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Intrapleural Fibrinolysis and DNase versus Video-Assisted Thoracic Surgery (VATS) for the treatment of pleural empyema (FIVERVATS): a randomised, controlled trial - surgery as first line treatment

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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 fibrinolyticum 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 e.g. 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-reviewed journals and presented at various national and international conferences.

Trial registration number NCT04095676

STRENGTHS AND LIMITATIONS OF THIS STUDY

- The study can potentially change and strengthen the treatment of patients' community acquired complicated parapneumonic effusion and pleural empyema
- 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, but not feasible due to the high number of patients needed for such a study

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 one 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 (e.g. 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 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, length of hospital stay (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 on 01 November 2021, finish inclusion 30 April 2023 and all patients has completed 1 year of follow-up on 30 April 2024.

Inclusion and exclusion criteria

Inclusion criteria:

- 18 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 **or**
     b. gram stain positive **or**
     c. culture positive **or**
     d. acidic with pH < 7.2 **or**
     e. low pleural fluid glucose (< 2 mmol/L) in the absence of accurate pH measurement **or**
     f. septated pleural fluid on TUS

Exclusion criteria:

- Pregnant
- Breastfeeding
- Declared terminally ill or a predicted survival of less than 3 months
- Previous intrathoracic surgery (within <1 year on the ipsilateral side as where the parapneumonic effusion/pleural empyema is located)
- Previously (within <1 year) hospitalised with complex parapneumonic effusion (stage II) or pleural empyema (stage III)
- Ipsilateral pleural drainage during the current admission (excluding diagnostic thoracentesis)
- Contraindication to intrapleural therapy (e.g. allergy)
- Hospitalisation within 7 days prior to current hospitalization

Endpoints

Primary endpoint:

- LOS, which is defined as the time from first admission in the course of the hospitalization 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 score)
- LOS after commencement of study intervention
- Days at home up to 30 days after study intervention (DAH30)
- 30-day 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 (CCI)
- Need for additional thoracic surgery in first 12 months after hospitalization
- Consumption of painkillers during hospitalisation and within 12 months after hospitalization
- Lung physiology within 12 months after hospitalisation
- 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.

Blinding

Patients and responsible health care 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 (e.g. 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.

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-degree sideways position, using general anesthesia. 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. 20 ml of marcain is used as local analgetic and applied at the incision sites or as a nerve block. In the VATS group, suction on drain (- 10 cm H_20) 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 (e.g. no fever/fever, improved general condition)
- Paraclinical satisfactory response (with respect to decreases in leukocytes and CRP's)
- 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 (e.g. no fever/sub-febrile, improved general condition)
- Satisfactory biochemical response (with respect to a decrease in leukocytes and CRPs)
- Imaging (TUS, CT or Chest X-ray (CXR) in 2 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 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 one 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

<u>Costs within the 1st year after discharge:</u>

Calculated for the two groups regarding the following expenses:

- Re-admission
- Ambulatory services
- Medication
- Number of sick days
- Visit to a General Practitioner (GP)

<u>Patient satisfaction and functional level:</u>

- Data in the form of EQ5D and Sct. George Respiratory Questionnaire is collected at the following times:
    - Upon inclusion in the study
    - At discharge
    - Outpatient data: 1, 3, 6 and 12 months.

<u>Various parameters acquired from and after hospitalisation (including ambulant outpatient visits):</u>

- 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
- Lung function tests and walking tests
- Re-admission
- Miscellaneous paraclinical parameters (e.g. biochemistry, microbiology, pathology)

Data obtained from National Patient Register:

- Health-related costs and expenses (e.g. hospital admissions, outpatient visits, general practice consultations, use of physiotherapy)
- Prescribed medication
- Death (e.g. 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 out-patient-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 versus 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 two 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 version 17 (StataCorp LLC, Texas, USA). 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 confidence intervals. 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 (e.g. 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 (Research Electronic Data Capture), REDCap Consortium, Vanderbilt University Medical Center, 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 learned 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.

SUSAR (Suspected Unexpected Serious Adverse Events Reporting), 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.

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 II 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 (e.g. 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. Firstly, 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 (e.g. different sizes and type of drains used in the two groups). Many factors could potentially affect the outcomes following the intervention. To minimize 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. 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 (pigtails).

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.

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Contributors TDC, MBB and CBJ wrote the first draft of the protocol manuscript. TDC, MBB, CBJ, RHP, PBL, BMB planned the conceptualisation and the design of the study and the protocol. All authors contributed to development of the protocol and the critical revisions of the protocol and the current manuscript.

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Disclaimer The conduct, trial analyses, the composing of this manuscript and its final contents are solely the author's incumbency.

Competing interests

Thomas Decker Christensen has been on the speaker bureaus for AstraZeneca, Boehringer-Ingelheim, Pfizer, Roche Diagnostics, Takeda, Merck Sharp & Dohme (MSD) and Bristol-Myers Squibb and has been in an Advisory Board for Bayer and Merck Sharp & Dohme (MSD).

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Other authors: None declared

Patient consent for publication Not required

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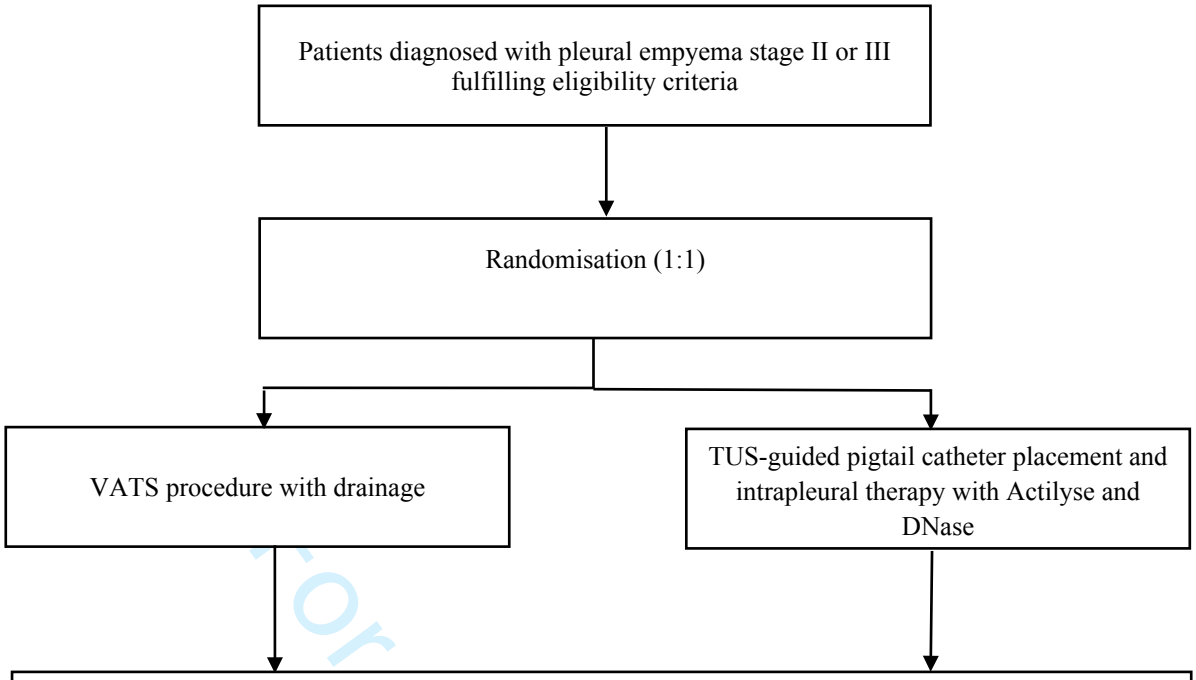

Follow-up

On treatment:

- Length of hospital stay, 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
- Need for additional intrapleural therapy
- Need for intensive care therapy
- Consumption of painkillers
- Lung function tests and walking tests
- Re-admission
- Miscellaneous paraclinical parameters (e.g. biochemistry, microbiology, pathology)

1, 3, 6 and 12 months after discharge:

- Need for additional surgery within 12 months after hospitalisation
- Need for additional intrapleural therapy within 12 months after hospitalisation
- Consumption of painkillers within 12 months after hospitalisation
- Lung function tests and walking tests
- Re-admission
- Miscellaneous paraclinical parameters
- Patient satisfaction and functional level (EQ5D and Sct. George)
- Health related costs and expenses (e.g. hospital admissions, outpatient visits, general practice consultations, use of physiotherapy)
- Prescribed medication
- Death (e.g. date, cause)

Figure 1 Trial schema. VATS, video assisted thoracoscopic surgery; TUS, thoracic ultrasound

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	4-5
	2b	Specific objectives or hypotheses	5
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	5
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	NA
Participants	4a	Eligibility criteria for participants	5-6
	4b	Settings and locations where the data were collected	5
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	8-11
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	7
	6b	Any changes to trial outcomes after the trial commenced, with reasons	NA
Sample size	7a	How sample size was determined	13-14
	7b	When applicable, explanation of any interim analyses and stopping guidelines	NA
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	7-8
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	7-8
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	7-8
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	7-8
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	8

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	NA
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	13-14
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	13-14
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	NA
	13b	For each group, losses and exclusions after randomisation, together with reasons	NA
Recruitment	14a	Dates defining the periods of recruitment and follow-up	NA
	14b	Why the trial ended or was stopped	NA
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	NA
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	NA
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	NA
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	NA
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	NA
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	NA
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	17-18
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	17-18
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	17-18
Other information			
Registration	23	Registration number and name of trial registry	2
Protocol	24	Where the full trial protocol can be accessed, if available	NA
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	21

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

BMJ Open

Intrapleural Fibrinolysis and DNase versus Video-Assisted Thoracic Surgery (VATS) for the treatment of pleural empyema (FIVERVATS): a randomised, controlled trial - surgery as first line treatment

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Intrapleural Fibrinolysis and DNase versus Video-Assisted Thoracic Surgery (VATS) for the treatment of pleural empyema (FIVERVATS): a randomised, controlled trial - surgery as first line treatment

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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 fibrinolyticum 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 e.g. 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-reviewed journals and presented at various national and international conferences.

Trial registration number NCT04095676

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 health care expenses will be estimated using registries

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 one 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 (e.g. 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 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, length of hospital stay (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 January 2022, finish inclusion 30 June 2023 and all patients has completed 1 year of follow-up on 30 June 2024.

Inclusion and exclusion criteria

Inclusion criteria:

- 18 years or more on the day of hospitalization
- Must be able to provide informed consent
- Acute hospitalization 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 or
     b. gram stain positive or
     c. culture positive or
     d. acidic with pH < 7.2 or
     e. low pleural fluid glucose (< 2 mmol/L) in the absence of accurate pH measurement or
     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
- Breastfeeding
- 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) hospitalized 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)
- Hospitalization within 7 days prior to current hospitalization

- Previous allergic reaction to alteplase or DNase
- Use of alteplase therapy contraindicated:
  - Ongoing treatment with oral anticoagulant incl. new oral anticoagulants (e.g. warfarin (Marevan), Dabigatranetexilat (Pradaxa), Rivaroxaban (Xarelto), Apixaban (Eliquis), Endoxaban (Lixiana))
  - Significant ongoing bleeding or within last six months
  - Known haemorrhagic diathesis
  - Previous or suspected intracranial hemorrhage
  - Suspected subarachnoidal hemorrhage or condition following subarachnoidal hemorrhage from aneurysm
  - All forms of damage to the central nervous system (e.g. cerebral tumors, aneurysm, intracranial / spinal surgery)
  - Recent (within 10 days) cardiac resuscitation, birth, or perforation of non-compressible blood vessel (e.g. puncture of v. subclavia, v. jugularis)
  - Severe, uncontrolled arterial hypertension
  - Bacterial endocarditis, pericarditis
  - Acute pancreatitis
  - Documented ulcerative gastrointestinal disease within last 3 months, esophagal varices, arterial aneurysm, arterio-venous malformations
  - Tumor / malignancy with an increased risk of hemorrhage
  - Severe liver disease, including liver failure cirrhosis, portal hypertension (esophagal 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 hospitalization 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 score)
- LOS after commencement of study intervention
- Days at home up to 30 days after study intervention (DAH30, which is defined as days at home up to 30 days after surgery, i.e. if the discharge is done 5 days after surgery, the DAH30 is 25).
- 30-day 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 (CCI)
- Need for additional thoracic surgery which has to be related to the parapneumonic process in first 12 months after hospitalization
- Consumption of painkillers during hospitalisation and within 12 months after hospitalization
- Pulmonary function tests and six minute 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 health care 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 (e.g. 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 three days
- intrapleural Pulmozyme® (DNase) 5 mg twice daily for three days

Both drugs are administered twice daiyly through the pigtail catheter and are left for one hour in the pleural cavity by blocking the drain (e.g. closing the three-way-stopcock / use of a pean forceps). The installation of the drugs in the pleural cavity is performed seperately with a time interval between administrations of at least two hours. Actilyse® (alteplase) is preparred 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 the syringe until the total volume of fluid in the syringe is 30 ml. Following this preparation the mixture is injected into the pleural cavity using the pigtail catheter. Pulmozyme® (DNase) is prepared by drawing 5 ml Pulmozyme® (DNase) (1mg/ml) (5 ml = 2 Pulmozyme cannisters) into a 50 ml syringe. This mixture is further diluted by drawing isotonic NaCl into the syringe until the total volume of fluid in the syringe is 30 ml. 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-degree sideways position, using general anesthesia. 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. 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 H_20) 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 (e.g. no fever/fever, improved general condition)
- Paraclinical satisfactory response (with respect to decreases in leukocytes and CRP's)
- 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 (e.g. 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 (CXR) in 2 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 one 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 1st year after discharge:

Calculated for the two groups regarding the following expenses:

- Re-admission

- Ambulatory services
- Medication
- Number of sick days
- Visit to a General Practitioner (GP)

Patient satisfaction and functional level:

- Data in the form of EQ5D and Sct. George Respiratory Questionnaire is collected at the following times:
  - Upon 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 is registered electronically both during hospitalization in the electronic patient record and after discharge using the National Patient Register.
- Lung function tests and walking tests

- Re-admission
- Miscellaneous paraclinical parameters (e.g. biochemistry, microbiology, pathology)

Data obtained from National Patient Register:

- Health-related costs and expenses (e.g. hospital admissions, outpatient visits, general practice consultations, use of physiotherapy)
- Prescribed medication
- Death (e.g. 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 out-patient-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 versus 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 two 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 version 17 (StataCorp LLC, Texas, USA). 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 confidence intervals. 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 (e.g. 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 (Research Electronic Data Capture), REDCap Consortium, Vanderbilt University Medical Center, 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 learned 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.

SUSAR (Suspected Unexpected Serious Adverse Events Reporting), 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 length of hospital stay.

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 II 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 (e.g. 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. Firstly, 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 (e.g. different sizes and type of drains used in the two groups). Many factors could potentially affect the outcomes following the intervention. To minimize 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 favor of the VATS arm because crossover from fibrinolytics to surgery is more likely than crossover 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 (pigtails).

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.

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Contributors TDC, MBB and CBL wrote the first draft of the protocol manuscript. TDC, MBB, CBL, RHP, PBL, BMB planned the conceptualisation and the design of the study and the protocol. All authors contributed to development of the protocol and the critical revisions of the protocol and the current manuscript.

All the authors 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

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Disclaimer The conduct, trial analyses, the composing of this manuscript and its final contents are solely the author's incumbency.

Competing interests

Thomas Decker Christensen has been on the speaker bureaus for AstraZeneca, Boehringer-Ingelheim, Pfizer, Roche Diagnostics, Takeda, Merck Sharp & Dohme (MSD) and Bristol-Myers Squibb and has been in an Advisory Board for Bayer and Merck Sharp & Dohme (MSD).

René Horsleben Petersen has received a speaker's fee from Medtronic and on the advisory board for AstraZeneca.

Christian B. Laursen has received a speaker's fee from AstraZeneca.

Morten Bendixen has received a teaching fee from Pulmonx Corporation.

Peter B. Licht has received a speaker's fee from Johnson & Johnson.

Other authors: None declared

Patient consent for publication Not required

Ethics approval The Scientific Ethics Committees for Denmark and the Danish Data Protection Agency has provided permission to complete the program. Information about the subjects is protected under the Personal Data Processing Act and the Health Act.

Provenance and peer review Not commissioned; externally peer reviewed

Supplemental material None

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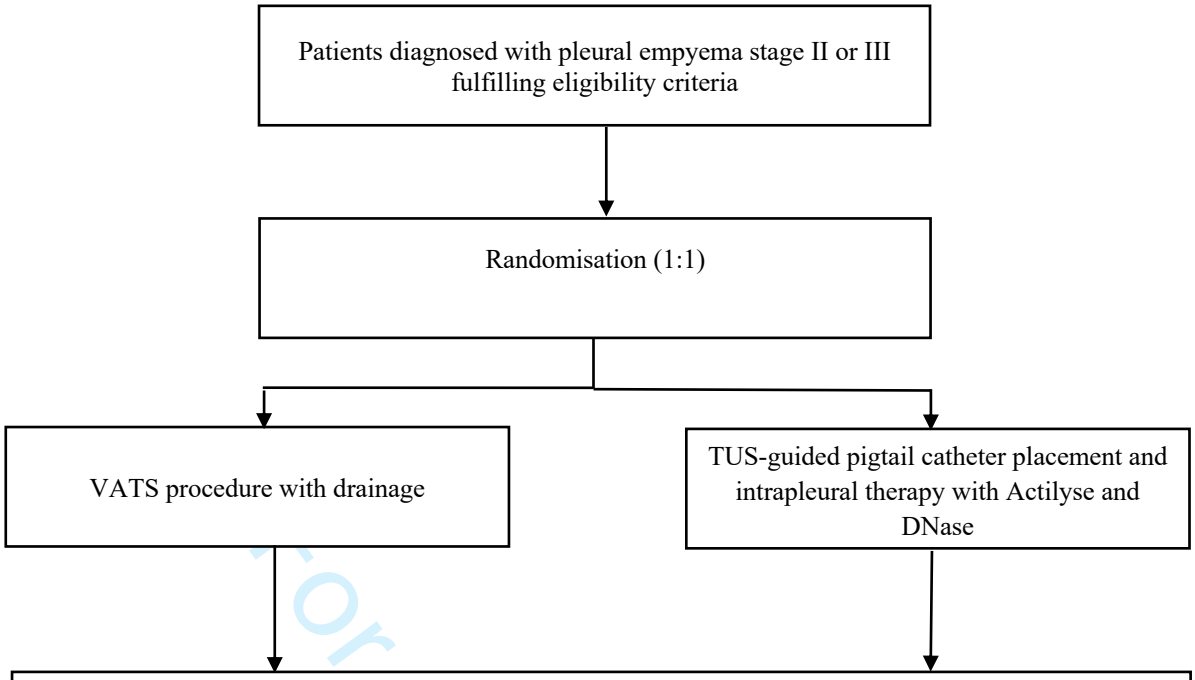
Figure legends

Figure 1 Trial schema. VATS, video assisted thoracoscopic surgery; TUS, thoracic ultrasound

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



Follow-up

On treatment:

- Length of hospital stay, 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
- Need for additional intrapleural therapy
- Need for intensive care therapy
- Consumption of painkillers
- Lung function tests and walking tests
- Re-admission
- Miscellaneous paraclinical parameters (e.g. biochemistry, microbiology, pathology)

1, 3, 6 and 12 months after discharge:

- Need for additional surgery within 12 months after hospitalisation
- Need for additional intrapleural therapy within 12 months after hospitalisation
- Consumption of painkillers within 12 months after hospitalisation
- Lung function tests and walking tests
- Re-admission
- Miscellaneous paraclinical parameters
- Patient satisfaction and functional level (EQ5D and Sct. George)
- Health related costs and expenses (e.g. hospital admissions, outpatient visits, general practice consultations, use of physiotherapy)
- Prescribed medication
- Death (e.g. date, cause)

Figure 1 Trial schema. VATS, video assisted thoracoscopic surgery; TUS, thoracic ultrasound

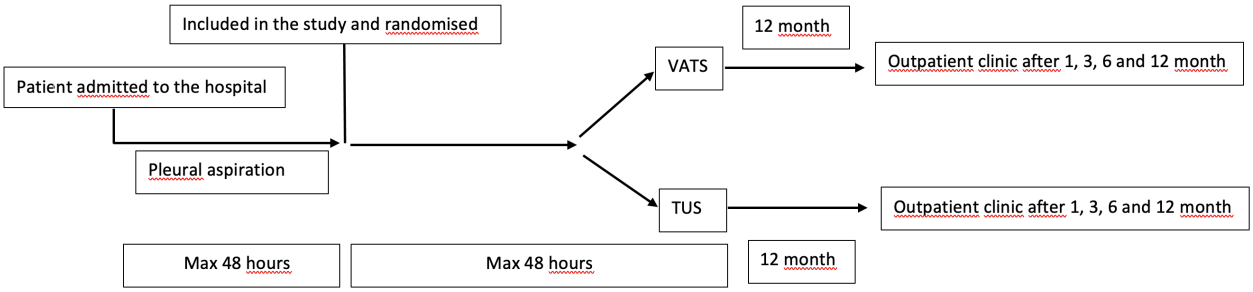


Figure 2 The trials time line. VATS, video assisted thoracoscopic surgery; TUS, thoracic ultrasound

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	4-5
	2b	Specific objectives or hypotheses	5
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	5
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	NA
Participants	4a	Eligibility criteria for participants	5-6
	4b	Settings and locations where the data were collected	5
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	8-11
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	7
	6b	Any changes to trial outcomes after the trial commenced, with reasons	NA
Sample size	7a	How sample size was determined	13-14
	7b	When applicable, explanation of any interim analyses and stopping guidelines	NA
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	7-8
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	7-8
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	7-8
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	7-8
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	8

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	NA
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	13-14
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	13-14
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	NA
	13b	For each group, losses and exclusions after randomisation, together with reasons	NA
Recruitment	14a	Dates defining the periods of recruitment and follow-up	NA
	14b	Why the trial ended or was stopped	NA
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	NA
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	NA
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	NA
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	NA
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	NA
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	NA
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	17-18
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	17-18
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	17-18
Other information			
Registration	23	Registration number and name of trial registry	2
Protocol	24	Where the full trial protocol can be accessed, if available	NA
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	21

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

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

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Primary Subject Heading:	Respiratory medicine
Secondary Subject Heading:	Surgery
Keywords:	Thoracic surgery < SURGERY, Respiratory infections < THORACIC MEDICINE, Clinical trials < THERAPEUTICS

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

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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 fibrinolyticum 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 e.g. 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-reviewed journals and presented at various national and international conferences.

Trial registration number NCT04095676

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 health care expenses will be estimated using registries

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 one 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 (e.g. 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 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, length of hospital stay (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:

- 18 years or more on the day of hospitalization
- Must be able to provide informed consent
- Acute hospitalization 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 or
     b. gram stain positive or
     c. culture positive or
     d. acidic with pH < 7.2 or
     e. low pleural fluid glucose (< 2 mmol/L) in the absence of accurate pH measurement or
     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
- Breastfeeding
- 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) hospitalized 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)
- Hospitalization within 7 days prior to current hospitalization

- Previous allergic reaction to alteplase or DNase
- Use of alteplase therapy contraindicated:
  - Ongoing treatment with oral anticoagulant incl. new oral anticoagulants (e.g. warfarin (Marevan), Dabigatranetexilat (Pradaxa), Rivaroxaban (Xarelto), Apixaban (Eliquis), Endoxaban (Lixiana))
  - Significant ongoing bleeding or within last six months
  - Known haemorrhagic diathesis
  - Previous or suspected intracranial hemorrhage
  - Suspected subarachnoidal hemorrhage or condition following subarachnoidal hemorrhage from aneurysm
  - All forms of damage to the central nervous system (e.g. cerebral tumors, aneurysm, intracranial / spinal surgery)
  - Recent (within 10 days) cardiac resuscitation, birth, or perforation of non-compressible blood vessel (e.g. puncture of v. subclavia, v. jugularis)
  - Severe, uncontrolled arterial hypertension
  - Bacterial endocarditis, pericarditis
  - Acute pancreatitis
  - Documented ulcerative gastrointestinal disease within last 3 months, esophagal varices, arterial aneurysm, arterio-venous malformations
  - Tumor / malignancy with an increased risk of hemorrhage
  - Severe liver disease, including liver failure cirrhosis, portal hypertension (esophagal 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 hospitalization 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 score)
- LOS after commencement of study intervention
- Days at home up to 30 days after study intervention (DAH30, which is defined as days at home up to 30 days after surgery, i.e. if the discharge is done 5 days after surgery, the DAH30 is 25).
- 30-day 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 (CCI)
- Need for additional thoracic surgery which has to be related to the parapneumonic process in first 12 months after hospitalization
- Consumption of painkillers during hospitalisation and within 12 months after hospitalization
- Pulmonary function tests and six minute 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 health care 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 (e.g. 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 three days
- intrapleural Pulmozyme® (DNase) 5 mg twice daily for three days

Both drugs are administered twice daiyly through the pigtail catheter and are left for one hour in the pleural cavity by blocking the drain (e.g. closing the three-way-stopcock / use of a pean forceps). The installation of the drugs in the pleural cavity is performed seperately with a time interval between administrations of at least two hours. Actilyse® (alteplase) is preparred 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 the syringe until the total volume of fluid in the syringe is 30 ml. Following this preparation the mixture is injected into the pleural cavity using the pigtail catheter. Pulmozyme® (DNase) is prepared by drawing 5 ml Pulmozyme® (DNase) (1mg/ml) (5 ml = 2 Pulmozyme cannisters) into a 50 ml syringe. This mixture is further diluted by drawing isotonic NaCl into the syringe until the total volume of fluid in the syringe is 30 ml. 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-degree sideways position, using general anesthesia. 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. 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 H_20) 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 (e.g. no fever/fever, improved general condition)
- Paraclinical satisfactory response (with respect to decreases in leukocytes and CRP's)
- 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 (e.g. 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 (CXR) in 2 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 one 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 1st year after discharge:

Calculated for the two groups regarding the following expenses:

- Re-admission

- Ambulatory services
- Medication
- Number of sick days
- Visit to a General Practitioner (GP)

Patient satisfaction and functional level:

- Data in the form of EQ5D and Sct. George Respiratory Questionnaire is collected at the following times:
  - Upon 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 is registered electronically both during hospitalization in the electronic patient record and after discharge using the National Patient Register.
- Lung function tests and walking tests

- Re-admission
- Miscellaneous paraclinical parameters (e.g. biochemistry, microbiology, pathology)

Data obtained from National Patient Register:

- Health-related costs and expenses (e.g. hospital admissions, outpatient visits, general practice consultations, use of physiotherapy)
- Prescribed medication
- Death (e.g. 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 out-patient-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 versus 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 two 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 version 17 (StataCorp LLC, Texas, USA). 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 confidence intervals. 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 (e.g. 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 (Research Electronic Data Capture), REDCap Consortium, Vanderbilt University Medical Center, 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 learned 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.

SUSAR (Suspected Unexpected Serious Adverse Events Reporting), 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 length of hospital stay.

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 II 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 (e.g. 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. Firstly, 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 (e.g. different sizes and type of drains used in the two groups). Many factors could potentially affect the outcomes following the intervention. To minimize 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 favor of the VATS arm because crossover from fibrinolytics to surgery is more likely than crossover 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 (pigtails).

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.

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Contributors TDC, MBB and CBL wrote the first draft of the protocol manuscript.

TDC, MBB, CBL, RHP, PBL, BMB planned the conceptualisation and the design of the study and the protocol.

TDC, MBB, CBL, RHP, PBL, BMB, JUSJ, MC, KN, LBM, UB, MHB, ZS, SL, SMWH, EOB, BN and NMR contributed to development of the protocol and the critical revisions of the protocol and the current manuscript.

TDC, MBB, CBL, RHP, PBL, BMB, JUSJ, MC, KN, LBM, UB, MHB, ZS, SL, SMWH, EOB, BN and NMR 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.

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Disclaimer The conduct, trial analyses, the composing of this manuscript and its final contents are solely the author's incumbency.

Competing interests

Thomas Decker Christensen has been on the speaker bureaus for AstraZeneca, Boehringer-Ingelheim, Pfizer, Roche Diagnostics, Takeda, Merck Sharp & Dohme (MSD) and Bristol-Myers Squibb and has been in an Advisory Board for Bayer and Merck Sharp & Dohme (MSD).

René Horsleben Petersen has received a speaker's fee from Medtronic and on the advisory board for AstraZeneca.

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Other authors: None declared

Patient consent for publication Not required

Ethics approval The Scientific Ethics Committees for Denmark and the Danish Data Protection Agency has provided permission to complete the program. Information about the subjects is protected under the Personal Data Processing Act and the Health Act.

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Supplemental material None

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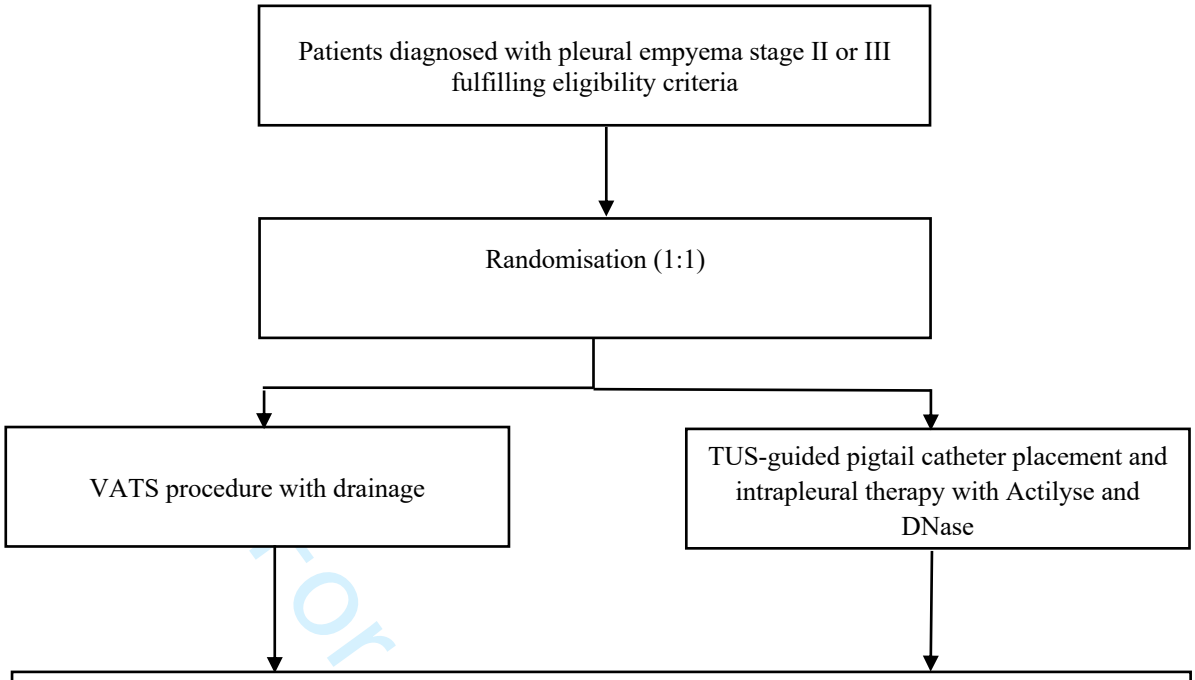
Figure legends

Figure 1 Trial schema. VATS, video assisted thoracoscopic surgery; TUS, thoracic ultrasound

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



Follow-up

On treatment:

- Length of hospital stay, 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
- Need for additional intrapleural therapy
- Need for intensive care therapy
- Consumption of painkillers
- Lung function tests and walking tests
- Re-admission
- Miscellaneous paraclinical parameters (e.g. biochemistry, microbiology, pathology)

1, 3, 6 and 12 months after discharge:

- Need for additional surgery within 12 months after hospitalisation
- Need for additional intrapleural therapy within 12 months after hospitalisation
- Consumption of painkillers within 12 months after hospitalisation
- Lung function tests and walking tests
- Re-admission
- Miscellaneous paraclinical parameters
- Patient satisfaction and functional level (EQ5D and Sct. George)
- Health related costs and expenses (e.g. hospital admissions, outpatient visits, general practice consultations, use of physiotherapy)
- Prescribed medication
- Death (e.g. date, cause)

Figure 1 Trial schema. VATS, video assisted thoracoscopic surgery; TUS, thoracic ultrasound

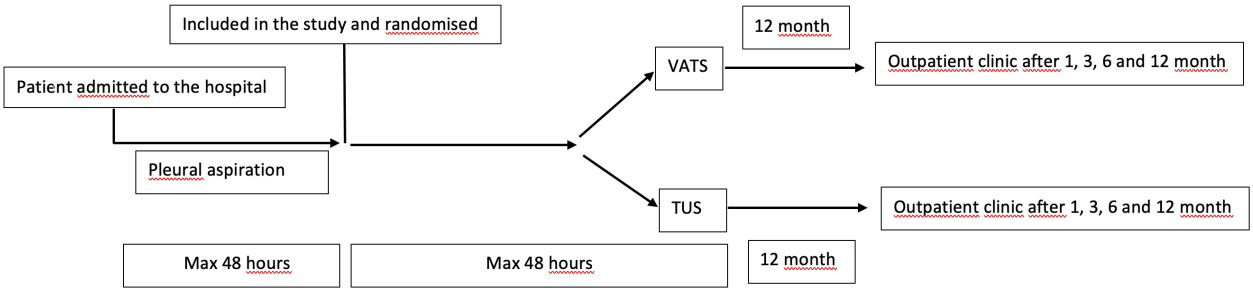


Figure 2 The trials time line. VATS, video assisted thoracoscopic surgery; TUS, thoracic ultrasound

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Reported on page no.
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2 + 18
	2b	All items from the World Health Organization Trial Registration Data Set	2 + 18
Protocol version	3	Date and version identifier	NA
Funding	4	Sources and types of financial, material, and other support	24
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1+22-24
	5b	Name and contact information for the trial sponsor	
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	24 (no role)
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	17-18+24
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4
	6b	Explanation for choice of comparators	5+20
Objectives	7	Specific objectives or hypotheses	5

Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	5
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5+22-24
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	5-7
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9-12
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	17-18
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	NA
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	11-12
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	7-8
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	5+Figure 1 +2
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	15-16
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	NA
Methods: Assignment of interventions (for controlled trials)			
Allocation:			

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	8-9
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	8-9
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	8-9
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	9
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	12-15
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	12-15
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	16-17
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	16
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	16
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	16

Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	17-18
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	17-18
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	17-18
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	17-18
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	18-19+25
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	18-19
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	9+Figure 2
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	16-17
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	25
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	16-17
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA

Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	18
	31b	Authorship eligibility guidelines and any intended use of professional writers	NA (we do not use professional writers)
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	18
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Attached as a file
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.