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A randomised study to assess the feasibility of treating patients with pleural infection according to the RAPID score, compared with usual care based on the British Thoracic Society Pleural Disease Guidelines

Submission date 02/09/2025	**Recruitment status** Recruiting	[X] Prospectively registered [X] Protocol [_] Statistical analysis plan [_] Results [_] Individual participant data [X] Record updated in last year
Registration date 03/11/2025	**Overall study status** Ongoing	
Last Edited 03/11/2025	**Condition category** Respiratory	

Plain English summary of protocol

Background and study aims

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 1 in 5 people, and patients stay in hospital for an average of 14 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 stay 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 from 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 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 change treatment and therefore benefit patients. To prove this, we need to conduct a large study. Before doing this, it is essential that we know such a study would be possible, and that changing treatment according to RAPID score is acceptable to patients and doctors.

We aim to conduct a study where patients are randomised (assigned by computer) to standard treatment or treatment which is driven by the RAPID score. We will measure whether this is

acceptable to patients and answer key questions which will help us know if a larger, definitive study is possible. We will interview patients who are willing to be part of the study, and some who decide not to, to understand what is important to them when treating this disease and their reasons for taking part or not. This will help us to understand what should be measured in a bigger study to best improve patient care.

Who can participate?
Patients with pleural infection who over 18 years old and meet inclusion/exclusion criteria

What does the study involve?
Participants assigned to the standard care group will be admitted to hospital and treated with intravenous antibiotics and chest drain insertion. Within 72 hours, the treating team will decide whether escalation of treatment to either intrapleural enzyme therapy (IET) or surgery, based on predefined progression criteria, including infection markers on the blood and radiological findings (Chest x ray or thoracic ultrasound). In this arm, all treatment will be delivered based on the British Thoracic Society Guidelines 2023.
Participants assigned to the RAPID-driven group will have their RAPID score calculated.
Low-risk group (0 – 2): participants will receive short-term pleural drainage (chest drain insertion for 24–48 hours) or therapeutic pleural aspiration alongside antibiotics. They will then be discharged with an early outpatient review at 3 ± 2 days and provided with a 24/7 phone number to study fellow to call if any issues arise.
Intermediate–high-risk group (3 – 7): participants will receive chest drain insertion, immediate intrapleural enzyme therapy (IET), and parallel surgical referral. The treating doctors will reassess the patient after 72 hours; if there is no response to treatment according to predefined criteria, surgery will be offered.
Participants will be asked to fill out a diary recording breathlessness and pain scores, as well as quality of life scores, during their hospital stay and at home. Follow up visits will occur in person at 2 and 4 weeks post hospital discharge and at 12 weeks over the phone. During follow up visits, participants will have bloods, chest x-rays, and chest ultrasound scans as part of routine care, to check on their clinical progress and assess if any further treatment is required.
If participants are willing and indicate this on the consent form, they will be invited to participate in a single interview with the research team to explore their experience and assess acceptability of both the RAPID driven care arm, and the trial overall.

What are the possible benefits and risks of participating?
Clinical outcomes in pleural infection remain poor; there is a 1- year mortality of 20%, increasing up to 40% among elderly populations, and 20% of patients fail initial medical treatment and require surgery. Treatment is also burdensome; 25% require hospital admission for more than 1 month, and there is a median hospital stay of 12–15 days. The cost of treatment in the NHS is approximately £4,000 per patient, equating to £58 million per year, driven by prolonged hospital stay. More efficient care, targeting treatments such as surgery and intrapleural therapy to those that need it most, is likely to improve costs and reduce hospital admission.
Currently, all patients with pleural infection are treated in a stepwise manner with initial chest tube drainage and antibiotics, and only those not showing a good response to treatment after three to five days go on to have more aggressive therapy in the form of Video-assisted thoracoscopic surgery (VATS) or IET. This generic and non-specific treatment approach is likely to be inefficient. Early Identification of patients with the poorest clinical outcomes (need for surgery, death, long hospital stay) would therefore be of high clinical value. This would allow the targeting of more interventional treatments early in the disease course to those who need it most.
While this is a feasibility study, and thus any clinical impact and change in practice will need to await results of the feasibility study, and then a definitive study in this area, the proposal is

designed with patient benefit central to the purpose of the study.
Given the above, 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:
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. 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.
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.
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.
The RAPTOR-F feasibility study does not introduce any additional clinical risk to participants. All treatment modalities to be used including chest drain insertion, therapeutic aspiration, intrapleural enzyme therapy (IET), antibiotics, and surgery are established, clinically approved interventions recommended in the British Thoracic Society (BTS) guidelines and routinely delivered as part of standard NHS care.

Where is the study run from?
The study is co-ordinated by the University of Oxford (UK)

When is the study starting and how long is it expected to run for?
December 2024 to September 2026

Who is funding the study?
National Institute for Health and Social Care Research (NIHR, UK), RfPB application number NIHR207229

Who is the main contact?
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Contact information

Type(s)

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Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

Integrated Research Application System (IRAS)
336017

Protocol serial number
CPMS 59220; Grant Code: NIHR207229

Study information

Scientific Title
RAPID driven Treatment of Pleural Infection (feasibility study): RAPTOR – f

Acronym
RAPTOR-f

Study objectives
Objectives:
1. To deliver a randomised feasibility study of usual care versus RAPID driven care in 30 patients from 4 UK centres with pleural infection.
2. To measure recruitment rate, recruitment proportion (number eligible versus number randomised) and completeness of key outcomes.
3. To conduct qualitative interviews with clinicians and patients to understand the reasons for not entering the study and the acceptability of management using RAPID.
4. To understand key patient priorities in the treatment of pleural infection.

Hypothesis:
We hypothesise that a RAPID score driven treatment algorithm is superior to the standard treatment approach, which treats all patients in an unselected manner (British Thoracic Society Guidelines, 2023). Because using the RAPID score to directly guide the treatment pathway represents a fundamentally different management strategy, a feasibility study is required to address key uncertainties. These include recruitment feasibility, acceptability to patients and healthcare professionals, and identification of the most appropriate outcomes for a larger, definitive study in the future.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 13/06/2025, Wales REC3 (Health and Care Research Wales, Floor 4, Crown Building, Cathays Park, Cardiff, CF10 3NQ, UK; +44 (0)2920 230457; wales.REC3@wales.nhs.uk), ref: 25/WA/0161

Study design
Randomized controlled trial

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Pleural infection

Interventions
Intervention arm:
The intervention in this study is treatment driven by the baseline RAPID score (post-randomisation). Patients with a higher RAPID score (and thus higher predicted mortality) will be triaged to more aggressive treatment early in the disease, and those with lower predicted mortality will be treated less aggressively.

The RAPID score will be calculated post-randomisation, and the treatment algorithm will proceed as follows:
A. Low risk (RAPID score 0 to 2):
1. Pleural drainage: temporary chest tube insertion for 24 to 48 hours or therapeutic pleural aspiration (short-term drainage) will be used if safe to do.
2. Admission for drainage for a maximum of 24 to 48 hours, a patient will be sent home after the senior clinician review and if deemed safe to go home after meeting the discharge criteria below and no signs of treatment failure (see below objective criteria for treatment failure).
3. Broad-spectrum antibiotics governed by the setting of the infection, hospital policy and the pleural fluid culture results.
4. Review in clinic after 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.
5. 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 an outpatient which will prompt urgent review by the pleural service locally.

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

B. Intermediate + high-risk (RAPID score 3 to 7):
1. All participants in this arm will be admitted to hospital for chest tube insertion to drain the infected pleural fluid.
2. They will be covered by broad-spectrum antibiotics governed by the setting of the infection, hospital policy and the pleural fluid culture results.
3. They will be having an early installation of Intrapleural enzyme therapy via the chest drain within 24 hours of the chest drain insertion if deemed safe and possible.

4. At the same time of the chest drain insertion a referral to local thoracic surgical services will be made to allow assessment for surgery and planning of the surgical procedures within 48 hours post admission.

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. While in patients and during the initial admission all participants will have Intravenous antibiotics.
3. The intravenous antibiotics will be switched to oral antibiotics 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 while in hospital to prevent clotting formation as people with a pleural infection do have a high tendency to develop clots.
5. All participants will have regular analgesia prescribed including NSAIDS or paracetamol in conjunction with opioids to relieve the pain from chest, drain insertion or other pleural procedures.
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 and facilities.
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 collection of the infected pleural fluid in the pleural cavity on images including; chest radiograph or ultrasound and/or CT) as judged by the local investigator AND
2. At least one of the following criteria (more than one may apply):
2.1. Clinical evidence of ongoing sepsis with persistent high-grade temperature, increasing heart rate and low blood pressure.
2.2. Lack of significant response to the inflammatory markers on the blood including; 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) OR peripheral blood white-cell count value (from 48 hours after treatment) as judged by local principal 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:
1. Chest drain removed.
2. No clinical features of ongoing sepsis as above.
3. Significantly reduced inflammatory markers according to local physician review.
4. Significant reduction in pleural fluid on radiology according to local physician review.
5. Switched to oral antibiotics (at local physician's discretion).

Follow up (applicable to both arms):
1. On discharge, all patients should be followed up in the pleural clinic on 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. All participants will have 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 for total treatment (as per national standards).

Follow up (Intervention arm only - low RAPID score group):
For the participants who fall into the low-risk group, a clinical review will be arranged in 3 days +/- 2 days after discharge where blood (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.

Intervention Type
Mixed

Primary outcome(s)
The feasibility of recruitment, data collection and acceptability of the participants and of healthcare professionals of randomisation, assessed using:
1. Recruitment, retention rate, the proportion of participants screened who consented to be randomised and who consented to be interviewed, data completeness/availability and participant completion assessed at recruitment completion.
2. Semi- structured interviews with a proportion of the randomised participants and healthcare professionals at 4 to 6 weeks post hospital discharge

The primary outcome will be defined as successful if ≥50% of the eligible patients are willing to be randomised and ≥50% of the healthcare professionals and participants agreed to take part in the interviews at recruitment completion

Key secondary outcome(s))
1. Length of hospital stay strategies: completeness of data regarding the time of the participants staying in hospital over 3 months from randomisation until discharge
2. Mortality rate over 3 months (all cause): proportion of participants who died (all cause) over 3 months post randomisation until the end of the study
3. Need for IET: proportion of participants who required IET post randomisation from time of admission until discharge
4. Need for surgery: proportion of participants who required surgery post randomisation from

time of admission until discharge
5. Medical treatment failure: proportion of participants who did not respond to medical treatment (pleural fluid drainage + IET) and required surgery post randomisation from time of admission until discharge
6. Need for repeat intervention and admission: number of participants who need further pleural procedure, e.g. chest drain insertion or therapeutic thoracocentesis and proportion of the participants who required re admission to hospital until the end of the study
7. Duration of antibiotics: completeness of data regarding the use of antibiotics from day of starting antibiotics up to 6 weeks post discharge
8. Time to complete recovery and return to normal function measured using SF36 at 4- and 12-weeks post randomisation
9. Health related quality of life measured using EQ5D 5l questionnaire at baseline, 2-, 4- and 12-weeks post randomisation
10. Breathlessness and pain measured using 100 mm VAS score post randomisation and until discharge from hospital
11. Feasibility of delivering the intervention arm (RAPID driven arm) measured using time of failure of medical treatment to surgery (VATS, thoracotomy) or time from ICD insertion to IET at end of the study
12. Healthcare utilisation: number of pleural procedures and days in hospital post randomisation during hospital stay
13. The pattern of computed tomography of the chest (CT chest) in pleural infection to assess for consolidation during hospital stay
14. Radiological changes following treatment: chest x- Ray to assess for pleural thickening at 12 weeks post-randomisation
15. The proportion of participants with an elevated level of pleural fluid and blood biomarkers (suPAR, PAI-1, IL 1+2, and NET) in serial samples taken on day 1 (randomisation day), 3 and 5 (post-randomisation) who did not respond to medical treatment

Completion date
30/09/2026

Eligibility

Key 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:
3.1. Purulent or
3.2. Gram positive or
3.3. Culture positive (pleural fluid or biopsy) or
3.4. Acidic with a pH<7.2 or
3.5. Low pleural fluid glucose <4.4 mmol/L or 72mg/dL(non-diabetic) or LDH ≥ 900 iu/L OR
3.6. (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

Participant type(s)
Patient

Healthy volunteers allowed

No

Age group
Adult

Lower age limit
18 years

Sex
All

Key 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)

Date of first enrolment
05/11/2025

Date of final enrolment
01/06/2026

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
Oxford University Hospitals NHS Foundation Trust
John Radcliffe Hospital
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Study participating centre

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Sponsor information

Organisation
University of Oxford

ROR
https://ror.org/052gg0110

Funder(s)

Funder type
Government

Funder Name
National Institute for Health and Care Research

Alternative Name(s)
National Institute for Health Research, NIHR Research, NIHRresearch, NIHR - National Institute for Health Research, NIHR (The National Institute for Health and Care Research), NIHR

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
The data-sharing plans for the current study are unknown and will be made available at a later date

IPD sharing plan summary
Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Participant information sheet	version 2.0	03/06/2025	06/10/2025	No	Yes
Protocol file	version 3.0	26/09/2025	06/10/2025	No	No
Study website	Study website	11/11/2025	11/11/2025	No	Yes