Memorial Healthcare System
OFFICE OF HUMAN RESEARCH

CLINICAL TRIAL PROTOCOL

Prospective Randomized Trial of Intrapleural Fibrinolytic Therapy to Enhance Chemical Pleurodesis

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Memorial Regional Hospital
Memorial Hospital West

CONFIDENTIAL

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LIST OF ABBREVIATIONS:

MHS	Memorial Healthcare System
TSP	Talc slurry pleurodesis
RSP	Radiographically satisfactory pleurodesis
NS	Normal saline
tPA	Tissue plasminogen activator
CxR	Chest x-ray radiography
CT	Computed tomography
MPE	Malignant pleural effusions
PAI-1	Plasminogen activator inhibitor-1
TNF-α	Tumor necrosis factor-alpha
MCP-1	Monocyte chemoattractant protein-1,
TGF-β	Transforming growth factor-beta
IL-8	Interleukin- 8
SOB	Shortness of Breath
VA	Visual assessment
REDCap	Research Electronic Data Capture
RSP	Radiographically Satisfactory Pleurodesis

1.0 STATEMENT OF COMPLIANCE

This document is a protocol for a prospective, randomized, double-blind, controlled trial to evaluate the efficacy of supplementing standard talc slurry pleurodesis with intrapleural cathflo activase for management of patients with recurrent pleural effusion. The study will be conducted in compliance with U.S. and international standards of Good Clinical Practice, applicable Federal regulations, International Conference on Harmonization guidelines and all applicable institutional research requirements. Collection, recording, and reporting of data will be accurate and will ensure the privacy, health, and welfare of research subjects during and after the study.

2.0 ABSTRACT

Recurrent pleural effusion is a common health problem, affecting approximately 1.5 million people each year in the United States. It causes breathlessness, pain and reduced physical capacity and can require surgical interventions. A long-standing treatment option is called pleurodesis, in which the surface of the lung is induced to adhere to the chest wall, obliterating the pleural space to prevent fluid build-up. Talc slurry pleurodesis (TSP) is one of the most common techniques used to accomplish this result. With TSP a drain is placed in the pleural space (chest tube), followed by instillation of sterile talc in a saline suspension. The talc is a sclerosing agent that induces scar formation between the visceral and parietal pleural membranes. Although effective, sometimes development of septations and loculations can produce suboptimal results. In patients with complex pleural effusion and empyema (infection in the pleural space), intrapleural administration of fibrinolytic medication such as cathflo activase (Alteplase®) is used to break down pleural loculations and improve pleural fluid drainage. To our knowledge, fibrinolytic therapy has never been used to manage loculated collections that develop with TSP. It is currently unknown if supplementing TSP with cathflo activase will improve results or impair pleurodesis compared to use of TSP alone.

This protocol describes a prospective, randomized, double-blind controlled trial comparing TSP alone to the combination of TSP with cathflo activase for achieving optimal results with pleurodesis for recurrent pleural effusion. Patients who sign informed consent will be randomly assigned to receive either TSP alone (talc, 5 gm in 50 ml NS) with placebo (50 ml NS) or TSP with cathflo activase (4 mg in 50 ml NS) through the chest pleural catheter. Follow-up lasts for three months. The primary outcome is achievement of a "Radiographically Satisfactory Pleurodesis" (RSP) by day three post-procedure, defined as chest tube drainage of less than 100 cc over 24 hours *and* a chest x-ray showing similar or less pleural space opacification than on the day TSP was performed (baseline, day 0). Secondary outcomes include the proportion of patients who achieve RSP, time needed to achieve RSP, duration of chest tube drainage, length of hospital stay after initiation of TSP, proportion of patients requiring repeat TSP, change in serum hemoglobin during therapy, objective assessments of pain and dyspnea, and potential complications. The incremental cost effectiveness of talc slurry pleurodesis with cathflo activase compared to without cathflo activase will be assessed using a static decision tree model, which will be constructed using the TreeAge Pro software. This study will recruit 136 patients, with an interim analysis for efficacy after 50 patients, and aims to help develop the future standard for management of patients requiring pleurodesis for their symptomatic pleural effusion.

3.0 INTRODUCTION

A pleural effusion is an accumulation of fluid in the chest around the lung, and is a common clinical problem, with an incidence of approximately 1.5 million per year in the United States.(1) Large collections compress the underlying lung and contribute to significant morbidity by affecting a patient's ability to breathe easily. A variety of conditions contribute to the development of a pleural effusion, such as heart, kidney and liver failure, cancer, and pneumonia. Often, drainage of the effusion is sufficient. But if the underlying cause cannot be corrected the effusion will return and more definitive management is indicated. Options for definitive management of a recurring pleural effusion are either an indwelling catheter to facilitate repeated drainage (e.g. PleurX®) or pleurodesis to prevent reaccumulation of fluid by sealing the pleural space.(2–5) Pleurodesis occurs in response to inflammation, which can be intentionally induced through either mechanical/surgical abrasion or application of a chemical irritant. Chemical pleurodesis is a convenient option because it can be done by injection of the chemical in suspension through a small drainage tube into the pleural space, rather than requiring surgery. Many agents have been used to promote pleurodesis, including sterile talc, tetracycline, doxycycline, bleomycin, silver nitrate and povidone iodine.(2)

Chemical pleurodesis is effective but can be incomplete, sometimes leaving the patient with a partially sealed pleural space and multiple pockets ("loculations") of fluid. This is probably the result of uneven distribution of the chemical irritant, incomplete contact of the chemical with the pleural membranes, and ongoing fluid production that creates pockets, or loculations, that separate the pleural membranes and prevent adhesion formation.(6) Fluid in the pleural space is often protein rich and partially organized with fibrin "clots". The Thoracic Surgery Division at the Memorial Healthcare System (MHS) has had extensive experience with intrapleural administration of cathflo activase (Alteplase®) to improve drainage of complex pleural effusions. This experience led to the hypothesis that cathflo activase given along with the chemical pleurodesis agent would improve results by 1) improving distribution and contact of the chemical agent with the pleural membranes generating a more uniform inflammatory response, and 2) prevent loculations from forming and therefore lead to a more complete pleurodesis. The Division started using cathflo activase with talc slurry in April 2014 and reviewed results as of December, 2016. 57 patients with benign or malignant effusions were treated and pleurodesis was performed 62 times (eight patients had bilateral pleurodesis). Because it was not done as part of a formal protocol, there was considerable variability in dosing and timing of cathflo activase, but our review suggested that results were at least as good as pleurodesis without cathflo activase and that there was no incidence of serious complication such as bleeding or respiratory failure. Following this review the protocol was modified to specify a cathflo activase dose of 4 mg. Since then, more than 150 additional patients with benign and malignant effusions have been treated with the combination of cathflo activase and TSP without apparent complication. A prospective randomized evaluation of this strategy is indicated to formally evaluate its efficacy.

3.1. Literature Review

Pleurodesis has a long history as the standard of care for palliation of malignant pleural effusions (MPE). By sealing the visceral and parietal pleura together there is no residual potential space in which fluid can accumulate, thus preventing development of large effusions that compromise

breathing. Chemical or physical irritation of the pleural space causes an inflammatory response and subsequent fibrin adhesion and fibrotic tissue formation, leading to pleurodesis.(2–4) The sclerosing agent is applied either during an operation called thoracoscopy, in which small incisions are made and the agent is sprayed directly onto the pleural surfaces (poudrage), or is injected in a suspension through an existing drainage tube in the pleural space (slurry).

Many chemicals have been tried for inducing pleurodesis. The agents used most often have been talc, bleomycin, tetracycline, and doxycycline.(2) A Cochrane review concluded that talc is the most effective agent,(7) but recent availability has been limited. In a prospective non-randomized study of 109 patients, Stefani and colleagues concluded that talc poudrage was superior to talc slurry using chest X-rays after the procedure to examine pleural fluid re-accumulation.(8) A presumptive disadvantage with talc slurry is that the talc is distributed unevenly in the pleural space. Maneuvers to promote uniform distribution such as frequent patient repositioning while the slurry dwells in the pleural space have been recommended, but there is no evidence that this improves distribution or results.(9–11)

Intrapleural fibrinolytic therapy was first described in the late 1940's. Tillet et al. (12) used a partially purified streptococcal concentrate containing streptokinase and streptococcal DNase intrapleurally in patients with fibrinous pleurisy and empyema and reported that it breaks down fibrin in the pleural space. Recombinant cathflo activase, or Alteplase®, is a recognized systemic treatment for myocardial infarction, pulmonary embolism and thromboembolic stroke.(13) Similar to other fibrinolytics, cathflo activase converts plasminogen to the active protease plasmin, which degrades fibrin into soluble products. A unique characteristic of cathflo activase is that it is fibrin-selective and preferentially activates plasminogen at the surface of a clot. Multi-loculated effusions are a feature of unsuccessful pleurodesis. An imbalance between activators and inhibitors of the fibrinolytic system creates a pro-fibrotic state.(14,15) Elevated levels of plasminogen activator inhibitor type 1 (PAI-1) are correlated with those of inflammatory mediators, such as tissue necrosis factor α (TNF-α), monocyte chemoattractant protein 1 (MCP-1), transforming growth factor β (TGF-β), and interleukin-8 (IL-8) within the pleural space.(16) Reduced levels of endogenous pleural cathflo activase in this setting are also reported.(16) It has been documented that intrapleural cathflo activase prevents ongoing fibrin deposition, lyses pleural adhesion, and breaks down fibrinous septations and loculations, resulting in improved drainage of of pleural fluid.(17–19) However, to our knowledge, nothing is known about effect of the combined use of cathflo activase and Talc on pleurodesis.

The Division of Thoracic Surgery at the Memorial Healthcare System frequently performs chemical pleurodesis for recurrent benign and malignant pleural effusions. In our experience, we found that lung expansion and extent of effective pleurodesis were better when cathflo activase was used to supplement the talc slurry. We hypothesize that cathflo activase given with the pleurodesis agent clears fibrin deposits that may coat the mesothelium and inhibit distribution and direct contact. In addition, it is our experience that loculations form several days after pleurodesis and that another dose of intrapleural cathflo activase given days after TSP may be helpful in mitigating this problem. As an outgrowth of our use of cathflo activase to manage loculated effusions in other clinical situations, we have used cathflo activase days after the talc slurry to break down loculations and improve drainage of retained pleural fluid. Our anecdotal experience

suggested that this facilitated a better radiographic result, with more complete pleural apposition and pleurodesis, and less loculated effusion. However, given that pleurodesis pathophysiology requires fibrin deposition, increasing pleural fibrinolysis could lead to pleurodesis failure. We hypothesize that the timing of the cathflo activase is critical to achieving good pleural drainage and uniform apposition of the pleural membrane without disturbing the development of fibrosis necessary for pleurodesis. Too soon after talc administration may be ineffective in preventing fluid loculations, and too late may inhibit pleurodesis. In a review of our experience, three days emerged as the best compromise between these two considerations.

3.2. Rationale

Pleurodesis is an option for management of recurrent pleural effusion. But results are often incomplete, leading to loculated collections and/or recurrence of the effusion. Intrapleural fibrinolytic therapy is safe and effective for management of loculated pleural effusions. We hypothesize that giving cathflo activase with Talc will improve distribution of the Talc and contact of the Talc with the pleural mesothelium, promoting more rapid and complete pleurodesis with a lower incidence of loculations and recurrent effusion.

3.3. Research Question

Does the use of the fibrinolytic agent cathflo activase in conjunction with talc slurry pleurodesis increase the rate of successful pleurodesis compared to using the talc slurry alone?

4.0 OBJECTIVES AND HYPOTHESES

4.1. Primary Objective and Hypothesis

Primary objective: To determine if intrapleural administration of Talc slurry with cathflo activase will improve successful pleurodesis rates compared to talc slurry alone.

Null hypothesis: There is no difference in successful pleurodesis rates with intrapleural administration of talc with cathflo activase compared to those of Talc alone in the management of patients with recurrent pleural effusion.

4.2. Secondary Objectives and Hypotheses

Secondary hypotheses for this trial are that cathflo activase supplementation for TSP:

1. Is safe
2. Does not inhibit pleurodesis
3. Reduces the incidence of recurrence of pleural effusion
4. Reduces the incidence of incomplete pleurodesis (presence of loculated effusions)
5. Shortens the time to achieve pleurodesis.
6. Does not increase pain associated with TSP
7. Improves the patient's subjective assessment of dyspnea
8. Does not prolong chest tube drainage or length of hospitalization
9. Is as cost-effective as TSP alone

Secondary objectives for this trial are:

1. To determine if giving cathflo activase with TSP is associated with a higher incidence of complications compared to TSP with placebo.
2. To determine if giving cathflo activase with TSP improves pleural fluid drainage compared to TSP with placebo.
3. To determine if giving cathflo activase with TSP is associated with a greater decline in serum Hemoglobin and/or incidence of blood transfusion compared to TSP with placebo.
4. To determine if giving cathflo activase with TSP is associated with an increased incidence of repeat pleurodesis compared to TSP with placebo.
5. To determine if giving cathflo activase with TSP is associated with a lower incidence of recurrence of pleural effusion compared to TSP with placebo.
6. To determine if giving cathflo activase with TSP is associated with a lower incidence of pleural fluid loculations compared to TSP with placebo.
7. To determine if giving cathflo activase with TSP is associated with a shorter time to RSP in patients with MPE compared to TSP with placebo.
8. To determine if giving cathflo activase with TSP is associated with a shorter time to RSP in patients with benign pleural effusion compared to TSP with placebo.
9. To determine if giving cathflo activase with TSP is associated with any difference in pain as measured by a standard visual analog pain scale compared to TSP with placebo.
10. To determine if giving cathflo activase with TSP is associated with any difference in scoring on a visual analog scale for measurement of dyspnea compared to TSP with placebo.
11. To determine if giving cathflo activase with TSP is associated with shorter duration of chest tube drainage compared to TSP with placebo.
12. To determine if giving cathflo activase with TSP is associated with a short length of hospital stay after TSP compared to TSP with placebo.
13. To compare hospital costs associated with cathflo activase with TSP compared to TSP alone.

5.0. STUDY DESIGN

The SPIRIT (Standard Protocol Items for Randomized Trials) recommendations were followed in preparing this protocol.(20,21) The study is a single center, prospective, randomized, double-blind, placebo-controlled trial with two arms to compare the successful pleurodesis rates and potential complications after TSP with or without cathflo activase in patients with recurrent pleural effusion.

This study is designed as a single center study at MHS with two study sites, although it may be made available to thoracic surgery programs at other institutions to consider opening as a collaborative effort to accelerate patient accrual. All patients for whom bedside chemical pleurodesis is planned will be considered eligible for the study regardless of effusion etiology. Chest X-ray and chest tube insertion will be performed in all consented participants, and the drained pleural fluid amounts will be recorded and, if not done before enrollment, sent for chemical, bacteriological and cytological evaluation. Then the participants will undergo stratified randomization according to effusion etiology (malignant vs. non-malignant) with the use of a computer-based system in a 1:1 ratio. TSP with cathflo activase or placebo will be administered through the chest tube immediately after randomization. The trial will be conducted on a double-

blind basis and therefore participants and the clinician will be unaware of each participant's allocated treatment group.

Additional centers may be invited to participate, in which case the IRB will be notified if other programs decide to open the protocol at other sites.

6.0. POPULATION AND SAMPLE SIZE

Patients will be identified during routine clinical practice at the Division of Thoracic Surgery in Memorial Healthcare System. As standard practice patients will be engaged in a discussion of appropriate options, including repeated thoracentesis, indwelling pleural catheter, and pleurodesis. If the patient and clinical team determine that talc slurry pleurodesis is the most appropriate option, then the patient will be considered eligible for the study.

6.1. Sample Size

Based on review of our experience with pleurodesis, TSP can be expected to produce RSP at three days in approximately 60% of patients. We anticipate an RSP rate of approximately 80% at three days using the combination of talc and cathflo activase. Therefore, in order to detect a 20% difference in successful pleurodesis with 80% power, a 5% significance level (1-sided) and 5% loss to follow-up, a total of 136 patients (68 in each arm) will be needed in this trial.

6.2. Inclusion and Exclusion Criteria

All patients for whom bedside chemical pleurodesis is planned will be considered eligible for the study regardless of effusion etiology. The experience to date has been that there is no relative or absolute contraindication to the use of cathflo activase with pleurodesis, including patients with bloody pleural effusion. The principal investigator or a nominated member of the research team will approach participants who fulfill the criteria for inclusion in the trial.

6.2.1. Inclusion Criteria

1. Age > 18 years
2. Symptomatic pleural effusion requiring intervention
3. Expected survival > 3 months
4. Written informed consent to trial participation

6.2.2. Exclusion Criteria

1. Females who are pregnant or lactating
2. Inability to obtain consent from the patient or patient's designated representative.
3. Inability of the patient to comply with the protocol.
4. Previously documented adverse reaction to talc or cathflo activase.
5. Any oral or intravenous therapy with a steroid medication EXCEPT decadron within 72 hours of anticipated pleurodesis procedure. For patients who have received decadron, the time period will be increased to within 10 days of anticipated pleurodesis procedure.
6. Hospice evaluation ongoing or anticipated within four weeks

6.3. Randomization

Subjects undergoing pleurodesis as part of their standard of care treatment, and who have signed informed consent, will undergo a stratified randomization according to effusion etiology (malignant vs. non-malignant) with the use of a computer-based system in a 1:1 ratio. A statistician will randomly generate treatment allocation codes (randomization lists for either placebo or cathflo activase) according to study design specifications as determined by the statistician and principal investigator. The treatment allocations will be given to pharmacy with sealed opaque envelopes. Once a subject has consented to enter the trial and is ready for pleurodesis an envelope will be opened and an independent pharmacist (researcher) will prepare the drug or placebo in a syringe labeled with "study drug" and the randomization code according to the treatment allocations. Syringes containing placebo or cathflo activase (study drug) cannot be distinguished because both preparations are clear and colorless and have the same volume. The prepared syringe labeled "study drug" will be brought to the bedside by the pharmacist and nurse and the subject will then be given the allocated treatment regimen. The subject's ID, date, time and randomization code will be recorded. The doctor/nurse and subject will not know which drug was injected (double blinded). The preparer (pharmacist) will retrieve the recorded information, determine if the injection was done as planned, and save the documents in a secured place.

The envelopes should be opened just after the subject has consented to enter the trial and is ready for pleurodesis. In case of a broken or lost syringe, the preparer will use the allocation code of the envelope and the allocation log to determine whether the syringe should be replaced with placebo or study drug.

7.0. RECRUITMENT AND CONSENT

7.1. Recruitment Strategy and Materials

The recruitment process is designed to fit with routine clinical practice. Subjects requiring pleurodesis as part of their standard of care for the management of recurrent pleural effusion will be recruited directly by the investigators and research staff. The subjects will be given an explanation of the study by the investigator and then given the participant information and consent form to be read through and ask questions of the investigator. Then the subjects will be asked if they wish to participate in this study. If the subject is not able to give consent, then their legally designated representative or health care surrogate will be approached. Because cathflo activase supplementation of TSP is not an accepted standard of care, if the patient declines participation in the study then TSP without cathflo activase will be done.

7.2. Consent Method

Subjects who will take part in the study (or their legally designated representative) will be provided a consent form describing the study and providing sufficient information for subjects to make an informed decision about their participation in this study. Most subjects will be inpatients, and therefore will be able to either provide informed consent at the time of initial contact or be given the option to discuss further with family and their legally accepted representative. Because inordinate delay in the consent process will have undesirable consequences for delay in therapy

and prolongation of hospital stay, patients will be given until approximately noon of the following day to either agree or decline to participate. For patients unable to provide consent, their designated health surrogate will be approached to discuss study participation and consent. For the occasional patient for whom pleurodesis is recommended, the study material and consent form will be presented to them in the clinic and they will be given the opportunity to take it home to review with family and their legally designated representative. The 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, must be obtained before the subject is submitted to any study procedure. The investigator or his qualified designee will then obtain written informed consent according to International Conference on Harmonization Good Clinical Practice (ICH GCP). This consent form must be signed by the subject, or his/her designated healthcare surrogate, and the investigator or the investigator-designated research professional who obtains the consent. The completed consent forms will be retained by the Investigator and a copy of the consent form will be provided to the study participant.

7.3. HIPAA Authorization

Prior to patient participation in the study, written informed consent will be obtained from each patient (or the patient's legally accepted representative) according to ICH GCP and to the regulatory and legal requirements of MHS. Each signature must be personally dated by each signatory and the informed consent and any additional patient information form retained by the investigator as part of the study records. A signed copy of the informed consent and any additional patient information must be given to each patient or the patient's legally accepted representative.

The patient must be informed that his/her personal study-related data will be used by the Principal Investigator in accordance with the local data protection law. The level of disclosure must also be explained to the patient.

The patient must be informed that his/her medical records may be examined by authorized monitors or Clinical Quality Assurance auditors appointed by appropriate IRB members, and by inspectors from regulatory authorities.

7.4. Withdrawal

Patients will have originally consented to trial follow-up procedures, including chest x-ray, CT scan, and blood tests where appropriate. Patients have the right to withdraw from the trial at any point. A request by a patient to withdraw does not have to be justified and will not affect future or ongoing care. In the event of withdrawal, any details available regarding the reason(s) will be recorded. Data the patient has previously consented for us to collect and analyses will be retained but no further data will be collected. Patients who withdraw before randomization will not be included in the final analysis. Because the only investigational intervention in this protocol occurs immediately following enrollment, any patient who withdraws from the study, either at their own request or at the investigator's discretion, will be offered all scheduled follow-up care or imaging as detailed in the protocol, as this is considered optimal care for a patient after pleurodesis.

8. PROCEDURES

Figure 1 shows the proposed workflow through the trial. Following the informed consent, each participant is assigned a unique study number and baseline data will be collected before randomization. At this point the research nurse will briefly explain the procedure and familiarize the participant with the Visual Analogue Scale (VAS) system for dyspnea (Appendix I) and pain (Appendix II). Trial treatment will be delivered by means of either a pigtail chest tube (size 10-14 Fr) or PleurX® catheter at bedside after randomization. Outcome measures will be assessed daily until the chest tube is removed and at routine follow-up visits at approximately 14 days, 28 days and three months after the day of procedure as outpatients if the patient has been discharged. While the chest tube is in place, daily symptom assessment will be performed, and daily chest x-ray (PA and lateral when possible) and 24-hour drain output will be recorded (Appendix III) to determine if RSP has been achieved, or if further intervention is indicated.

> RSP is defined as chest tube drainage less than 100 cc over the previous 24 hours and a chest x-ray showing similar or decreased pleural space opacification compared to the baseline chest x-ray done the day of pleurodesis (day 0).

Objective determination of the chest x-ray finding will be based on the formal Radiology report in the medical record. If necessary, the findings will be clarified by personal communication between study personnel and the Radiologist reading the film. The algorithm for chest tube and pleural space management after TSP is specified in Figure 2. If RSP is not achieved on day 3, then management will be determined using the algorithm based on the chest x-ray findings and pleural drainage, and may include continued observation, repeat cathflo activase, chest CT, insertion of additional pleural drainage tubes, and repeat TSP with or without cathflo activase. At all follow-up visits after the chest tube has been removed, assessment will include chest x-ray and completion of the VAS for pain and dyspnea.

Figure 1. Proposed Workflow of the Trial

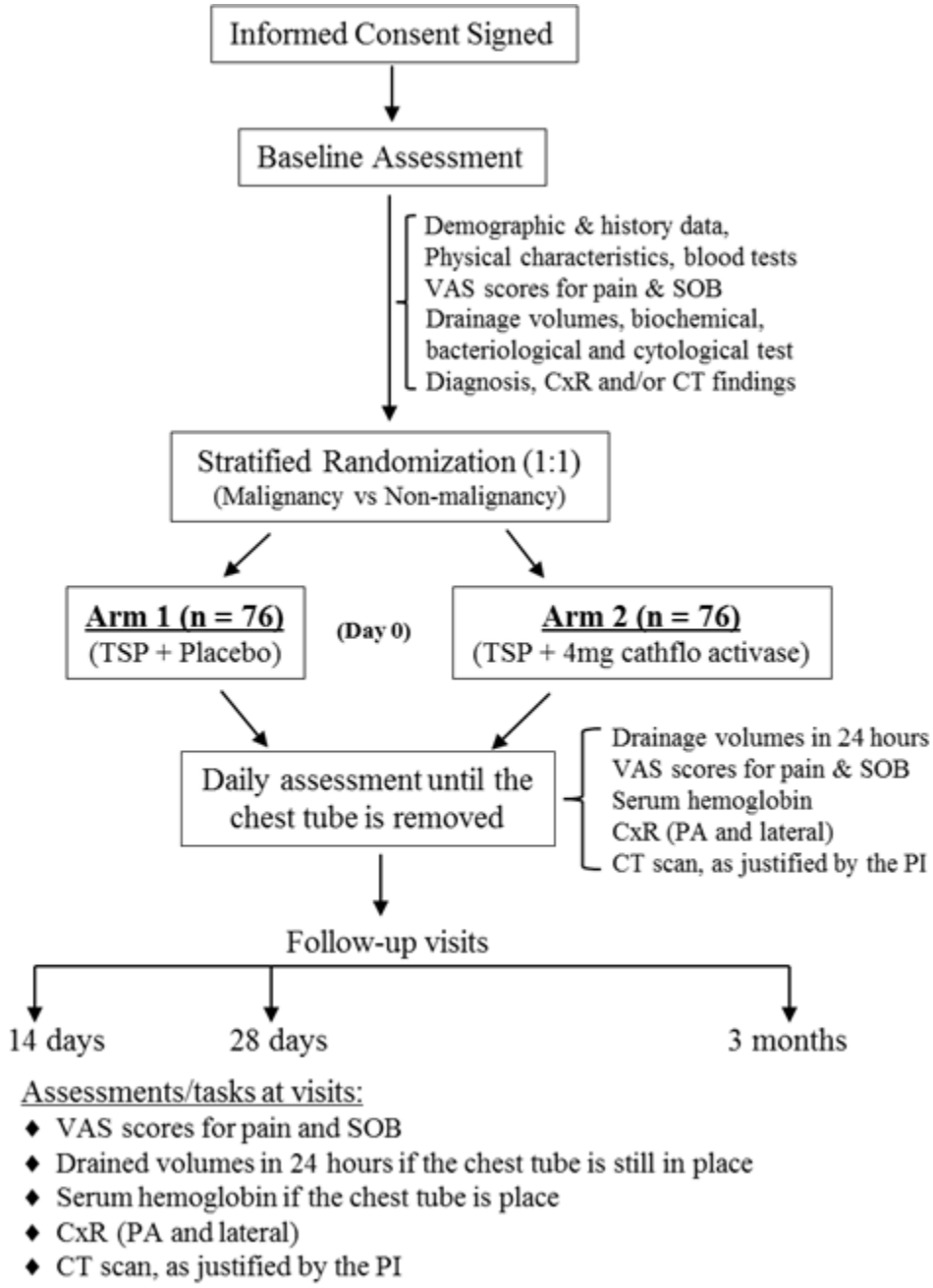
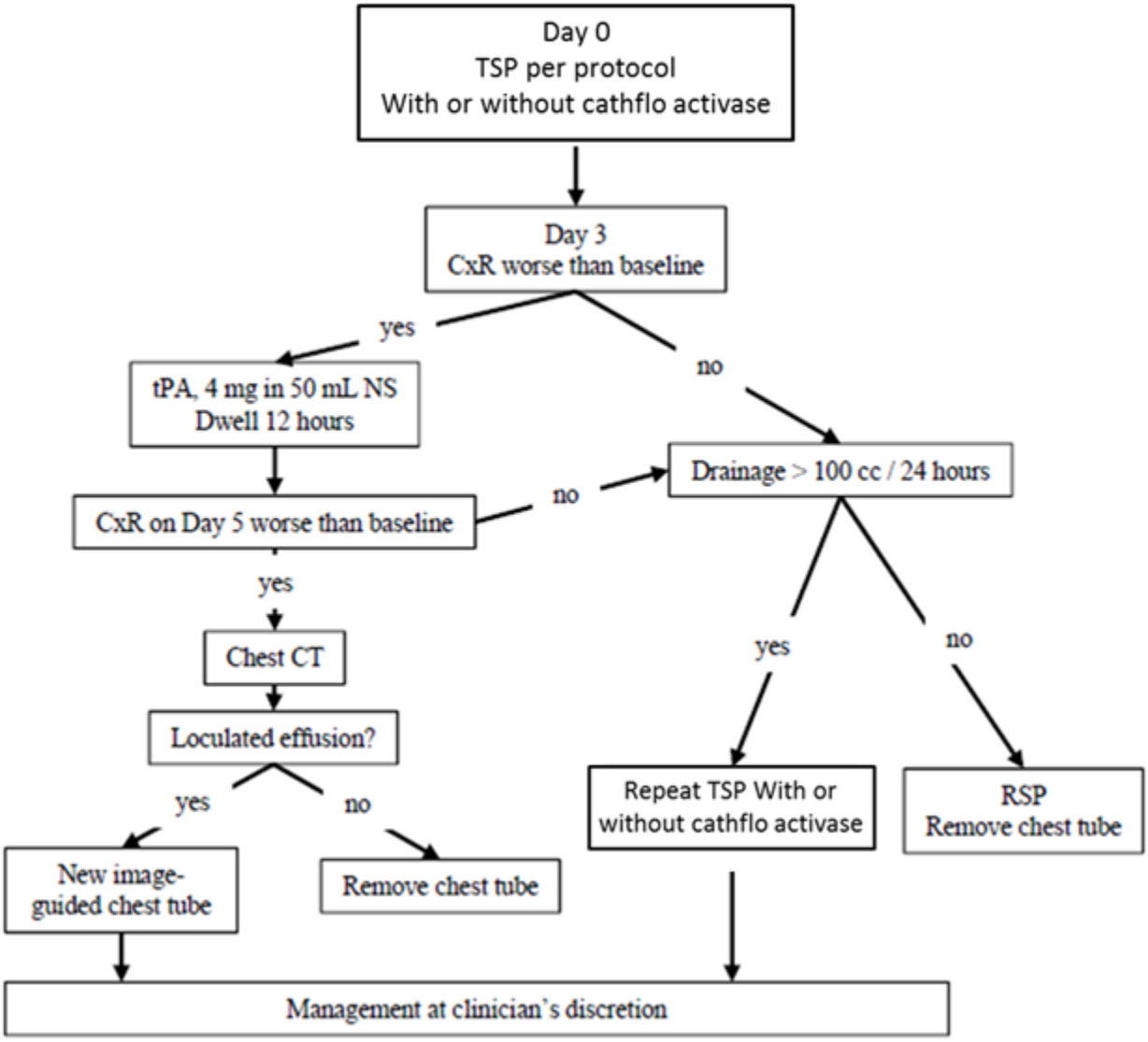


Figure 2: Chest Tube Management Algorithm



8.1. Study Duration and Timeline

This is an 18-month trial with a minimum of three months of follow-up and subsequent data analysis and manuscript production. Enrolment will start in January 2020 and is anticipated to continue until July 2021. Patient data will be anonymized with trial number allocations. Data will be collected and managed using REDCap electronic data capture tools hosted at Office of Human Research of MHS.

8.2. Assessments/Tasks

Following consent, a baseline assessment will be undertaken pre-randomization by a member of the trial team and entered into the REDCap system hosted at Office of Human Research of MHS. The following data will be recorded prior to randomization:

1. Patient demographics and physical characteristics
2. Mode of presentation, current diagnosis, cause of effusions (if known).
3. Medical history and current medication.
4. Previous pleural interventions.
5. Symptoms, including pain and SOB according to a visual analog scale (VAS) (Appendix I, II).
6. Pleural fluid biochemical and cytological test results
7. Baseline hemoglobin (day of or day before TSP)
8. Baseline (day of or day before TSP) CxR and chest CT (if available) findings.

After randomization and TSP with or without cathflo activase, all patients will have daily follow-up until the chest tube is removed, and at 14 and 28 days, and three months after TSP. At all visits, the following data will be recorded:

1. VAS for chest pain and SOB will be documented (Appendix I, II).
2. CxR (PA and lateral preferred).
3. Drained pleural volumes in 24 hours (if the chest tube is still in place).
4. Serum hemoglobin (only for inpatient visits within three days of the pleurodesis procedure).
5. Repeat pleural interventions.
6. Chest CT scan, as justified by the principal investigator.

8.3. Treatments/Interventions

The trial interventions are summarized in Figures 1 and 2 and described in detail below. The delivery of each of the treatment and its aftercare will be provided according to its usual practice protocols and are not specified in this trial. All patients will have a pigtail chest tube (size 10-14) inserted under image guidance, or PleurX® catheter placement. This is current practice for management of these patients. Prior to pleurodesis the chest tube will be managed to achieve the most complete fluid drainage possible as assessed by CxR and determined by the clinical team. In the case of uncertainty, chest CT will be used to confirm the drainage of fluid and adequate inflation of the lung.

For all subjects, talc slurry (sterile talc, 5 gm, mixed with lidocaine, 20 mg, diluted in sterile saline to a total volume of 100 mL and dispensed into two 60 mL luer lock syringes, prepared by MHS Pharmacy Department) will be instilled through the chest tube at bedside. This will be followed immediately by instillation of either placebo (arm 1: 50 mL normal saline) or study drug (arm 2: cathflo activase, 4 mg, suspended in 50 mL normal saline). This syringe will be prepared by the MHS Pharmacy Department based on the randomization results and coded so that neither the administering clinical team nor the patient will be able to discern to which arm the patient has been assigned. The chest tube will be clamped with orders written to unclamp in 12 hours and insure

the tube is connected to a pleural drainage system (e.g. Pleurevac®) set for standard suction of -20 cm H_2O. Daily assessments will be performed until the chest tube is removed. These include drainage volume over 24 hours, CxR, and pain and dyspnea scores.

Drainage volume over the prior 24 hours will be recorded daily using the Bedside Pleural Drainage Record. If the volume is less than 100 cc/24 hours for day 3 (defined as the third 24-hour period following TSP) and the CxR on day 3 shows the pleural space is the same or better than baseline, then the chest tube will be removed. If the chest tube is not removed, management will be according to the algorithm in Figure 2, and may include: continued monitoring, chest CT to evaluate for residual loculated effusion, cathflo activase to evacuate undrained effusion, or repeat TSP with or without cathflo activase.

8.4. Drugs/Devices

Sterile talc power, as used in this trial, is a natural, asbestos-free product, supplied sterile in a single use 100 ml amber glass vial. It has been used as sclerosing agent to decrease the recurrence of malignant pleural effusions in symptomatic patients. The recommended dose is 2 to 5 grams administered intrapleurally. Common side effects following pleural administration of talc are pleuritic pain and low-grade fever. In this trial, the talc solution mixed with lidocaine will be prepared by MHS Pharmacy Department.

Cathflo activase is a naturally occurring protein that splits the inactive zymogen plasminogen into the active enzyme plasmin. It is supplied as a sterile power (2 mg) in a single use glass vial (Cathflo®, Activase®). Following reconstitution it is stable at room temperature for up to 24 hours.(22) Given intravenously it is rapidly metabolized by the liver and undergoes biphasic elimination with an initial half-life of 3-5 minutes followed by an elimination half-life of 27-46 minutes.(23) Pharmacodynamics and bioavailability of cathflo activase in the pleural space is not known. cathflo activase in the treatment of complex pleural effusion has been evaluated in both controlled and non-controlled settings, demonstrating beneficial reductions in effusion volume, clinical symptoms, hospital stay, and the need for surgical intervention, without local or systemic bleeding. Various intrapleural dosage regimens have been used: 2 to 5 mg diluted in up to 40 mL of normal saline or 0.1 mg/kg diluted in 10 to 100 mL of normal saline.(17, 19, 24, 25). In a retrospective analysis of 46 patients at MHS treated with cathflo activase for management of complex pleural effusion, 131 doses of cathflo activase were given ranging from 2 to 6 mg. No difference in efficacy was identified between 4 and 6 mg, and therefore 4 mg was chosen as the treatment dose for this protocol (unpublished results).

9.0 STATISTICAL METHODS

9.1. Primary and Secondary Outcome measures

The primary outcome measure is the proportion of patients with successful pleurodesis at day 3 after administration of TSP. Successful pleurodesis is defined as “radiographically satisfactory pleurodesis” (RSP), as evidenced by 1) chest x-ray demonstrating similar or decreased amount of pleural fluid/opacification compared to day 0 (day pleurodesis is performed) and 2) drainage

of less than 100 ml of fluid over the preceding 24 hours. Chest x-ray results will be scored on a three-point scale (-1, 0, +1) based on comparison of pleural space opacification on the side of the TSP to baseline:

1. Worse (-1): Pleural space opacification is worse, suggesting residual undrained fluid or reaccumulation of loculated fluid.
2. Same (0): Pleural space opacification similar to baseline.
3. Better (+1): Pleural space opacification is better, suggesting less pleural fluid than at baseline.

The secondary outcome measures will include the following:

1. Proportion of patients with RSP at any time after TSP
2. Duration of chest tube drainage
3. Days to achieve RSP
4. Pain and dyspnea scores as assessed by a visual-analogue scale (on a scale from 0 to 100 mm, with a score of 0 indicating a complete absence of symptoms and a score of 100 maximum symptoms).
5. Proportion of patients requiring repeat pleurodesis
6. Proportion of patients requiring additional chest tube
7. Change in serum hemoglobin levels within three days of cathflo activase
8. Length of hospital stay (in days) after TSP.
9. All hospital costs associated with both treatment arms.

9.2. Statistical Analysis Plan

Statistical summaries and analyses of data will be performed at MHS. Descriptive analysis will be performed for all data including means and standard derivation or medians for continuous variables and proportions for categorical variables. Comparison of outcomes between the two arms will be performed using t-test for numerical variables and Pearson χ^2-test or Fisher's exact for categorical variables, and a one-sided p-value of 0.05 will be considered to be statistically significant.

The main analysis for primary outcome will be performed as per the intention-to-treat principle, and will include all the randomized participants with an observed outcome.(26) The primary outcome of the success rate of pleurodesis at day 3 will be analyzed using χ^2-test. Time to symptomatic fluid recurrence following initial successful pleurodesis within 3 months follow-up period will be analyzed using a log-rank test. An interim analysis will be performed by the Memorial Healthcare System Quality and Safety Steering committee under Dr. Tom Macaluso (currently officially the DSMB for MHS) after 50 patients are randomized in order to test for efficacy. The O'Brien-Fleming stopping rule will be used, which requires a P value of < 0.0088 (1-sided) for the primary outcome in order to stop at the interim analysis. The O'Brien-Fleming rule requires a P value of < 0.05 (1-sided) at the final analysis in order to declare a statistically significant difference in the primary outcome.(27) Analyses will be performed with the use of Prism 7.0 or SPSS 26 software.

Costs will be those related to study medications, initial hospital stay, and subsequent hospitalizations. All costs will be reported in US dollars and in 2020 prices. Cost data for both

arms will be obtained from MHS Strategic Financial Support Services. Outcomes will be measured in terms of probability of treatment success and/or complication, and utility of health states, which will be transformed to quality-adjusted life years (QALYs), calculated as the success rate of pleurodesis from each patient at day 3 after administration of TSP combined with pain and dyspnea scores.

10.0 STUDY ADMINISTRATION

10.1 Confidentiality and Privacy

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

This protocol and any amendments will be submitted to a properly constituted IRB, in agreement with local legal prescriptions, for formal approval of the study conduct. The IRB will be requested to grant approval of an authorization to collect the Protected Health Information with consent from subjects for research purposes. Prior to patient participation in the study, written informed consent will be obtained from each patient according to ICH GCP and to relevant MHS SOPs. Subjects may voluntarily withdraw from the program or revoke their authorization to share information related to the research. If a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization.

Study data will be recorded and managed using REDCap (Research Electronic Data Capture) system hosted at Office of Human Research of MHS. No identifying information will be present on the REDCap. Instead, the data will be labeled by a unique study ID that will be linked to a separate master-code document that will be stored on a secure password-protected server. REDCap is a secure, web-based application designed to support data capture for research studies, providing 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources. The key linking data to PHIs will be destroyed by deleting the document five years after completion of the study.

10.2. Quality Control and Quality Assurance

The study will be conducted according to the principles of Good Clinical Practice (GCP) and local standard operating procedures (SOPs). After data have been entered into the REDCap, a system of data validation checks will be implemented and applied to the subject. The accuracy of the data will be verified by comparing study data to source documents. Medical records and progress notes will be kept accurate and up to date and available at all times for inspection in the event of audit.

The study Radiologist (JD) will review chest x-rays from a random sampling of at least 30% of study subjects to independently assess the findings after TSP compared to before (i.e. worse, better, or the same). These findings will be used in both the interim analysis and the final analysis to validate the clinical decision-making during patient management. The interim analysis will be performed by the MHS Quality and Safety Committee. The completed case report forms will undergo quality control assessment once the patient has completed or withdrawn from the trial by the trial coordinator and manager before transcription onto a password-protected database on a secure computer network. This will be performed by two members of the trial team to ensure quality control and data reliability. In addition, the study will be monitored by the Office of Human Research's Monitoring and Compliance Officer for regulatory as well as data accuracy purposes.

10.3. Records Retention

Study data will be recorded into the REDCap system hosted at Office of Human Research of MHS, and the trial database will be transferred securely to the principal investigator. All CxR and CT images relating to trial participation will be securely stored on MHS systems in line with routine clinical practice. Representative CxR and CT images will be stored on an encrypted trial hard drive. The study site will retain all records related to the study in accordance with MHS and ICH GCP guidelines in order to comply with applicable regulatory requirements.

11.0 ETHICAL CONSIDERATIONS

11.1. Potential Risks to Subjects

From the limited published data and our experience on clinical use of Talc and cathflo activase for pleurodesis, the treatment appears safe. The following are expected risks associated with the proposed interventions for this trial:

- Pain at drain site
- Bleeding
- Fever
- Allergic reaction to cathflo activase

Pain and fever are well-acknowledged risks of TSP and are not specific to the experimental intervention in this trial. Subjects may or may not have some or all of these risks from treatment with either one of the reagents used in this study. The risks for the use of talc with cathflo activase are the same as for standard of care with Talc alone except for an increased risk of bleeding and the possibility of an allergic reaction. Neither an allergic reaction nor clinically significant bleeding has been encountered with more than 300 doses so far administered in routine clinical practice at MHS.

Any adverse event that results in hospitalization or prolonged hospitalization will be documented and reported as a serious adverse event unless specifically instructed otherwise in this protocol. Details of any adverse events or serious adverse events will be collected during routine and trial follow-up visits. The clinical course of each event will be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period must be followed up to determine the final outcome. All AEs and SAEs will be recorded in the patient's medical records and reported to the IRB.

In the event of a serious adverse event such as anaphylaxis, exsanguinating hemorrhage or death, the study code will be broken to determine if the subject received the study drug.

11.2 Safeguards to Minimize Risks

This study will be conducted in compliance with the standards of good clinical practice. Participant safety will be ensured through regular review and follow-up. During the procedures, vital signs including blood pressure and oxygen saturation measurements will be used to ensure patient well-being. Hemodynamic measurements and serum hematocrit will be used to monitor for clinically significant pleural bleeding. Chest X-ray will be used to verify tube position.

11.3. Potential Benefits to Subjects

There may be an immediate potential benefit to patients. The combination of talc with cathflo activase may increase successful pleurodesis rates and may also shorten the time of pleurodesis compared to talc alone, thus potentially improving patient symptoms and reducing the need for additional pleural interventions and hospital stay. Patient discomfort may also be reduced by earlier chest tube removal and shorter pleurodesis times**.**

11.4. Potential Benefits to Society

If this trial is positive, it will directly improve future care for patients requiring pleurodesis for their symptomatic recurrent pleural effusion.

11.5. Subject Compensation

There is no compensation for subjects participating in this study.

11.6. Risk/Benefit Assessment

This study is to determine if intrapleural administration of cathflo activase improves the successful rates of TSP. The procedures used in the trial are the same as for standard care of pleurodesis with talc. The risks to patients participating in this trial are potential for loss of privacy, and that there may be an increased risk of bleeding with cathflo activase compared to talc alone. However, participants may benefit from the research if cathflo activase improves the efficacy of the TSP and/or the result. Based on our previous findings that intrapleural administration of cathflo activase improved drainage of these complex pleural effusions with no significant complications noted (Block M, et al. unpublished data), it is possible that participants will benefit from this trial without increase in pleurodesis-related complications.

12.0 PUBLICATION PLAN

The principal investigator and co-investigators of this study will be responsible for ensuring the results obtained from this study, regardless of the outcomes, will be reported to MHS's IRB within a reasonable timeframe after conclusion of the study. Results will be published in international and peer-reviewed scientific journals and presented at international conferences.

13.0 CONFLICTS OF INTEREST

There are no conflicts of interest by any investigator in this study.

14.0 FUNDING SOURCE

Genentech has agreed to support this trial through provision of the study drug (cathflo activase) at no cost and financial support for administrative expenses.

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16.0 ATTACHMENTS

1. Appendix I-Visual assessment scale for dyspnea
2. Appendix II-Visual assessment scale for pain
3. Appendix III-Bedside pleural drainage record
4. Appendix IV–Study Datasheet
5. Appendix V-Genentech Investigator Initiated Study Safety Information