STUDY TITLE: Fibrinolytic Therapy versus Medical Thoracoscopy for Treatment of Pleural Infection: A Randomized Clinical Trial

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Protocol Document: Fibrinolytic Therapy versus Medical Thoracoscopy for Treatment of Pleural Infection: A Randomized Clinical Trial

Study Team:

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Overall Objective:

The purpose of this prospective randomized clinical trial is to compare two currently accepted standard-of-care treatment strategies: medical thoracoscopy as compared to instillation of intrapleural tissue plasminogen activator (TPA) and human recombinant deoxyribonuclease (DNase) for the management of complicated pleural infections in adults as defined as complicated parapneumonic effusions or pleural empyema.

Introductory Statement and Background:

Pleural infection (empyema or complex parapneumonic effusion [CPPE]) represents one of the common clinical diagnoses encountered in clinical practice in the United States (US) and worldwide. The incidence of pleural infection continues to rise with an annual incidence of approximately 65,000 in the US and United Kingdom (UK).[1] It is associated with substantial morbidity and mortality as well as increased hospital costs despite advances in medical diagnostic and therapeutic strategies.[2-4] The overall mortality of pleural infection approaches 20% and it is above 30% in elderly patients over 65 years and immunocompromised patients.[1,5-8]

Treatment of CPPE or empyema requires antibiotics and drainage of the pleural cavity.[3] However, in about 30% of cases, it is difficult to remove the fluid due to loculations, septations and increased viscosity of the pleural fluid, and around 20% will need surgical intervention to adequately treat the pleural infection.[9,10]

Rationale:

The intrapleural therapy of combined tissue plasminogen activator (tPA) and human recombinant deoxyribonuclease (DNase) in the management of pleural infection has been shown to improve the chest radiographic appearance at day 7 in the Multi-center Intra-pleural Sepsis Trial (MIST2).[9] However, this approach is expensive, with a substantial hospital stay (around 12 days), and had a no significant decrease in the rate of surgery referral as compared to placebo.[9]

Although two randomized studies have shown that around 80% of patients with pleural infection can be successfully managed medically, early surgical intervention is still considered a first-line treatment for pleural infection in some regions around the world [9,10]. This approach has been justified on the basis of improved clinical outcome and shorter hospital stays for patients managed in this way.[11-15]

Video-assisted thoracoscopic surgery (VATS) has been suggested as a surgical invasive approach to clear potentially infected material from the pleural space. In one small randomized and another non-randomized prospective trial comparing VATS with intercostal drainage plus intrapleural streptokinase, VATS was associated with decreased hospital stays and overall costs.[16,17] However, there are several limitations that need to be mentioned. First, these two trials were under-powered studies without appropriate sample size calculation. Second, VATS was compared to intrapleural streptokinase. The intrapleural activity of endogenous plasminogen activator inhibitor (PAI-1) in the pathogenesis of pleural infection is important since this mediator not only directly inhibits streptokinase but has also been shown to contribute to the severity of loculation and poor outcomes with intrapleural fibrinolytic therapy.[18-20] Third, large case series have shown that VATS is usually performed on a younger and less comorbid population (i.e. highly selected patients), compared to the unselected population of patients (which are usually sicker, elderly and have multiple comorbidities) with pleural infection seen in the fibrinolytic studies.[9,10, 11,21] Moreover, failure to respond to medical fibrinolytic therapy might

necessitate invasive surgical intervention, such as VATS, or even open thoracotomy, at a later stage of the pleural infection where adequate clearance of the dense septations and thickening within and around the pleural cavity is needed to reverse lung restriction and improve compliance. However, clinical outcomes are unpredictable, with some patients having no long-term sequelae but others showing permanent impairment of lung function.

Medical thoracoscopy (MT) is a minimally invasive procedure that can be used to treat pleural infection through improving clearance by mechanical adhesiolysis and targeted drain placement. MT can also be used in patients who are not fit for general anesthesia by using local anesthesia and sedation. MT has shown to be safe and effective in the treatment of pleural infection in observational studies.[22-25] However, to date, there are no randomized controlled trials addressing the potential role of early MT versus fibrinolytic therapy in empyema and complicated pleural infection.

Proposal:

Specific Aim 1:

To compare the efficacy of early medical thoracoscopy versus fibrinolytic therapy (tPA/DNase) in patients with complicated parapneumonic effusions or pleural empyema.

Methods and Procedures:

Study Design

This prospective randomized trial will be conducted at UF Health Shands Hospital in accordance with Good Clinical Practice Standards and under IRB supervision. A large number of patients with pleural infection are treated at our institution, with a multidisciplinary team comprised of experienced interventional pulmonologists, chest radiologists and thoracic surgeons. We plan to enroll a total of 60 patients with pleural infection that will be randomized utilizing a computerized system to either medical thoracoscopy (thoracoscopy group) or fibrinolytic therapy (fibrinolytic group).

Patient Population

Subjects (> 18 years of age) with either CPPE or empyema will be screened for inclusion. Screening logs recording reasons for non-trial entry will be kept.

CPPE is defined as non-purulent effusion in a patient with clinical evidence of infection such as fever and/or elevated blood leukocyte count and/or elevated CRP, with pleural fluid pH ≤ 7.2 (measured by blood-gas analyzer), or pleural fluid glucose < 60 mg/dl or pleural fluid LDH >1000 IU/L[26]. Empyema is defined as pus within the pleural space and/or presence of bacteria on pleural fluid Gram stain or culture.

For patients to be considered for the trial they need to fulfill one of the following criteria: 1) CPPE along with evidence of septated pleural effusion on pleural ultrasonography and/or chest CT scan [27] (Figure 1) or 2) empyema.

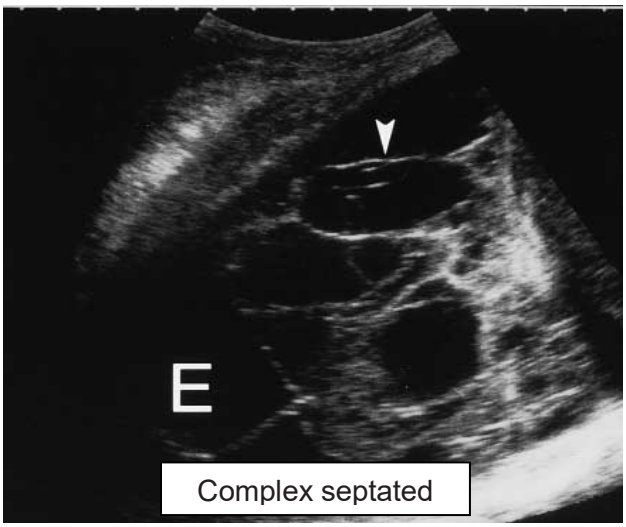

Figure 1. Throracic ultrasound showing complex pleural effusion along with septation (arrowhead)

Prescreening / Study exclusion criteria are as follows:

1) age <18 years;
2) pregnancy
3) inability to give informed written consent;
4) previous thoracic surgery or thrombolytic therapy for pleural infection;
5) medical thoracoscopy cannot be performed within 48 hours;

6) inability to tolerate procedure due to hemodynamic instability or severe hypoxemia;
7) inability to correct coagulopathy;
8) presence of a homogeneously echogenic effusion on pleural US[27] (Figure 2).

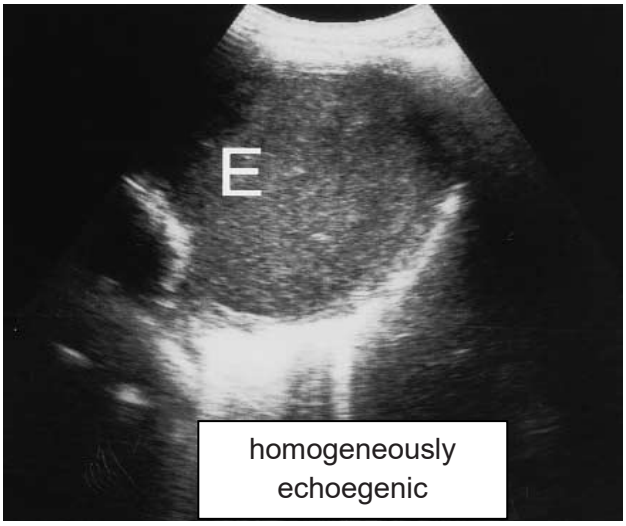

Figure 2. Thoracic ultrasound showing homogeneously echogenic loculated effusion

Patients who agree to participate in the trial will sign an informed consent. Next, all patients will undergo diagnostic thoracentesis as per standard of care. In addition to standard of care testing on pleural fluid, an additional 10 mLs of fluid will be collected to check for markers like interleukin-8 and vascular endothelial growth factor. All patients will receive intravenous antibiotics according to local hospital guidelines and local microbiology results. Intravenous antibiotics will be changed to oral consolidation therapy by the managing consultant in light of the clinical response. Antibiotic therapy will be continued for between 2 and 6 weeks, as required per standard of care.

Following diagnostic thoracentesis and confirmation of pleural infection, participants will be randomly assigned to either receive thoracoscopy (treatment arm) or fibrinolytic therapy (control arm). (Figure 3)

Pleural effusion will be defined as loculated if it (1) has a lobulated shape with a convex boarder or (2) it is compartmentalized or accumulated in a fissure or a non-dependent portion of the pleura. On chest ultrasound the pleural effusion will be defined as loculated if it has fibrin

strands or septa floating inside the anechoic/hypoechoic pleural effusion(s) along with the presence of defined multiple pockets in the pleural cavity. [28]

Pain scores and general physical status will be assessed using a participant-completed 100-mm visual analog scale (VAS) upon randomization, at 6 weeks (via phone call) and 12 weeks follow up.

Study Protocol I- Thoracoscopy (Treatment Arm)

Patients will undergo medical thoracoscopy (rigid or semi-rigid) within 48 hours of randomization. A single port (with a maximum of 2 ports) will be placed and thoracoscopy will be performed under monitoring as per standard protocols, with the patient in a lateral decubitus position. The pleura will be carefully inspected through the thoracoscope under direct visualization. Adhesiolysis will be attempted and pleural irrigation will be done. At the end of the procedure, a drain will be inserted and connected to an underwater seal with a negative pressure suction. As per standard of care, a chest CT without contrast will be performed when chest tube drainage is < 75 mLs and if there was no evidence of significant pleural effusion (<200 ml), the catheter will be removed [29] The fluid volume will be calculated by measuring the maximum perpendicular distance between the surface and the chest wall right above the diaphragm with at maximum inspiration in the most dependent position.[29] Any need for additional drainage or administration of fibrinolytic or surgery will be considered treatment failure.

II-Fibrinolytic Therapy (Control Arm)

A chest tube (14-French or less) will be inserted under ultrasonography into the most dependent area of the pleural effusion or into the largest loculation in patients with multi-loculated effusions. The dose of DNase (Pulmozyme, Genentech, USA) will be 5 mg and the dose of tPA (Actilyse, Genentech, USA) will be 10 mg, each in 50 ml of 0.9% NaCl. The tPA and DNase will not be mixed together in one syringe. Concurrent tPA and DNase will be administered intrapleurally through the chest tube followed by saline flush. The tube will then be clamped for 120 minutes and after which it will be connected back to wall suction. The intrapleural therapy will be given twice daily for a maximum of 6 doses. As per standard of care, a chest CT without contrast will be performed when chest tube drainage is < 75 mLs and if there was no evidence of significant

pleural effusion (<200 ml), the catheter will be removed [29]. Any need for additional drainage or more doses of fibrinolytic from the existing drainage over and above the 6 doses mentioned or surgery will be considered treatment failure.

Study Outcome

Primary outcome measure:

- Duration of hospital stay after intervention, as defined as thoracoscopy in the treatment arm and first dose of fibrinolytic in the control arm

Secondary outcome measures:

- Number of days with chest tube drainage
- Total length of hospital stay
- Failure rate of assigned treatment necessitating intervention defined as any of the following:

1-Surgical intervention (VATS, open thoracotomy) in either arm
2-Need of additional chest tube and/or fibrinolytic therapy in the medical thoracoscopy arm due to clinical non-responsiveness
3-Need of additional chest tube in the fibrinolytic therapy arm due to clinical non-responsiveness

- Adverse events
    - Pleural bleeding defined as drop in serum hematocrit requiring blood transfusion or causing hemodynamic instability
    - Significant pain requiring escalation of analgesia
- In-hospital and 30-day mortality
- Change in pleural fluid volume on chest CT scan from randomization (day 0) to prior to chest tube removal measured by radiologist (Mohammed) blinded to treatment allocation using image J software. Volume of pleural effusion will be obtained by examination of radiographic images obtained during the standard-of-care CT examination.
- Infectious biomarker (CRP) from randomization (day 0), at removal of chest tube and 12 weeks as per standard of care
- Total costs of each treatment modality in each treatment site

Sample Size and Statistical Analysis

The difference in length of post-intervention hospital stay of 2 days between the two treatment arms would be clinically important.

This rationale was based on previous large VATS case series reported by Luh and colleagues[30] in which the mean postoperative stay was 7.2 d ± 3.2 d versus 11.8 d±9.4 d from randomization to fibrinolytic therapy until discharge in the MIST2 trial[9] and 10 d ± 1.8 d from first intrapleural treatment dose until discharge reported by Piccolo and colleagues.[31]

To demonstrate this difference with 5% significance and 80% power, a minimum of 30 patients will be needed in each study group. Baseline characteristics will be compared between the two groups using Chi square, *t* tests, and Mann-Whitney U tests as appropriate. All data will be analyzed according to the intention-to-treat principle. A p value of ≤ 0.05 will be considered statistically significant.

Significance

To our knowledge, there are no randomized clinical trials evaluating the efficacy of early medical thoracoscopy versus fibrinolytic therapy in patients with pleural infection. This study should clarify the role of early medical thoracoscopy in patients with complicated parapneumonic effusions or pleural empyema. Currently, many centers worldwide primarily treat patients with pleural infection by placing a chest tube with pleural fibrinolysis. In case of failure of such an approach, which means that several treatment days are lost, a more invasive procedure is needed. By this time, significant pleural septae have formed, and often a surgical VATS or thoracotomy under general anesthesia becomes necessary. Therefore, this pivotal study could lead to changes in the management of patients with pleural empyema/CPPE.

Human Subjects Will Be Used

The research team will explain the details about the study to the patient. This discussion will also serve to answer any questions that the subject may have. Potential risks will be minimized by providing adequate time and opportunity for the subjects to review and ask questions about the study prior to consenting to participate. The subject will have an option to opt out of the

study at any point of time without any obligations or loss of treatments through UF Health Shands Hospital or other treatment centers.

All collected data will be de-identified and linked to the subject by a unique identifying number. The data will be secured by the research team and will not affect patient care in any manner. The investigators will not use or disclose the means of record identification for any other purpose. The protected health information (PHI) will not be reused or disclosed to any other person or entity except for other research for which the use of the PHI would be permitted under the Privacy Rule.

After enrollment, a number will be assigned to the subject. This number will be used for all study documents to maintain the privacy of the subject. The subjects will have the phone numbers of the study team members for any questions or concerns that might arise throughout the study period.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by the IRB for the study. The formal consent of a subject, using the IRB-approved consent form, will be obtained before that subject is submitted to any study procedure.

No Animals or Biohazardous Materials Will Be Used.

Risks and Benefits

If successful, this study may improve standard of care treatment for pleural infection by clarifying which of two standard-of-care procedures produces superior clinical outcomes including decreased length of stay and decreased need for adjuvant / subsequent treatments following initial treatment for pleural infection.

Risk associated with thoracentesis:

a. Pain during placement (minor and controlled with anesthesia)

b. Bleeding. During insertion of the needle, a blood vessel in the skin or chest wall may be accidentally nicked. Bleeding is usually minor and stops on its own. Sometimes,

bleeding can cause a bruise on the chest wall. Rarely, bleeding can occur into or around the lung and may require a chest tube or surgery.

- **Collapsed lung.** When the needle is being placed, it may puncture the lung. This hole may seal quickly on its own. If the hole does not seal over, air can leak out and build up around the lung. This build-up of air can cause part or all of the lung on that side to collapse (pneumothorax). If this happens, the doctor can place a chest tube between the ribs into the chest to remove the air that is leaking from the lung

Risks associated with sedation:

a. Drowsiness, slurred speech, tremor, fatigue, and low blood pressure, increase carbon dioxide in your blood, slowing of the heart rate, anxiety, confusion, dizziness and shivering

b. .Respiratory depression. Trained medical professionals with extensive experience and expertise will administer these medications and will be responsible for monitoring the participant during the course of the procedure.

Risks associated with thoracoscopy:

a. Chest pain (5%). The nerves between the ribs are bruised after the procedure, which can cause some persistent pain.

b. Air leak from lung (1-5%). A small hole develops in the lung. This means the chest tube has to stay in longer.

c. Bleeding (< 1%). Usually it is minor and settles quickly. Bleeding is more common if you have been taking blood thinning drugs.

d. Heart problems (< 1%). A brief minor strain may be put on the heart. This can cause abnormal beating of the heart, fluid to accumulate in the lungs, a heart attack, or the heart may stop beating.

e. Low oxygen levels (< 1%). Participants will be administered oxygen if needed.

f. Death(< 1%) as a result of this procedure is uncommon.

Risks associated with chest tubes:

a. ***Pain during placement*—**Discomfort often occurs as the chest tube is inserted. Doctors try to lessen any pain or discomfort by giving a local numbing medicine. The discomfort usually decreases once the tube is in place.

b. ***Bleeding (<5%)*—**During insertion of the tube, a blood vessel in the skin or chest wall may be accidentally nicked. Bleeding is usually minor and stops on its own. Rarely, bleeding can occur into or around the lung and may require surgery. Usually bleeding can just be watched with the chest tube in place.

c. ***Infection (< 5%)*—**Bacteria can enter around the tube and cause an infection around the lung. The longer the chest tube stays in the chest, the greater the risk for infection. The risk of infection is decreased by special care in bandaging the skin at the point where the tube goes into the chest.

Risks associated with fibrinolytic therapy:

a. Pain (15%)-While the medications are in the pleural space, participants may feel some discomfort. Usually such pain can be relieved by analgesics.

b. Bleeding (5%)-While medications are in the pleural space, participants may experience bleeding inside the pleural space. Usually, it resolves with stopping medications. Rarely, blood transfusion might be need or require surgery.

Privacy risks: As with any study, there is a risk that personal health information, collected during the course of research, may be disclosed. The research team will to everything within their power to mitigate and minimize this risk. The data collected both written and electronic will be held securely in a locked cabinet and secure server behind the UF Health firewall respectively. Only the study individual will be contacted and the questionaries' administered in the privacy of a secluded clinic room. The data collected will be restricted to only the minimum amount necessary to accomplish the aim of the study.

Risks associated with psychological stress: Participants may feel embarrassed or uncomfortable responded to questions. Participants will be informed that they may refuse to answer any of the questions and may take a break at any time during the study. Participants are also free to withdraw from the study at any time.

Conflict of Interest

All research personnel associated with this protocol report no actual or perceived conflicts of interest.

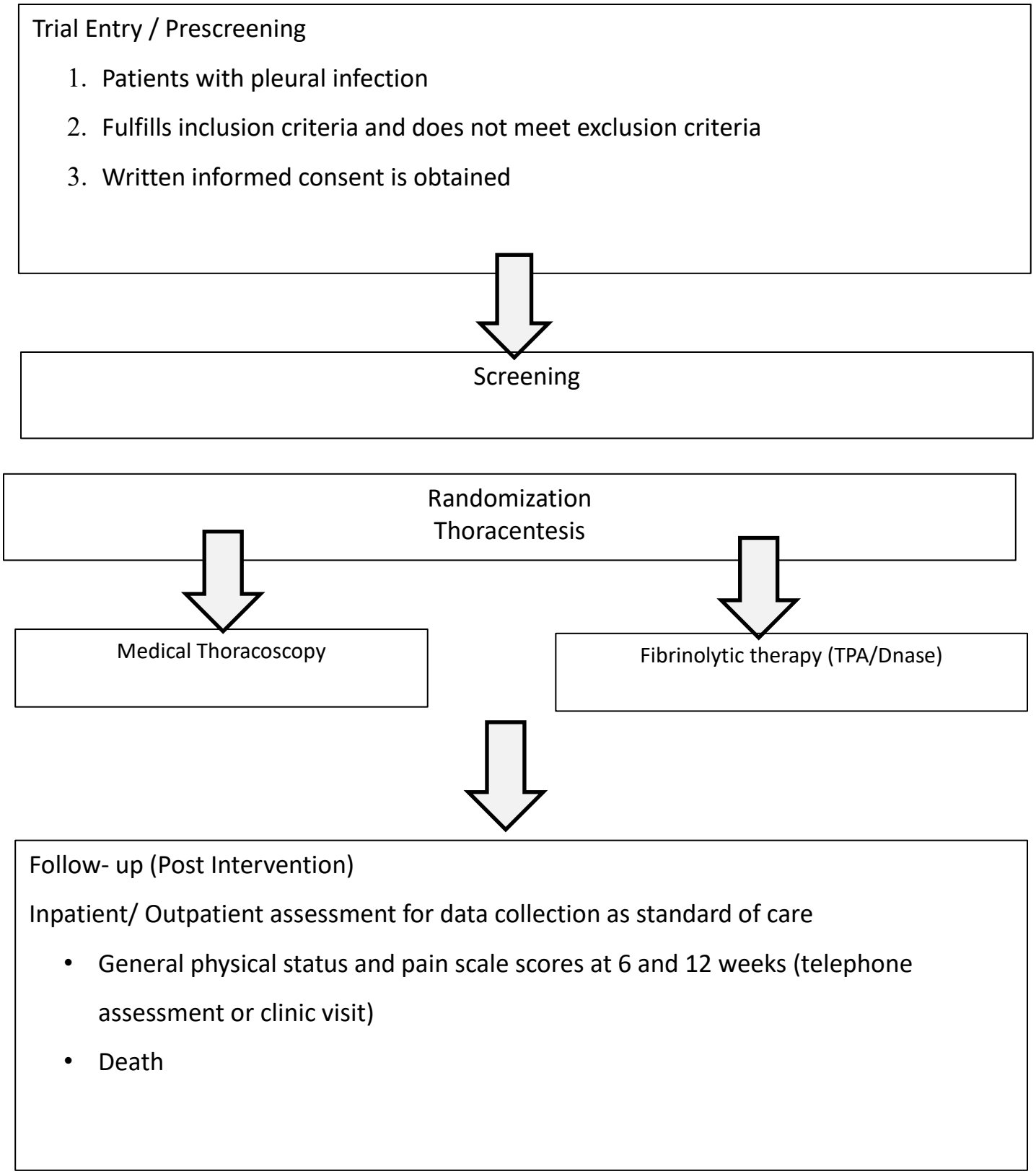

Figure 3. Proposed Study Protocol

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