ISRCTN16328099 https://doi.org/10.1186/ISRCTN16328099

The Fourth Multicentre Intrapleural Sepsis Trial (MIST-4) - a randomised clinical randomised effectiveness study comparing early video assisted thoracic surgery and early intrapleural enzyme therapy in adult patients with pleural infection

Submission date 08/01/2026	**Recruitment status** Recruiting	[X] Prospectively registered [ ] Protocol [ ] Statistical analysis plan [ ] Results [ ] Individual participant data [X] Record updated in last year
Registration date 27/02/2026	**Overall study status** Ongoing	
Last Edited 10/03/2026	**Condition category** Respiratory	

Plain English summary of protocol

Background and study aims

Pleural infection is a severe complication of pneumonia, where infected fluid collects around the lungs. Around 40 new cases are diagnosed daily in the UK, increasingly among the elderly. Standard treatment includes antibiotics, chest tube drainage under local anaesthetic, and a hospital stay of approximately 2 weeks. However, 20% of patients either die within a year or require surgery when initial treatment fails. Surgery, while effective, carries significant risks, particularly for older or frail patients where mortality can reach 35%.

Two less invasive treatment options are now available: Intrapleural Enzyme Therapy (IET), which enhances fluid drainage via the chest tube, and Video-Assisted Thoracoscopic Surgery (VATS), a keyhole surgical approach. Both have shown promise, but their comparative effectiveness has never been tested in a large, direct trial. Currently, choice of treatment varies by hospital and clinician. Evidence suggests that delays in administering effective therapy result in poorer outcomes, including death and prolonged hospitalisation.

A prior feasibility study showed that patients were willing to be randomised to either IET or VATS and that both treatments could be delivered promptly. Patients in that study identified reducing death, repeat procedures, and hospital stay as top priorities.

We now plan a definitive randomised trial to compare early IET versus early VATS in 604 patients across UK hospitals.

Who can participate?

Patients aged 18 years and over with pleural infection

What does the study involve?
Participants will be randomly allocated to either treatment. The primary outcome will be the need for further treatment—a key concern for patients.

What are the possible benefits and risks of participating?
The main risk of taking part is unexpected side effects from one of the drugs (IET) or a surgical complication (VATS) described in detail below. Both these treatments are already used in the NHS for patients, and so we know a lot about their complications and how to deal with them. Participants will be monitored closely for any such problems, and if they occur, they will be promptly treated by the team of nurses and doctors looking after them and the study team will be notified. If any unforeseen complications are felt to be a result of the medications given through the chest tube, they will be stopped immediately.

Where is the study run from?
Oxford Respiratory Trials Unit (UK)

When is the study starting and how long is it expected to run for?
January 2026 to October 2029

Who is funding the study?
National Institute for Health and Care Research (NIHR) (UK)

Who is the main contact?
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Integrated Research Application System (IRAS)
1012038

Sponsor's protocol code number
19390

Central Portfolio Management System (CPMS)
57993

Study information

Scientific Title
The Fourth Multicentre Intrapleural Sepsis Trial (MIST-4) - a randomised clinical randomised effectiveness study comparing early video assisted thoracic surgery and early intrapleural enzyme therapy in adult patients with pleural infection

Acronym
MIST4

Study objectives
Primary objectives:
To compare treatment failure of initial randomised intervention (either VATS or IET) over 90 days post randomisation

Secondary objectives:
1. To compare health-related quality of life between randomised groups
2. To compare total length of hospital stay between randomised groups
3. To compare total duration of antibiotics between randomised groups
4. To compare time to intervention between randomised groups
5. To compare complication burden between randomised groups

6. To compare recovery and independence between randomised groups
7. To compare the percentage of patients with adverse events between groups
8. To compare the percentage of deaths between randomised groups
9. To compare average patient reported– pain / breathlessness between randomised groups
10. To compare lung function between randomised groups
11. Radiological improvement compared to baseline between randomised groups
12. Cost effectiveness of IET compared to surgery

Ethics approval required
Ethics approval required

Ethics approval(s)
notYetSubmitted

Primary study design
Interventional

Allocation
Randomized controlled trial

Masking
Open (masking not used)

Control
Active

Assignment
Single

Purpose
Treatment

Study type(s)
Efficacy, Safety, Treatment

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

Interventions
Randomisation to one of two arms in a 1:1 ratio, utilising sealed envelope randomisation software:
1. Intrapleural Enzyme Therapy (or IET) – this involves giving six doses of IET therapy (DNase and alteplase) through a chest tube.
2. Keyhole surgery to drain infected fluid – known as Video Assisted Thoracoscopic Surgery (VATS).

Both treatments are established and used routinely in hospitals every day; follow-up activity for both arms will follow standard of care.

Intervention Type
Drug

Phase
Phase IV

Drug/device/biological/vaccine name(s)
Alteplase, dornase alfa

Primary outcome(s)
Treatment failure of initial randomised intervention (either VATS or IET) over 90 days post randomisation. Treatment failure is any of the following:
1. Any further pleural intervention required after initial intended treatment:
1.1. Further chest tube insertion
1.2. Surgical intervention (further VATS debridement, thoracotomy, thoracostomy)
1.3. Any additional intrapleural therapy including IET (any dose in the VATS group, and further doses beyond 6 doses in the IET group) and saline irrigation
2. Death (all cause)
3. Re-admission post discharge for pleural infection related events
4. Re-escalation of antibiotics from oral to intravenous or re-initiation of antibiotic treatment once initial treatment course completed

Key secondary outcome(s))
1. Quality of life measured using EQ-5D-5L +bolt ons at baseline, 2 weeks and 90 days
2. Length of hospital stay - randomisation to 90 days – including re-admission in relation to the initial in-patient episode at 90 days
3. Total days of antibiotics at 90 days, measured using patients' medical records
4. Days to intervention (IET/surgical treatment) from randomisation, measured using patients' medical records
5. Complications measured using the Comprehensive Complication Index (CCI) at 30 days
6. Days at Home up to 30 days after randomisation (DAH-30) measured using patients' medical records
7. Adverse events(AEs) by average number of AEs and percentage of participants with at least one AE (assessed from intervention) at 90 days
8. Death (all cause) at 12 months measured using patients' medical records
9. Pain measured using validated 100 mm Visual Analogue Scale (VAS) at baseline, Day 1 post trial intervention, discharge, weekly post randomisation from 2 weeks and 90 days
10. Spirometry (FEV1% predicted) at 2 weeks post randomisation and 90 days
11. Objective measurement of pleural shadowing on chest x-ray (CXR) or CT at baseline, 2 weeks and 90 days
12. Cost by incremental cost per quality-adjusted life year (QALY) gained at baseline to 90 days, measured using patients' medical records

Completion date
31/10/2029

Eligibility

Key inclusion criteria
All patients will initially be treated with chest drain insertion for up to 24 hours, and only those with residual pleural collections will be randomised (MIST-3 demonstrated that with an identical

recruitment strategy, 15% of patients required no further treatment), hence this will enrich the population for those who stand to benefit most from intervention. Pleural infection will be diagnosed on BTS guideline criteria.

1. Aged 18 years or above.
2. Clinical presentation compatible with pleural infection plus, pleural fluid requiring drainage which is:
2.1. Purulent OR
2.2. Culture positive OR
2.3. Acidic (pH <7.2) OR*
2.4. Pleural contrast enhancement on CT or septation on ultrasound
3. Fail initial (12 to 24 hours) drainage treatment, defined as clinically significant residual pleural collection on chest imaging (chest radiograph, ultrasound, or CT)
4. Clinical Frailty Score ≤6**
5. Participant is willing and able to give informed consent for participation in the trial.

*In the absence of pleural fluid pH measurement access or concern over accuracy – a PF LDH >1000, glucose <2.0mmol/L may be adequate alternatives particularly in the presence of other radiological features such as septations on thoracic ultrasound or pleural contrast enhancement on CT (if done).

** Patients will be included if they are potentially fit for surgical intervention, using deliberately broad criteria to minimise selection bias. Only those who are clearly unfit for surgery (pre-morbid Clinical Frailty Scale >6) will be excluded. Patients with significant comorbidities (e.g., renal or cardiac failure) will remain eligible. Participants randomised to surgery who are later deemed unfit will still be analysed in the intention-to-treat population, consistent with the previous feasibility trial.

Healthy volunteers allowed
No

Age group
Mixed

Lower age limit
18 years

Upper age limit
100 years

Sex
All

Total final enrolment
0

Key exclusion criteria
1. Has previously received an intrapleural fibrinolytic and/or DNase for this episode of pleural infection
2. Has previously received large volume saline flushes akin to irrigation for this episode of pleural infection*

3. Has a known sensitivity to tPA or DNase.
4. Has had a previous pneumonectomy on the side of the infection.
5. Coincidental major bleed within the last 7 days.
6. Clinically significant renal or hepatic impairment in the view of the recruiting clinician e.g. CKD 5 on dialysis or advanced cirrhosis.
7. Participant with life expectancy of less than 3 months due to other disease (for example, known malignancy with poor prognosis).
8. Female participant of childbearing age who is pregnant, lactating or planning pregnancy during the trial.
9. Scheduled elective surgery (i.e. not for this episode of pleural infection) or other procedures requiring general anaesthesia within 30 days of prospective enrolment.
10. Significant irreversible coagulopathy that in the local investigator's opinion would prevent the participant from safely receiving IET.
11. Participation in another interventional clinical trial for pleural infection.
* Standard intrapleural saline flush regimens to maintain tube patency (e.g. 20 ml qds / 30 ml tds) are permitted

Date of first enrolment
01/04/2026

Date of final enrolment
01/07/2028

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
-
-
-
England
-

Sponsor information

Organisation
Oxford Respiratory Trials Unit

Funder(s)

Funder type

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

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