



BMJ Open Intrapleural fibrinolysis and DNase versus video-assisted thoracic surgery (VATS) for the treatment of pleural empyema (FIVERVATS): protocol for a randomised, controlled trial – surgery as first-line treatment

Thomas Decker Christensen ¹, Morten Bendixen,² Søren Helbo Skaarup,³ Jens-Ulrik Jensen,^{4,5} Rene Horsleben Petersen,^{5,6} Merete Christensen,⁶ Peter Licht,⁷ Kirsten Neckelmann,⁷ Bo Martin Bibby,⁸ Lars B Møller,⁹ Uffe Bodtger ^{10,11}, Morten Hornemann Borg,¹² Zaigham Saghir,^{4,5} Sten Langfeldt,¹³ Stefan M W Harders,¹⁴ Eihab O Bedawi,¹⁵ Babu Naidu,^{16,17} Najib Rahman,¹⁵ Christian B Laursen^{18,19}

To cite: Christensen TD, Bendixen M, Skaarup SH, *et al*. Intrapleural fibrinolysis and DNase versus video-assisted thoracic surgery (VATS) for the treatment of pleural empyema (FIVERVATS): protocol for a randomised, controlled trial – surgery as first-line treatment. *BMJ Open* 2022;**12**:e054236. doi:10.1136/bmjopen-2021-054236

► Prepublication history for this paper is available online. To view these files, please visit the journal online (<http://dx.doi.org/10.1136/bmjopen-2021-054236>).

Received 06 June 2021

Accepted 11 February 2022



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For numbered affiliations see end of article.

Correspondence to

Dr Thomas Decker Christensen; tdc@clin.au.dk

ABSTRACT

Introduction Pleural empyema is a frequent disease with a high morbidity and mortality. Current standard treatment includes antibiotics and thoracic ultrasound (TUS)-guided pigtail drainage. Simultaneously with drainage, an intrapleural fibrinolytic can be given. A potential better alternative is surgery in terms of video-assisted thoracoscopic surgery (VATS) as first-line treatment. The aim of this study is to determine the difference in outcome in patients diagnosed with complex parapneumonic effusion (stage II) and pleural empyema (stage III) who are treated with either VATS surgery or TUS-guided drainage and intrapleural therapy (fibrinolytic (Alteplase) with DNase (Pulmozyme) as first-line treatment.

Methods and analysis A national, multicentre randomised, controlled study. Totally, 184 patients with a newly diagnosed community acquired complicated parapneumonic effusion or pleural empyema are randomised to either (1) VATS procedure with drainage or (2) TUS-guided pigtail catheter placement and intrapleural therapy with Actilyse and DNase. The total follow-up period is 12 months. The primary endpoint is length of hospital stay and secondary endpoints include for example, mortality, need for additional interventions, consumption of analgesia and quality of life.

Ethics and dissemination All patients provide informed consent before randomisation. The research project is carried out in accordance with the Helsinki II Declaration, European regulations and Good Clinical Practice Guidelines. The Scientific Ethics Committees for Denmark and the Danish Data Protection Agency have provided permission. Information about the subjects is protected under the Personal Data Processing Act and the Health Act. The trial is registered at www.clinicaltrials.gov, and monitored by the regional Good clinical practice monitoring unit. The results of this study will be published in peer-

Strengths and limitations of this study

- The study is a national, multicentre, randomised, controlled trial.
- Patients and providers are not blinded to the intervention.
- The primary endpoints are length of hospital stay—mortality would have been preferred.
- Patients will be followed for 12 months after inclusion in this study.
- The use of medication and healthcare expenses will be estimated using registries.

reviewed journals and presented at various national and international conferences.

Trial registration number NCT04095676.

INTRODUCTION

Pleural empyema is a disease with an infection inside the chest cavity, often as complication to bacterial pneumonia. In Europe community-acquired pneumonia is estimated to result in at least 1 million hospitalisations on a yearly basis, of whom 20%–40% develop parapneumonic effusion and 5%–10% pleural empyema.¹ Patients often have a high prevalence of co-morbidities and experience a long duration of hospitalisation. The disease carries a significant morbidity and mortality rate of approximately 15% within 1 year.²

Community-acquired bacterial infection in the pleural cavity has been characterised and divided into three clinical stages: simple

parapneumonic effusion (stage I), complicated parapneumonic effusion (stage II) and pleural empyema (stage III).³

While stage I has an overall good prognosis when treated with antibiotics, in stages II–III supplementary invasive treatment is needed. The invasive treatment is aimed at removing the infection, provide expansion of the lung, and additionally to avoid irreversible damage (eg, trapped lung) and reduce morbidity.⁴

Current standard treatment for these stages is drainage with thoracic ultrasound (TUS)-guided pigtail and antibiotics. Simultaneously with drainage, an intrapleural fibrinolyticum can be given, but the indication and evidence for this is debated.^{2 5 6} Fibrinolyticum (alteplase) combined with DNase has been found to have a positive effect in selected patients, but despite this, the median length of the hospital stay (LOS) were nearly 12 days.⁷

Today, video-assisted thoracoscopic surgery (VATS) can be performed with a very low morbidity and mortality.⁸ In a Cochrane review on surgical versus non-surgical treatment of pleura empyema, two studies with adult patients were included. However, neither study had a size or methodological quality that makes it possible to conclude whether surgery, especially minimal invasive surgery as VATS, should be included as part of the standard treatment of pleural empyema.^{9–12}

The theoretical advantage of surgery as first line treatment is in providing rapid, definitive treatment and insuring optimal drain placement. Experience so far suggest reduction in mortality, LOS, and late complications.⁸

LOS is associated with success or failure of the initial empyema treatment, and has accordingly been used in nearly all randomised, controlled empyema trials.^{2 6 13}

In conclusion, treatment needs to be improved due to the high morbidity and mortality and the increasing incidence of the disease. Today, the choice of treatment is random, based on local preferences resulting in non-optimal outcome for these very sick patients.

Aim of the study

To determine the difference in outcome in patients diagnosed with complex parapneumonic effusion (stage II) and pleural empyema (stage III) who are treated either with VATS surgery or TUS guided drainage and intrapleural therapy (fibrinolytic (Alteplase) with DNase (Pulmozyme)) as first line treatment.

METHODS AND ANALYSIS

Design

A randomised, controlled study, not blinded (open label), national multicentre study including all thoracic surgical departments and all relevant respiratory departments in Denmark.

Time plane

We anticipate starting including patients at earliest on 01 April 2022, finish inclusion 30 September 2023 and all patients has completed 1 year of follow-up on 30 September 2024.

Inclusion and exclusion criteria

Inclusion criteria

- ▶ Eighteen years or more on the day of hospitalisation.
- ▶ Must be able to provide informed consent.
- ▶ Acute hospitalisation within the last 48 hours.
- ▶ Meeting diagnostic criteria for community acquired pleural infection using the following criteria:
 1. A clinical presentation compatible with pleural infection AND
 2. Has pleural fluid which is either:
 - a. Purulent pleural fluid.
 - b. Gram stain positive.
 - c. Culture positive.
 - d. Acidic with pH <7.2.
 - e. Low pleural fluid glucose (<2mmol/L) in the absence of accurate pH measurement.
 - f. Septated pleural fluid on ultrasound.

Exclusion criteria

- ▶ Pregnancy. Prior to inclusion of fertile women (defined as the period from menarche to postmenopause) a negative pregnancy test must be available.
- ▶ Breast feeding.
- ▶ Declared terminally ill or a predicted survival of less than 3 months.
- ▶ Previous intrathoracic surgery (within <1 year on the same side of the thorax as where the parapneumonic effusion/pleural empyema is located).
- ▶ Previously (within <1 year) hospitalised with with complex parapneumonic effusion (stage II) or pleural empyema (stage III).
- ▶ Drainage during the current admission on the same side of the thorax (excluding diagnostic pleural puncture).
- ▶ Hospitalisation within 7 days prior to current hospitalisation.
- ▶ Previous allergic reaction to alteplase or DNase.
- ▶ Use of alteplase therapy contraindicated:
 - Ongoing treatment with oral anticoagulant including new oral anticoagulants (eg, warfarin (Marevan), Dabigatranetexilat (Pradaxa), Rivaroxaban (Xarelto), Apixaban (Eliquis), Endoxaban (Lixiana)).
 - Significant ongoing bleeding or within last 6 months.
 - Known haemorrhagic diathesis.
 - Previous or suspected intracranial haemorrhage.
 - Suspected subarachnoidal haemorrhage or condition following subarachnoidal haemorrhage from aneurysm.
 - All forms of damage to the central nervous system (eg, cerebral tumours, aneurysm, intracranial/spinal surgery).

- Recent (within 10 days) cardiac resuscitation, birth, or perforation of non-compressible blood vessel (eg, puncture of v. subclavia, v. jugularis).
- Severe, uncontrolled arterial hypertension.
- Bacterial endocarditis, pericarditis.
- Acute pancreatitis.
- Documented ulcerative gastrointestinal disease within last 3 months, esophageal varices, arterial aneurysm, arteriovenous malformations.
- Tumour/malignancy with an increased risk of haemorrhage.
- Severe liver disease, including liver failure cirrhosis, portal hypertension (esophageal varices), and active hepatitis.
- Large operation or significant trauma within previous 3 months.

Endpoints

Primary endpoint

- ▶ LOS, which is defined as the time from first admission in the course of the hospitalisation and to the completion of treatment defined as time of discharge from hospital without need of any additional invasive treatment.

Secondary endpoints

- ▶ LOS when patients are stratified in subgroups (Stage, TUS score, RAPID (Renal (urea), Age, fluid Purulence, Infection source, Dietary (albumin)) score).
- ▶ LOS after commencement of study intervention.
- ▶ Days at home up to 30 days after study intervention (DAH30, which is defined as DAH30 after surgery, that is, if the discharge is done 5 days after surgery, the DAH30 is 25).
- ▶ Thirty days and in-hospital mortality.
- ▶ Time from randomisation to commencement of intervention.
- ▶ Drainage time measured (in days).
- ▶ Proportion of patients where primary intervention could be considered as definitive treatment.
- ▶ Complications ranked by Clavien-Dindo classification and Comprehensive Complication Index.
- ▶ Need for additional thoracic surgery which has to be related to the parapneumonic process in first 12 months after hospitalisation.
- ▶ Consumption of painkillers during hospitalisation and within 12 months after hospitalisation.
- ▶ Pulmonary function tests and 6min walk test performed 1, 3, 6 and 12 months after inclusion in the study.
- ▶ Quality of life and patient reported outcomes within 12 months after hospitalisation
- ▶ Health related costs within 12 months after hospitalisation.

Randomisation

Patients will be randomised 1:1 to either:

1. VATS procedure with drainage, including rinse with saline.
2. TUS-guided pigtail catheter placement and intrapleural therapy with fibrinolyticum (alteplase) and DNase, including rinse with saline.

Block randomisation with varying block size will be used to get an equal number of patients in both groups. There will be stratification for each surgical centre in the randomisation. The randomisation is conducted via a REDCap (Research Electronic Data Capture), (REDCap Consortium, Vanderbilt University Medical Center, Tennessee, USA). [Figure 1](#) shows the trial flow and [figure 2](#) display the flow of the patients.

Blinding

Patients and responsible healthcare staff will not be blinded. Research staff not involved in the treatment of the included patients are blinded to treatment allocations until data analyses are complete. Assessment of different scoring systems (eg, TUS and radiology score) are blinded to the extent that it is practically possible.

Patient population and selection

All patients admitted during the diagnosis of pleural empyema or pleural effusion without specification (diagnostic codes: DJ 86, DJ 86.1, DJ 86.9, DJ 90.9). Stages II and III will be potential candidates, whether they are hospitalised at a Regional Hospital or at a University Hospital.

Intervention

Drain and intrapleural therapy group

Pigtail is applied as soon as possible and within 48 hours after randomisation. Drain placement is carried out using TUS. Operators (conductors of the procedure) must have relevant training and competencies corresponding to the specialist level within the relevant specialty and be approved by the steering committee to conduct the procedure. A pigtail catheter (minimum 10F) is inserted. Operator determines the size of drain and whether drain placement is done with one-step or Seldinger technic. Pain management is registered and performed according the local practice at the department.

The intrapleural therapy consists of treatment with the following two drugs:

- ▶ Intrapleural Actilyse (alteplase) 10 mg twice daily for 3 days.
- ▶ Intrapleural Pulmozyme (DNase) 5 mg twice daily for 3 days.

Both drugs are administered twice daily through the pigtail catheter and are left for 1 hour in the pleural cavity by blocking the drain (eg, closing the three-way stopcock/use of a pean forceps). The installation of the drugs in the pleural cavity is performed separately with a time interval between administrations of at least 2 hours. Actilyse (alteplase) is prepared by diluting 10 mg Actilyse (alteplase) in the solvent liquid (10 mL) supplied alongside the drug in a 50 mL syringe. This mixture is further diluted by drawing isotonic NaCl into

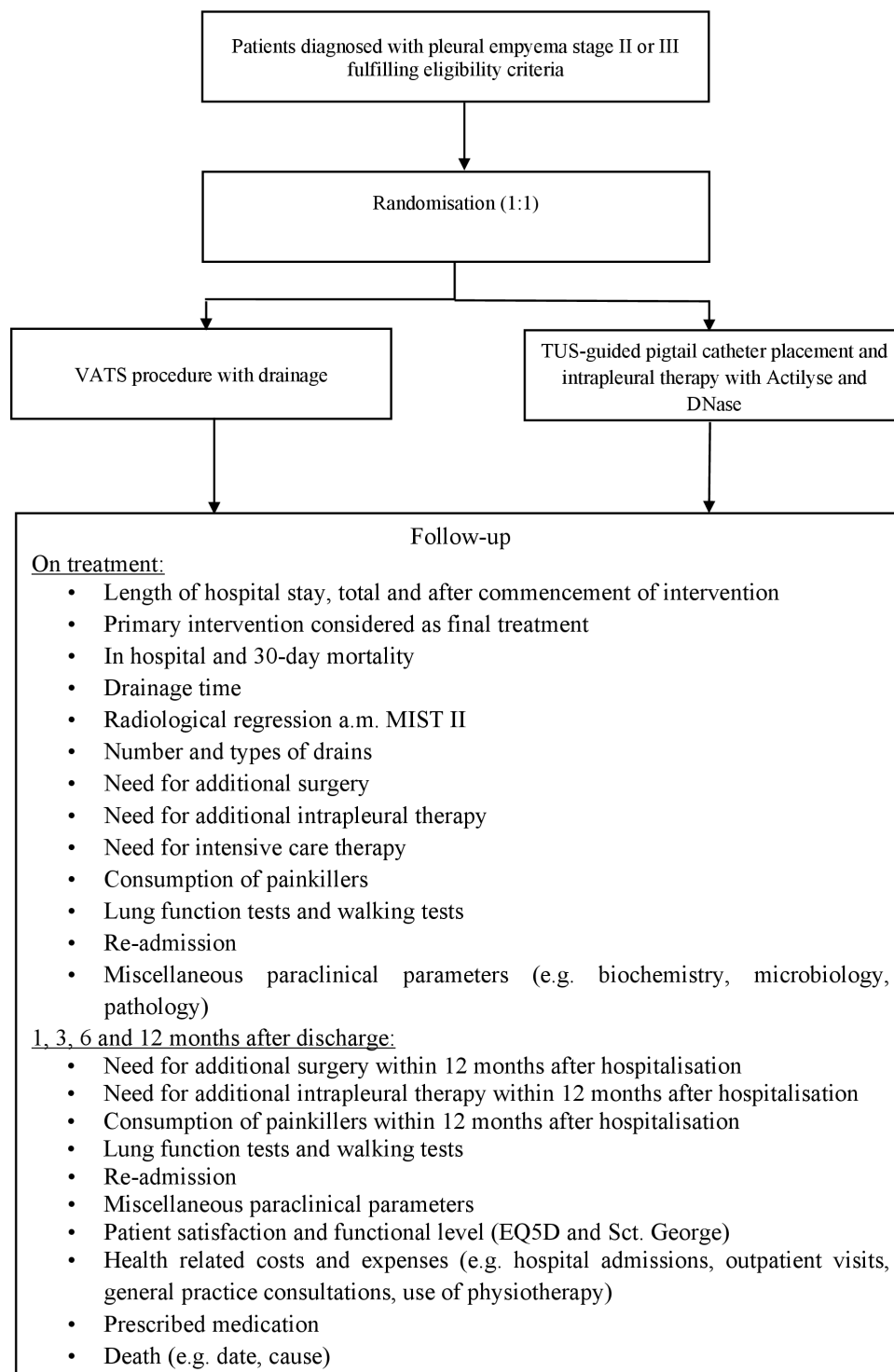


Figure 1 Trial schema. EQ5D, European Quality of life - 5 Dimensions; MIST, Multicenter Intrapleural Sepsis Trial; TUS, thoracic ultrasound; VATS, video-assisted thoracoscopic surgery.

the syringe until the total volume of fluid in the syringe is 30mL. Following this preparation the mixture is injected into the pleural cavity using the pigtail catheter. Pulmozyme (DNase) is prepared by drawing 5mL Pulmozyme (DNase) (1mg/mL) (5mL=2 Pulmozyme cannisters) into a 50mL syringe. This mixture is further diluted by drawing isotonic NaCl into the syringe until the total volume of fluid in the

syringe is 30mL. Following this preparation the mixture is injected into the pleural cavity using the pigtail catheter.

VATS group

The VATS procedure must be commenced as soon as possible and no later than 48 hours after randomisation. The surgery is performed with the patient in a 90° sideways position, using

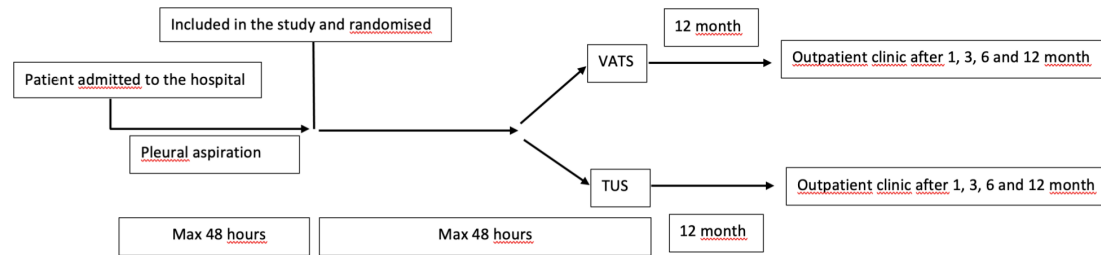


Figure 2 The trials time line. TUS, thoracic ultrasound; VATS, video-assisted thoracoscopic surgery.

general anaesthesia. Access is obtained through one to three ports, followed by purification and possibly decortication, and insertion of one pleural drain (sizes 24–32F) at the end of surgery. A 20 mL Marcain is used as local analgetic and applied at the incision sites or as a nerve block. Additional pain management is registered and performed according to the local practice at the department. In the VATS group, suction on drain (10 cm H₂O) is applied in at least the first day after the procedure. Operator must have relevant training and competencies corresponding to the specialist level within the relevant specialty and be registered and approved by the steering committee.

After the procedure

Randomised patients are transferred to a specialised department of Respiratory Medicine or remain in the department of Thoracic Surgery. Following completed intervention, the chest tubes in both groups are flushed with 30 mL normal saline three times daily to ensure tube patency.

Antibiotics

The empiric antibiotic treatment used in all centres is in accordance with the national guidelines from the Danish Society for Respiratory Medicine. Treatment is initiated as intravenous treatment. Type of antibiotic treatment can be subsequently adjusted depending on results of microbiological tests. Change to oral treatment can be done when all of the following three criteria are met:

- ▶ Clinical improvement of the patient (eg, no fever/fever, improved general condition).
- ▶ Paraclinical satisfactory response (with respect to decreases in leukocytes and C reactive protein (CRP)).
- ▶ Drain/pigtail is removed.

This means that 14 days intravenous treatment will not be given as standard. The duration of intravenous antibiotic treatment will, therefore, be individualised based on the application of the above criteria. The overall duration of treatment of antibiotic is 6 weeks as standard.

Other treatments and supportive care

All patients are:

- ▶ Offered specialised lung physiotherapy.
- ▶ Screened for and given additional nutritional support.
- ▶ Treated with painkillers in accordance with departmental guidelines.
- ▶ Given thrombosis prophylactic treatment in accordance with national guidelines.

Need for additional salvage thoracic surgery or non-surgical pleural procedures

Following the primary intervention subsequent decisions during the admission to perform salvage thoracic surgery or additional non-surgical pleural procedures is made in accordance with the national guidelines from the Danish Society for Cardiothoracic Surgery and Danish Society for Respiratory Medicine.

Removal of chest tube/pigtail

The decision to remove the drain/pigtail is made by the clinician attending the patient. The following criteria are used as a guide for discontinuation of drain/pigtail in both groups:

- ▶ Clinical improvement of the patient (eg, no fever/subfebril, improved general condition).
- ▶ Satisfactory biochemical response (with respect to a decrease in leukocytes and CRPs).
- ▶ Imaging (TUS, CT or chest X-ray in two planes) without significant residual effusion (<100 mL).
- ▶ Drain with clear pleural fluid by rinsing.

In both groups removal of drain/pigtail does not await the results of any of the obtained cultures of the pleural fluid. As such the presence of negative cultures is not used as removal criteria.

Discharge from hospital

In current usual practice in Denmark, patients with pleural empyema are typically discharged when:

- ▶ The drain/pigtail has been removed.
- ▶ Antibiotic treatment has been changed from intravenous to oral treatment without signs of subsequent clinical or paraclinical treatment within 1 day following the change.

These principles are also used in the study.

Data recording

Prior to informed consent obtained as part of screening for study participation

- ▶ Data needed to determine whether inclusion criteria are met (see above).
- ▶ Data needed to determine whether any exclusion criteria are present (see above).

Baseline patient data: age, gender, comorbidities, medication, performance status, previously recorded lung function, etc.

Surgical and TUS data: used time, specific type of procedure, operator, drain size, complications, etc.

Drain data: Length of drain treatment, daily output / input, removal criteria, no. of drains used, etc.

Costs during hospitalisation

Calculated for the two groups regarding the following expenses:

- ▶ VATS group:
 - Utensils used during surgery.
 - Time of the procedure
 - Consumption of staff resources.
 - Hospitalisation time.
 - Medicine.
- ▶ Drain group:
 - Equipment used during the procedure.
 - Procedure time.
 - Consumption of human/staff resources.
 - Fibrinolyticum and DNase (amount used).
 - Hospitalisation time
 - Medicine.

Costs within the first year after discharge

Calculated for the two groups regarding the following expenses:

- ▶ Readmission.
- ▶ Ambulatory services.
- ▶ Medication
- ▶ Number of sick days
- ▶ Visit to a General Practitioner.

Patient satisfaction and functional level

- ▶ Data in the form of European Quality of life - 5 Dimensions (EQ5D) and Sct. George Respiratory Questionnaire is collected at the following times:
 - On inclusion in the study.
 - At discharge.
 - Outpatient data: 1, 3, 6 and 12 months.

Various parameters acquired from and after hospitalisation (including ambulant outpatient visits)

- ▶ Hospitalisation time, total and after commencement of intervention.
- ▶ Primary intervention considered as final treatment.
- ▶ In hospital and 30-day mortality.
- ▶ Drainage time.
- ▶ Radiological regression a.m. MIST II.
- ▶ Number and types of drains.
- ▶ Need for additional surgery during and within 12 months after hospitalisation.
- ▶ Need for additional intrapleural therapy during and within 12 months after hospitalisation.
- ▶ Need for intensive care therapy.
- ▶ Consumption of painkillers during hospitalisation and within 12 months after hospitalisation which is registered electronically both during hospitalisation in the electronic patient record and after discharge using the National Patient Register.
- ▶ Lung function tests and walking tests.

- ▶ Readmission.
- ▶ Miscellaneous paraclinical parameters (eg, biochemistry, microbiology, pathology).

Data obtained from national patient register

- ▶ Health-related costs and expenses (eg, hospital admissions, outpatient visits, general practice consultations, use of physiotherapy).
- ▶ Prescribed medication
- ▶ Death (eg, date, cause).

Outpatient follow-up after discharge

In conjunction with participation in the project, in addition to any common local controls, outpatient follow-up is performed at the regional respiratory medicine outpatient clinic after 1, 3, 6 and 12 months after discharge.

Sample size and power calculation

The study is based on assumptions and knowledge about LOS, both from national and international publications. We calculated the sample size based on the following assumptions: the main effect target is the difference between the total time (primary endpoint) between the two groups of patients (VATS vs drainage). The distribution of the hospitalisation time is expected to be skewed to the right, so that a logarithmic transformation is needed to achieve normality.

We assume a median hospitalisation period in the drainage group of 12 days, a minimum clinically relevant difference in hospitalisation of 2 days, 80% power and coefficient of variation (CV) of 40%.

Significance level is set to 0.05. Thus, 77 patients in each group must be included. To account for excluded patients (set at 20%), we expect to include 92 patients in each group. A total of 184 patients is to be included.

In terms of showing clinically relevant non-inferiority with a difference in hospitalisation of 1 day with an 80% power, and CV of 40%, 70 patients is needed in each group. This is based on a true improvement of 1 hospitalisation day. Based on the annual number of patients diagnosed with pleura empyema in Denmark, we find it feasible to include the needed number of patients in the trial during the inclusion period.

Data analysis

Data extractions are made from REDCap database, and data analysis is performed using STATA V.17 (StataCorp). Endpoints will be described for the individual group by median and percentile, assuming data is not normally distributed.

Differences between the groups in the primary endpoint are determined by t-test at the log-entry time and reported as median ratios with associated CIs. Patients dying during the admission is omitted from the analysis if the primary endpoint. Whether death before discharge affects the primary endpoint is assessed using survival analysis as sensitivity analysis. We expect that the distribution between stages II and III will be 75% and 25%, respectively, and whether there is a difference

between stages II and III will be assessed as secondary analysis. When repeating measurements (eg, quality of life), repeated measurements ANOVA are used with treatment and time as systematic effects and patient as random effect. All data are analysed primarily according to the intention to treat principle, but there will also be one per protocol analysis regarding the above-mentioned endpoints. Comparison will take place between the two groups (drainage and VATS).

Data collection media

- ▶ REDCap, REDCap Consortium, Vanderbilt University Medical Centre, Tennessee, USA.
- ▶ Electronic patient record (EPJ in Region Midt, EPJ in Region North, EPJ (COSMIC) in Region South and EPJ (EPIC Health Platform) in the Capital Region and Region Zealand).
- ▶ Health related costs are retrieved via the National Patient Register (LPR).

Handling and archiving data

All data are entered in a Case Report Form in RedCap, which is a professional database that provides a user-friendly interface. The REDCap data management system is secure, fully compliant with all regulatory guidelines, and includes a complete audit-trail for data entry validation. Through these mechanisms, as well as relevant training for all involved parties, patient confidentiality will be safeguarded. REDCap is available for free at both Odense University Hospital, Copenhagen and Aarhus University.

When handling, processing and archiving data collected, the Data Inspectorate's guidelines are followed, which implies that all personal data are deleted at the end of the project. The collected data is stored at the Department of Cardiothoracic and Vascular Surgery, Aarhus University Hospital and at Department of Pulmonology, Odense University Hospital.

Data monitoring

The study will be monitored by the Good Clinical Practice Units at the participating centres. An independent Data Monitoring Committee comprised of two clinical researchers not actively involved in the study and a research statistician will be established. This committee will meet on a regular basis to assess data of included patients, with a special emphasis on serious adverse or unforeseen events.

Events and side effects

All unintended events and adverse events throughout the treatment period and until the last call after 30 days are recorded. All adverse events are recorded in the patients case report form.

All serious adverse events (SAE) must be reported by the investigator to the sponsor within 24 hours after the investigator has learnt about the serious incident. SAE is understood to mean an event or side effect that results in death, is life threatening, causes hospitalisation

or prolonged hospitalisation, resulting in significant or permanent invalidity or incapacity.

All SAEs must be followed until the problem is resolved or until it is decided that participation in the trial was not the cause.

Suspected unexpected serious adverse events reporting (SUSAR), which is mortal or life threatening, is entered in the registration form (report of SAE/SUSAR) and will be reported to the Scientific Ethics Committees for Central Denmark Region and/or Region of Southern Denmark within 7 days.

Patient and public involvement

The patients were not directly involved in the development of the research question and study design, but indirectly fueled the idea to this study because many patients over the years who were diagnosed with pleural empyema repeatedly informed that they were frustrated with long-lasting treatments and hospital stays. As a result, we have designed the study aiming to improve and speed up their treatment and reduce their LOS.

We are also in the process of designing 'spin-off' studies with a qualitative focus, which will help to design future studies including patient reported outcome measurements, which has also been deemed relevant by patients themselves.

Potential patients/the public will be informed of the trial using social medias and news columns. All patients included in the trial will be informed of the results of the study. The burden of the intervention is assessed by the patients using health quality assessment schemes. Patient advisors are, if relevant, thanked in the acknowledge section.

ETHICS AND DISSEMINATION

All patients provide informed consent before randomisation. The research project is carried out in accordance with the Helsinki II Declaration, European regulations and Good Clinical Practice Guidelines. The Scientific Ethics Committees for Denmark and the Danish Data Protection Agency have provided permission. Information about the subjects is protected under the Personal Data Processing Act and the Health Act. The trial is registered at www.clinicaltrials.gov, and monitored by the regional Good Clinical Practice monitoring unit. The results of this study will be published in peer-reviewed journals and presented at various national and international conferences.

DISCUSSION

Pleural empyema is a frequent disease with a high morbidity and mortality. Community-acquired bacterial infection in the pleural cavity has been divided into three clinical stages (I–III).³ The treatment of stage I is drainage, however, the optimal treatment of



stage II and III has not been established and the treatment is primarily based on local preferences and not evidence-based.

In our study, we want to find the optimal method for treating patients with pleural empyema stage II and III—either a VATS procedure or TUS guided drainage and intrapleural therapy (fibrinolytic (Alteplase) with DNase (Pulmozyme)).

The theoretical advantage of surgery as first line treatment is that patients undergo rapid, definitive treatment and insurance of optimal drain placement. Early and definite surgery can potentially reduce mortality, LOS, and cause fewer late complications.⁹

If this trial is positive for the primary and/or the secondary outcomes, it will change and strengthen the treatment of patients with community acquired bacterial pleural infection, both nationally and internationally. We investigate both clinical parameters, patient satisfaction and economical aspects (cost-effectiveness) in relation to pleura empyema treatment, so it will cover many aspects of this disease. We have established a nationwide study with participation of all relevant departments and all relevant specialties (eg, pulmonology and thoracic surgery), and the trial will therefore have a high internal and external validity. This is a significant plus in terms of methodological quality, and the results of the study will widely be applicable and can easily be implemented in the daily clinical practice.

We have decided to have LOS as the primary endpoint, since it is an objective measurement depicting the clinical status of the patient, and LOS is a clinically relevant endpoint used in multiple trials assessing treatment of complicated parapneumonic effusions and pleural empyema.^{2 6 13}

This study has some limitations. First, the primary endpoint should preferably have been 1-year mortality and secondary endpoint severe morbidity. However, this would have required inclusion of a large number of patients, which would have required a very long inclusion time due to the relatively small number of inhabitants in Denmark and hence the small number of patients with pleural empyema. This could have been solved by including patients from other countries making the study internationally—however, this was beyond the resources provided for this project.

Second, patients and providers should ideally be blinded to the intervention, but this was however not deemed clinically feasible (eg, different sizes and type of drains used in the two groups). Many factors could potentially affect the outcomes following the intervention. To minimise some of the main factors we chose that the patients following the intervention at each site would be placed at the same department and all these departments had staff with specialised competencies in the management of the patient population. Standards for the antibiotic treatment and drain removal has been included in the protocol, since any local differences in both factors may affect the chosen outcomes.

A drawback is that in intent to treat analysis there is potential bias in favour of the VATS arm because cross-over from fibrinolytics to surgery is more likely than cross-over from surgery to the Intrapleural Fibrinolysis and DNase group although this does occur.

Lastly, we potentially introduce a systematic bias concerning chest tube as the VATS group receives large-bore chest tubes (drain), and the TUS group receive small-bore chest tubes (pigtales).

In summary, this national, multicentre, randomised, controlled trial will investigate whether antibiotics and early goal directed VATS as first-line treatment should be considered the standard regimen of patients with complicated parapneumonic effusion and pleural empyema. It will hopefully benefit the initial management and treatment of this patient population making the treatment based on evidence instead of local preferences.

Author affiliations

¹Department of Cardiothoracic and Vascular Surgery & Department of Clinical Medicine, Aarhus University Hospital, Aarhus, Denmark

²Department of Cardiothoracic and Vascular Surgery, Aarhus University Hospital, Aarhus, Denmark

³Department of Respiratory Diseases and Allergy, Aarhus University Hospital, Aarhus, Denmark

⁴Department of Internal Medicine, Respiratory Medicine Section, Herlev and Gentofte Hospital, Copenhagen, Denmark

⁵Institute for Clinical Medicine, Faculty of Health Sciences, University of Copenhagen, Copenhagen, Denmark

⁶Department of Cardiothoracic Surgery, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark

⁷Department of Cardiothoracic Surgery, Odense University Hospital, Odense, Denmark

⁸Department of Public Health, Section for Biostatistics, Aarhus University, Aarhus, Denmark

⁹Department of Cardiothoracic Surgery, Aalborg University Hospital, Aalborg, Denmark

¹⁰Department of Internal Medicine & Department of Respiratory Medicine, Zealand University Hospital, Naestved-Slagelse Hospital, Naestved, Denmark

¹¹Institute of Regional Health Research, University of Southern Denmark, Odense, Denmark

¹²Department of Respiratory Medicine & Clinical Institute, Aalborg University Hospital, Aalborg, Denmark

¹³Department of Radiology, Aarhus University Hospital, Aarhus, Denmark

¹⁴Department of Radiology, Odense University Hospital, Odense, Denmark

¹⁵NIHR Oxford Biomedical Research Centre, University of Oxford, Oxford, UK

¹⁶Department of Thoracic Surgery, Queen Elizabeth Hospital, Birmingham, UK

¹⁷Institute of Inflammation and Ageing, University of Birmingham, Birmingham, UK

¹⁸Department of Respiratory Medicine, Odense University Hospital, Odense, Denmark

¹⁹Odense Respiratory Research Unit (ODIN), Department of Clinical Research, University of Southern Denmark, Odense, Denmark

Twitter Zaigham Saghir @ZaighamSaghir

Collaborators Steering committee: Department of Cardiothoracic and Vascular Surgery & Department of Clinical Medicine, Aarhus University Hospital: TDC, MB. Department of Cardio-thoracic Surgery, Rigshospitalet, Copenhagen University Hospital: RHP. Department of Cardiothoracic and Vascular Surgery, Odense University Hospital: PL. Department of Cardiothoracic Surgery, Aalborg University Hospital: LBM. Department of Respiratory Medicine, Odense University Hospital: CBL. Department of Respiratory Medicine, Aarhus University Hospital: SHS. Department of Respiratory Medicine, Herlev-Gentofte Hospital, Copenhagen University Hospital: J-UJ. Biostatistical Advisory Service (BIAS), Faculty of Health Sciences, Aarhus University: BMB. International collaborators and advisory board: NIHR Oxford Biomedical Research Centre, University of Oxford, Oxford, UK: NR,

EOB. Department of Thoracic Surgery, Queen Elizabeth Hospital Birmingham, UK & Institute of Inflammation and Ageing, University of Birmingham, UK: BN. Monitoring committee: Department of Respiratory Medicine, Odense University Hospital: J Davidsen. Department of Cardiothoracic and Vascular Surgery, Odense University Hospital: M Stenger. Participating Centres and investigators: Department of Cardiothoracic and Vascular Surgery & Department of Clinical Medicine, Aarhus University Hospital: TDC, MB. Department of Cardio-thoracic Surgery, Rigshospitalet, Copenhagen University Hospital: RHP, MC. Department of Cardiothoracic and Vascular Surgery, Odense University Hospital: PL, K Nickelmann. Department of Cardiothoracic Surgery, Aalborg University Hospital: LBM. Department of Respiratory Medicine, Odense University Hospital: CBL, V Panou. Department of Respiratory Medicine, Aarhus University Hospital: SHS. Department of Respiratory Medicine, Herlev-Gentofte Hospital, Copenhagen University Hospital: J-UJ. Department of Respiratory Medicine, Aalborg University University: MHB. Hospital Department of Respiratory Medicine, Holstebro Hospital: P Gjørup. Department of Respiratory Medicine, Viborg-Skive Hospital: A Kristensen. Department of Respiratory Medicine, Horsens Hospital: MC. Department of Respiratory Medicine, Randers Hospital: J Bak. Department of Respiratory Medicine, Lillebaelt Hospital, Kolding: J Dalberg. Department of Acute Medicine, Aabenrå Hospital: CB Mogensen. Department of Respiratory Medicine, Esbjerg Hospital: TT Jensen. Department of Respiratory Medicine, Naestved-Slagelse Hospital U Boedtger. Department of Acute Medicine, Odense University Hospital: S Posth. Department of Radiology, Aarhus University Hospital: SL. Department of Radiology, Odense University Hospital: SMWH.

Contributors TDC, MB and CBL wrote the first draft of the protocol manuscript. TDC, MB, CBL, RHP, PL, BMB planned the conceptualisation and the design of the study and the protocol. TDC, MB, CBL, RHP, PL, BMB, J-UJ, MC, KN, LBM, UB, MHB, ZS, SL, SMWH, EOB, BN and NR contributed to development of the protocol and the critical revisions of the protocol and the current manuscript. TDC, MB, CBL, RHP, PL, BMB, J-UJ, MC, KN, LBM, UB, MHB, ZS, SL, SMWH, EOB, BN and NR have made substantial contributions to the conception and design of the work; drafting the work and revising it critically for important intellectual content; made final approval of the version to be published; made agreement to be accountable for his/her contributions of the work in ensuring that questions related to the accuracy or integrity of the work are appropriately investigated and resolved.

Funding This work was supported by the Novo Nordisk Foundation (grant no: 0065455) and Skibsreder Per Henriksen, R. og Hustrus Fond.

Competing interests TDC has been on the speaker bureaus for AstraZeneca, Boehringer-Ingelheim, Pfizer, Roche Diagnostics, Takeda, Merck Sharp and Dohme (MSD) and Bristol-Myers Squibb and has been in an Advisory Board for Bayer and Merck Sharp and Dohme (MSD). RHP has received a speaker's fee from Medtronic and on the advisory board for AstraZeneca. CBL has received a speaker's fee from AstraZeneca. MB has received a teaching fee from Pulmonx Corporation. PL has received a speaker's fee from Johnson & Johnson.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Consent obtained directly from patient(s).

Provenance and peer review Not commissioned; externally peer reviewed.

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ORCID iDs

Thomas Decker Christensen <http://orcid.org/0000-0001-6509-8510>

Uffe Bodtger <http://orcid.org/0000-0002-1231-9209>

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