MEMORIAL HEALTHCARE SYSTEM
INFORMED CONSENT FOR RESEARCH

STUDY TITLE: Prospective Randomized Trial of Intrapleural Fibrinolytic Therapy to Enhance Chemical Pleurodesis

Name of Participant: _____

Study Doctor(s): Mark Block, MD; Francisco Tarrazzi, MD; Syed Razi, MD; Catherine Tami, APRN; Krystina Serpa, APRN; Jenessey Gonzalez, APRN

INFORMATION ABOUT THIS CONSENT FORM

We are asking you to take part in a research study. This form gives you information that will help you decide if you would like to take part. All information included in this form is important, but there are several points that you should pay special attention to:

- *Your participation is completely voluntary*. This means that you do not have to participate in this study if you do not want to. Even if you decide to take part, you can leave at any time if you change your mind.

- *We are asking you to take part in research*. Research is done by doctors to learn new information about diseases and how to treat them. Research is different from regular medical care, which involves treatments that have already been tested.

- *The purpose of this study* is to determine if adding the drug cathflo activase to the standard solution of talc powder (talc slurry) will improve results of talc slurry pleurodesis for the treatment of recurring pleural effusions. Cathflo activase is a naturally occurring enzyme that dissolves blood clots, and it has been used to treat patients who have pleural effusions that do not drain easily. We hope that with the information obtained from this study, we will learn which technique works best.

- *The potential risks of this study* are the risks of allergic reactions and bleeding. All patients in this study will undergo talc slurry pleurodesis and will therefore be exposed to risks associated with this procedure. Talc slurry pleurodesis has been used for decades all over the world and is widely considered safe and effective. Rare serious complications include an allergic reaction to the talc, and lung swelling as a reaction to the talc. Common and less serious side effects include pain that lasts for a few hours, and fever. You may or may not have any of these side effects. There may be other risks that are unknown.

- *The potential benefits of this study* are to shorten the time it takes to achieve effective pleurodesis, and to improve the results of pleurodesis, thus potentially improving your symptoms, reducing the need for additional pleural interventions and shortening your hospital stay. If this trial is positive, it will directly improve future care for patients requiring pleurodesis for their symptomatic pleural effusion.

- *The alternative to participation* is that you do not have to participate in this study. You will receive the treatment (TSP only or TSP+ cathflo activase) that is most appropriate for you, regardless of whether you are in the study or not.

- Please read this entire form carefully. You may also ask the research staff to read this form to you. This form may have words or phrases that are difficult to understand. If you have questions about any parts of this form, please ask the research staff to explain them to you. You may wish to talk about this study with others (for example, your friends, family, or other doctors). If you decide to take part in this study, you will be asked to sign this form. Please make sure you understand what the study is about before signing the form. If you agree to take part, you will be given a copy of this form to keep.

PURPOSE OF THE STUDY

The purpose of this research study is to compare the potential benefits of supplementing standard talc slurry pleurodesis with intrapleural administration of cathflo activase for the management of patients with recurrent pleural effusion. We are going to observe how long it takes to complete pleurodesis, and how good the results are in terms of left-over pockets of fluid or recurrence of the effusion, and any complications or discomfort that you experience. You will be randomly assigned to either standard talc slurry pleurodesis or talc slurry pleurodesis with cathflo activase, both approved hospital treatments.

The researchers will need to collect personal data about you and relevant health information, laboratory and radiography results. Chest x-rays (CxR) and chest CT scans will be done as a routine part of the pleurodesis treatment, and the results will be collected for the research. We may also wish to collect some of the drained fluid (which would otherwise be discarded) for research purposes. We hope that with the information obtained from this study, we can develop a better way to stop pleural effusions with pleurodesis. If this trial is positive, it will directly improve care for patients with recurrent pleural effusion, to the benefit of ~1.5 million patients per year.

STUDY PARTICIPANTS

Participation in this study is completely voluntary. You do not have to participate if you do not want to. If you agree to participate now and change your mind later, you can leave this study at any point. If you leave this study, there will be no penalty and you will not lose any benefits to which you are otherwise entitled. The attitude of your doctor toward you will not change and you will continue to receive standard medical care.

Who can take part in this study?

All patients for whom bedside chemical pleurodesis is planned will be considered eligible for the study regardless of the cause of the pleural effusion. The experience so far on hundreds of patients receiving this treatment has been that there is no reason to avoid the use of cathflo activase with pleurodesis, including evidence of bleeding in the pleural effusion.

To be eligible for this study, you have to meet the following criteria:

- Age > 18 years
- Symptomatic pleural effusion requiring intervention

- Expected survival > 3 months
- Written informed consent to trial participation

You will not be eligible for this study if you meet any of the following criteria:

- Females who are pregnant or lactating
- Previously documented adverse reaction to talc or cathflo activase.
- Oral or intravenous steroid therapy
- Inability to give informed consent or comply with the protocol

How many people will take part in this study?

We expect that 136 people from Memorial Healthcare System will participate in this study.

Participants will be assigned to two groups. 76 will be assigned to standard talc slurry pleurodesis (TSP) group and 76 will be assigned to the talc slurry pleurodesis with cathflo activase (TSP + cathflo activase) group. The assignment to the groups will be random (by chance), just like flipping a coin. If you choose to take part and meet the study requirements, you will be enrolled in the study, and you will have a 50:50 chance of undergoing talc pleurodesis or talc with cathflo activase pleurodesis.

The trial will be conducted on a double-blind basis, which means that you and your doctor will not be able to choose which group you will be assigned to, and neither you nor your doctor will know to which group you have been assigned.

STUDY PARTICIPATION

What will happen to me on this study?

If your doctors determine that talc slurry pleurodesis is the best treatment for your pleural effusion, then one of the study investigators will talk to you, take a medical history from you and assess your suitability for the study. They will then give you this information sheet to read, and you will be given time to consider this, ask questions, and discuss it with your family and friends. If you decide to take part you will be asked to read and sign this form. You will have a 50:50 chance of receiving the cathflo activase with the talc pleurodesis. If you have effusions on both sides, you will be randomized separately for each side. We will undertake the assigned treatment as soon as possible to ensure quick relief of your symptoms. The research nurse will briefly explain the procedure and familiarize you with the Visual Analogue Scales (VAS) used to assess your symptoms of pain and shortness of breath (SOB). We may collect some of the drained fluid (which would otherwise be discarded) for further examination. Trial treatment will be delivered to you by means of either a small drain inserted into your chest cavity. This is current practice for management of patients with pleural effusion and is not specific to this trial.

For all participants, talc slurry (sterile talc, 5 gm, mixed with lidocaine, 20 mg, diluted in sterile saline to a total volume of 50 mL and dispensed into a 60 mL luer lock syringe, prepared by MHS Pharmacy Department) will be instilled through the chest tube at bedside. This will be followed immediately by

instillation of either placebo (50 mL normal saline) if you are assigned to TSP group or study drug (cathflo activase, 4 mg, suspended in 50 mL normal saline) if you are assigned to TSP + cathflo activase group. 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.

You will be closely monitored for any potential side effects that may occur with either treatment by the research coordinator. Daily assessments to include drainage volume over 24 hours, chest x-Ray (CxR), and pain and dyspnea scores will be made until the chest tube is removed. If the drainage volume is less than 100 cc/24 hours for the third day after the talc slurry is given (defined as the third 24 hour period following TSP) and the CxR on day 3 shows the pleural space is as clear or more clear than the CxR before the talc was given, then the chest tube will be removed. If the chest tube is not removed, monitoring will be continued and additional tests such as a chest CT may be done. It may be necessary to insert an additional drain if there is a pocket of fluid that has not drained, to give cathflo activase by itself to improve drainage, or to repeat the talc slurry pleurodesis if the drainage does not slow down enough.

Follow up will be conducted at the Division of Thoracic Surgery offices at Memorial Healthcare System. Follow up evaluations will be done at 14 days, 28 days and three months after the pleurodesis. If you have been discharged from the hospital then you will be asked to return for an appointment in the office. At these visits a CxR will be done and you will be asked questions about your breathing, chest pain, and any problems you have encountered since you were last seen by one of study team members.

However, if you develop symptoms at any point, call the Thoracic Surgery team at the phone number below and we will arrange extra appointments and appropriate treatment immediately. If you find that you need to change your study appointment date or time please let us know as soon as possible.

If you do not agree to take part in the study, your doctor will decide the best treatment for you. You will receive the treatment (TSP only or TSP+ cathflo activase) that is most appropriate for you, regardless of whether you are in the study or not.

How much of my time will be needed?

If you participate in this study, you will be expected to complete three follow up visits after the day of the procedure as an outpatient if you have been discharged. Your first follow up appointment will be 10-14 days after the drainage tube is removed from your chest, then the standard schedule for follow up will be 28 ± 4 days, and then three months. You will be expected to allow the study team to contact you by phone or bedside visit if you are still in the hospital for scheduling your appointments. At these visits you will be asked questions about your breathing, chest pain, and any problems you have encountered since we last reviewed you. You may have a CxR and/or CT scan during your follow up visits.

How long will I be on this study?

We will follow you up through the course of your treatment to see if the treatment is successful. Your participation will end after your 3 month follow up visit. However, if you have problems related to the study treatment, we will follow you until it is resolved.

Will I be told the results of the tests done for this study?

We will share the clinically relevant test results with you.

RISKS AND BENEFITS

What are the risks associated with this study?

Medicine is not an exact science. No one can promise that you will benefit from the study treatment. Your disease condition may not respond to the treatment or may cause a bad result. Some of these bad results can cause injuries that will not heal or they can even lead to death. There are risks that we know of and expect but there can also be new risks that we are not aware of yet.

For participants involved in this study, the known or expected risks include:

- Pain at drain site
- Bleeding
- Infection
- Pneumothorax
- Fever
- Loss of confidentiality and privacy

These are well-acknowledged risks of talc slurry pleurodesis. You 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 with the exception of an increased risk of bleeding, although clinically significant bleeding has not been encountered with more than 300 doses so far administered in routine clinical practice. Rarely, allergic reactions can occur. There may be other risks that are unknown.

What will be done to protect me from these risks?

This study will be conducted in compliance with the standards of good clinical practice. The researchers will try to protect you and minimize these risks by using procedures already being performed on the patients for treatment purposes. 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. You will be also closely monitored for any potential risks by the research team. Any personal or health information will be kept private and confidential. It will be stored securely and only authorized persons can access to it.

What will happen if I get hurt or become sick as a result of taking part in this study?

There is a minimal risk that you may be hurt or become sick as a result of taking part in this study. If you are hurt, become sick, or experience any side effects, tell your study doctor and your regular doctor as soon as possible.

If you are hurt, medical care will be provided to you. All of that medical care will be charged and paid for in the same way it would be if you were not part of the study. Neither the study sponsor, nor the investigating doctors, nor the Memorial Healthcare System will pay for that care. Signing this consent

form does not take away any of your legal rights. It does not release anyone from liability for negligence.

Funds to pay for pain, expenses, lost wages, and other damages caused by the injury are not routinely available. If you need help paying for losses or care caused by such an injury, ask the study doctor or a social worker about how you might get help.

If I take part in this study, can I also participate in other studies?

Being in several studies at the same time, or even at different times, may increase the risks to you. It may also affect the results of the studies. Before you take part in multiple studies, talk to the doctors involved in each study.

Will I benefit from taking part in this study?

You may benefit as a result of your participation in this study. The study is primarily aimed at assessing the outcome of these two different management options for recurrent pleural effusions, to see which one is better. So you may benefit from improved results with improvement in your symptoms, reducing the need for additional pleural interventions, and shortening your hospital stay. Your discomfort may also be improved by earlier chest rube removal and shorter pleurodesis times. There is, however, no guarantee that you will benefit from your participation in this study.

Will I be told if the researchers find out new information that might affect my willingness to take part in this study?

The researchers will tell you if they learn any important information that may change your willingness to continue to take part in the study. You may also be asked to sign a new consent form that will include the new information.

OTHER OPTIONS

What are my options if I do not want to take part in this study?

You do not have to take part in this study. If you do not take part, there may be other ways to treat your recurrent pleural effusion. These include in-patient repeated thoracentesis, indwelling pleural catheter, and talc pleurodesis without cathflo activase. You will still receive the appropriate medical care from your doctor, including the above described standard talc slurry pleurodesis treatment as required. Always talk to your doctor before starting any other treatment. Your healthcare providers' attitude about you or your care will not be affected by this decision.

CONFIDENTIALITY OF RECORDS

How will the researchers protect my privacy?

Your participation in this study will be kept as confidential as possible within the law. Any personal or health information will be kept private and confidential. It will be stored securely and only authorized persons, who are aware that it must be kept confidential, will have access to it. Your study details will be given a number so your identity will not be revealed. The trial records will be kept in the Department of Thoracic Surgery of MHS during the study and in a locked archive for at least 5 years from the time

the study is closed. They may be destroyed at any time thereafter.

Could any data or specimens collected from me be used in future research?

We may remove all identifying information from the data or specimens collected from you and use the de-identified data or specimens for future research studies or share with other investigators for future research. Since there will be no way to link the data or specimens to you, we will not ask you to sign an additional informed consent form.

AUTHORIZATION TO RELEASE PROTECTED HEALTH INFORMATION

Authorization (permission) to use or disclose (release) identifiable health information for research.

This research study will use records of current and/or future identifiable health information. This information will come from the records of your hospital, doctors' offices, clinics, or other places you get healthcare. This information also comes from your healthcare billing records or insurance records. It includes information about the cost of your treatments and care. The information you allow to be disclosed and used is described in the "What will happen to me on this study?" section of the consent for this study. It is also the information described in the consent under the section about coverage of research-related injuries (if applicable). This information will be used for the purpose of meeting the goals of this study. You allow the use and disclosure of this information to

- the researchers, doctors taking part in the study and their assistants;
- Memorial Healthcare System Institutional Review Board;
- the Food and Drug Administration (FDA);
- people and organizations acting for any of the above.

Other people or organizations that help with this research may also get your medical information. They may get your blood, or body tissue samples, or slides or imaging studies. These other people and organizations include central laboratories, central review centers, and central reviewers.

If it applies to your case, you give permission to use or disclose information about:

- Acquired Immunodeficiency Syndrome (AIDS)
- Human Immunodeficiency Virus (HIV) infection
- mental or behavioral health or psychiatric care
- or treatment for drug or alcohol abuse.

You are letting Memorial Healthcare System and your healthcare facilities and providers give this information to the people, organizations, and parties listed above. You are also allowing (blood or body tissue samples or imaging studies) to be sent to a central laboratory to help with this study.

The term “Protected Health Information” means the information about your health that is protected under the law. It includes new and existing medical records and test results that contain information that could be used to identify you. It means medical records that include ways to identify you, such as your name, address, telephone number, date of birth, medical record number, and/or social security number. This may include information in your medical record and information created or collected during this study. It includes long-term information about your general health status and the status of your disease.

Federal and state laws require your records to be kept private. However, no one can promise complete confidentiality. Your Protected Health Information will sometimes be used or disclosed in the ways described in this form. In addition, after the researcher discloses your records to others then the law may no longer protect the privacy of your records listed above.

The results of this study may be published, but those publications will not identify you. Scientific data from this study may be presented at meetings. It may be published so that the information may be used to help others. Your participation in the study will not be made known and will be kept strictly confidential.

This authorization is voluntary. You do not have to give it. But, if you will not allow the use and disclosure of your identifiable health information, you will not be allowed to be part of this study. You can cancel this authorization at any time. But if you cancel after you have started the study, you will be removed from the study. Your canceling this authorization will not affect any use or disclosure made before the cancellation. That information will continue to be used in the study. Blood and body fluids you gave to the study may continue to be used. It will not change any action that anyone had made because he or she relied on your authorization. It means that no new Protected Health Information about you will be used or disclosed. You may cancel this authorization by giving a written notice to:

Dr. Mark I. Block

1150 N 35th Ave #660

Hollywood, FL 33021

Phone: 954-265-1125

Until this study is over, you will not be given study information about yourself. You will not be told which study treatment you are getting. That has been kept secret from you during the study so that your beliefs about the drug will not change the results. You will be able to get this information at the end of the study.

This authorization does not have a fixed ending date. It stays in effect until it is canceled.

FINANCIAL INFORMATION

What are the costs associated with the study?

Genentech (manufacturer of cathflo activase) is providing the drug for free. All of your medical care will be charged and paid for in the same way it would be if you were not part of the study, and you will not be charged extra for taking part in the study.

If you do not have health insurance, or if you think your health insurance will not pay for research related costs, talk to the study doctor or call your health insurance provider before taking part in this study.

Will I be paid for being in this study?

You will not receive any monetary compensation for your participation in this study. If you have any questions about this, please feel free to discuss this with the study doctor or study staff.

Could anyone profit financially from the study results?

The study is primarily aimed at assessing the outcome of the two different management options for recurrent pleural effusion, and there is no financial support for this study. You will not receive any financial benefits from any commercial products that may result from this study. The investigators do not have any financial interest in entities that may or may not benefit from the outcome of this study.

ENDING THE STUDY

What do I have to do to stop participating in the study?

You can leave the study at any time. You can leave even before the study procedures are completed. There is no penalty and you will not lose any benefits to which you are otherwise entitled. The attitude of your doctor will not change and you will continue to receive standard medical treatment.

To withdraw from the study, please send a written note to the study doctor. The contact information for the study doctor is provided in the section “Contact Information” of this form.

Can the study doctor remove me from the study?

You may be taken out of the study if:

1. Staying in the study would be harmful to you.
2. You need treatment not allowed in the study.
3. You fail to follow instructions.
4. You become pregnant (females).
5. The study is canceled.

We may learn about new things that might make you want to stop being in the study. If this happens, you will be informed. You can then decide if you want to continue to be in the study.

Even if you stop taking part in the study your medical information will still be collected and shared as part of the study. This is to try to find out the long term results of the care you got while you were part of the study. However, none of your future medical information will be used or shared as part of the study, if you request that.

CONTACT INFORMATION

Who do I contact if I have question about this study?

You can contact the Principal Investigator (PI) if you have any questions at any point in the study. Let the Principal Investigator know if you have a research-related problem or injuries at any time during the study. The Principal Investigator's contact information is below:

Dr. Mark I. Block

1150 N 35th Ave #660

Hollywood, FL 33021

Phone: 954-265-1125

If you have any questions about your rights in this study, you may contact in writing or by telephone:

The Chairman of the Institutional Review Board

Memorial Healthcare System

3501 Johnson Street, Hollywood, Florida 33021

Telephone number (954) 265-1857.

Where can I get more information?

If you want more information about this study, ask your study doctor. You may also visit the following Web site at http://clinicaltrials.gov/ to learn more information about participating in research studies. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

STATEMENT OF CONSENT

I have read and fully understand this form. The study has been explained to me. All of my questions were answered to my satisfaction. I sign this form freely and voluntarily. I agree to freely take part in this study. **A copy of this signed form will be given to me if I decide to take part.**

_____ _____

PRINT NAME OF PARTICIPANT DATE

_____ _____

SIGNATURE OF PARTICIPANT (18 and older) DATE

_____ _____

PRINT NAME OF AUTHORIZED REPRESENTATIVE RELATIONSHIP/AUTHORITY

_____ _____

SIGNATURE OF AUTHORIZED REPRESENTATIVE DATE

_____ _____

SIGNATURE OF CONSENTING PERSONNEL DATE

STATEMENT OF INVESTIGATOR:

I have discussed the nature of this research study and its possible benefits, risks, and alternatives with the participant (and/or his/her authorized representative). I have answered all of the participant's (and/or his/her authorized representative's) questions. The participant (and his/her authorized representative) stated that this information was understood to their satisfaction.

_____

PRINT NAME OF INVESTIGATOR

_____ _____

SIGNATURE OF INVESTIGATOR DATE

Each person who signs the consent must personally enter the date for his/her signature.