

Strategy for Prompt and Effective Thoracentesis in the Emergency Department:

A Multicenter Randomized Clinical Trial

ACRONYM: SPEEDTAP

*Investigators*

Sandra Thun Langsted, MD, PhD-candidate

and

Associate professor Kasper Glerup Lauridsen, MD, PhD, FERC, FAHA

Associate professor Jesper Bo Weile, MD, PhD

Søren Helbo Skaarup, MD, PhD

Bo Løfgren, MD, PhD, FESC, FAHA, Consultant, Head of Department

ClinicalTrials.gov number: NCT06180603

Committee on health Research Ethics – Central Denmark Region:

1-10-72-111-23.

## Indholdsfortegnelse

|  |           |
|--|-----------|
| <b>List of abbreviations</b> .....   | <b>4</b>  |
| <b>Overview</b> .....  | <b>5</b>  |
| <b>Trial overview</b> .....  | <b>7</b>  |
| <b>Trial sites</b> .....   | <b>8</b>  |
| <b>Revision chronology</b> .....   | <b>9</b>  |
| <b>1. Introduction</b> .....   | <b>10</b> |
| <b>2. Hypothesis</b> .....   | <b>11</b> |
| <b>3. Trial design</b> .....   | <b>11</b> |
| 3.1 Study setting .....  | 11        |
| 3.2 Randomization and allocation.....  | 11        |
| 3.3 Interventions.....   | 12        |
| 3.3.1 Manual fluid removal by the emergency physician (Intervention).....      | 12        |
| 3.3.2 Standard of care - thoracentesis by a radiologist (Control) .....        | 12        |
| 3.3.3 Assessments of chest discomfort and breathlessness .....                 | 12        |
| 3.3.4 Patients' experience questionnaire .....                                 | 13        |
| 3.3.5 Criteria for modification of interventions for a given participants..... | 13        |
| 3.4 Blinding.....  | 14        |
| 3.5 Clinical personnel.....  | 14        |
| <b>4. Setting and patient population</b> .....                                 | <b>14</b> |
| 4.1 Inclusion criteria .....   | 14        |
| 4.2 Exclusion criteria.....  | 14        |
| <b>5. Outcomes</b> .....   | <b>15</b> |
| 5.1 Primary outcome: .....   | 15        |
| 5.2 Secondary outcomes.....  | 15        |
| 5.2.1 Efficacy endpoint .....  | 15        |
| 5.2.2 Safety endpoints .....   | 16        |
| <b>6. Sample size calculation and statistical analyses plan</b> .....          | <b>16</b> |
| 6.1 Sample size calculation.....   | 16        |
| 6.2 Statistical analysis plan .....  | 17        |
| 6.3 Missing data .....   | 18        |
| 6.4 Subgroup analysis.....   | 18        |

|  |           |
|--|-----------|
| <b>7. Data collection and management .....</b>         | <b>18</b> |
| 7.1 Data collection process.....                       | 18        |
| 7.2 Overview of variables .....                        | 19        |
| <b>8. Participant timeline .....</b>                   | <b>23</b> |
| 8.1 Screening and enrollment.....                      | 23        |
| 8.2 Screening log .....                                | 23        |
| 8.3 SPIRIT flow diagram.....                           | 24        |
| <b>9.ETHICAL.....</b>                                  | <b>25</b> |
| 9.1 Potential benefits.....                            | 25        |
| 9.2 Consent.....                                       | 25        |
| 9.3 Ethical review committee .....                     | 26        |
| 9.4 Risk, side effects and other disadvantages .....   | 26        |
| 9.5 Insurance .....                                    | 27        |
| <b>10.Financial statement .....</b>                    | <b>27</b> |
| 10.1 Funding.....                                      | 27        |
| <b>11. Publication and feasibility .....</b>           | <b>27</b> |
| 11.1 Investigator and publication.....                 | 27        |
| 10.2 Feasibility.....                                  | 27        |
| <b>References .....</b>                                | <b>29</b> |
| <b>Appendix 1: Draft of CONSORT flow diagram .....</b> | <b>30</b> |

## **List of abbreviations**

CRF = Case report form

CONSORT = Consolidated standards of reporting trials

CPR-number = Civil registration number

CT= Computed tomography

CXR = Chest x-ray

ED = Emergency Department

TBD = To be disclosed

GCS = Glasgow Coma Scale

RR = Respiratory Rate

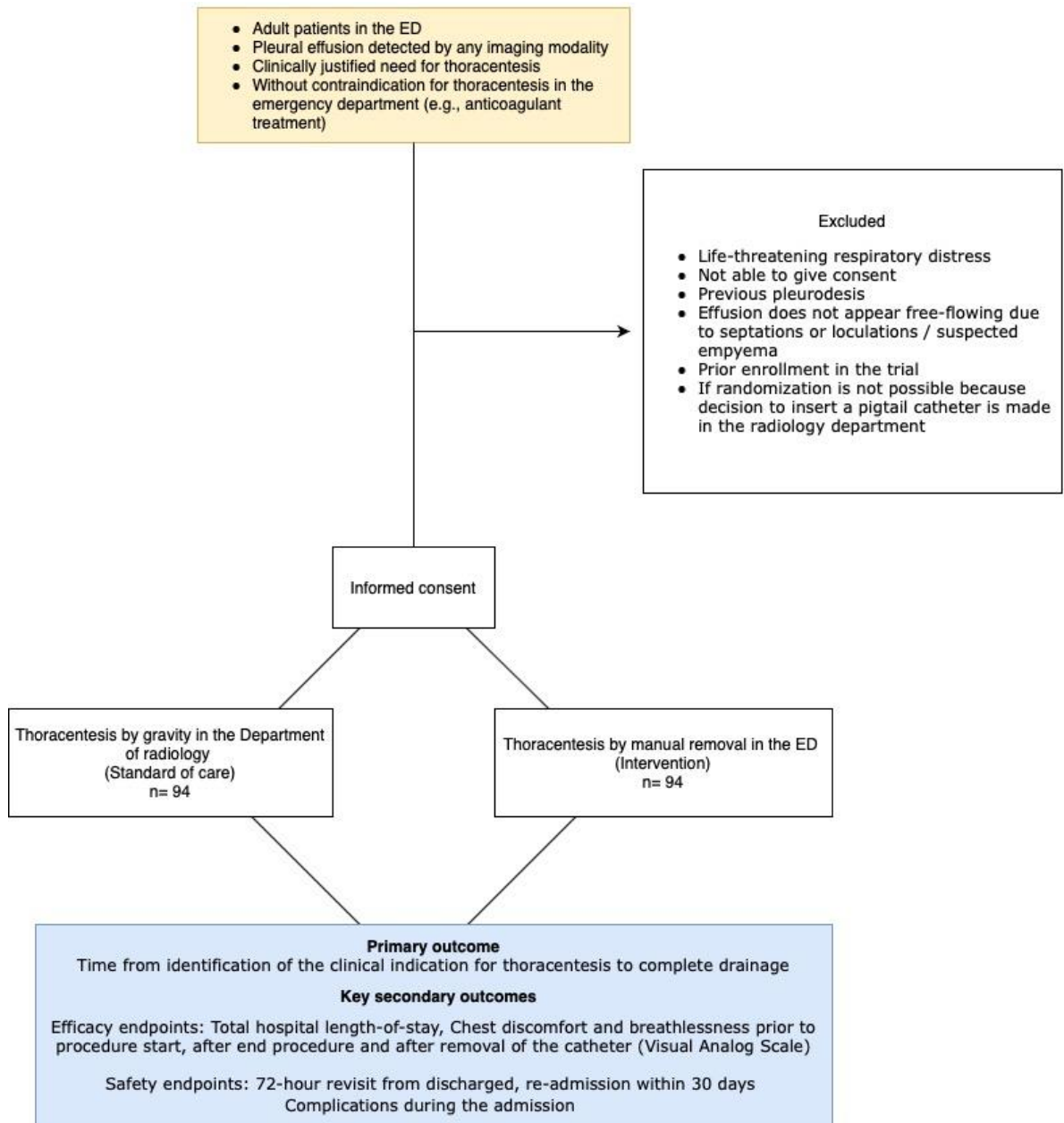
## Overview

|                           |  |
|---------------------------|--|
| Registry and trial number | Clinicaltrials.gov (TBD)   |
| Date of registration      | TBD  |
| Funding                   | “Puljen til styrkelse af sundhedsforskning i Region Midtjylland” and Eva Merete Falck Crones Fond  |
| Primary investigator      | Sandra Thun Langsted   |
| Contact                   | Sandra Thun Langsted, sandln@rm.dk   |
| Title                     | Strategy for Prompt and Effective Thoracentesis in the Emergency Department: A Multicenter Randomized Clinical Trial   |
| Country of recruitment    | Denmark  |
| Condition studied         | Patients with pleura effusion requiring thoracentesis  |
| Intervention              | Manual fluid removal using a syringe   |
| Comparator                | Passive fluid removal using gravity  |
| Inclusion criteria        | <ol style="list-style-type: none"><li>1) Patients <math>\geq</math> 18 years admitted to the ED</li><li>2) Pleural effusion detected by any imaging modality</li><li>3) Clinically justified need for thoracentesis</li><li>4) Without contraindication for thoracentesis in the emergency department (e.g., anticoagulant treatment)</li></ol>  |
| Exclusion criteria        | <ol style="list-style-type: none"><li>1) Life-threatening respiratory distress</li><li>2) Not able to give consent</li><li>3) Previous pleurodesis</li><li>4) Effusion does not appear free-flowing due to septations or loculations / suspected empyema</li><li>5) Prior enrollment in the trial</li><li>6) If randomization is not possible because decision to insert a pigtail</li></ol> |

catheter is made in the radiology department

|                         |   |
|-------------------------|---|
| Study type              | Interventional<br>Randomized (1:1)<br>Intervention model: Parallel group<br>Masking: Open-labelled  |
| Date of first screening | 1. November 2023  |
| Target sample size      | 188   |
| Recruitment status      | Not started   |
| Primary outcome         | Time from randomization to removal of catheter  |
| Key secondary outcomes  | Efficacy endpoints <ul style="list-style-type: none"><li>• Total hospital length-of-stay</li><li>• Chest discomfort and breathlessness prior to procedure start, after end procedure and after removal of the catheter</li></ul> Safety endpoints <ul style="list-style-type: none"><li>• 72-hour revisit from discharged. Defined as any unplanned hospital stay within 72 hours from previous hospital discharge</li><li>• Re-admission within 30 days</li><li>• Complications during the admission</li></ul> |

## Trial overview



## **Trial sites**

### **Aarhus University Hospital**

Akutafdelingen, Aarhus Universitetshospital  
Palle Juul-Jensens Boulevard 99  
8200 Aarhus N

### **Horsens Regional Hospital**

Akutafdelingen, Regionshospitalet Horsens  
Sundvej 30  
8700 Horsens

### **Randers Regional Hospital**

Akutafdelingen, Regionshospitalet Randers  
Skovlyvej 9, 8930 Randers NØ

### **Gødstrup Regional Hospital**

Akutafdelingen, Regionshospitalet Gødstrup  
Hospitalsparken 15,  
7400 Herning

### **Viborg Regional Hospital**

Akutafdelingen, Regionshospitalet Viborg  
Heibergs Alle 5B  
8800 Viborg

## Revision chronology

Version 2.1: 04.01.2024

Added clinical.gov number and Committee on health Research Ethics number

## 1. Introduction

Shortness of breath due to pleural effusion is a common reason for admission to the Emergency Department (ED)<sup>1,2</sup>. Patients admitted to the ED with pleural effusion requiring thoracentesis are most often referred to the Department of Radiology. However, performing thoracentesis in the ED enables a number of possible advantages such as reducing treatment delay and thereby reducing time to symptom relief and alleviating the burden on the radiology department's workload. Additionally, today, following insertion of a pigtail catheter most often fluid is drained passively into a collecting bag by gravity. An alternative option is active removal of fluid using a syringe connected to a three-way stopcock. Previous studies have reported that manual drainage is both safe and reduce time to complete fluid drainage to less than 30 minutes<sup>3-5</sup>. Both methods are used as standard of care in the clinical setting. However, no one has ever tested the effectiveness of the two treatment methods against each other in an ED setting. Hence, the decision on treatment method is influenced primarily by clinician's personal preference, with little regard to solid evidence.

Only one study has investigated manual versus passive drainage<sup>4</sup>. The outcome in this study was in relation to patient reported pain 5 minutes post thoracentesis. Patients were predominately from an outpatient setting or on a regular ward. The study found no significant difference in pain but reported that manual drainage took significantly shorter time<sup>4</sup>. However, the investigation of combining manual fluid removal in an ED setting for optimizing patient care remains unexplored in terms of complete drainage time, length of stay and patient satisfaction.

The aim of this study is to investigate how ultrasound-guided bedside thoracentesis with manual fluid removal in the ED performed by emergency physicians compared to the present standard thoracentesis performed by radiologists affects time to complete pleural effusion drainage.

## **2.Hypothesis**

We hypothesize that thoracentesis with manual drainage performed in the ED compared to current standard treatment results in reduced time to complete drainage.

## **3.Trial design**

### *3.1 Study setting*

This is a prospective, randomized, investigator-initiated, multicenter clinical superior study

investigating two different thoracentesis methods for patients requiring thoracentesis the ED.

Enrollment will take place in the five EDs in the Central Denmark Region: Randers Regional

Hospital, Horsens Regional Hospital, Gødstrup Regional Hospital, Viborg Regional Hospital, and

Aarhus University Hospital.

### *3.2 Randomization and allocation*

Patients fulfilling all inclusion criteria and no exclusion criteria will be randomized in a 1:1 ratio to

either manual fluid removal by an emergency physician or insertion of pigtail catheter in the

radiology department using blocks with random sizes of 4, 6 or 8 stratified according to site to

balance the group allocation across study sites. Randomization will be performed via the web-

based system provided in REDCap by Aarhus University ensuring allocation concealment.<sup>6,7</sup>

Unique randomization numbers (Study ID) for each patient will be generated according to each

site. The randomized sequence of Study ID will be generated using online randomization software.

Inclusion in the study can occur around the clock.

Enrollment and randomization will be performed by the treating physician directly into the

REDCap site. The treating physician will register data in REDCap including patient identifier (i.e.,

Danish Central Personal Register number), site and inclusion/exclusion criteria and register trial

specific data in the electronic medical record to notify the enrollment of the patient in the trial.

This includes timing of enrollment and allocation.

### *3.3 Interventions*

#### *3.3.1 Manual fluid removal by the emergency physician (Intervention)*

In the intervention group, thoracentesis will be performed bedside using ultrasound in the ED by a physician with competences to independently perform thoracentesis or by a physician in training supervised by a physician with competences and experience in thoracentesis. The procedure will be performed according to current guidelines.<sup>8</sup> Fluid is manually drained using a syringe connected to a three-way stopcock which is connected to a collecting bag without the use of manometry<sup>5</sup>.

The fluid will be manually drained into the collecting bag. Specimens will routinely be sent for analysis.

The intent of all thoracentesis is complete drainage of the pleural space. When performing manual fluid removal, the drainage will only be terminated early if requested by the patient due to e.g., intolerable pain or refractory cough. Manual drainage will be stopped if > 1.5 L fluid is drained and the drain will be left in-situ for later manual evacuation of remaining fluid upon discretion of the treating physician. By the end of the procedure, the catheter is removed and an airtight bandage will be placed. Chest x-ray will not routinely be performed post procedure.

#### *3.3.2 Standard of care - thoracentesis by a radiologist (Control)*

In the control group, patients needing thoracentesis will be referred to the radiology department.

Thoracentesis will be performed according to local guidelines<sup>8</sup>. Specimens will be sent for analysis. Chest x-ray will not be routinely performed post-procedure.

#### *3.3.3 Assessments of chest discomfort and breathlessness Visual Analog Scale*

The effect of the thoracentesis on chest discomfort and breathlessness in both groups will be accessed. Patient will be asked to rate their current degree of chest discomfort and breathlessness on a scale prior to procedure start, during the procedure and after removal of the catheter.

*3.3.4 Patients' experience questionnaire*

Patients in both groups will upon removal of the catheter be handed a questionnaire about their experienced with the procedure.

*3.3.5 Criteria for modification of interventions for a given participants*

The clinical team may at any time deviate from the protocol if they find it to be in the interest of the patient. The clinician caring for the patient will 24-hour have the telephone number of a member of the research group regarding any protocol related issues. The reason for the protocol deviation should be documented in the electronic patient journal.

Protocol violations are defined as follows:

| Intervention group   | Major protocol deviation   | Documentation                     |
|----------------------|--|-----------------------------------|
| Manual fluid removal | <ul style="list-style-type: none"> <li>• If patient is referred to the radiology department</li> <li>• If the catheter is inserted but not manually drained</li> </ul> | Reason for the protocol violation |
| Standard of care     | <ul style="list-style-type: none"> <li>• If the catheter is inserted in the ED with or without manual drainage</li> </ul>  | Reason of the protocol violation  |

### 3.4 Blinding

Due to the nature of the intervention, the clinician will not be blinded to the intervention. Patients will be informed about the study aims to investigate the efficacy of two thoracentesis method but due to the nature of the intervention they will not be blinded to the comparator or outcomes.

### 3.5 Clinical personnel

The clinical personnel in the involved radiology departments and EDs will be informed about the background and objectives of the study, the inclusion and exclusion criteria, the interventions, and the procedures. Information about the project will be sent to their e-mails and the project will be presented on staff-meetings.

## 4. Setting and patient population

The physician and nurses working in the ED will screen the patients for the inclusion criteria listed in table 1.

**Table 1: In- and exclusion criteria**

| <i>4.1 Inclusion criteria</i>   | <i>4.2 Exclusion criteria</i>  |
|---|--|
| <ul style="list-style-type: none"><li>• Patients <math>\geq</math> 18 years admitted to the ED</li><li>• Pleural effusion detected by any imaging modality (e.g., bedside ultrasound, chest x-ray, computed tomography)</li><li>• Clinically justified need for thoracentesis<ul style="list-style-type: none"><li>○ Symptomatic relief</li><li>○ Define the etiology of the effusion</li></ul></li></ul> | <ul style="list-style-type: none"><li>•</li><li>• Life-threatening respiratory distress</li><li>• Not able to give consent</li><li>• Previous pleurodesis</li><li>• Effusion does not appear free-flowing due to septations or loculations / suspected empyema</li><li>• Prior enrollment in the trial</li></ul> |

|  |  |
|--|--|
| <ul style="list-style-type: none"> <li>• Without contraindication for thoracentesis in the emergency department (e.g., anticoagulant treatment)</li> </ul> | <ul style="list-style-type: none"> <li>• If randomization is not possible because decision to insert a pigtail catheter is made in the radiology department</li> </ul> |
|--|--|

## 5. Outcomes

### 5.1 Primary outcome:

Time from identification of the clinical indication for thoracentesis defined by time patient is randomized to complete drainage defined by removal of pigtail catheter.

### 5.2 Secondary outcomes

*Secondary outcomes will be divided into efficacy endpoints and safety endpoints:*

#### 5.2.1 Efficacy endpoint

- Time from indication(randomization) to procedure start (defined as the use of ultrasound to determine the insertion site – the time will be noted on the paper-CRF)
- Duration of procedure defined as catheter in- catheter out
- Time from admission to the ED
  - To indication
  - To procedure start
  - Removal of catheter
- Total volume drained
- Time from admission to discharge from the ED
- Total hospital length-of-stay

- Patient will be asked to rate their current degree of chest discomfort and breathlessness prior to procedure start, after end procedure and after removal of the catheter:
  - Breathlessness
  - Chest discomfort
- Patient satisfaction with the procedure by completing a questionnaire following removal of the catheter
- Number of cases where the operator decided not to perform thoracentesis despite the presence of pleural effusion

#### 5.2.2 Safety endpoints

- 72-hour revisit from discharged. Defined as any unplanned hospital stay within 72 hours from previous hospital discharge
- Re-admission within 30 days
- Complications during the admission
  - Pneumothoraxes requiring intervention
  - Bleeding (e.g hemothorax, bleeding that require surgical intervention or transfusion, hematoma, minor diffuse bleeding)
  - Re-expansion pulmonary edema
  - Infection

## 6. Sample size calculation and statistical analyses plan

### 6.1 Sample size calculation

Previous published data have found a mean drainage time of 10.5 min, 14.9 min and 16.4 min<sup>4,5</sup>

for manual fluid removal, however, these studies are based on patients from the outpatient clinic

or internal medicine ward referred to the interventional radiology department and do not reflect the reality of an busy ED. We assume an estimate for the mean manual fluid drainage time of 6 hours. Based on unpublished data from the **business intelligence data warehouse** from 161 thoracentesis performed in Randers Regional Hospital at either the ED or referred from the ED to the radiology department found a median drainage time of 24.5 hours. The mean was influenced by a small number of patients with a long drainage time. We therefor believe that 24.5 h are more likely to represent a true mean in the clinical setting. We therefor assume a mean of 24.5 h (SD 42.8) in our control group. Using a two-sample student t-test, type I error rate of 5% and a power of 80%, we calculated that a total sample size of 170 patients would be required to detect a 75% reduction in hours from the control group to in the intervention group in patient with pleural effusion requiring thoracentesis. To account for a dropout of approximately 10% the total sample size is increased to a total of 188 patients which will require 94 patients in each group.

The study is not powered for safety but complications will be followed and registered. If one study site does not include patients for various reasons patient inclusion will continue in other study sites until the number of anticipated patients is reached.

## ***6.2 Statistical analysis plan***

The statistical reporting will adhere to the CONSORT guidelines. All test will be two-sided, a p-value of 0.05 will be considered statistically significant and confidence intervals will be 95%.

Patient inclusion and exclusion will be outlined in a CONSORT flow chart (appendix 1).

Both a per-protocol and intention-to-treat analysis will be conducted. For the primary analysis an intention-to-treat analysis will be performed. The population will be defined as all randomized participants for whom consent was obtained. The two groups will be compared in relation to

baseline characteristics using descriptive data. Dichotomous data will be reported as numbers (percent) and continuous data will be reported as median (quartile 1; quartile 3). The two groups will be compared using generalized linear mixed effect models<sup>9</sup>. In general, if data is severely non-normally distributed, appropriate statistical testing will be performed.

### ***6.3 Missing data***

Missing data will be reported. We expect few missing data for the primary outcome. Missing data will be handled by excluding patients with missing values for the primary analysis. Multiple imputation will not be conducted.

### ***6.4 Subgroup analysis***

This study is not powered to detect subgroup differences and these will be considered exploratory and hypothesis generating. Subgroup analysis will include 1) Difference in time to complete drainage depending on ED arrival (day/evening or night) 2) Difference in time to complete drainage depending on ED arrival (week day or weekends) 3) Difference in chest discomfort and breathlessness among different etiologies (heart failure, cancer, infection) and thoracentesis method.

## **7. Data collection and management**

### ***7.1 Data collection process***

A paper case report form (paper-CRF) will be placed at the patient's bedside collecting data on the procedure (e.g indication, site, time of procedure start, time of the insertion of the catheter), and patient symptoms (chest discomfort and breathlessness). The treating physician or nurse will help complete the form.

Further data will be obtained from the electronic medical journal by the research team as described in section “overview of variables below”. A trained member of the research team ( i.e. primary investigator or site investigator) will be responsible for data collection and entry into the eCRF from the electronic medical journal and from the paper-CRF. Data will be entered directly into REDCap from the electronic medical journal. The paper-CRF and e-CRF will both be developed and tested and validated before enrollment start to optimize the use.

For some variables it will be possible to use routinely collected data passed on from the regional data warehouse. These data will be linked to REDCap data by using the personal identification number. All data will be collected longitudinally using the personal identification number as key identifier. Consent forms will be stored securely according to legal regulations. Data handling will comply with General Data Protection Regulation (European Union 2016/679), national requirements and the Danish Data Protection Act (ACT 502 of 23<sup>rd</sup> May 2018), the Danish Health Act and the general rules of the Declaration of Helsinki.

## 7.2 Overview of variables

Below is provided an overview of the included variables

| Variable   | Collection  | Source       | Purpose       |
|--|-------------|--------------|---------------|
| <b>Before consent, all screened patients</b>   |             |              |               |
| Site   | Prospective | e-CRF        | Screening log |
| Treating physician   | Prospective | Consent form | Screening log |
| <b>INCLUSION CRITERIA</b>  |             |              |               |
| Emergency Department contact   | Prospective | e-CRF        | Screening log |
| Age > 18 years   | Prospective | e-CRF        | Screening log |
| Pleural effusion detected on UL, chest X-ray, CT   | Prospective | e-CRF        | Screening log |
| Clinically justified need for thoracentesis  | Prospective | e-CRF        | Screening log |
| Without contraindication for thoracentesis in the emergency department (e.g anticoagulant treatment) | Prospective | e-CRF        | Screening log |

|  |               |              |                           |
|--|---------------|--------------|---------------------------|
|  |               |              |                           |
| EXCLUSION CRITERIA   |               |              |                           |
| Life threatening respiratory distress  | Prospective   | e-CRF        | Screening log             |
| Not able to give consent   | Prospective   | e- CRF       | Screening log             |
| Previous pleurodesis   | Prospective   | e-CRF        | Screening log             |
| Unacceptable high bleeding risk for thoracentesis according to local guidelines                                    | Prospective   | e-CRF        | Screening log             |
| Effusion does not appear free-flowing due to septations or loculations / suspected empyema                         | Prospective   | e-CRF        | Screening log             |
| Prior enrollment   | Prospective   | e-CRF        | Screening log             |
| If randomization is not possible because decision to insert a pigtail catheter is made in the radiology department | Prospective   | e-CRF        | Screening log             |
| REASONS FOR NON-INCLUSION  |               |              |                           |
| No physician on duty to perform thoracentesis  | Prospective   | e-CRF        | Screening log             |
| To busy  | Prospective   | e-CRF        | Screening log             |
| Other reasons  | Prospective   | e-CRF        | Screening log             |
| Age  | Retrospective | BI-data      | Screening log             |
| Sex  | Retrospective | BI-data      | Screening log             |
| Length of stay   | Retrospective | BI-data      | Screening log             |
| Drainage time (catheter in- catheter out)  | Retrospective | MR           | Screening log             |
| <b>After consent, only included patients</b>   |               |              |                           |
| Study ID   | Prospective   | e-CRF        | Screening log             |
| Unique patient identifier (CPR number)   | Prospective   | e-CRF        | Screening log             |
| <i>Treating physician data</i>   |               |              |                           |
| Name   | Prospective   | eCRF         | Baseline characteristics  |
| Seniority (specialist, resident, etc.)   | Prospective   | eCRF         | Baseline characteristics  |
| Ultrasound certified   | Prospective   | eCRF         | Baseline characteristics  |
| Number of thoracenteses within the last year   | Prospective   | eCRF         | Baseline characteristics  |
| <i>Patient registration data</i>   |               |              |                           |
| Site   | Prospective   | eCRF         | Baseline characteristics  |
| Unique patient identifier (CPR number)   | Prospective   | eCRF         | Identifier                |
| Full name, patient   | Prospective   | Consent form | Identifier                |
| E-mail, patient  | Prospective   | Consent form | Study results information |
| Date and time of consent   | Prospective   | Consent form | Study time origin         |
| Date and time for randomization  | Prospective   | eCRF         | Primary outcome           |

|   |                            |                             |   |
|---|----------------------------|-----------------------------|---|
| <i>Patient demographics and characteristics</i>                         |                            |                             |   |
| Age   | Retrospective <sup>c</sup> | BI -data <sup>A</sup> or MR | Baseline characteristics                                |
| Sex   | Retrospective              | BI -data or MR              | Baseline characteristics                                |
| Height  | Retrospective              | BI -data or MR              | Baseline characteristics                                |
| Weight  | Retrospective              | BI -data or MR              | Baseline characteristics                                |
| Co-morbidities  | Retrospective              | BI -data or MR              | Baseline characteristics                                |
| Prior thoracentesis within the last year                                | Retrospective              | BI -data or MR              | Baseline characteristics                                |
| <i>Procedure-related data</i>   |                            |                             |   |
| Date and time for procedure start                                       | Prospective                | Paper – CRF                 | Baseline characteristics                                |
| Duration of the thoracentesis (catheter in-catheter out)                | Prospective                | Paper – CRF                 | Primary outcome   |
| Indication  | Prospective                | Paper – CRF                 | Baseline characteristics                                |
| Side  | Prospective                | Paper – CRF                 | Baseline characteristics                                |
| Number needle passes  | Prospective                | Paper – CRF                 | Assess complication risk                                |
| Pleural effusion color  | Prospective                | Paper – CRF                 | Baseline characteristics                                |
| Complication during the procedure                                       | Prospective                | Paper – CRF                 | Baseline characteristics                                |
| Reason for stopping prematurely   | Prospective                | Paper – CRF                 | Protocol violation                                      |
| Reason for letting the drain remain in the patient (intervention group) | Prospective                | Paper – CRF                 | Protocol violation                                      |
| Date and time for procedure finished                                    | Prospective                | Paper – CRF                 | Protocol violation                                      |
| <i>Medical history</i>  |                            |                             |   |
| Medication (anticoagulants/antiplatelets, diuretics, analgesic)         | Retrospective              | BI- data or MR              | Baseline characteristics and to asses complication risk |
| Pausing of anticoagulants/antiplatelets                                 | Retrospective              | BI- data or MR              | Baseline characteristics and to asses complication risk |
| <i>Bioanalytic</i>  |                            |                             |   |
| Biochemistry analyses   | Retrospective              | BI- data or MR              | Baseline characteristics                                |

|  |               |                      |                                 |
|--|---------------|----------------------|---------------------------------|
|  |               |                      | and to assess complication risk |
| Arterial gas   | Retrospective | BI- data or MR       | Baseline characteristics        |
| <i>Triage and ED metrics</i>   |               |                      |                                 |
| Arrival date and time  | Retrospective | BI data              | Secondary outcome               |
| Chief complaint  | Retrospective | BI data or MR        | Baseline characteristics        |
| Vital signs parameters ( temperature, saturation, puls, blood pressure, GCS, RR) | Retrospective | BI data or MR        | Baseline characteristics        |
| Triage color   | Retrospective | BI data or MR        | Baseline characteristics        |
| Air supplement   | Retrospective | BI data or MR        | Baseline characteristics        |
| Timestamp when seen by a physician   | Retrospective | BI data or MR        | Baseline characteristics        |
| Physician responsible for the patient  | Retrospective | BI data or MR        | Baseline characteristics        |
| Date and time of transfer to another department                                  | Retrospective | BI data or MR        | Secondary outcome               |
| Date and time of discharge home  | Retrospective | BI data or MR        | Secondary outcome               |
| <i>Etiology</i>  |               |                      |                                 |
| Microbiology   | Retrospective | BI- data or MR       | Etiology                        |
| Pathology  | Retrospective | BI – data or MR      | Etiology                        |
| <i>Outcomes</i>  |               |                      |                                 |
| Time from randomization to removal of catheter                                   | Retrospective | Paper-CRF or MR      | Primary outcome                 |
| Time from indication to start of thoracentesis                                   | Prospective   | Paper-CRF or MR      | Baseline characteristics        |
| Duration of procedure  | Prospective   | Paper-CRF or MR      | Baseline characteristics        |
| Total time for fluid drainage  | Retrospective | Paper-CRF or MR      | Assess safety                   |
| Time to discharge from the ED  | Retrospective | Paper-CRF or BI data | Secondary outcome               |
| Total hospital length-of-stay  | Retrospective | Paper-CRF or BI data | Secondary outcome               |
| Patient reported symptoms<br>Breathlessness<br>Chest discomfort                  | Prospective   | Paper- CRF           | Secondary outcome               |
| Patients' experience   | Prospective   | Questionnaire        | Secondary outcome               |
| 72-hour revisits   | Retrospective | BI data              | Assess safety                   |
| Re-admission within 30 day   | Retrospective | BI data              | Assess safety                   |
| Complications during admission <sup>B</sup>                                      | Retrospective | BI or MR             | Assess safety                   |

<sup>A</sup> BI data = business intelligence data <sup>B</sup>MR= Medical Record

<sup>B</sup>Complications: for specific complications please see under outcome

<sup>C</sup> data will be expected to be filled out on the paper-CRF however some missing data are expected especially for patients with thoracentesis performed in the radiology department. For those patients' data will be obtain by looking at the procedure note from the radiology department

## **8. Participant timeline**

### *8.1 Screening and enrollment*

Patients will be screened prospectively by the treating physicians. All patients with pleural effusion requiring thoracentesis at the participating sites will be entered into a screening log. They will be checked for inclusion criteria and exclusion criteria. Upon fulfillment of all inclusion criteria and no exclusion criteria the treating physician will ask for informed consent, enroll and randomize the patient (for further details please see under "*consent*" below). The screening log will be updated daily by a member of the research team (primary investigator, member of the trial team or site investigator). For those who are not randomized a specific reason for non-inclusion/exclusion is documented.

Patients fulfilling inclusion criteria and no exclusion but are not randomized for various reasons will be deemed "inclusion failure". Inclusion failures will be monitored to access potential selection bias. For those who are deemed "inclusion failures" will the following variables be obtained in order to evaluate selection bias: Age, gender, duration of drainage time, hospital length of stay. Screening log data will be used in the study to describe patient flow in the CONSORT diagram.

### *8.2 Screening log*

Physicians may fail to include all patients with pleura effusions requiring thoracentesis. Therefore, all patients at the participating sites with a for procedure codes KGAA10, KTGA30 or KTGA30B (from the emergency department and referral form the ED to the radiology department) will retrospectively be entered into the screening log if they were not included in the study.

### 8.3 SPIRIT flow diagram

Schedule of enrollment, intervention and assessment

|  | Enrollment | Randomization | Post-randomization |              | Follow-up      |         |
|--|------------|---------------|--------------------|--------------|----------------|---------|
| TIME POINT   | -T1        | 0             | T1                 | ED discharge | Discharge home | 30 days |
| <b>ENROLLMENT</b>  |            |               |                    |              |                |         |
| Screened for eligibility   | x          |               |                    |              |                |         |
| Screening log  | x          |               |                    |              |                |         |
| Informed consent   |            | x             |                    |              |                |         |
| Randomization  |            | x             |                    |              |                |         |
| <b>INTERVENTIONS</b>   |            |               |                    |              |                |         |
| Manual fluid removal in the ED   |            |               | x                  |              |                |         |
| Standard of care (SOC) – referral to the radiology department  |            |               | x                  |              |                |         |
| <b>ASSESSMENTS</b>   |            |               |                    |              |                |         |
| Case Report Form   |            |               | x                  |              |                |         |
| Retrospective data retrieval<br>Baseline characteristics<br>Vital parameters<br>Medical history<br>Complications<br>Microbiology<br>Pathology<br>Admission metrics<br>Removal of catheter<br>Readmission |            |               |                    | x            | x              | x       |
| Manual record review<br>Baseline characteristics<br>Vital parameters<br>Medical history<br>Complications<br>Microbiology<br>Pathology  |            |               |                    | x            | x              | x       |

|                     |  |  |  |  |  |  |
|---------------------|--|--|--|--|--|--|
| Removal of catheter |  |  |  |  |  |  |
|---------------------|--|--|--|--|--|--|

## 9. ETHICAL

### 9.1 Potential benefits

The introduction section provides details on the potential benefits of manual aspiration in an ED setting. In brief, to the best of our knowledge, no randomized controlled trial has investigated combining manual fluid removal in an ED setting for optimizing patient care. It remains unexplored in terms of complete drainage time, length of stay, patient satisfaction and safety, therefore a true clinical equipoise exist.

### 9.2 Consent

All participants are required to give informed consent prior to enrollment. Participants admitted to the ED and fulfilling the inclusion criteria will be asked for informed consent before enrollment and randomization. Participants will receive oral and written information and will receive the brochure "Volunteer's right in a health science research project" ("Forsøgspersoners rettigheder i et sundhedsvidenskabeligt projekt"). The patient will be asked for consent to obtain relevant health information from the electronic patient record during the admission and 30 days follow-up. The informed consent form gives the trial team, as well as any regulatory authority, direct access to obtain information from the patient's medical records, including electronic records, in order to access information about the trial participant's health condition, as required for the completion of the research project and for monitoring purposes, including self-monitoring, quality control and surveillance, which they are obligated to perform.

Trial information and the consent request will take place in an undisturbed room and the patient will have the opportunity to request an assessor. For ethical reasons, treatment of pleura effusions is an acute problem where treatment must be initiated without much delay in order to prevent

respiratory decline. Therefore, is it not possible to give 24 hours of time for consideration. We therefore need patients to provide consent within a timeframe of one hour (from information about the study until consent). However more time can be requested if needed.

The treating physician who obtains the consent will have sufficient knowledge about the patient and the trial. Patients declining to participate in the study will receive treatment according to hospital standard of care.

If a patient who has already consented, at some point denies future participation in the trial, no additional data will be collected but all data collected up until the point of withdrawal will be included consistent with Danish law.

In this study, no biological material will be collected and no biobank will be established. Consent forms will be stored securely, according to legal regulations.

### *9.3 Ethical review committee*

The trial will be approved by the regional ethics committees in Central Region Denmark

### *9.4 Risk, side effects and other disadvantages*

The study investigates two routinely used draining methods in the clinic. There are no reported disadvantages of the intervention compared to standard of care. Thoracentesis is generally considered a low-risk procedure with a reported overall complication rate 0.98%<sup>10</sup>. However, complication such as pneumothorax, bleeding or infection may occur but no studies have reported any increase for of these for patients receiving the intervention over the standard of care<sup>4,5</sup>. More importantly, the patients have a clinical need for thoracentesis independently of the study so no additional intervention is introduced. If patients allocated to the control arm deteriorate or experience respiratory failure in the waiting for thoracentesis by the radiologist a thoracentesis will be performed in the ED. If the emergency physician for some reason cannot perform

thoracentesis, the patients will then be referred to the radiology department for urgent thoracentesis.

### *9.5 Insurance*

The patients in the study are covered by the Danish patient insurance<sup>11</sup>.

## **10. Financial statement**

### *10.1 Funding*

This investigator-initiated study is funded by the Central Denmark Region (with 1.100.000 DK) and Eva Merete Falck Crones Fond (20.000). The funding is covering wage costs for the primary investigator and are held in a research account at the Emergency Department at Randers Regional Hospital. The primary investigator is employed at the Central Denmark Region. The primary investigator declares no conflict of interest.

## **11. Publication and feasibility**

### *11.1 Investigator and publication*

Sandra Thun Langsted, MD, PhD-student, is the lead investigator. Bo Løfgren, MD, PhD, FESC, FAHA, Associate professor, Kasper Glerup Lauridsen, MD, PhD, FERC, FAHA, Associate professor, Jesper Bo Weile, MD, PhD and Søren Helbo, MD, PhD has committed themselves as scientific mentors on the project. The lead investigator will be responsible for recruitment, data collection, analyzing and preparation of papers. The trial protocol will be registered at [www.clinicaltrials.gov](http://www.clinicaltrials.gov) where the results; positive, negative or inconclusive will be published. Regardless of the study outcome the results will be submitted to an international peer-reviewed journal.

### *10.2 Feasibility*

The investigators behind the study have the necessary expertise to ensure successful conduction and have experience from previous randomized clinical trials<sup>12-14</sup>. This study is conducted

between EDs in Central Denmark Region. Each participating site will have a site-investigator that will help with recruitment and data collection. Sandra Thun Langsted, MD, PhD-student will serve as primary investigator on the project, which role will be surveillance on the study conduction, data handling and ensure sufficient information to the clinical staff performing thoracentesis.

## References

1. Markus Fally JKP, Katrine Fjællegaard, Karin Armbruster, Simon Reuter, Uffe Bødtger. Pleuraeffusion. Danish Respiratory Society <https://lungemedicin.dk/pleuraeffusion/>
2. Rasmussen KMB, Hertz P, Laursen CB, et al. Ensuring Basic Competence in Thoracentesis. *Respiration*. 2019;97(5):463-471. doi:10.1159/000495686
3. Senitko M, Ray AS, Murphy TE, et al. Safety and Tolerability of Vacuum Versus Manual Drainage During Thoracentesis: A Randomized Trial. *Journal of bronchology & interventional pulmonology*. 2019;26(3):166-171. doi:10.1097/LBR.0000000000000556
4. Lentz RJ, Shojaee S, Grosu HB, et al. The Impact of Gravity vs Suction-driven Therapeutic Thoracentesis on Pressure-related Complications: The GRAVITAS Multicenter Randomized Controlled Trial. *Chest*. 2020;157(3):702-711. doi:10.1016/j.chest.2019.10.025
5. Lentz RJ, Lerner AD, Pannu JK, et al. Routine monitoring with pleural manometry during therapeutic large-volume thoracentesis to prevent pleural-pressure-related complications: a multicentre, single-blind randomised controlled trial. *The lancet respiratory medicine*. 2019;7(5):447-455. doi:10.1016/S2213-2600(18)30421-1
6. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)—A metadata-driven methodology and workflow process for providing translational research informatics support. *Journal of biomedical informatics*. 2009;42(2):377-381. doi:10.1016/j.jbi.2008.08.010
7. Harris PA, Taylor R, Minor BL, et al. The REDCap consortium: Building an international community of software platform partners. *Journal of biomedical informatics*. 2019;95:103208-103208. doi:10.1016/j.jbi.2019.103208
8. thoracentesis. 103.7.3. Pleuradrænage, fælles radiologisk instruks, RM. <https://e-dok.rm.dk/edok/admin/GUI.nsf/desktop.html?Open>
9. Senn SJ, Lewis RJ. Treatment Effects in Multicenter Randomized Clinical Trials. *JAMA : the journal of the American Medical Association*. 2019;321(12):1211-1212. doi:10.1001/jama.2019.1480
10. Ault MJ, Rosen BT, Scher J, Feinglass J, Barsuk JH. Thoracentesis outcomes: a 12-year experience. *Thorax*. 2015;70(2):127-132. doi:10.1136/thoraxjnl-2014-206114
11. Indenrigs- og Sundhedsministeriet. Bekendtgørelse af lov om klage- og erstatningsadgang inden for sundhedsvæsenet. <https://www.retsinformation.dk/eli/lt/2011/1113>
12. Adelborg K, Dalgas C, Grove EL, Jørgensen C, Al-Mashhadi RH, Løfgren B. Mouth-to-mouth ventilation is superior to mouth-to-pocket mask and bag-valve-mask ventilation during lifeguard CPR: A randomized study. *Resuscitation*. 2011;82(5):618-622. doi:10.1016/j.resuscitation.2011.01.009
13. Schmidt AS, Lauridsen KG, Adelborg K, et al. Cardioversion Efficacy Using Pulsed Biphasic or Biphasic Truncated Exponential Waveforms: A Randomized Clinical Trial. *Journal of the American Heart Association*. 2017;6(3):n/a. doi:10.1161/JAHA.116.004853
14. Bang C, Hansen C, Lauridsen KG, et al. Rapid use of high-sensitive cardiac troponin I for ruling-in and ruling-out of acute myocardial infarction (RACING-MI): study protocol. *Open heart*. 2019;6(1)doi:10.1136/openhrt-2018-000995

**Appendix 1: Draft of CONSORT flow diagram**

