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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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2 **Intraleural Fibrinolysis and DNase versus Video-Assisted Thoracic Surgery**
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4 **(VATS) for the treatment of pleural empyema (FIVERVATS):**
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6 **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

1
2 The theoretical advantage of surgery as first line treatment is in providing rapid, definitive treatment
3 and insuring optimal drain placement. Experience so far suggest reduction in mortality, length of
4 hospital stay (LOS), and late complications.⁸
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9 LOS is associated with success or failure of the initial empyema treatment, and has accordingly been
10 used in nearly all randomised, controlled empyema trials.^{2 6 13}
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13 In conclusion, treatment needs to be improved due to the high morbidity and mortality and the
14 increasing incidence of the disease. Today, the choice of treatment is random, based on local
15 preferences resulting in non-optimal outcome for these very sick patients.
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21 22 **Aim of the study**

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24 To determine the difference in outcome in patients diagnosed with complex parapneumonic effusion
25 (stage II) and pleural empyema (stage III) who are treated either with VATS surgery or TUS guided
26 drainage and intrapleural therapy (fibrinolytic (Alteplase) with DNase (Pulmozyme®)) as first line
27 treatment.
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33 34 35 36 **METHODS AND ANALYSIS**

37 38 **Design**

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40 A randomised, controlled study, not blinded (open label), national multicentre study including all
41 thoracic surgical departments and all relevant respiratory departments in Denmark
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47 48 **Time plane**

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50 We anticipate starting including patients on 01 November 2021, finish inclusion 30 April 2023 and
51 all patients has completed 1 year of follow-up on 30 April 2024.
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55 56 57 **Inclusion and exclusion criteria**

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59 Inclusion criteria:
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- 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

34 Exclusion criteria:

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- 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

- 1
2 2. TUS-guided pigtail catheter placement and intrapleural therapy with fibrinolyticum
3
4 (alteplase) and DNase, including rinse with saline
5

6 Block randomisation with varying block size will be used to get an equal number of patients in both
7
8 groups. There will be stratification for each surgical centre in the randomisation. The randomisation
9
10 is conducted via a REDCap (Research Electronic Data Capture), (REDCap Consortium, Vanderbilt
11
12 University Medical Center, Tennessee, USA). Figure 1 shows the trial flow.
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16 17 18 **Blinding**

19
20 Patients and responsible health care staff will not be blinded. Research staff not involved in the
21
22 treatment of the included patients are blinded to treatment allocations until data analyses are
23
24 complete. Assessment of different scoring systems (e.g. TUS and radiology score) are blinded to the
25
26 extent that it is practically possible.
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30 31 32 **Patient population and selection**

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34 All patients admitted during the diagnosis of pleural empyema or pleural effusion without
35
36 specification (diagnostic codes: DJ 86, DJ 86.1, DJ 86.9, DJ 90.9). Stages II and III will be potential
37
38 candidates, whether they are hospitalised at a Regional Hospital or at a University Hospital.
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42 43 44 **Intervention**

45 *Drain and intrapleural therapy group*

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47 Pigtail is applied as soon as possible and within 48 hours after randomisation. Drain placement is
48
49 carried out using TUS. Operators (conductors of the procedure) must have relevant training and
50
51 competencies corresponding to the specialist level within the relevant specialty and be approved by
52
53 the steering committee to conduct the procedure. A pigtail catheter (minimum 10F) is inserted.
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55 Operator determines the size of drain and whether drain placement is done with one-step or Seldinger
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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 H₂O) is applied in at least the first day after the procedure. Operator must have relevant training and competencies corresponding to the specialist level within the relevant specialty and be registered and approved by the steering committee.

After the procedure

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

Antibiotics

The empiric antibiotic treatment used in all centres is in accordance with the national guidelines from the Danish Society for Respiratory Medicine. Treatment is initiated as intravenous treatment. Type of antibiotic treatment can be subsequently adjusted depending on results of microbiological tests.

Change to oral treatment can be done when all of the following three criteria are met:

- Clinical improvement of the patient (e.g. no fever/fever, improved general condition)
- Paraclinical satisfactory response (with respect to decreases in leukocytes and CRP's)
- Drain/pigtail is removed

1
2 This means that 14 days intravenous treatment will not be given as standard. The duration of
3
4 intravenous antibiotic treatment will therefore be individualised based on the application of the above
5
6 criteria. The overall duration of treatment of antibiotic is 6 weeks as standard.
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10 11 *Other treatments and supportive care*

12
13 All patients are:

- 14
15 - Offered specialised lung physiotherapy
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17 - Screened for and given additional nutritional support
- 18
19 - Treated with painkillers in accordance with departmental guidelines
- 20
21 - Given thrombosis prophylactic treatment in accordance with national guidelines
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27 28 *Need for additional salvage thoracic surgery or non-surgical pleural procedures*

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30 Following the primary intervention subsequent decisions during the admission to perform salvage
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32 thoracic surgery or additional non-surgical pleural procedures is made in accordance with the national
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34 guidelines from the Danish Society for Cardiothoracic Surgery and Danish Society for Respiratory
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36 Medicine.
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41 42 *Removal of chest tube/pigtail*

43
44 The decision to remove the drain/pigtail is made by the clinician attending the patient. The following
45
46 criteria are used as a guide for discontinuation of drain/pigtail in both groups:

- 47
48 • Clinical improvement of the patient (e.g. no fever/sub-febrile, improved general condition)
- 49
50 • Satisfactory biochemical response (with respect to a decrease in leukocytes and CRPs)
- 51
52 • Imaging (TUS, CT or Chest X-ray (CXR) in 2 planes) without significant residual effusion (<
53
54 100 ml)
- 55
56 • Drain with clear pleural fluid by rinsing
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1
2 In both groups removal of drain / pigtail does not await the results of any of the obtained cultures of
3
4 the pleural fluid. As such the presence of negative cultures is used as removal criteria.
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8 9 *Discharge from hospital*

10
11 In current usual practice in Denmark, patients with pleural empyema are typically discharged when:

- 12
13 - The drain/pigtail has been removed
- 14
15 - Antibiotic treatment has been changed from intravenous to oral treatment without signs of
16
17 subsequent clinical or paraclinical treatment within one day following the change
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19

20 These principles are also used in the study.
21
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23 24 **Data recording**

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26
27 Prior to informed consent obtained as part of screening for study participation:

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29 • Data needed to determine whether inclusion criteria are met (see above)
- 30
31 • Data needed to determine whether any exclusion criteria are present (see above)
- 32
33

34 Baseline patient data: age, gender, comorbidities, medication, performance status, previously
35
36 recorded lung function etc.
37

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

39
40 Drain data: Length of drain treatment, daily output / input, removal criteria, no. of drains used etc.

41
42
43 Costs during hospitalisation:

44
45 Calculated for the two groups regarding the following expenses:

- 46
47 • VATS Group:
 - 48
49 ○ Utensils used during surgery
 - 50
51 ○ Time of the procedure
 - 52
53 ○ Consumption of staff resources
 - 54
55 ○ Hospitalisation time
 - 56
57 ○ Medicine
 - 58
59
 - 60

- 1
- 2 • Drain group:
- 3
- 4 ○ Equipment used during the procedure
- 5
- 6 ○ Procedure Time
- 7
- 8 ○ Consumption of human/staff resources
- 9
- 10 ○ Fibrinolyticum and DNase (amount used)
- 11
- 12 ○ Hospitalisation time
- 13
- 14 ○ Medicine
- 15
- 16
- 17
- 18
- 19

20 Costs within the 1st year after discharge:

21 Calculated for the two groups regarding the following expenses:

- 22
- 23
- 24
- 25 • Re-admission
- 26
- 27 • Ambulatory services
- 28
- 29 • Medication
- 30
- 31 • Number of sick days
- 32
- 33 • Visit to a General Practitioner (GP)
- 34
- 35
- 36
- 37
- 38

39 Patient satisfaction and functional level:

- 40
- 41 • Data in the form of EQ5D and Sct. George Respiratory Questionnaire is collected at the
- 42 following times:
- 43
- 44 ○ Upon inclusion in the study
- 45
- 46 ○ At discharge
- 47
- 48 ○ Outpatient data: 1, 3, 6 and 12 months.
- 49
- 50
- 51
- 52
- 53
- 54

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

- 56
- 57 • Hospitalisation time, total and after commencement of intervention
- 58
- 59 • Primary intervention considered as final treatment
- 60

- 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

1
2 target is the difference between the total time (primary endpoint) between the two groups of patients
3
4 (VATS versus drainage). The distribution of the hospitalisation time is expected to be skewed to the
5
6 right, so that a logarithmic transformation is needed to achieve normality.
7

8
9 We assume a median hospitalisation period in the drainage group of 12 days, a minimum clinically
10
11 relevant difference in hospitalisation of two days, 80% power, and coefficient of variation (CV) of
12
13 40%.
14

15
16 Significance level is set to 0.05. Thus, 77 patients in each group must be included. To account for
17
18 excluded patients (set at 20%), we expect to include 92 patients in each group. A total of 184 patients
19
20 is to be included.
21

22
23 In terms of showing clinically relevant non-inferiority with a difference in hospitalisation of 1 day
24
25 with an 80% power, and CV of 40%, 70 patients is needed in each group. This is based on a true
26
27 improvement of 1 hospitalisation day. Based on the annual number of patients diagnosed with pleura
28
29 empyema in Denmark, we find it feasible to include the needed number of patients in the trial during
30
31 the inclusion period.
32
33

34 35 36 **Data analysis** 37

38
39 Data extractions are made from RedCap database, and data analysis is performed using STATA
40
41 version 17 (StataCorp LLC, Texas, USA). Endpoints will be described for the individual group by
42
43 median and percentile, assuming data is not normally distributed.
44

45
46 Differences between the groups in the primary endpoint are determined by t-test at the log-entry time
47
48 and reported as median ratios with associated confidence intervals. Patients dying during the
49
50 admission is omitted from the analysis if the primary endpoint. Whether death before discharge
51
52 affects the primary endpoint is assessed using survival analysis as sensitivity analysis. We expect that
53
54 the distribution between stages II and III will be 75% and 25%, respectively, and whether there is a
55
56 difference between stages II and III will be assessed as secondary analysis. When repeating
57
58 measurements (e.g. quality of life), repeated measurements ANOVA are used with treatment and time
59
60

1
2 as systematic effects and patient as random effect. All data are analysed primarily according to the
3
4 intention to treat principle, but there will also be one per protocol analysis regarding the above-
5
6 mentioned endpoints. Comparison will take place between the two groups (drainage and VATS).
7
8
9

10 11 **Data collection Media**

- 12
13 • REDCap (Research Electronic Data Capture), REDCap Consortium, Vanderbilt University
14
15 Medical Center, Tennessee, USA
- 16
17 • Electronic patient record (EPJ in Region Midt, EPJ in Region North, EPJ (COSMIC) in
18
19 Region South and EPJ (EPIC Health Platform) in the Capital Region and Region Zealand).
- 20
21 • Health related costs are retrieved via the National Patient Register (LPR).
22
23
24
25
26

27 28 **Handling and archiving data**

29 All data are entered in a Case Report Form in RedCap, which is a professional database that provides
30
31 a user-friendly interface. The REDCap data management system is secure, fully compliant with all
32
33 regulatory guidelines, and includes a complete audit-trail for data entry validation. Through these
34
35 mechanisms, as well as relevant training for all involved parties, patient confidentiality will be
36
37 safeguarded. REDCap is available for free at both Odense University Hospital, Copenhagen and
38
39 Aarhus University.
40
41

42
43 When handling, processing and archiving data collected, the Data Inspectorate's guidelines are
44
45 followed, which implies that all personal data are deleted at the end of the project. The collected data
46
47 is stored at the Department of Cardiothoracic and Vascular Surgery, Aarhus University Hospital and
48
49 at Department of Pulmonology, Odense University Hospital.
50
51

52 53 54 **Data monitoring**

55
56
57 The study will be monitored by the Good Clinical Practice Units at the participating centres. An
58
59 independent Data Monitoring Committee comprised of two clinical researchers not actively involved
60

1
2 in the study and a research statistician will be established. This committee will meet on a regular basis
3
4 to assess data of included patients, with a special emphasis on serious adverse or unforeseen events.
5
6
7

8 9 **Events and side effects**

10 All unintended events and adverse events throughout the treatment period and until the last call after
11
12 30 days are recorded. All Adverse Events are recorded in the patients Case Report Form.
13
14

15 All Serious Adverse Events (SAE) must be reported by the investigator to the sponsor within 24 hours
16
17 after the investigator has learned about the serious incident. SAE is understood to mean an event or
18
19 side effect that results in death, is life threatening, causes hospitalisation or prolonged hospitalisation,
20
21 resulting in significant or permanent invalidity or incapacity.
22
23

24 All SAEs must be followed until the problem is resolved or until it is decided that participation in the
25
26 trial was not the cause.
27
28

29 SUSAR (Suspected Unexpected Serious Adverse Events Reporting), which is mortal or life
30
31 threatening, is entered in the registration form (Report of SAE / SUSAR) and will be reported to the
32
33 Scientific Ethics Committees for Central Denmark Region and / or Region of Southern Denmark
34
35 within 7 days.
36
37
38
39
40

41 **ETHICS AND DISSEMINATION**

42 All patients provide informed consent before randomisation. The research project is carried out in
43
44 accordance with the Helsinki II Declaration, European regulations and Good Clinical Practice
45
46 Guidelines. The Scientific Ethics Committees for Denmark and the Danish Data Protection Agency
47
48 have provided permission. Information about the subjects is protected under the Personal Data
49
50 Processing Act and the Health Act. The trial is registered at www.clinicaltrials.gov, and monitored
51
52 by the regional Good Clinical Practice monitoring unit. The results of this study will be published in
53
54 peer-reviewed journals and presented at various national and international conferences.
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DISCUSSION

Pleural empyema is a frequent disease with a high morbidity and mortality. Community acquired bacterial infection in the pleural cavity has been divided into three clinical stages (I - III).³ The treatment of stage I is drainage, however the optimal treatment of stage II and III has not been established and the treatment is primarily based on local preferences and not evidence-based.

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

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

If this trial is positive for the primary and/or the secondary outcomes, it will change and strengthen the treatment of patients with community acquired bacterial pleural infection, both nationally and internationally. We investigate both clinical parameters, patient satisfaction and economical aspects (cost-effectiveness) in relation to pleural 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

1
2 small number of inhabitants in Denmark and hence the small number of patients with pleural
3
4 empyema. This could have been solved by including patients from other countries making the study
5
6 internationally – however, this was beyond the resources provided for this project.
7

8
9 Second, patients and providers should ideally be blinded to the intervention, but this was however
10
11 not deemed clinically feasible (e.g. different sizes and type of drains used in the two groups). Many
12
13 factors could potentially affect the outcomes following the intervention. To minimize some of the
14
15 main factors we chose that the patients following the intervention at each site would be placed at the
16
17 same department and all these departments had staff with specialised competencies in the
18
19 management of the patient population. Standards for the antibiotic treatment and drain removal has
20
21 been included in the protocol, since any local differences in both factors may affect the chosen
22
23 outcomes. Lastly, we potentially introduce a systematic bias concerning chest tube as the VATS
24
25 group receives large-bore chest tubes (drain), and the TUS group receive small-bore chest tubes
26
27 (pigtailed).
28
29
30

31
32 In summary, this national, multicentre, randomised, controlled trial will investigate whether
33
34 antibiotics and early goal directed VATS as first line treatment should be considered the standard
35
36 regimen of patients with complicated parapneumonic effusion and pleural empyema. It will
37
38 hopefully benefit the initial management and treatment of this patient population making the
39
40 treatment based on evidence instead of local preferences.
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SMW Harders.

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).

1 René Horsleben Petersen has received a speaker's fee from Medtronic and on the advisory board for
2 AstraZeneca.
3

4 Christian B. Laursen has received a speaker's fee from AstraZeneca.
5

6 Morten Bendixen has received a teaching fee from Pulmonx Corporation.
7

8 Peter B. Licht has received a speaker's fee from Johnson & Johnson.
9

10 Other authors: None declared
11
12

13 **Patient consent for publication** Not required
14
15

16 **Ethics approval** The Scientific Ethics Committees for Denmark and the Danish Data Protection
17 Agency has provided permission to complete the program. Information about the subjects is
18 protected under the Personal Data Processing Act and the Health Act.
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23 **Provenance and peer review** Not commissioned; externally peer reviewed
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32 **Supplemental material** None
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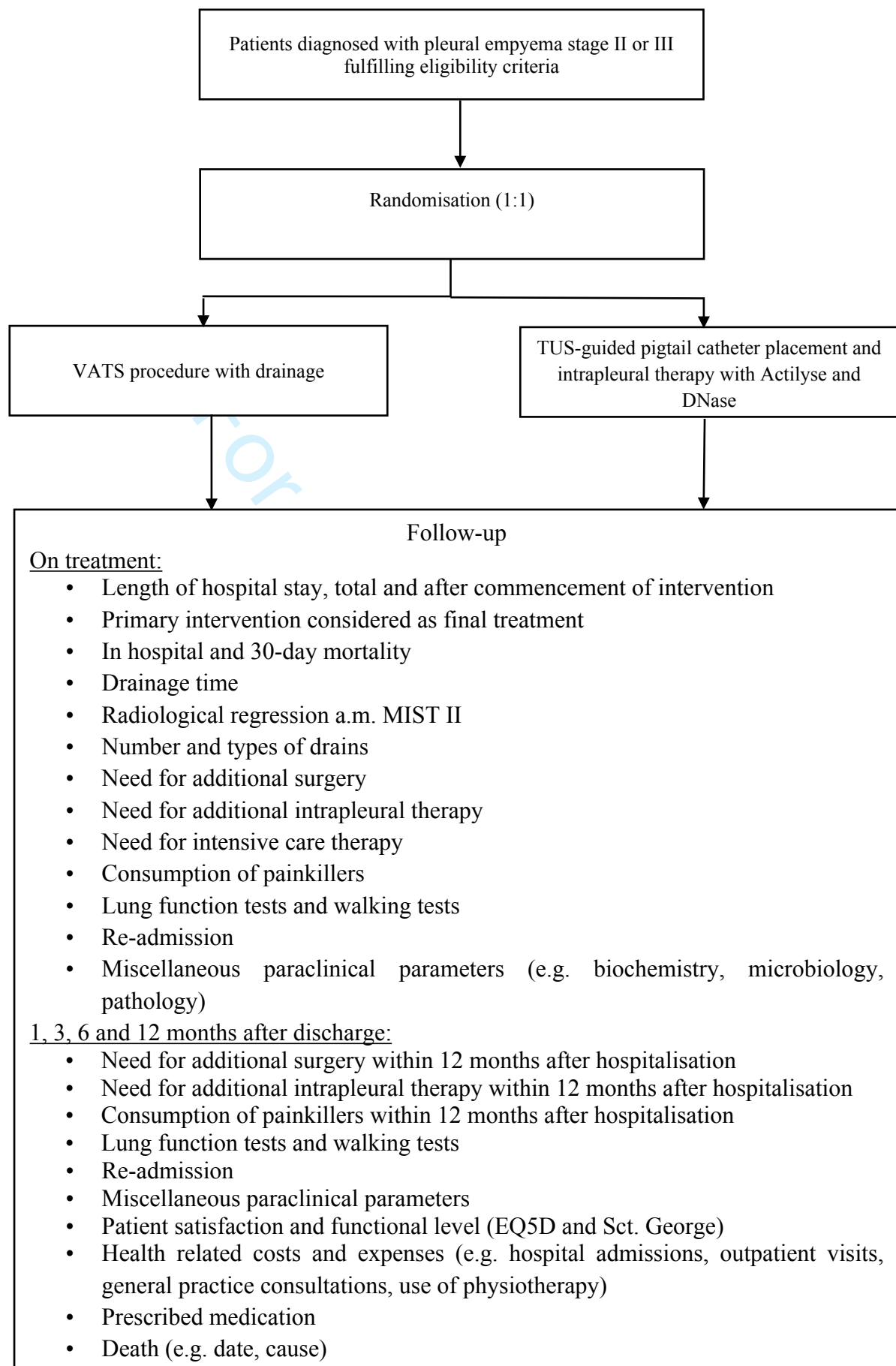


Figure 1 Trial schema. VATS, video assisted thoracoscopic surgery; TUS, thoracic ultrasound



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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2021-054236.R1
Article Type:	Protocol
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Manuscripts

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2 **Intraleural Fibrinolysis and DNase versus Video-Assisted Thoracic Surgery**
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4 **(VATS) for the treatment of pleural empyema (FIVERVATS):**
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6 **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

For peer review only

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

1
2 The theoretical advantage of surgery as first line treatment is in providing rapid, definitive treatment
3 and insuring optimal drain placement. Experience so far suggest reduction in mortality, length of
4 hospital stay (LOS), and late complications.⁸
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9 LOS is associated with success or failure of the initial empyema treatment, and has accordingly been
10 used in nearly all randomised, controlled empyema trials.^{2 6 13}
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13 In conclusion, treatment needs to be improved due to the high morbidity and mortality and the
14 increasing incidence of the disease. Today, the choice of treatment is random, based on local
15 preferences resulting in non-optimal outcome for these very sick patients.
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20 21 22 **Aim of the study**

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

37 38 **Design**

39 A randomised, controlled study, not blinded (open label), national multicentre study including all
40 thoracic surgical departments and all relevant respiratory departments in Denmark
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48 **Time plane**

49 We anticipate starting including patients at earliest on 01 January 2022, finish inclusion 30 June
50 2023 and all patients has completed 1 year of follow-up on 30 June 2024.
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57 **Inclusion and exclusion criteria**

58 Inclusion criteria:
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- 1
- 2 • 18 years or more on the day of hospitalization
- 3
- 4 • Must be able to provide informed consent
- 5
- 6 • Acute hospitalization within the last 48 hours
- 7
- 8 • Meeting diagnostic criteria for community acquired pleural infection using the following
- 9 criteria:
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- 11
- 12
- 13 1) A clinical presentation compatible with pleural infection AND
- 14
- 15 2) Has pleural fluid which is either:
- 16
- 17 a. purulent pleural fluid or
- 18
- 19 b. gram stain positive or
- 20
- 21 c. culture positive or
- 22
- 23 d. acidic with pH < 7.2 or
- 24
- 25 e. low pleural fluid glucose (< 2 mmol/L) in the absence of accurate pH measurement or
- 26
- 27 f. septated pleural fluid on ultrasound
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34 Exclusion criteria:

- 35
- 36 • Pregnancy. Prior to inclusion of fertile women (defined as the period from menarche to
- 37 postmenopause) a negative pregnancy test must be available
- 38
- 39 • Breastfeeding
- 40
- 41 • Declared terminally ill or a predicted survival of less than 3 months
- 42
- 43 • Previous intrathoracic surgery (within <1 year on the same side of the thorax as where the
- 44 parapneumonic effusion/pleural empyema is located
- 45
- 46 • Previously (within <1 year) hospitalized with with complex parapneumonic effusion (stage
- 47 II) or pleural empyema (stage III)
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- 49 • Drainage during the current admission on the same side of the thorax (excluding diagnostic
- 50 pleural puncture)
- 51
- 52 • Hospitalization within 7 days prior to current hospitalization
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- 1
- 2 • Previous allergic reaction to alteplase or DNase
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- 4 • Use of alteplase therapy contraindicated:
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- 6 - Ongoing treatment with oral anticoagulant incl. new oral anticoagulants (e.g. warfarin
- 7 (Marevan), Dabigatranetexilat (Pradaxa), Rivaroxaban (Xarelto), Apixaban (Eliquis),
- 8 Endoxaban (Lixiana))
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- 11 - Significant ongoing bleeding or within last six months
- 12
- 13 - Known haemorrhagic diathesis
- 14
- 15 - Previous or suspected intracranial hemorrhage
- 16
- 17 - Suspected subarachnoidal hemorrhage or condition following subarachnoidal hemorrhage
- 18 from aneurysm
- 19
- 20 - All forms of damage to the central nervous system (e.g. cerebral tumors, aneurysm,
- 21 intracranial / spinal surgery)
- 22
- 23 - Recent (within 10 days) cardiac resuscitation, birth, or perforation of non-compressible
- 24 blood vessel (e.g. puncture of v. subclavia, v. jugularis)
- 25
- 26 - Severe, uncontrolled arterial hypertension
- 27
- 28 - Bacterial endocarditis, pericarditis
- 29
- 30 - Acute pancreatitis
- 31
- 32 - Documented ulcerative gastrointestinal disease within last 3 months, esophageal varices,
- 33 arterial aneurysm, arterio-venous malformations
- 34
- 35 - Tumor / malignancy with an increased risk of hemorrhage
- 36
- 37 - Severe liver disease, including liver failure cirrhosis, portal hypertension (esophageal
- 38 varices), and active hepatitis
- 39
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- 41 - Large operation or significant trauma within previous 3 months
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57 Endpoints

58 Primary endpoint:

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- 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.

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Secondary endpoints:

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- 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

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Randomisation

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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 daiily 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 prepared by diluting 10 mg Actilyse® (alteplase) in the solvent liquid (10 ml) supplied alongside the drug in a 50 ml syringe.

This mixture is further diluted by drawing isotonic NaCl into 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 H₂O) is applied in at least the first day after the procedure.

1
2 Operator must have relevant training and competencies corresponding to the specialist level within
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4 the relevant specialty and be registered and approved by the steering committee.
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8 9 *After the procedure*

10 Randomised patients are transferred to a specialised department of Respiratory Medicine or remain
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12 in the department of Thoracic Surgery. Following completed intervention, the chest tubes in both
13
14 groups are flushed with 30 ml normal saline three times daily to ensure tube patency.
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18 19 20 *Antibiotics*

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22 The empiric antibiotic treatment used in all centres is in accordance with the national guidelines from
23
24 the Danish Society for Respiratory Medicine. Treatment is initiated as intravenous treatment. Type
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26 of antibiotic treatment can be subsequently adjusted depending on results of microbiological tests.
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29 Change to oral treatment can be done when all of the following three criteria are met:

- 30
31
- 32 • Clinical improvement of the patient (e.g. no fever/fever, improved general condition)
 - 33 • Paraclinical satisfactory response (with respect to decreases in leukocytes and CRP's)
 - 34 • Drain/pigtail is removed
- 35
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38 This means that 14 days intravenous treatment will not be given as standard. The duration of
39
40 intravenous antibiotic treatment will therefore be individualised based on the application of the above
41
42 criteria. The overall duration of treatment of antibiotic is 6 weeks as standard.
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46 47 48 *Other treatments and supportive care*

49 All patients are:

- 50
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- 52 - Offered specialised lung physiotherapy
 - 53 - Screened for and given additional nutritional support
 - 54 - Treated with painkillers in accordance with departmental guidelines
 - 55 - Given thrombosis prophylactic treatment in accordance with national guidelines
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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

1
2 Prior to informed consent obtained as part of screening for study participation:
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- 4 • Data needed to determine whether inclusion criteria are met (see above)
- 5
- 6 • Data needed to determine whether any exclusion criteria are present (see above)
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9 Baseline patient data: age, gender, comorbidities, medication, performance status, previously
10 recorded lung function etc.

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12
13 Surgical and TUS data: used time, specific type of procedure, operator, drain size, complications etc.

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

17
18 Costs during hospitalisation:
19

20 Calculated for the two groups regarding the following expenses:
21

- 22 • VATS Group:
 - 23 ○ Utensils used during surgery
 - 24
 - 25 ○ Time of the procedure
 - 26
 - 27 ○ Consumption of staff resources
 - 28
 - 29 ○ Hospitalisation time
 - 30
 - 31 ○ Medicine
 - 32
- 33 • Drain group:
 - 34 ○ Equipment used during the procedure
 - 35
 - 36 ○ Procedure Time
 - 37
 - 38 ○ Consumption of human/staff resources
 - 39
 - 40 ○ Fibrinolyticum and DNase (amount used)
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 - 42 ○ Hospitalisation time
 - 43
 - 44 ○ Medicine
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55 Costs within the 1st year after discharge:
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57 Calculated for the two groups regarding the following expenses:
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- 59 • Re-admission
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- 1
- 2 • Ambulatory services
- 3
- 4 • Medication
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- 6
- 7 • Number of sick days
- 8
- 9 • Visit to a General Practitioner (GP)
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14 Patient satisfaction and functional level:

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- 16 • Data in the form of EQ5D and Sct. George Respiratory Questionnaire is collected at the
- 17 following times:
- 18
 - 19 ○ Upon inclusion in the study
 - 20
 - 21 ○ At discharge
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 - 24
 - 25 ○ Outpatient data: 1, 3, 6 and 12 months.
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30 Various parameters acquired from and after hospitalisation (including ambulant outpatient visits):

- 31
- 32 • Hospitalisation time, total and after commencement of intervention
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- 34 • Primary intervention considered as final treatment
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- 37 • In hospital and 30-day mortality
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- 39 • Drainage time
- 40
- 41 • Radiological regression a.m. MIST II
- 42
- 43 • Number and types of drains
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- 45
- 46 • Need for additional surgery during and within 12 months after hospitalisation
- 47
- 48 • Need for additional intrapleural therapy during and within 12 months after hospitalisation
- 49
- 50 • Need for intensive care therapy
- 51
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- 53 • Consumption of painkillers during hospitalisation and within 12 months after hospitalisation
- 54
- 55 which is registered electronically both during hospitalization in the electronic patient record
- 56
- 57 and after discharge using the National Patient Register.
- 58
- 59 • Lung function tests and walking tests
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- 1
- 2 • Re-admission
- 3
- 4 • Miscellaneous paraclinical parameters (e.g. biochemistry, microbiology, pathology)
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9 Data obtained from National Patient Register:

- 10 • Health-related costs and expenses (e.g. hospital admissions, outpatient visits, general practice
- 11 consultations, use of physiotherapy)
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- 13 • Prescribed medication
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- 15 • Death (e.g. date, cause)
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23 **Outpatient follow-up after discharge**

24 In conjunction with participation in the project, in addition to any common local controls, outpatient
25 follow-up is performed at the regional respiratory medicine out-patient-clinic after 1, 3, 6 and 12
26 months after discharge.
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32 **Sample size and power calculation**

33 The study is based on assumptions and knowledge about LOS, both from national and international
34 publications. We calculated the sample size based on the following assumptions: the main effect
35 target is the difference between the total time (primary endpoint) between the two groups of patients
36 (VATS versus drainage). The distribution of the hospitalisation time is expected to be skewed to the
37 right, so that a logarithmic transformation is needed to achieve normality.
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40 We assume a median hospitalisation period in the drainage group of 12 days, a minimum clinically
41 relevant difference in hospitalisation of two days, 80% power, and coefficient of variation (CV) of
42 40%.
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48 Significance level is set to 0.05. Thus, 77 patients in each group must be included. To account for
49 excluded patients (set at 20%), we expect to include 92 patients in each group. A total of 184 patients
50 is to be included.
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2 In terms of showing clinically relevant non-inferiority with a difference in hospitalisation of 1 day
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4 with an 80% power, and CV of 40%, 70 patients is needed in each group. This is based on a true
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6 improvement of 1 hospitalisation day. Based on the annual number of patients diagnosed with pleura
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8 empyema in Denmark, we find it feasible to include the needed number of patients in the trial during
9
10 the inclusion period.
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15 **Data analysis**

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17 Data extractions are made from RedCap database, and data analysis is performed using STATA
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19 version 17 (StataCorp LLC, Texas, USA). Endpoints will be described for the individual group by
20
21 median and percentile, assuming data is not normally distributed.
22
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25 Differences between the groups in the primary endpoint are determined by t-test at the log-entry time
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27 and reported as median ratios with associated confidence intervals. Patients dying during the
28
29 admission is omitted from the analysis if the primary endpoint. Whether death before discharge
30
31 affects the primary endpoint is assessed using survival analysis as sensitivity analysis. We expect that
32
33 the distribution between stages II and III will be 75% and 25%, respectively, and whether there is a
34
35 difference between stages II and III will be assessed as secondary analysis. When repeating
36
37 measurements (e.g. quality of life), repeated measurements ANOVA are used with treatment and time
38
39 as systematic effects and patient as random effect. All data are analysed primarily according to the
40
41 intention to treat principle, but there will also be one per protocol analysis regarding the above-
42
43 mentioned endpoints. Comparison will take place between the two groups (drainage and VATS).
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50 **Data collection Media**

- 51
52 • REDCap (Research Electronic Data Capture), REDCap Consortium, Vanderbilt University
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54 Medical Center, Tennessee, USA
- 55
56 • Electronic patient record (EPJ in Region Midt, EPJ in Region North, EPJ (COSMIC) in
57
58 Region South and EPJ (EPIC Health Platform) in the Capital Region and Region Zealand).
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- 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

1
2 side effect that results in death, is life threatening, causes hospitalisation or prolonged hospitalisation,
3
4 resulting in significant or permanent invalidity or incapacity.
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6 All SAEs must be followed until the problem is resolved or until it is decided that participation in the
7
8 trial was not the cause.
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10 SUSAR (Suspected Unexpected Serious Adverse Events Reporting), which is mortal or life
11
12 threatening, is entered in the registration form (Report of SAE / SUSAR) and will be reported to the
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14 Scientific Ethics Committees for Central Denmark Region and / or Region of Southern Denmark
15
16 within 7 days.
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22 **Patient and Public Involvement**

23
24 The patients were not directly involved in the development of the research question and study
25
26 design, but indirectly fueled the idea to this study because many patients over the years who were
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28 diagnosed with pleural empyema repeatedly informed that they were frustrated with long-lasting
29
30 treatments and hospital stays. As a result, we have designed the study aiming to improve and speed
31
32 up their treatment and reduce their length of hospital stay.
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35 We are also in the process of designing “spin-off” studies with a qualitative focus, which will help
36
37 to design future studies including patient reported outcome measurements, which has also been
38
39 deemed relevant by patients themselves.
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42 Potential patients/the public will be informed of the trial using social medias and news columns. All
43
44 patients included in the trial will be informed of the results of the study. The burden of the
45
46 intervention is assessed by the patients using health quality assessment schemes. Patient advisors
47
48 are, if relevant, thanked in the acknowledge section.
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52 **ETHICS AND DISSEMINATION**

53
54 All patients provide informed consent before randomisation. The research project is carried out in
55
56 accordance with the Helsinki II Declaration, European regulations and Good Clinical Practice
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2 Guidelines. The Scientific Ethics Committees for Denmark and the Danish Data Protection Agency
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4 have provided permission. Information about the subjects is protected under the Personal Data
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6 Processing Act and the Health Act. The trial is registered at www.clinicaltrials.gov, and monitored
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8 by the regional Good Clinical Practice monitoring unit. The results of this study will be published in
9
10 peer-reviewed journals and presented at various national and international conferences.
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15 **DISCUSSION**

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18 Pleural empyema is a frequent disease with a high morbidity and mortality. Community acquired
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20 bacterial infection in the pleural cavity has been divided into three clinical stages (I - III).³ The
21
22 treatment of stage I is drainage, however the optimal treatment of stage II and III has not been
23
24 established and the treatment is primarily based on local preferences and not evidence-based.
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26

27 In our study we want to find the optimal method for treating patients with pleural empyema stage II
28
29 and III – either a VATS procedure or TUS guided drainage and intrapleural therapy (fibrinolytic
30
31 (Alteplase) with DNase (Pulmozyme®)).
32
33

34 The theoretical advantage of surgery as first line treatment is that patients undergo rapid, definitive
35
36 treatment and insurance of optimal drain placement. Early and definite surgery can potentially reduce
37
38 mortality, LOS, and cause fewer late complications.⁹
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41 If this trial is positive for the primary and/or the secondary outcomes, it will change and strengthen
42
43 the treatment of patients with community acquired bacterial pleural infection, both nationally and
44
45 internationally. We investigate both clinical parameters, patient satisfaction and economical aspects
46
47 (cost-effectiveness) in relation to pleura empyema treatment, so it will cover many aspects of this
48
49 disease. We have established a nationwide study with participation of all relevant departments and
50
51 all relevant specialties (e.g. pulmonology and thoracic surgery), and the trial will therefore have a
52
53 high internal and external validity. This is a significant plus in terms of methodological quality, and
54
55 the results of the study will widely be applicable and can easily be implemented in the daily clinical
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57 practice.
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1 We have decided to have LOS as the primary endpoint, since it is an objective measurement depicting
2 the clinical status of the patient, and LOS is a clinically relevant endpoint used in multiple trials
3 assessing treatment of complicated parapneumonic effusions and pleural empyema.^{2 6 13}

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7
8 This study has some limitations. Firstly, the primary endpoint should preferably have been 1-year
9 mortality and secondary endpoint severe morbidity. However, this would have required inclusion of
10 a large number of patients, which would have required a very long inclusion time due to the relatively
11 small number of inhabitants in Denmark and hence the small number of patients with pleural
12 empyema. This could have been solved by including patients from other countries making the study
13 internationally – however, this was beyond the resources provided for this project.

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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 (pigtailed).

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

1
2 hopefully benefit the initial management and treatment of this patient population making the
3
4 treatment based on evidence instead of local preferences.
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25 **Contributors** TDC, MBB and CBL wrote the first draft of the protocol manuscript. TDC, MBB,
26
27 CBL, RHP, PBL, BMB planned the conceptualisation and the design of the study and the protocol.
28
29 All authors contributed to development of the protocol and the critical revisions of the protocol and
30
31 the current manuscript.
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34 All the authors have made substantial contributions to the conception and design of the work;
35
36 drafting the work and revising it critically for important intellectual content; made final approval of
37
38 the version to be published; made agreement to be accountable for his/her contributions of the work
39
40 in ensuring that questions related to the accuracy or integrity of the work are appropriately
41
42 investigated and resolved
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56
57 solely the author's incumbency.
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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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Provenance and peer review Not commissioned; externally peer reviewed

Supplemental material None

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25 **Figure legends**

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27 **Figure 1** Trial schema. VATS, video assisted thoracoscopic surgery; TUS, thoracic ultrasound
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32 **Figure 2** The trials time line. VATS, video assisted thoracoscopic surgery; TUS, thoracic
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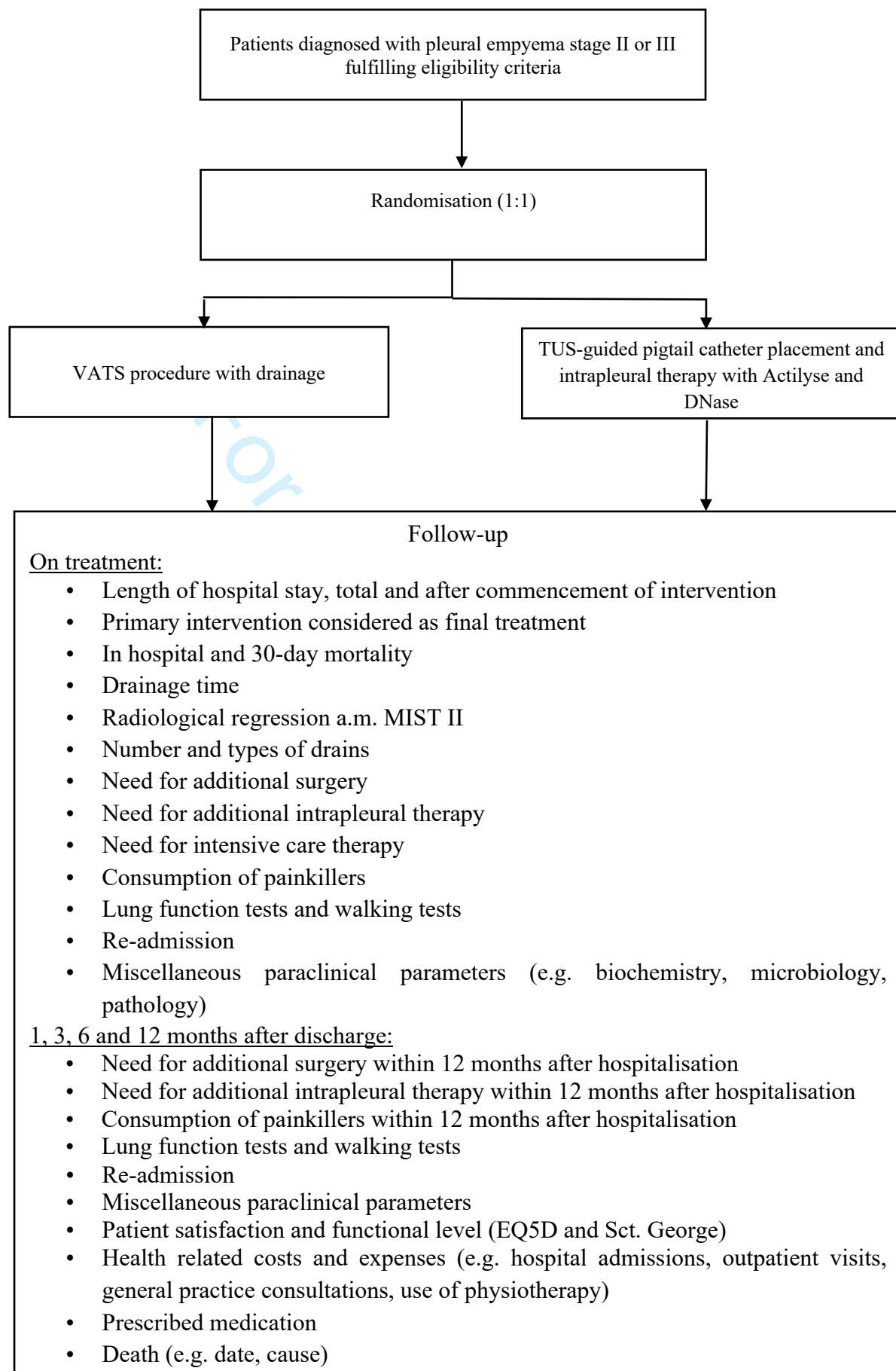


Figure 1 Trial schema. VATS, video assisted thoracoscopic surgery; TUS, thoracic ultrasound

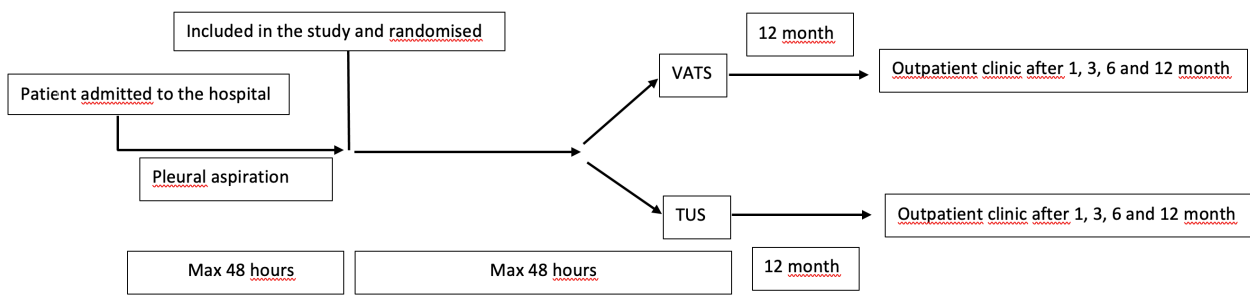


Figure 2 The trials time line. VATS, video assisted thoracoscopic surgery; TUS, thoracic ultrasound



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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2021-054236.R2
Article Type:	Protocol
Date Submitted by the Author:	10-Feb-2022
Complete List of Authors:	<p>Christensen , Thomas Decker ; Aarhus University Hospital, Department of Cardiothoracic and Vascular Surgery & Department of Clinical Medicine Bendixen, Morten ; Aarhus University Hospital, Department of Cardiothoracic and Vascular Surgery, Skaarup, Søren ; Aarhus University Hospital, Department of Respiratory Diseases and Allergy Jensen, Jens-Ulrik; Herlev and Gentofte Hospital , Department of Internal Medicine, Respiratory Medicine Section; Faculty of Health Sciences, University of Copenhagen, Institute for Clinical Medicine Petersen, Rene ; Copenhagen University Hospital, Rigshospitalet, Department of Cardiothoracic Surgery; Faculty of Health Sciences, University of Copenhagen, Institute for Clinical Medicine Christensen, Merete; Copenhagen University Hospital, Rigshospitalet, Department of Cardiothoracic Surgery Licht, Peter; Odense University Hospital, Department of Cardiothoracic Surgery Neckelmann, Kirsten; Odense University Hospital, Department of Cardiothoracic Surgery Bibby, Bo; Aarhus University, Department of Public Health, Section for Biostatistics Møller, Lars ; Aalborg University Hospital, Department of Cardiothoracic Surgery Bodtger, Uffe; Zealand University Hospital & , Department of Internal Medicine, Roskilde, Denmark & Department of Respiratory Medicine, Naestved-Slagelse Hospital, ; University of Southern Denmark, Institute of Regional Health Research Borg, Morten ; Aalborg University Hospital, Department of Respiratory Medicine & Clinical Institute Saghir, Zaigham ; Herlev and Gentofte Hospital , Department of Internal Medicine, Respiratory Medicine Section; Institute for Clinical Medicine, Faculty of Health Sciences, University of Copenhagen Langfeldt, Sten; Aarhus University Hospital, Department of Radiology Harders, Stefan ; Odense University Hospital, Department of Radiology Bedawi, Eihab ; NIHR Oxford Biomedical Research Centre Naidu, Babu; Queen Elizabeth Hospital, Department of Thoracic Surgery; University of Birmingham, Institute of Inflammation and Ageing Rahman, Najib; University of Oxford, NIHR Oxford Biomedical Research</p>

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

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Manuscripts

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2 **Intrapleural Fibrinolysis and DNase versus Video-Assisted Thoracic Surgery**
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4 **(VATS) for the treatment of pleural empyema (FIVERVATS):**
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7 **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

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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

1
2 The theoretical advantage of surgery as first line treatment is in providing rapid, definitive treatment
3 and insuring optimal drain placement. Experience so far suggest reduction in mortality, length of
4 hospital stay (LOS), and late complications.⁸
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8
9 LOS is associated with success or failure of the initial empyema treatment, and has accordingly been
10 used in nearly all randomised, controlled empyema trials.^{2 6 13}
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13
14 In conclusion, treatment needs to be improved due to the high morbidity and mortality and the
15 increasing incidence of the disease. Today, the choice of treatment is random, based on local
16 preferences resulting in non-optimal outcome for these very sick patients.
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20 21 22 **Aim of the study**

23
24 To determine the difference in outcome in patients diagnosed with complex parapneumonic effusion
25 (stage II) and pleural empyema (stage III) who are treated either with VATS surgery or TUS guided
26 drainage and intrapleural therapy (fibrinolytic (Alteplase) with DNase (Pulmozyme®)) as first line
27 treatment.
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36 **METHODS AND ANALYSIS**

37 38 **Design**

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40 A randomised, controlled study, not blinded (open label), national multicentre study including all
41 thoracic surgical departments and all relevant respiratory departments in Denmark
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48 **Time plane**

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50 We anticipate starting including patients at earliest on 01 April 2022, finish inclusion 30 September
51 2023 and all patients has completed 1 year of follow-up on 30 September 2024.
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56

57 **Inclusion and exclusion criteria**

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59 Inclusion criteria:
60

- 1
- 2 • 18 years or more on the day of hospitalization
- 3
- 4 • Must be able to provide informed consent
- 5
- 6 • Acute hospitalization within the last 48 hours
- 7
- 8 • Meeting diagnostic criteria for community acquired pleural infection using the following
- 9 criteria:
- 10
- 11
- 12
- 13 1) A clinical presentation compatible with pleural infection AND
- 14
- 15 2) Has pleural fluid which is either:
- 16
- 17 a. purulent pleural fluid or
- 18
- 19 b. gram stain positive or
- 20
- 21 c. culture positive or
- 22
- 23 d. acidic with pH < 7.2 or
- 24
- 25 e. low pleural fluid glucose (< 2 mmol/L) in the absence of accurate pH measurement or
- 26
- 27 f. septated pleural fluid on ultrasound
- 28
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34 Exclusion criteria:

- 35
- 36 • Pregnancy. Prior to inclusion of fertile women (defined as the period from menarche to
- 37 postmenopause) a negative pregnancy test must be available
- 38
- 39 • Breastfeeding
- 40
- 41 • Declared terminally ill or a predicted survival of less than 3 months
- 42
- 43 • Previous intrathoracic surgery (within <1 year on the same side of the thorax as where the
- 44 parapneumonic effusion/pleural empyema is located
- 45
- 46 • Previously (within <1 year) hospitalized with with complex parapneumonic effusion (stage
- 47 II) or pleural empyema (stage III)
- 48
- 49 • Drainage during the current admission on the same side of the thorax (excluding diagnostic
- 50 pleural puncture)
- 51
- 52 • Hospitalization within 7 days prior to current hospitalization
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- 1
- 2 • Previous allergic reaction to alteplase or DNase
- 3
- 4 • Use of alteplase therapy contraindicated:
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- 6 - Ongoing treatment with oral anticoagulant incl. new oral anticoagulants (e.g. warfarin
- 7 (Marevan), Dabigatranetexilat (Pradaxa), Rivaroxaban (Xarelto), Apixaban (Eliquis),
- 8 Endoxaban (Lixiana))
- 9
- 10
- 11 - Significant ongoing bleeding or within last six months
- 12
- 13 - Known haemorrhagic diathesis
- 14
- 15 - Previous or suspected intracranial hemorrhage
- 16
- 17 - Suspected subarachnoidal hemorrhage or condition following subarachnoidal hemorrhage
- 18 from aneurysm
- 19
- 20 - All forms of damage to the central nervous system (e.g. cerebral tumors, aneurysm,
- 21 intracranial / spinal surgery)
- 22
- 23 - Recent (within 10 days) cardiac resuscitation, birth, or perforation of non-compressible
- 24 blood vessel (e.g. puncture of v. subclavia, v. jugularis)
- 25
- 26 - Severe, uncontrolled arterial hypertension
- 27
- 28 - Bacterial endocarditis, pericarditis
- 29
- 30 - Acute pancreatitis
- 31
- 32 - Documented ulcerative gastrointestinal disease within last 3 months, esophageal varices,
- 33 arterial aneurysm, arterio-venous malformations
- 34
- 35 - Tumor / malignancy with an increased risk of hemorrhage
- 36
- 37 - Severe liver disease, including liver failure cirrhosis, portal hypertension (esophageal
- 38 varices), and active hepatitis
- 39
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- 41 - Large operation or significant trauma within previous 3 months
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57 Endpoints

58 Primary endpoint:

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- 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.

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Secondary endpoints:

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- 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

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Randomisation

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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 daiily 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 prepared by diluting 10 mg Actilyse® (alteplase) in the solvent liquid (10 ml) supplied alongside the drug in a 50 ml syringe.

This mixture is further diluted by drawing isotonic NaCl into 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 H₂O) is applied in at least the first day after the procedure.

1
2 Operator must have relevant training and competencies corresponding to the specialist level within
3
4 the relevant specialty and be registered and approved by the steering committee.
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8 9 *After the procedure*

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11 Randomised patients are transferred to a specialised department of Respiratory Medicine or remain
12
13 in the department of Thoracic Surgery. Following completed intervention, the chest tubes in both
14
15 groups are flushed with 30 ml normal saline three times daily to ensure tube patency.
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18 19 20 *Antibiotics*

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22 The empiric antibiotic treatment used in all centres is in accordance with the national guidelines from
23
24 the Danish Society for Respiratory Medicine. Treatment is initiated as intravenous treatment. Type
25
26 of antibiotic treatment can be subsequently adjusted depending on results of microbiological tests.
27
28

29 Change to oral treatment can be done when all of the following three criteria are met:

- 30
31
- 32 • Clinical improvement of the patient (e.g. no fever/fever, improved general condition)
 - 33 • Paraclinical satisfactory response (with respect to decreases in leukocytes and CRP's)
 - 34 • Drain/pigtail is removed
- 35
36
37

38 This means that 14 days intravenous treatment will not be given as standard. The duration of
39
40 intravenous antibiotic treatment will therefore be individualised based on the application of the above
41
42 criteria. The overall duration of treatment of antibiotic is 6 weeks as standard.
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46 47 48 *Other treatments and supportive care*

49 All patients are:

- 50
51
- 52 - Offered specialised lung physiotherapy
 - 53 - Screened for and given additional nutritional support
 - 54 - Treated with painkillers in accordance with departmental guidelines
 - 55 - Given thrombosis prophylactic treatment in accordance with national guidelines
- 56
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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

1
2 Prior to informed consent obtained as part of screening for study participation:
3

- 4 • Data needed to determine whether inclusion criteria are met (see above)
- 5
- 6 • Data needed to determine whether any exclusion criteria are present (see above)
- 7

8
9 Baseline patient data: age, gender, comorbidities, medication, performance status, previously
10 recorded lung function etc.

11
12
13 Surgical and TUS data: used time, specific type of procedure, operator, drain size, complications etc.

14
15
16 Drain data: Length of drain treatment, daily output / input, removal criteria, no. of drains used etc.

17
18 Costs during hospitalisation:
19

20 Calculated for the two groups regarding the following expenses:
21

- 22 • VATS Group:
 - 23 ○ Utensils used during surgery
 - 24
 - 25 ○ Time of the procedure
 - 26
 - 27 ○ Consumption of staff resources
 - 28
 - 29 ○ Hospitalisation time
 - 30
 - 31 ○ Medicine
 - 32
- 33 • Drain group:
 - 34 ○ Equipment used during the procedure
 - 35
 - 36 ○ Procedure Time
 - 37
 - 38 ○ Consumption of human/staff resources
 - 39
 - 40 ○ Fibrinolyticum and DNase (amount used)
 - 41
 - 42 ○ Hospitalisation time
 - 43
 - 44 ○ Medicine
 - 45
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55 Costs within the 1st year after discharge:
56

57 Calculated for the two groups regarding the following expenses:
58

- 59 • Re-admission
- 60

- 1
- 2 • Ambulatory services
- 3
- 4 • Medication
- 5
- 6
- 7 • Number of sick days
- 8
- 9 • Visit to a General Practitioner (GP)
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- 11
- 12
- 13

14 Patient satisfaction and functional level:

- 15
- 16 • Data in the form of EQ5D and Sct. George Respiratory Questionnaire is collected at the
- 17 following times:
- 18
 - 19 ○ Upon inclusion in the study
 - 20
 - 21 ○ At discharge
 - 22
 - 23
 - 24
 - 25 ○ Outpatient data: 1, 3, 6 and 12 months.
 - 26
 - 27
 - 28
 - 29

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

- 31
- 32 • Hospitalisation time, total and after commencement of intervention
- 33
- 34 • Primary intervention considered as final treatment
- 35
- 36
- 37 • In hospital and 30-day mortality
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- 39 • Drainage time
- 40
- 41 • Radiological regression a.m. MIST II
- 42
- 43 • Number and types of drains
- 44
- 45
- 46 • Need for additional surgery during and within 12 months after hospitalisation
- 47
- 48 • Need for additional intrapleural therapy during and within 12 months after hospitalisation
- 49
- 50 • Need for intensive care therapy
- 51
- 52
- 53 • Consumption of painkillers during hospitalisation and within 12 months after hospitalisation
- 54
- 55 which is registered electronically both during hospitalization in the electronic patient record
- 56
- 57 and after discharge using the National Patient Register.
- 58
- 59 • Lung function tests and walking tests
- 60

- 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.

1
2 In terms of showing clinically relevant non-inferiority with a difference in hospitalisation of 1 day
3
4 with an 80% power, and CV of 40%, 70 patients is needed in each group. This is based on a true
5
6 improvement of 1 hospitalisation day. Based on the annual number of patients diagnosed with pleura
7
8 empyema in Denmark, we find it feasible to include the needed number of patients in the trial during
9
10 the inclusion period.
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13
14

15 **Data analysis**

16
17 Data extractions are made from RedCap database, and data analysis is performed using STATA
18
19 version 17 (StataCorp LLC, Texas, USA). Endpoints will be described for the individual group by
20
21 median and percentile, assuming data is not normally distributed.
22
23

24 Differences between the groups in the primary endpoint are determined by t-test at the log-entry time
25
26 and reported as median ratios with associated confidence intervals. Patients dying during the
27
28 admission is omitted from the analysis if the primary endpoint. Whether death before discharge
29
30 affects the primary endpoint is assessed using survival analysis as sensitivity analysis. We expect that
31
32 the distribution between stages II and III will be 75% and 25%, respectively, and whether there is a
33
34 difference between stages II and III will be assessed as secondary analysis. When repeating
35
36 measurements (e.g. quality of life), repeated measurements ANOVA are used with treatment and time
37
38 as systematic effects and patient as random effect. All data are analysed primarily according to the
39
40 intention to treat principle, but there will also be one per protocol analysis regarding the above-
41
42 mentioned endpoints. Comparison will take place between the two groups (drainage and VATS).
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50 **Data collection Media**

- 51
52 • REDCap (Research Electronic Data Capture), REDCap Consortium, Vanderbilt University
53
54 Medical Center, Tennessee, USA
- 55
56 • Electronic patient record (EPJ in Region Midt, EPJ in Region North, EPJ (COSMIC) in
57
58 Region South and EPJ (EPIC Health Platform) in the Capital Region and Region Zealand).
59
60

- 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

1
2 side effect that results in death, is life threatening, causes hospitalisation or prolonged hospitalisation,
3
4 resulting in significant or permanent invalidity or incapacity.
5

6 All SAEs must be followed until the problem is resolved or until it is decided that participation in the
7
8 trial was not the cause.
9

10 SUSAR (Suspected Unexpected Serious Adverse Events Reporting), which is mortal or life
11
12 threatening, is entered in the registration form (Report of SAE / SUSAR) and will be reported to the
13
14 Scientific Ethics Committees for Central Denmark Region and / or Region of Southern Denmark
15
16 within 7 days.
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22 **Patient and Public Involvement**

23
24 The patients were not directly involved in the development of the research question and study
25
26 design, but indirectly fueled the idea to this study because many patients over the years who were
27
28 diagnosed with pleural empyema repeatedly informed that they were frustrated with long-lasting
29
30 treatments and hospital stays. As a result, we have designed the study aiming to improve and speed
31
32 up their treatment and reduce their length of hospital stay.
33
34

35 We are also in the process of designing “spin-off” studies with a qualitative focus, which will help
36
37 to design future studies including patient reported outcome measurements, which has also been
38
39 deemed relevant by patients themselves.
40
41

42 Potential patients/the public will be informed of the trial using social medias and news columns. All
43
44 patients included in the trial will be informed of the results of the study. The burden of the
45
46 intervention is assessed by the patients using health quality assessment schemes. Patient advisors
47
48 are, if relevant, thanked in the acknowledge section.
49
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52 **ETHICS AND DISSEMINATION**

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54 All patients provide informed consent before randomisation. The research project is carried out in
55
56 accordance with the Helsinki II Declaration, European regulations and Good Clinical Practice
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1
2 Guidelines. The Scientific Ethics Committees for Denmark and the Danish Data Protection Agency
3
4 have provided permission. Information about the subjects is protected under the Personal Data
5
6 Processing Act and the Health Act. The trial is registered at www.clinicaltrials.gov, and monitored
7
8 by the regional Good Clinical Practice monitoring unit. The results of this study will be published in
9
10 peer-reviewed journals and presented at various national and international conferences.
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12
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14 15 **DISCUSSION**

16
17
18 Pleural empyema is a frequent disease with a high morbidity and mortality. Community acquired
19
20 bacterial infection in the pleural cavity has been divided into three clinical stages (I - III).³ The
21
22 treatment of stage I is drainage, however the optimal treatment of stage II and III has not been
23
24 established and the treatment is primarily based on local preferences and not evidence-based.
25
26

27 In our study we want to find the optimal method for treating patients with pleural empyema stage II
28
29 and III – either a VATS procedure or TUS guided drainage and intrapleural therapy (fibrinolytic
30
31 (Alteplase) with DNase (Pulmozyme®)).
32
33

34 The theoretical advantage of surgery as first line treatment is that patients undergo rapid, definitive
35
36 treatment and insurance of optimal drain placement. Early and definite surgery can potentially reduce
37
38 mortality, LOS, and cause fewer late complications.⁹
39
40

41 If this trial is positive for the primary and/or the secondary outcomes, it will change and strengthen
42
43 the treatment of patients with community acquired bacterial pleural infection, both nationally and
44
45 internationally. We investigate both clinical parameters, patient satisfaction and economical aspects
46
47 (cost-effectiveness) in relation to pleura empyema treatment, so it will cover many aspects of this
48
49 disease. We have established a nationwide study with participation of all relevant departments and
50
51 all relevant specialties (e.g. pulmonology and thoracic surgery), and the trial will therefore have a
52
53 high internal and external validity. This is a significant plus in terms of methodological quality, and
54
55 the results of the study will widely be applicable and can easily be implemented in the daily clinical
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57 practice.
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1 We have decided to have LOS as the primary endpoint, since it is an objective measurement depicting
2 the clinical status of the patient, and LOS is a clinically relevant endpoint used in multiple trials
3 assessing treatment of complicated parapneumonic effusions and pleural empyema.^{2 6 13}

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6
7
8 This study has some limitations. Firstly, the primary endpoint should preferably have been 1-year
9 mortality and secondary endpoint severe morbidity. However, this would have required inclusion of
10 a large number of patients, which would have required a very long inclusion time due to the relatively
11 small number of inhabitants in Denmark and hence the small number of patients with pleural
12 empyema. This could have been solved by including patients from other countries making the study
13 internationally – however, this was beyond the resources provided for this project.

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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 (pigtailed).

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

1
2 hopefully benefit the initial management and treatment of this patient population making the
3
4 treatment based on evidence instead of local preferences.
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25 **Contributors** TDC, MBB and CBL wrote the first draft of the protocol manuscript.

26
27 TDC, MBB, CBL, RHP, PBL, BMB planned the conceptualisation and the design of the study and
28
29 the protocol.
30

31 TDC, MBB, CBL, RHP, PBL, BMB, JUSJ, MC, KN, LBM, UB, MHB, ZS, SL, SMWH, EOB, BN
32
33 and NMR contributed to development of the protocol and the critical revisions of the protocol and
34
35 the current manuscript.
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38 TDC, MBB, CBL, RHP, PBL, BMB, JUSJ, MC, KN, LBM, UB, MHB, ZS, SL, SMWH, EOB, BN
39
40 and NMR have made substantial contributions to the conception and design of the work; drafting
41
42 the work and revising it critically for important intellectual content; made final approval of the
43
44 version to be published; made agreement to be accountable for his/her contributions of the work in
45
46 ensuring that questions related to the accuracy or integrity of the work are appropriately
47
48 investigated and resolved.
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60

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8 **Competing interests**

9
10 Thomas Decker Christensen has been on the speaker bureaus for AstraZeneca, Boehringer-
11
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13
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16

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21

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39
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16 17 **REFERENCES**

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30 **Figure legends**

31 **Figure 1** Trial schema. VATS, video assisted thoracoscopic surgery; TUS, thoracic ultrasound
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36 **Figure 2** The trials time line. VATS, video assisted thoracoscopic surgery; TUS, thoracic
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38 ultrasound
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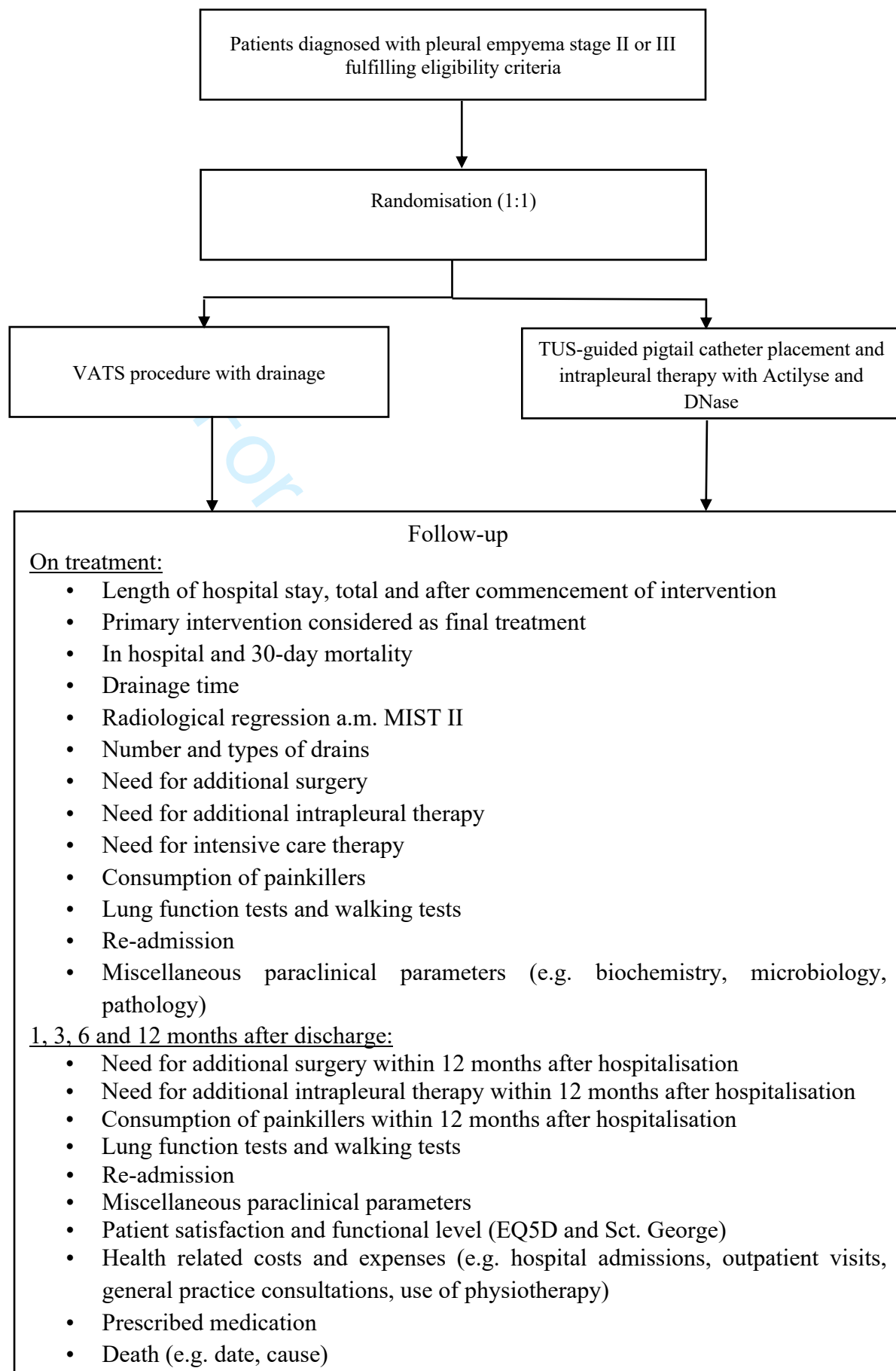


Figure 1 Trial schema. VATS, video assisted thoracoscopic surgery; TUS, thoracic ultrasound

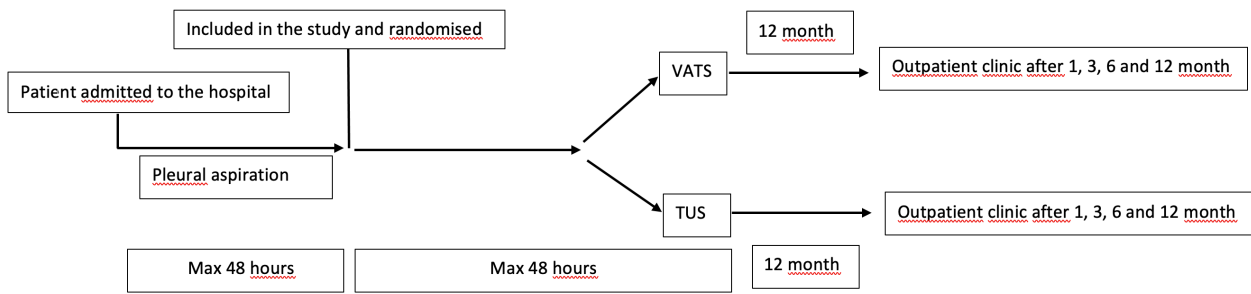


Figure 2 The trials time line. VATS, video assisted thoracoscopic surgery; TUS, thoracic ultrasound

For peer review only



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

1			
2	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)
3			
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6			
7			
8	Methods: Participants, interventions, and outcomes		
9			
10	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
11			
12			
13			
14	Eligibility	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)
15	criteria		
16			
17			
18			
19	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered
20			
21			
22		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)
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26		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)
27			
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31		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial
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34	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
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42	Participant	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)
43	timeline		
44			
45			
46			
47	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
48			
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51	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size
52			
53			

54 **Methods: Assignment of interventions (for controlled trials)**

56 Allocation:

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2	Sequence	16a	Method of generating the allocation sequence (eg, computer-generated	8-9
3	generation		random numbers), and list of any factors for stratification. To reduce	
4			predictability of a random sequence, details of any planned restriction	
5			(eg, blocking) should be provided in a separate document that is	
6			unavailable to those who enrol participants or assign interventions	
7				
8				
9	Allocation	16b	Mechanism of implementing the allocation sequence (eg, central	8-9
10	concealme		telephone; sequentially numbered, opaque, sealed envelopes),	
11	nt		describing any steps to conceal the sequence until interventions are	
12	mechanis		assigned	
13	m			
14				
15	Implement	16c	Who will generate the allocation sequence, who will enrol participants,	8-9
16	ation		and who will assign participants to interventions	
17				
18				
19	Blinding	17a	Who will be blinded after assignment to interventions (eg, trial	9
20	(masking)		participants, care providers, outcome assessors, data analysts), and	
21			how	
22				
23		17b	If blinded, circumstances under which unblinding is permissible, and	NA
24			procedure for revealing a participant's allocated intervention during the	
25			trial	
26				
27				
28	Methods: Data collection, management, and analysis			
29				
30	Data	18a	Plans for assessment and collection of outcome, baseline, and other	12-15
31	collection		trial data, including any related processes to promote data quality (eg,	
32	methods		duplicate measurements, training of assessors) and a description of	
33			study instruments (eg, questionnaires, laboratory tests) along with their	
34			reliability and validity, if known. Reference to where data collection	
35			forms can be found, if not in the protocol	
36				
37				
38		18b	Plans to promote participant retention and complete follow-up, including	12-15
39			list of any outcome data to be collected for participants who discontinue	
40			or deviate from intervention protocols	
41				
42	Data	19	Plans for data entry, coding, security, and storage, including any	16-17
43	management		related processes to promote data quality (eg, double data entry; range	
44			checks for data values). Reference to where details of data	
45			management procedures can be found, if not in the protocol	
46				
47				
48	Statistical	20a	Statistical methods for analysing primary and secondary outcomes.	16
49	methods		Reference to where other details of the statistical analysis plan can be	
50			found, if not in the protocol	
51				
52		20b	Methods for any additional analyses (eg, subgroup and adjusted	16
53			analyses)	
54				
55		20c	Definition of analysis population relating to protocol non-adherence (eg,	16
56			as randomised analysis), and any statistical methods to handle missing	
57			data (eg, multiple imputation)	
58				
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2 **Methods: Monitoring**

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4 Data 21a Composition of data monitoring committee (DMC); summary of its role 17-18
 5 monitoring and reporting structure; statement of whether it is independent from the
 6 sponsor and competing interests; and reference to where further details
 7 about its charter can be found, if not in the protocol. Alternatively, an
 8 explanation of why a DMC is not needed

10

11 21b Description of any interim analyses and stopping guidelines, including 17-18
 12 who will have access to these interim results and make the final
 13 decision to terminate the trial

14

15 Harms 22 Plans for collecting, assessing, reporting, and managing solicited and 17-18
 16 spontaneously reported adverse events and other unintended effects of
 17 trial interventions or trial conduct

19

20 Auditing 23 Frequency and procedures for auditing trial conduct, if any, and 17-18
 21 whether the process will be independent from investigators and the
 22 sponsor

23

24 **Ethics and dissemination**

25

26 Research 24 Plans for seeking research ethics committee/institutional review board 18-19+25
 27 ethics (REC/IRB) approval

29 approval

30 Protocol 25 Plans for communicating important protocol modifications (eg, changes 18-19
 31 amendments to eligibility criteria, outcomes, analyses) to relevant parties (eg,
 32 investigators, REC/IRBs, trial participants, trial registries, journals,
 33 regulators)

36

37 Consent or 26a Who will obtain informed consent or assent from potential trial 9+Figure 2
 38 assent participants or authorised surrogates, and how (see Item 32)

39

40 26b Additional consent provisions for collection and use of participant data NA
 41 and biological specimens in ancillary studies, if applicable

42

43 Confidentialit 27 How personal information about potential and enrolled participants will 16-17
 44 y be collected, shared, and maintained in order to protect confidentiality
 45 before, during, and after the trial

46

47 Declaration 28 Financial and other competing interests for principal investigators for 25
 48 of interests the overall trial and each study site

50

51 Access to 29 Statement of who will have access to the final trial dataset, and 16-17
 52 data disclosure of contractual agreements that limit such access for
 53 investigators

54

55 Ancillary and 30 Provisions, if any, for ancillary and post-trial care, and for compensation NA
 56 post-trial care to those who suffer harm from trial participation

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1			
2	Disseminatio	31a	Plans for investigators and sponsor to communicate trial results to
3	n policy		participants, healthcare professionals, the public, and other relevant
4			groups (eg, via publication, reporting in results databases, or other data
5			sharing arrangements), including any publication restrictions
6			
7		31b	Authorship eligibility guidelines and any intended use of professional
8			writers
9			
10			NA (we do
11			not use
12			professional
13		31c	Plans, if any, for granting public access to the full protocol, participant-
14			level dataset, and statistical code
15			
16			18
17	Appendices		
18			
19	Informed	32	Model consent form and other related documentation given to
20	consent		participants and authorised surrogates
21	materials		
22			Attached as
23	Biological	33	Plans for collection, laboratory evaluation, and storage of biological
24	specimens		specimens for genetic or molecular analysis in the current trial and for
25			future use in ancillary studies, if applicable
26			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](https://creativecommons.org/licenses/by-nc-nd/3.0/)" license.