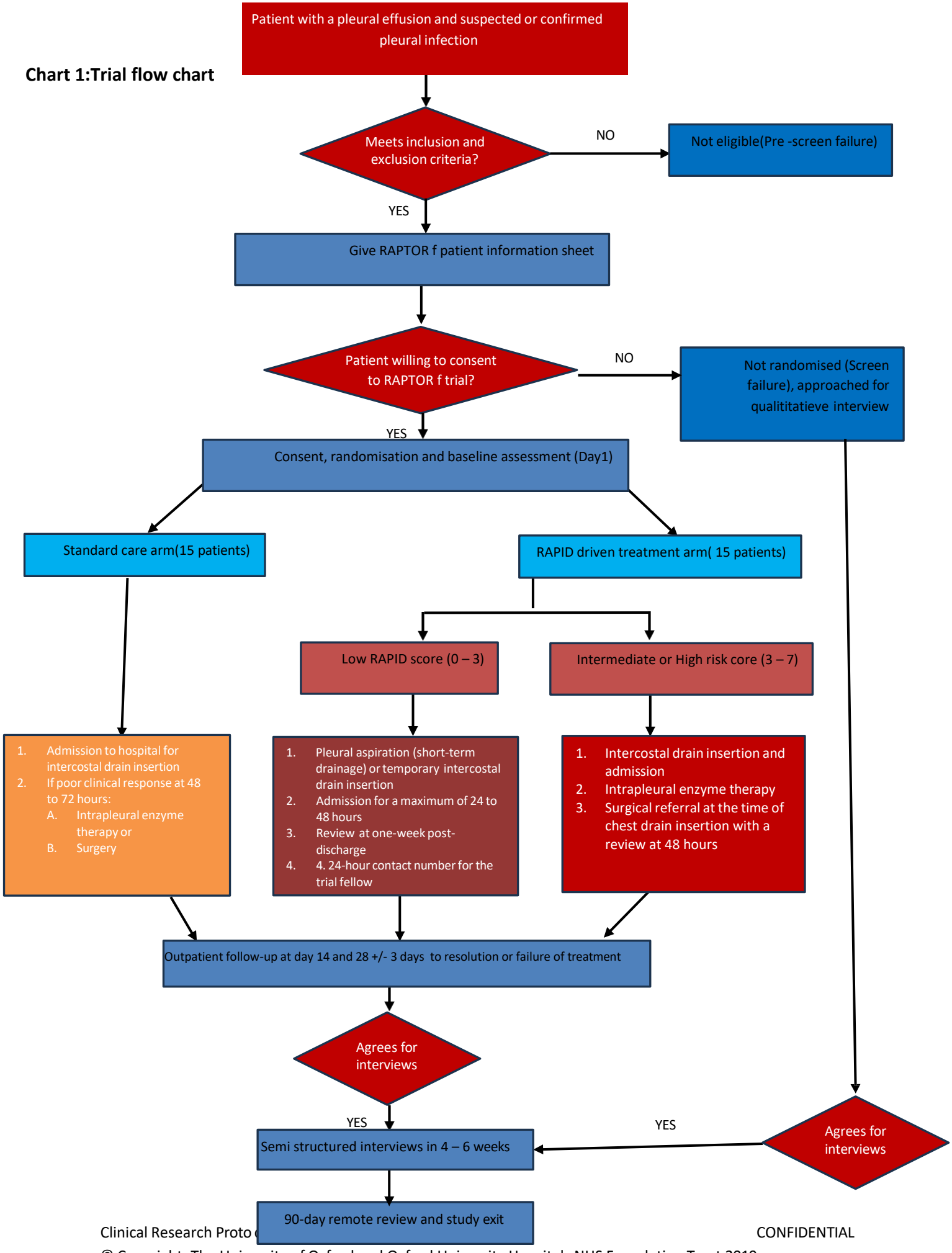
5. CT chest will be transferred in a secured USB, Compact Disk or other appropriate password-protected device to Oxford Centre to assess for a radiological pattern of pleural infection e.g., consolidation (within 1 week prior to randomisation)

6. EQ-5D quality of life questionnaire, VAS for chest pain and shortness of breath

### 9.5. Randomisation

Following consent and baseline assessment, randomisation will occur via a secure web-based system Sealed Envelope by a member of the RAPTOR f research team at the site. Randomisation will occur once the pleural infection has been confirmed by the documented inclusion criteria. This may occur after the therapeutic pleural aspiration or once a chest drain has been inserted or with a high suspicion of pleural infection. Participants will be randomly allocated to one of two arms of the study in a 1:1 ratio to either standard care or RAPID-driven treatment, see study flow diagram (Chart 1). Randomisation will be randomly generated by the Sealed Envelope software to reduce selection bias.

**Chart 1:Trial flow chart**



### 9.6. Blinding and code-breaking

There is no blinding in this study, hence no un-blinding procedures or code-breaking are required.

### 9.7. Description of study intervention(s), comparators and study procedures (post-randomisation and inpatient period)

**Intervention arm**

In the intervention arm, treatment will be determined according to the calculated baseline RAPID score.

Patients with a higher RAPID score (and thus higher predicted mortality and morbidity (7,12)) will be triaged to more aggressive treatment early in the disease, and those with lower predicted mortality and morbidity will be treated less aggressively.

***A. Low risk (RAPID score 0 to 2):***

Patients will be treated as follows:

1. **Pleural drainage**: therapeutic pleural aspiration (drain to dryness) using a Rocket kit will be suggested as the initial treatment. If the patient has already had a chest tube inserted prior to randomisation (as randomisation can occur for 24 hours after drain insertion), then patients will be admitted for drainage for a proposed maximum of 24 to 48 hours, with the removal of the drain as soon as possible, provided there is no residual collection of pleural fluid on the chest-x-ray (CXR) or thoracic ultrasound or CT scan before drain removal. No specific size of drain is specified, and local practice should be followed.
2. **Broad spectrum antibiotics**: see below for the expected standard of care in both intervention groups concerning antibiotics, which are as per NHS standard care for pleural infection. Use of early oral antibiotics to promote discharge is recommended in this group.
3. **Review at 3 days +_ 2 days post-discharge** with bloods including full blood count, CRP (C-reactive protein), liver and renal profile, ultrasound scan and chest x ray.
4. **Patient contact:** All patients will receive a 24-hour contact number (to the study fellow) who can be contacted should there be any concern or deterioration when at home which will prompt urgent review by the pleural service locally.

If at any point a patient is considered to have ***failed treatment*** on the basis of predefined criteria (see below), they will then be treated as per the intermediate/high-risk group below and will be admitted to hospital.

***B. Intermediate + high-risk (RAPID score 3 to 7)***

The intermediate and high-risk groups have been combined for the treatment algorithm; there are similar numbers of patients in the combined intermediate and high risk group and the low-risk group (7). Patients in this category will be treated as follows:

1. **Pleural drainage:** all patients will be admitted to hospital for chest drain insertion and remain in hospital for as long as is clinically required while the tube is in situ. No specific size of drain is specified, and local practice should be followed.
2. **Broad spectrum antibiotics:** see below; IV antibiotics can be given while the patient is admitted.
3. **Adjunctive therapy:**
    a. Intrapleural enzyme therapy (tPA / DNase) should be started as soon as possible after drain insertion and randomisation, assuming there are no contraindications. if there is no risk of bleeding.

b. In parallel, referral to local thoracic surgical services made at the time of randomisation, and the need for surgery clinically revisited at 48 hours post-randomisation.
c. In patients where there are contraindications to intrapleural enzyme therapy, immediate surgical intervention in suitable patients should be considered.

**Standard care arm:**

In the standard care group, the RAPID score ***will not be routinely calculated***, and all patients will undergo treatment as per current national guidelines (BTS 2023) (1). This is summarized as follows:

1. **Pleural drainage:** all patients will be admitted to the hospital for chest drain insertion and subsequent drainage
2. **Broad spectrum antibiotics**: see below
3. **Clinical review** of progression will occur 48 to 72 hours after randomisation and initial above treatment. If there is evidence of poor clinical response (on the objective criteria listed below), the patient will be escalated to either intrapleural therapy or surgical intervention according to patient suitability and clinician choice / usual practice.

**Treatment applicable to both arms**

A number of treatments should be considered best practice and routine management in patients with pleural infection and will be applied to both groups (intervention and standard care). These treatments follow the NHS standard of care for pleural infection and are as follows:

1. **Broad spectrum antibiotics** to cover both aerobic and anaerobic organisms, and according to infection setting (community or hospital acquired infection), to be focused once culture results are available if positive as per local treatment guidelines or policies.
2. **Intravenous antibiotics** should be given during initial admission (if admitted)
3. **Switch to oral antibiotics** should occur once there has been a good clinical response with biochemical and radiological improvement, OR if the patient is intended for outpatient treatment (e.g. low RAPID group).
4. **Prophylactic low molecular weight heparin** should be administered as per local protocols if the patient is admitted.
5. **Analgesics** including NSAIDS or paracetamol in conjunction with opioids if needed will be provided for pain relief from pleural procedures and chest drains.
6. **Nutritional support** (supplements, dietician referral, nasogastric feeding) should be considered as clinically appropriate.
7. **Chest drain management**; for all patients who have chest drain during treatment, flushes and thoracic suction should be used according to local practice.
8. **Clinical review** should be conducted every day by the treating physician**.**

**Treatment failure Criteria**

During treatment and follow-up, the following objective criteria will be used to record if the patient is failing treatment and requires further intense treatment including re-admission, intrapleural enzyme therapy or surgical intervention. These criteria apply to any patient at any point from randomization to four weeks follow-up, and regardless of which treatment arm they have been randomised to (and **applied in general around 72 hours post randomisation for standard care and medium-high RAPID score in the intervention arm and at day 3 +_ 2 days post-discharge for low RAPID score group or at any other time if the treating physician feels they failed medical therapy** ). This measure is in place to ensure patient safety and objectivity of decision-making.

The treatment failure criteria are **BOTH** of the following:

1. The presence of a **significant residual pleural collection** on radiology (chest radiograph, ultrasound and/or CT) as judged by the local investigator AND
2. **At least one** of the following criteria (more than one may apply):
    a. Clinical evidence of **ongoing sepsis** with persistent fever, tachycardia or hypotension.
    b. A **serum CRP** (C-reactive protein) that fails to fall by more than or equal to 50% compared to the baseline value (from 48 hours after treatment).
    c. Lack of significant response in the **peripheral blood white-cell count value** (from 48 hours after treatment) as judged by local investigators.

To ensure objective decision-making and patient safety we will suggest applying **objective discharge criteria** for both arms as the total length of hospital stay is a potentially important primary outcome in the large-scale trial is prove this approach is safe. Discharge will occur **only once all** of the following are met:

a. Chest drain removed.
b. No clinical features of sepsis syndrome.
c. Significantly reduced inflammatory markers according to local physician review.
d. Significant reduction in pleural fluid on radiology according to local physician review.
e. Switched to oral antibiotics (at local physician's discretion).

### 9.8. Inpatient assessment (post-randomisation and before discharge home)

During the inpatient stay, the following data will be collected from all of the participants and recorded into the electronic study database:

1. **Bloods:** including full blood count (FBC), C reactive protein (CRP), liver and renal profile are advisable to be carried out every other day in the first week and weekly or twice per week if staying more than one week as part of usual NHS care (not requested specifically for the study) and based on treating physician discretion.
2. **Imaging:** Thoracic Ultrasound on day 3 (+/- 1 day) and 5 (+/- 1 day) or at the time of discharge, and chest x ray on day 3 (+/- 1 day) or as needed based on the discretion of the treating physician.
3. Cumulative volume of pleural fluid drainage (over the entire time of the drain being in situ)
9. **Antibiotics:** treatment received including types of antibiotics, and duration of intravenous antibiotics if available
10. Any chest tube displacement or blockage
11. Details of treatments given – e.g. whether all intrapleural treatment was completed, any missed or adjustment doses, date and type of surgery, reason surgical intervention was not undertaken, time from randomisation until surgery
12. Time from chest drain insertion to IET and/or surgery
13. Details of any subsequent pleural interventions while inpatient
14. Requirement for surgery due to treatment failure on objective criteria

### 9.9. Subsequent Visits (Outpatient follow up)

**Follow Up (applicable to both arms)**

1. On discharge, all patients should be followed up in pleural clinic at day 14 and 28 +/- 3 days post discharge with assessments of blood parameters (CRP, liver and renal profile, FBC), chest x-ray and thoracic ultrasound as per standard NHS care.
2. A telemedicine review via phone will occur at 90 +_ 3 days post-discharge to collect longer-term outcomes.

3. ***The total length of antibiotic treatment given*** will be determined by local physicians and clinical response, but it is suggested to be at least 3 weeks total treatment (as per national standards).

**Follow Up (Intervention arm only)**

In the intervention arm, a clinical review will be arranged in 3 days +/- 2 days after discharge for low RAPID score group participants where bloods (CRP, full blood count, renal and liver profile), thoracic ultrasound and chest x ray will be conducted and the treatment failure criteria will be applied at the time of follow up, should any of these criteria full filled, the participant will be admitted to hospital and treated as intermediate to high score group.

Below is the summary of assessments in each outpatient visit which will be recorded into electronic CRF (REDCap).

| **Assessment** | **Day 3 +/-2 days follow up (Low RAPID score group only), post discharge** | **14 days +_ 3 days follow up** | **28 days +_ 3 days follow up** | **90 days +_ follow up (phone call)** |
|---|---|---|---|---|
| Clinical assessment (review symptoms and clinical examination) | Yes | Yes | Yes | NA |
| Thoracic ultrasound | Yes (part of the research) | Yes (standard care) | Yes (standard care) | NA |
| Blood (FBC, U and Es, liver function and CRP) – standard NHS care | Yes | Yes | Yes | NA |
| Chest x ray | Yes | Yes | Yes | Yes (remote review) |
| Readmissions to hospital | Yes | Yes | Yes | Yes (remote review) |
| Requirement for further chest drain insertion | Yes | Yes | Yes | Yes (remote review) |
| Requirement for surgery | Yes | Yes | Yes | Yes (remote review) |
| Mortality rate | Yes | Yes | Yes | Yes (remote review) |
| Health related quality of life using EQ-5D-5L | NA | Yes | Yes | Yes (remote review) |
| Assessment of functional ability (SF36) | Na | Yes | Yes | Yes (remote review) |
| VAS score pain and breathlessness | NA | Yes | NA | Yes (remote review) |

## 9.10. Health-related quality of life questionnaires

All patients will be asked to fill in a health-related quality of life (EQ-5D) questionnaire, time to return to normal function (SF36) and a VAS scoresheet for chest pain and breathlessness.

***EQ-5D-5L***

The EQ-5D is a 5-domain questionnaire which gives an overall assessment of an individual's quality of life at a particular time point. There are five questions, and it is envisaged this should take between 1-2 minutes to complete. These assessments will take place in person at baseline, 14 days +/- 3, 28 days +/-3 days and remotely in 90 days +/- 3 days.

***VAS score***

RAPTOR – f study uses 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 – 45 seconds per scale. These will be collected at baseline, day 28 +/-3 days in person and day 90 +/- 3 days (remotely)

**SF36**

This survey assesses eight health concepts: physical functioning, bodily pain, role limitations due to physical health problems, role limitations due to personal or emotional problems, general mental health, social functioning, energy/fatigue, and general health perceptions. It takes 6 to 8 minutes to fill out, this assessment will take place at day 28 +_ 3 days and day 90+_ 3 days.

## 9.11. Embedded Qualitative Interviews

An important aspect of a feasibility study is the participant's experience of the study processes, interventions and follow-up is an important aspect of the RATOR f feasibility study. A selection of patients who were eligible for the RAPTOR f study (both those who accepted randomisation and those who did not) will be invited to semi-structured interviews. A selection of healthcare professionals (Respiratory/pleural or general physicians) who were responsible for the clinical care of participants in the RAPTOR f study will be invited towards the end of the recruitment period.

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

***Patient interviews***

Patients who accepted randomisation will be given the interview specific participants information sheet (PIS) at 14 days post-discharge (at the time of the first clinic visit for all participants and the second clinic visit for the low risk group). The interviews will take place 4 to 6 weeks after study recruitment to allow time for recovery of the participant.

For those who did not accept randomisation, the members of the clinical team will explore their willingness to take part in a qualitative interview while they are inpatient or when attend their clinic follow up. If they are willing, they will be given the participant information sheet r the qualitative study and the team will seek their permission to pass on their contact details to the study fellow Dr Elsheikh via secured email system. The research team will then contact them to arrange an interview, which will be conducted at a time convenient to the patient participant at 4 to 6 weeks after hospital discharge, in order to ensure recovery.

Participants will be invited to online interviews via Microsoft Teams or a telephone call if unable to access online audio team call. The interview will be conducted at a time convenient for the patient. Interviewees will be asked to provide remote verbal informed consent at time of to the interview., Professional translation services will be provided for non-English speakers.

The interview topic guides (for patients and for healthcare professionals) have been developed in collaboration with a pleural infection PPI group and submitted for ethical approval. The interviews will explore the following topics: acceptability of study design (e.g. recruitment, consenting, randomisation) and treatment arms; factors influencing study participation; the impact of pleural infection and study participation on the quality of life and carers; and important health outcomes.

A sample of up to 12patients who were eligible for enrolment in the RAPTOR f study will be invited to participate in interviews to ensure that that there is sufficient information for the topics covered in the interview guide and no new issues are emerging.

***Healthcare Professionals Interview***

Up to six healthcare professionals who will be significantly involved with the care of study participants, will be invited to participate in an interview near the end of the recruitment period. An information sheet will be provided to each of the Healthcare Professionals and a minimum of 24 hours to consider their participation. The process of obtaining consent for the interviews will mirror that used for the patient interviews, with written informed consent required prior to the commencement of the interview. This consent will include permission for the physician's comments to be recorded and for anonymised quotes to be included in the final report and any peer-reviewed literature arising from the project.

The interview topic guide will focus on the following areas:

- The experience of using the risk stratification tools, RAPID score to guide management of pleural infection.
- Suggested improvements to the study 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 study of this type? What are the barriers of recruitment and randomisation
- The study's perceived effect on patient outcomes and healthcare services, as well as recommendations for future research in this field.

As with the patients' interviews, the sample size of up to six physicians has been deemed sufficient to provide enough information for the topics covered in the interview guide and that no new issues are emerging.

***All interviews***

All interviews will last up to 60 minutes. This will be conducted by Dr. Elsheikh, or one of the members of the study team via online platforms e.g. Microsoft Teams, audio function or Telephone call for those who don't have access to the internet. It will be audio-recorded, professionally transcribed by transcription services, the transcripts will remain confidential during the transfer and storage process, the company will destroy the audio-files and any copies they held of the transcript. The transcription company will be approved by, and contracted to, the university. Transcripts will be securely returned to study team, checked and any remaining identifying information removed, then to uploaded to data management software. The data will be thematically analysed under the supervision of Dr Margaret Glogowska.

### 9.12. Sample Handling

Samples for routine clinical care will be conducted as per local hospital practice and NHS standard care. Research samples from all participants consenting to provide samples (blood and pleural fluid) will be collected and transported to the coordinating centre for analysis as per study-specific processing procedures.

#### 9.12.1. Bloods

All blood tests (e.g. CRP, FBC) performed during the RAPTOR f feasibility study are part of the NHS standard care for patients with pleural and systemic infection. These tests will include full blood count, , C-reactive protein, and liver and renal function tests which are advisable to be taken on alternate days if feasible for the first 7 days and then once or twice per week as deemed appropriate by the treating physician if the participant stays over a week. These samples will be processed at each recruiting centre via normal laboratory processes. The results will be recorded on the case reports form.

In addition, all participants will be asked for specific consent for collection of repeated samples of blood (10 millilitres, about 2 teaspoonfuls) on days 1 (randomisation day) , 3 and 5 post -randomisation from all centres (Optional) if these are convenient to collect (e.g. if the patient has been discharged home, they will not be collected or day o sample only) and to avoid any discomfort for the patients all research samples will be collected at the same time of usual care samples. We will assess the levels of the biomarkers, including suPAR (Soluble Urokinase Plasminogen Activator Receptor) and PAI-1 (Plasminogen-Activator Inhibitor-1), cytokines ( Interleukins (IL) 1 and 2, and NE (Neutrophils elastase) assessments at baseline from all participants at baseline and we will repeat the measurement on day 3 and 5 if applicable and participant willing to donate the samples.

#### 9.12.2. Pleural fluid

As part of the NHS standard care for diagnosis and management of pleural infection, a diagnostic pleural aspiration is performed, which will occur before/or at the time of enrollment in RAPTOR f study. This includes pleural fluid total protein (TP), lactate dehydrogenase (LDH), glucose, pH, cytology and standard microbiology (culture and microscopy in white top containers or blood culture bottles), the results will be recorded in the study database system. If any of the above standard pleural fluid investigations were not

requested, they could be performed on this pleural fluid collected during chest tube insertion as per standard care or add on request to the laboratory after therapeutic aspiration.

In addition, all participants from all centres **(optional)** will be asked for specific consent for the collection of repeated samples of pleural fluid (100 ml) on days 1 ( randomisaiton day, 3 and 5, post – randomisation), if these are convenient to collect (e.g. if the patient has been discharged home, they will not be collected or day 1sample only) ,and to avoid any discomfort for the patients all research samples will be collected at the same time of usual care samples. These samples will be used for analysis of pleural fluid biomarkers, including suPAR (Soluble Urokinase Plasminogen Activator Receptor) and PAI-1 (Plasminogen-Activator Inhibitor-1), cytokines (Interleukins (IL) 1 and 2, and NE (Neutrophils elastase) assessments. They will also be consented **(optional)** to store and use the leftover samples after completing the analysis for the ethically approved future research. The participant will be assured that consent for the samples storage and use is not required for participation and enrolment into the clinical study.

## 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.
- 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. They 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.

Withdrawal of a participant from the study should be under the guidance of the principal investigator (in liaison with the CI). Withdrawal details will be recorded on the relevant CRF.
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 recorded as a file note/protocol deviation. Should a participant decide to withdraw, all efforts will be made to complete and report the observations as thoroughly as possible. For participants moving from the area, every effort should be made for the participant to be followed up at another centre, or for follow-up via GP.

Finally, the Investigator may discontinue a participant from the study arms at any time if the Investigator considers it necessary for any reason including:

I. Ineligibility (either arising during the study or retrospectively having been overlooked at screening)
II. Significant protocol deviation
III. Significant non-compliance with the study requirements

If the participant is withdrawn due to an adverse event directly related to the study, the Investigator will

arrange for follow-up visits or telephone calls until the adverse event has resolved or stabilised.

## 11. Definition of End of Study

The end of the study is the point at which all the data have been entered, follow-up completed, queries resolved, data lock complete and research samples analysed or at the discretion of the Study Steering Committee (SSC).

## 12. SAFETY REPORTING

All treatment modalities that will be used in the RAPTOR -f feasibility study (interventional and non-interventional treatments), including chest drain insertion, therapeutic aspiration, IET, antibiotics, and surgery have all been clinically approved and are part of the NHS routine standard usual care; therefore, only SAEs that are found to be directly related the a study procedure and not expected will be reported.

### 12.1. Definition of Serious Adverse Events

A serious adverse event is any untoward medical occurrence that:

- results in death
- is life-threatening
- requires inpatient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability/incapacity
- consists of a congenital anomaly or birth defect.

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

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

### 12.2. Reporting Procedures for Serious Adverse Events

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).

## 13. STATISTICS AND ANALYSIS

The plan for the statistical analysis of the study is outlined below. There will not be a separate SAP document in use for the trial, as the analysis is relatively simple.

### 13.1. Description of the Statistical Methods

#### 13.1.1. Analysis of the RAPTOR f feasibility study:

Feasibility parameters will be measured and reported, and include:

- Recruitment proportion (number of randomised patients divided by number of eligible patients)
- Randomisation acceptance rate (proportion of patients who are willing to be randomised over those eligible)
- Retention (number of participants who complete intended treatment, number of participants who complete intended follow up)

These will be reported and used to assess whether or not a definitive trial is feasible. Descriptive statistics will be used to describe the demographic characteristics between the two groups. For categorical variables, numbers (and proportions) will be reported for each treatment group and overall. For continuous variables, means and standard deviations (or medians in the interquartile range) will be reported for each treatment group and overall. As this feasibility study is not powered to draw definitive conclusions, comparisons between the two arms for clinical outcomes will be reported using descriptive statistics only. No statistical tests will be carried out. These will be based on multivariable linear (for continuous outcomes) or logistic (for binary outcomes) regression with adjustment for stratification factors and important prognostic factors and will be reported as adjusted differences in means (for continuous outcomes) or proportions (for binary outcomes). Treatment comparisons will be reported for the intention-to-treat population (all randomised participants will be analysed according to their allocated treatment group irrespective of which treatment they actually receive) as treatment effects together with 95% confidence intervals for the two main comparisons: (1) Standard care vs overall RAPID driven treatment (2) Low RAPID driven treatment arm vs moderate to high RAPID driven treatment arm. Compliance to the interventions will be reported.

To establish the feasibility of collecting accurate long-term outcomes in randomised participants, we will present the completeness of the outcomes across the duration of the trial. The outcome measures collected in this study will be used to inform the sample size for the future definitive large-scale phase III RCT if it is feasible to be undertaken.

Adverse events and serious adverse events will be reported by each arm in the intervention group on the safety population only (all patients who received the allocated treatment).

It is anticipated that STATA (StataCorp LP) or other appropriate validated statistical software will be used for analysis.

#### 13.1.2. Analysis of the embedded qualitative:

Interviews will be digitally audio-recorded, transcribed verbatim, and de-identified before being uploaded to data management software. The 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. Codes will then be grouped into categories, and data explored to identify connections and to develop a descriptive account of the dataset as a whole. The analysis will

focus on the acceptability of study processes to patients, individual and group equipoise, and the patient experience of pleural infection and treatment.

For the RAPTOR-f study and embedded qualitative interviews, we will use robust progression criteria (see Table 1) to assess the feasibility of progression to a definitive phase III trial; green indicates all criteria are met, and if met, a larger study will be declared feasible. If one or more criteria are amber, this will result in mitigations including:

- Review of qualitative data to identify barriers and potential mitigations
- Discussion of recruitment to date and barriers with the study management group
- Consideration of widening the recruited population and increasing centres

**Table 1**: Illustrate stop and go criteria for study progression, this will be applied for all centres, if any criteria are red, this will prompt major changes to the study or qualitative study design.

| Criteria | Green | Amber | Red |
|---|---|---|---|
| Recruitment proportion (number eligible versus number randomised) | >50% | 30% - 50% | < 30 |
| Average monthly recruitment* (pts/centre/month) | ≥1.0 | 0.5 – 0.9 | < 0.5 |
| Adherence to the allocated intervention group | ≥90% | 75% - 90% | < 75% |
| The proportion of key date completion (e.g Visual Analogue Score) | ≥98% | 75% - 97% | < 75% |
| Proportion completing study protocol (accounting for 10% expected attrition) | ≥90% | 75% - 90% | < 75% |
| Individual site recruitment (at 10 months) | ≥10 | 5 – 9 | < 5 |
| Proportion completing clinicians' interview | >50 % | 30% - 50% | < 30% |
| Proportion completing patients' interview | >50% | 30% - 50% | < 30% |

***** Once all centres have been greenlighted

### 13.2. Sample Size Determination

As a feasibility study, 30 patients are considered sufficient to demonstrate the feasibility of recruitment to a larger study. In addition, a potential sample size calculation for a definitive phase 3 trial is presented below to ensure the correct feasibility parameters of the recruitment rate are robustly addressed in the feasibility study.

The average hospital stay for pleural infection is 14 days (SD 10). Assuming RAPID driven treatment overall reduces hospital stay by 4 days (as 50% of the RAPID arm will be in the low-risk group and reducing the length of stay by 8 days is reasonable as such patients will be sent home within 24 to 48 hours of treatment), and assuming a clinically meaningful difference in hospital stay of more than 4 days

(SD 10 from previous studies), with 5% significance and 90% power, this would require 264 patients in total (132 randomised 1:1). In a definitive study of this design recruiting in 15 centres in the UK over 18 months recruitment, a rate of 1 patient/centre/month would provide sufficient patients.

For the feasibility RAPTOR study, a target of 30 patients in total (3-4 centres recruitment over 10 months at 1 patient/centre/month) is therefore reasonable.

This number should be sufficient to conduct meaningful qualitative interviews with patients/carers (in discussion with our qualitative co-applicant) and is also sufficient to show a definitive study is possible, with careful measurement of the number eligible / number consented / number randomised / number completing protocol.

### 13.3. Analysis populations

The study will be analysed on intention to treat, with included populations as specified in sections 12.2 and 12.3.

### 13.4. Decision points

No interim analysis will be conducted. The Study Steering Committee will review the recruitment rate regularly throughout the trial.

### 13.5. Stopping rules

No formal stopping rules are planned.

### 13.6. The Level of Statistical Significance

Not applicable

### 13.7. . Procedure for Accounting for Missing, Unused, and Spurious Data.

The study database will generate queries automatically during the data input process. The database will only be locked (allowing the commencement of final analysis) once the Study Steering Committee is satisfied that all data queries have been addressed as completely as possible. The incidence of missing data will be minimised by maintaining contact with participants to avoid missed appointments, and by completing eCRFs with the use of notes reviews or telephone contact if necessary. In such cases, appropriate consent must be in place.

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

Any changes/deviations from the statistical analysis outlined here will be described and justified in the final statistical report.

### 13.9. Health Economics Analysis

Initial Health Economic Analysis will be undertaken to inform a potential larger trial. It will be the subject of a specific Health Economic Analysis plan to be written during trial recruitment, using the parameters collected.

## 14. DATA MANAGEMENT

The study will utilise a secure web-based, study data management system designed for remote electronic data capture. Electronic Case Report Forms (e-CRFs) will be designed in accordance with the trial protocol to allow appropriate remote data capture.

It is the Investigator's responsibility to ensure the accuracy of all data entered and recorded in the eCRFs. The Delegation of Responsibilities Log will identify all study personnel responsible for data collection, entry, handling and managing the database.

### 14.1. 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, and include electronic patient records), clinical and office charts, laboratory and pharmacy records, and medical imaging.

Data required for the conduct and analysis of this study will be collected via paper participant facing electronic forms and clinician entered electronic CRFs (e-CRFs). This may be transcribed or summarised from source documents or may be collected directly in trial e-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).

Audio files of the patient and clinician interviews will be stored by the chief investigator or study co-coordinator and sent securely to the external transcription company by secure link. Once the transcript is received and provided that there is no error in the transcription, the company will destroy these files permanently and a copy of the audio-files will be stored by Oxford University for 5 years, and only members of the team involved with data collection and analysis will have access to the recordings and transcripts as per university policy.

Consent forms will be retained for participants consenting to be contacted for future research and samples retention.

### 14.2. Access to Data

Direct access will be provided to authorised representatives of the sponsor, host institution, to permit study-related monitoring, audits, and inspections of the study to ensure compliance.

### 14.3. Data Recording and Record-Keeping

Data will be entered into a secure, validated, GCP-compliant electronic data management system (REDCap). 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 Study Specific Procedures (SSPs) will be followed to maximise the completeness and accuracy study data.

Study documents (other than the signed consent form) and datasets will be de-identified with participants allocated a unique study-specific number or code, documents containing personal identifiable information (e.g. for the purposes of contacting participants about the interview study) will be kept securely and separately on university servers until the interview conducted after which you will no longer need to keep their phone number.

Participants who consent to qualitative interviews will require their contact information to be sent to the study research fellow Dr Elsheikh via a secured email system by a research nurse at the recruiting site to allow co-ordination of in-depth interviews.

All study documents will be stored securely. Both paper and electronic study data will be retained through an archiving service for a period of 5 years.

## 15. QUALITY ASSURANCE PROCEDURES

### 15.1. Risk assessment

All of the treatment modalities applied to the RAPTOR f study are part of the NHS care which have been proven safe, therefore there is no risk assessment planned.

### 15.2. Study monitoring

All data entry will be conducted on the online database, with remote monitoring conducted by the study management group. The REDCap database has an integrated system for reviewing data queries and errors, which will be monitored throughout and discussed with the respective recruiting sites.

### 15.3. 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 SMG 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 SSC charter will be written detailing the requirements of this committee and its members.

## 16. PROTOCOL DEVIATIONS

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

## 17. SERIOUS BREACHES

The Medicines for Human Use (Clinical Trials) Regulations contain a requirement for the notification of "serious breaches" to the MHRA within 7 days of the Sponsor becoming aware of the breach.

A serious breach is defined as “A breach of GCP or the study protocol which is likely to affect to a significant degree:

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

(b) the scientific value of the study”.

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

## 18. ETHICAL AND REGULATORY CONSIDERATIONS

### 18.1. Declaration of Helsinki

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

### 18.2. Guidelines for Good Clinical Practice

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

### 18.3. 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), HRA (where required), and host institution(s) 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.

### 18.4. Other Ethical Considerations

Eligible participants will be given detailed information and the opportunity to discuss the study further with a member of the study team. Participants are generally given 24 hours of ‘thinking time’ thereafter to consider enrolling in a study. 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 the collection of subsequent data sheets. All will be appropriately de-identified.

Verbal consent will be taken from participants, non-randomised patients and healthcare professionals to be enrolled in the qualitative study.

18.5 **Reporting**

The CI shall submit a report 12 months after commencing the study, or on request, an Annual Progress Report to the host organisation, funder (where required) and Sponsor. In addition, an end of study notification and final report will be submitted to the REC, the host organisation and the Sponsor.

### 18.6. Participant Confidentiality

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

### 18.7. Expenses and Benefits

All of the study procedures are part of the NHS standard care therefore there is no extra expenses expected however for healthcare professionals or participants interviews; we will provide a thank you vouchers for all of the participants. Which equate £ 20.

## 19. FINANCE AND INSURANCE

### 19.1. Funding

NIHR Research for Patient Benefit Programme, application number NIHR207229

### 19.2. Insurance

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

### 19.3. Contractual arrangements

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

## 20. PUBLICATION POLICY

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

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

Ownership of IP generated by employees of the University vests in the University. The University will ensure appropriate arrangements are in place as regards any new IP arising from the trial.

## 22. ARCHIVING

**22.1. Minimum archiving period**
The TMF including all essential documents, as well as any non-trial-specific records (e.g. SOPs, training records and equipment records), will be archived for at least 5 years after the completion of study-related activities.

**22.2. Trial Master File**
The study documents (including the Trial Master File (TMF) will be archived electronically on a secure, backed up, access restricted MSD-IT server for 5 years.

**22.3. Investigator Site File and participant medical records**
The Investigator Site Files will be archived at the participating sites in accordance with the site agreements, and with site local procedures. Where applicable, the medical records of trial participants are not archived and must be retained at the site for the minimum archiving period above and in accordance with requirements of the host healthcare provider (where that is the longer retention period).

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## 25. APPENDIX B: SCHEDULE OF STUDY PROCEDURES –

## 26. APPENDIX C: AMENDMENT HISTORY

| Amendment No. | Protocol Version No. | Date issued | Author(s) of changes | Details of Changes made |
|---|---|---|---|---|
| 1 | 2.0 | | Elsheikh | 1. Change protocol date and version from 03/06/2025, V2.1 to 09/09/2025, V3.0, all through protocol.<br>2. Typo correction: Change LDH ≥ 9000 IU/L to LDH ≥ 900 IU/L (pages 9, 21).<br>3. Sample collection timing: Change Day 0 to Day 1 (the day of randomisation) to align with patient assessments (pages 12, 19, 24, 25, 35, 36).<br>4. Thoracic ultrasound timing: Change from Day 2 ± 1 to Day 3 ± 1 (pages 22, 31).<br>5. Typo correction: Delete "1 days" (page 31).<br>6. Images transfer: Add "Compact Disk, or other appropriate password-protected electronic device" (page 27). |

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).