CEDARS-SINAI MEDICAL CENTER

CONSENT FORM FOR RESEARCH

Title: **STANDARD-DOSE APIXABAN AFTER VERY LOW-DOSE THROMBOLYSIS FOR ACUTE INTERMEDIATE-HIGH RISK ACUTE PULMONARY EMBOLISM "(SAFE-LYSE)"**

STUDY SUPPORT PROVIDED BY: BRISTOL-MYERS SQUIBB COMPANY (BMS)

PRINCIPAL INVESTIGATOR:

VICTOR TAPSON, MD	**CO-PRINCIPAL INVESTIGATOR**
AARON WEINBERG, MD	**CO-PRINCIPAL INVESTIGATOR**

STUDY CONTACT PHONE NUMBER AT CSMC: 310-423-4765 OR 310-423-4788

AFTER HOURS CONTACT (24 HOURS): 310-423-5000 AND ASK FOR PULMONARY EMBOLISM RESPONSE TEAM PHYSICIAN ON CALL

This research study is funded by Bristol-Myers Squibb Company (BMS). BMS only reimburses Cedars-Sinai Medical Center for the costs associated with running the study; BMS is not providing additional compensation to Cedars Sinai Medical Center or the Principal Investigator for their participation in the study.

1. WHAT IS THE PURPOSE OF THIS RESEARCH STUDY?

We are doing this study to see how much of the pulmonary embolism (clot) can be dissolved when treated with a very low dose of a thrombolytic drug (clot buster) along with standard anticoagulant therapy as compared to the standard of care anticoagulant therapy alone.

You are being asked to join in a clinical research study because you have a blood clot in one or both of your pulmonary arteries (large blood vessels in your chest) that is interfering with blood flow through your heart and lungs. Your doctor has decided that you need to have the blood clot dissolved.

The study will enroll up to 40 people in total.

This research study is designed to test the investigational use of Alteplase, or tPA. This drug is approved by the U.S. Food and Drug Administration (FDA) for breaking down blood clots. However, it is not approved by the FDA for the condition that is being studied at the low dose of the drug being administered in this study.

2. WHAT WILL HAPPEN DURING THE STUDY?

This section provides a general overview of what will happen during your participation in this study. Information included below should be considered along with the flowchart of procedures attached as an Appendix.

The flowchart shows a timeline for research-related or standard of care procedures that are involved in your participation in this study. **Research-related procedures** are those performed solely for the research. They would not be performed if you did not take part in the study. **Standard of care (routine)** procedures would be performed both as part of this study and if you do not participate in this study.

A table describing common medical procedures done solely for the purposes of monitoring and assessing your condition during this study is attached as an Appendix to the end of this consent form. Standard of care procedures that will be repeated or done at greater frequency are listed in the flow chart Appendix.

Overview of study:

- Your doctor will review your medical record, lab results and other test results to determine if you are able to participate in this study.
- You will be randomized to one of two treatment groups. See below for more detailed explanation.
- You will either receive study drug or placebo infusion along with Standard of Care heparin, a blood thinner drug.
- Your vital signs (temperature, respiratory rate, heart rate, blood pressure, and oxygen saturation level) will be measured immediately prior to the infusion and at 24 ± 6 hours after infusion completion.
- You will also be assessed for adverse events, including bleeding complications, during your hospitalization and if any occur, the information will be recorded in the study record.
- Within 24 ± 6 hours of completing infusion, a CT-angiogram and an echocardiogram (ultrasound test) will be performed to see how much clot has been dissolved. Some blood tests will also be repeated.
- After at least 24 hours of your drug administration, you will transition to an oral anticoagulant, apixaban (Eliquis). You will start on 10 mg twice a day for the first 7 days. You will then transition to 5 mg twice a day for 12 months. If your risk of bleeding is high, your doctor may delay your transition to apixaban.
- There are a total of seven (7) follow-up visits. Three visits will require a return to the doctor's clinic and four (4) will be conducted by phone or e-mail. During the clinic visits at 30 ± 15 days, 180 ± 15 days, and 365 ± 15 days after your procedure, you will be asked about your general health, have an echocardiogram (ECHO), a physical exam, an exercise test, and complete two quality of life questionnaires. At days, 3, 7, 90 ± 15 days, and 270 ± 15 days after your procedure, you will be contacted by phone or e-mail by study staff to review your general health and to complete two quality of life questionnaires.
- The two quality of life questionnaires include the Patient-Reported Outcomes Measurement Information System Physical Function 6 (PROMIS PF-6) and the Pulmonary Embolism Quality of Life (PEmb-QOL) surveys.

This is a randomized, double-blind research study.

- "**Randomized**" means that you will be assigned to a study group by chance, like flipping a coin. You will be randomized into one of 2 study groups, and will have an equal chance of being placed in one of the groups described above.
- **"Double-blind"** means neither you nor the researchers will know what group you are assigned to.

This study has 2 study groups:

- Group 1 will get the usual drug to treat pulmonary embolism (heparin) plus a placebo IV infusion.
- Group 2 will get the usual drug to treat pulmonary embolism (heparin) plus the study drug (tPA) IV infusion.

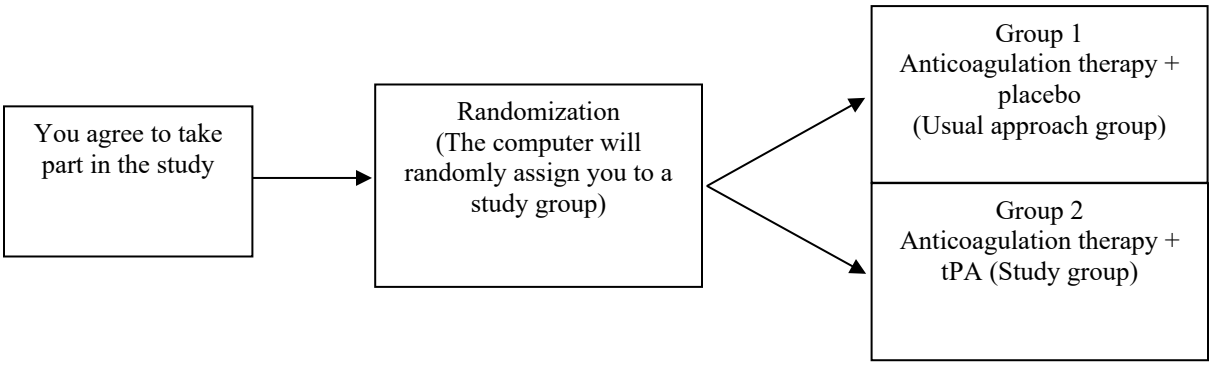
After initial treatment, all study participants will be transitioned to apixaban 10 mg twice a day for 7 days, followed by 5 mg twice a day for at least 6 months. If your doctor thinks it is safe and appropriate, the apixaban dose may be additionally decreased to 2.5 mg twice a day for the remaining 6 months.

A computer will randomly assign you to a study group. This is done because no one knows if the results experienced by the participants in one study group are better, the same, or worse than the results experienced by participants in the other. Once you are put in one group, you cannot switch to another group. Neither you nor your doctor can choose the group in which you will be placed.

Either of these different approaches could help your condition but could also cause side effects. This study will allow the researchers to learn whether the different approaches are better, the same, or worse than the current standard of care.

This is a placebo-controlled study. It will compare the effects (good or bad) of tPA against the effects of a placebo (an inactive substance, such as, a sugar pill) on the condition being studied in this research.

Another way to find out what will happen to you during the study is to read the chart below. Start reading at the left side and read across to the right, following the lines and arrows.



If you are assigned to the control group, you will be followed as you receive the care generally followed for individuals with your condition. Standard (routine) care for controls will involve IV infusions of heparin.

In order to properly follow the study's protocol (research plan), all participants will receive treatments and procedures that have been pre-determined by the protocol. In effect, the protocol describes which medications or procedures you will receive, rather than those decisions being made by your personal doctor or based on your preference. There may be options available outside of this study that you will not be able to receive while participating in this study. We do not believe you should be at any increased risk due to this limitation.

How long will you be in the study?
We think you will be in this study for/until about 1 year. The total time includes the days while you are in the hospital and the 7 follow-up visits (as indicated above – 3 in-clinic; 4 over the phone or by email) over the course of the year after your hospitalization.

3. WHAT ARE THE POSSIBLE RISKS?

Risks of common medical procedures performed solely for research purposes are described in a table attached to the end of this consent form as an Appendix. Side effects and risks of standard of care procedures are not described in this consent form.

This section describes the possible risks and/or discomforts we anticipate you could experience that are related to the study procedures.

Risks of heparin

Likely, Some May Be Serious (*Occurs in greater than 20% and up to 100 % of people***)**
- None

- **Less Likely, Some May Be Serious (***Occurs in >3% - 20 % of people)*
- Bleeding in various parts of the body
- Allergic reaction such as itching or hives, swelling in your face or hands, swelling or tingling in your mouth or throat, chest tightness, trouble breathing
- Abnormal blood clotting
- Decreased platelet count

Rare AND Serious (*Occurs in 3% or less of people* ***and*** *may require hospitalization or may be irreversible, long-term, life-threatening or fatal***)**
- Major bleeding

Heparin-induced Thrombocytopenia (HIT) is an immune system reaction from heparin which may cause a decrease of platelet counts and blood clots. HIT may occur up to several weeks after completing heparin therapy. You will not be enrolled in this study if you have a known history of HIT.

Risks of tPA

> In the lists below, "**Serious**," refers to those side effects that may require hospitalization, may be irreversible, long-term, life-threatening or fatal.

Likely, Some May Be Serious (*Occurs in greater than 20% and up to 100 % of people***)**
- None

Less Likely, Some May Be Serious (*Occurs in >3% - 20 % of people)*
- Bleeding in the brain
- Need for blood transfusion
- Bleeding in the stomach or intestinal tract
- Blood in urine
- Bruising
- Bleeding in other parts of the body

Rare AND Serious (*Occurs in 1% or less of people* ***and*** *may require hospitalization or may be irreversible, long-term, life-threatening or fatal***)**
- Allergic reaction, which can be severe, such as swelling of the airways, rash, or shock
- New case of ischemic stroke

Risks of apixaban

Likely, Some May Be Serious (*Occurs in greater than 20% and up to 100 % of people***)**
- None

- **Less Likely, Some May Be Serious (***Occurs in >3% - 20 % of people)*
- Bleeding in various parts of the body
- Clinically relevant non-major bleeding

Rare AND Serious (*Occurs in 3% or less of people* ***and*** *may require hospitalization or may be irreversible, long-term, life-threatening or fatal***)**
- Major bleeding
- Allergic reaction, which can be severe

In addition to the risks summarized above, the FDA has issued the following warning for apixaban:

FDA Blackbox warning: Increased risk of thromboembolic events (blood clots such as stroke) upon discontinuation of apixaban. Patients are at increased risk of thrombotic events when apixaban is discontinued prematurely (too early). If apixaban must be discontinued for a reason other than bleeding or completion of therapy, your doctor may consider administering another anticoagulant. Talk to your doctor before stopping apixaban.

FDA Blackbox warning: Risk of spinal/epidural hematoma: Additionally, patients on apixaban who receive neuraxial anesthesia (pain blockers administered into the central nervous system, such as the spine) or undergoing spinal puncture are at risk for spinal or epidural hematomas (collection of blood). This may result in long-term or permanent paralysis. Talk to your doctor about apixaban before receiving any spinal procedures.

Radiation Risk

This research study involves exposure to radiation from a CT Angiogram. The amount of radiation exposure from each CT Angiogram is approximately 6-10 Rem, which is within the typical range from similar diagnostic x-ray procedures. One of these procedures will be done as standard of care. and an additional one will only be done because of your participation in this research study. This research CT Angiogram involves radiation exposure that is not necessary for your medical care and is for research purposes only. This use involves minimal radiation risk and is necessary to obtain the research information desired.

CT Angiogram Contrast Risks:
The contrast (dye) solution that may be given for a CT scan may cause an allergic reaction (rare). Severe allergic reactions can be life threatening. CT contrast solution can cause kidney damage, especially if you are diabetic, dehydrated (lost body water) or elderly.

Reproductive and Lactation Risks

Taking part in this research study can affect an unborn baby. Therefore, you should not become pregnant or father a baby while on this study. If you or your partner is capable of becoming pregnant you will need to use birth control. Check with the researcher about approved birth control methods to use while participating in this study.

Women should not breastfeed a baby while on this study.

Participation in a Double-Blind Study
Participation in a double-blind study means that you may not be able to participate in other, similar trials since unblinding would generally only occur for emergent, life-threatening situations. We might not be able to tell you if you received the study drug or placebo in a situation where you would like to qualify for another research study. Because you may not know the study group to which you were assigned, in the future should you wish to participate in a different study that requires knowing what drug you received in this study, you may not be eligible to participate in the different study.

Follow-up Visit for Discontinuing Participants

While you are free to discontinue your participation at any time, we encourage you to complete a Final Study Visit. During this visit, we will conduct tests to collect safety data, and discuss any information that may be important to share with your treating physician.

4. ARE THERE BENEFITS IN TAKING PART IN THE STUDY?

If you agree to take part in this research study, there may or may not be direct medical benefit to you. The possible benefits of taking part in the research study is that your clot burden may be reduced more quickly with a low dose, clot-busting medication when given alongside your Standard of Care treatment for your condition. As a study subject, you will be seen more often and followed more closely at the clinic than is normal for a non-study subject who have pulmonary embolism. However, no benefit is guaranteed. It is possible that your condition may remain unchanged or even get worse.

We hope the information learned from this research study will benefit other individuals with pulmonary embolism in the future by helping us to learn if clots are sufficiently dissolved by giving a lower dosage of tPA.

5. WILL I BE INFORMED OF RESEARCH RESULTS?

The imaging procedure(s) in this study are for research purposes only. However, the techniques used are the same as those used in standard clinical imaging procedures. The imaging results may be shared with you and may be placed in your Cedars-Sinai medical record.

Unanticipated Incidental Findings
If, unexpectedly, we find that results of your research procedures could suggest important medical information and we determine there is something you or your doctors can do in response to this finding, we will contact you using the last contact information provided by you. If necessary, we may recommend additional clinical testing to confirm the research finding. The cost of any additional testing and any related treatment will be your responsibility.

6. WHY WOULD MY PARTICIPATION BE STOPPED?

Your participation in this study may be stopped at any time by the researcher or the sponsor without your consent for any reason, including:

- The study is stopped or suspended;
- Funding for the study is reduced, stopped or withdrawn;
- If it is in your best interest;
- You do not consent to continue in the study after being told of changes in the research that may affect you;
- You do not follow the study procedures;
- You decide to withdraw from the study for any reason;
- You become pregnant;
- You lose the ability to freely provide consent through imprisonment.

You may choose (or you may be required) to withdraw from certain parts of the study, but invited to continue with other parts. For example, you might stop taking a study drug, but continue with follow-up visits or allow us to continue to collect data from your medical records. Separate written

consent will be requested if your continued participation will involve procedures not described in this consent form.

7. ARE THERE ANY OTHER OPTIONS?

Your participation is voluntary, so you have the right to decline to participate or to withdraw from this research study at any time without any penalty or loss of benefits to which you would be entitled outside of the study. Choosing not to participate will not affect the care you receive at Cedars-Sinai Health System.

If you decide not to take part in this study, you have other choices. For example:

- you may choose to be treated following the usual clinical approach, which is receiving heparin IV infusions
- you may choose to take part in a different study at CSMC or elsewhere, if one is available
- you could decide not to be treated.

The researcher will discuss these options and their risks and benefits with you.

8. WILL MY INFORMATION BE KEPT CONFIDENTIAL?

We will do our best to make sure that the personal information collected as part of this study is kept private. However, we cannot guarantee total privacy. A copy of your research consent and authorization forms may be filed in your electronic medical record at CSMC. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other identifiable personal information will not be used. Organizations that may look at and/or copy your medical records for research oversight, quality assurance, and data analysis include: accrediting agencies, government and regulatory groups (such as Food and Drug Administration (FDA), Office for Human Research Protections (OHRP), etc.), safety monitors, companies that sponsor the study, and authorized representatives of the sponsor.

Attached to this consent form is an "Authorization Form" that outlines with whom your information may be shared for the purposes of this research and under what circumstances.

We might share your information and/or research samples collected in this study with other researchers at Cedars-Sinai, other academic institutions, or third party commercial entities for future research without additional informed consent from you. Information that identifies you will be removed and will not be shared with other researchers or anyone outside of Cedars-Sinai.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Website will not include information that can identify you. At most, the Website will include a summary of the results. You can search this Website at any time.

9. WHAT IF I BECOME ILL OR INJURED BECAUSE OF TAKING PART IN THIS STUDY?

Contact your study doctor at once if you feel that you are ill or have been injured because of taking part in this study. If it is a medical emergency, call 911 or go to an emergency room. Promptly notify your study doctor of your situation at the phone number listed on page 1 of this consent form.

Who pays for my research related illness or injury?
Cedars-Sinai has no plans to pay for costs associated with the treatment of research-related injury or illness. We will make every effort to seek reimbursement from your health plan. However, you will be responsible for any deductibles and co-payments required under your health plan and for any claims ultimately denied by your health plan. Financial assistance may be available under Cedars-Sinai's Charity Care Policy and Procedure. If you feel that you have had a research-related injury and need financial assistance, please contact the IRB Office at 310-423-3783. You do not waive any of your legal rights by signing this form.

10. FINANCIAL CONSIDERATIONS

Costs of Participation

Please review the attached Appendix flowchart for a listing of items, drugs and services that will be billed to you and/or your insurance and those that will be covered by the study sponsor.

Only items, drugs and services that are reasonable and necessary for your medical care throughout the study will be billed to your insurance. You remain responsible for all deductibles, co-pays, and balances under your health benefit plan. If your insurance company does not pay, you will be billed for those charges. You should check with your health benefit plan if you have questions or concerns about your insurance coverage.

Compensation for Participating

You will be paid $50 for each in-person follow-up visit. The payment will be issued after completion of the entire study. The total amount you will receive if you complete the whole study is $150. The cost of parking for Day 30, Day 180, and Day 365 visits will also be covered. If you do not complete the entire research study, you will only be paid for those visits and procedures you do complete. You may be required to complete a W-9 Form in order to receive payment. The W-9 Form will be maintained by our accounting department at Cedars-Sinai. Although any amount of payment may be reportable (check with a tax professional if you have questions about your obligations), if total payment by Cedars-Sinai is $600 or more in a calendar year, a 1099 Form will be filed with the IRS in accordance with federal tax law.

If you are a Cedars-Sinai employee, you should provide your employee identification number to the research team so that your payment can be appropriately processed through Payroll. For your own protection and to comply with tax laws, your payment for participation will be reported to the IRS together with other compensation you receive from Cedars-Sinai.

Financial Interest in the Research

The PI and institution have no potential financial conflict of interest with respect to this study.

11. WHAT IF I HAVE QUESTIONS OR PROBLEMS?

Please contact one of the investigators listed on the first page of this form for questions or concerns about the research.

If you have questions, problems, or concerns that you want to discuss with someone who is not associated with this study, or want to offer suggestions or feedback, please contact:

Cedars-Sinai Human Research Protection Program (HRPP) Phone: (310) 423-3783
Email: ResearchConcerns@cshs.org

The Cedars-Sinai HRPP has been established to protect the rights and welfare of research participants. You may also contact the Cedars-Sinai HRPP if you want to offer input or obtain information regarding the study.

12. CONSENT PROVISIONS

If you sign this form below, it means that:

(1) You have taken the time to carefully read and understand the information presented in this informed consent form; you should discuss it with others, and if appropriate seek a second opinion to make an informed decision;
(2) The information concerning the research study and its involved procedures has been fully explained to you and your questions have been answered to your satisfaction;
(3) You have received and understand all of the information you desire regarding your participation in the research study;
(4) You have considered the potential risks, any anticipated benefits and alternatives (and their relative risks and benefits) of participation;
(5) You are voluntarily agreeing to participate in this research study;
(6) You understand that by consenting to participate in the research, you are not giving up any of your legal rights (other than the postponement of your access to certain health information as described in this informed consent form);
(7) You understand that you have the right to be informed of significant new findings related to this research study which may affect your willingness to continue participating in this study; and
(8) You have been provided with a copy of the "Experimental Subject's Bill of Rights", if applicable to this research study, and have been provided with an opportunity to ask questions regarding the Bill of Rights.

We will give you a copy of this signed and dated consent form and the Experimental Subject's Bill of Rights.

SIGNATURE PAGE

Consent Form for Research and
Authorization for Use and Disclosure of Identifiable Health Information (Research)

SIGNATURE BY THE PARTICIPANT OR LEGAL REPRESENTATIVE

Main Research Study: *I hereby agree to participate in the research study described to me during the informed consent process and described in this informed consent form.* ***You will be given a signed copy of this form.***

_____

Name of Participant (Print) Signature Date Signed

If participant is unable to sign the form, please state the reason below:

_____

_____ _____ _____

Signature of Legal Representative Relationship to the Participant Date of Signature

Authorization for Use and Disclosure of Identifiable Health Information (Research)): *I hereby agree that my identifiable health information may be used and/or disclosed in accordance with this "Authorization for Use and Disclosure of Identifiable Health Information (Research)" form attached as Appendix to this form.*

_____

Name of Participant (Print) Signature Date Signed

If participant is unable to sign the form, please state the reason below:

_____

_____ _____ _____

Signature of Legal Representative Relationship to the Participant Date of Signature

SIGNATURE BY THE INVESTIGATOR: *I attest that all the elements of informed consent described in this form have been discussed fully in non-technical terms with the participant. I further attest that all questions asked by the participant were answered to the best of my knowledge.*

Name of Investigator (Print)	Signature	Date Signed

SIGNATURE BY THE INTERPRETER/WITNESS

(Signature of an interpreter is only required when a non-English speaking subject is consented with the assistance of an interpreter and an IRB-approved 'short form.' The witness may be any person who is conversant in both English and the language of the Non-English speaking subject, such as the interpreter (the certified hospital interpreter), study staff, a family member, or other person. The witness signs the consent forms to confirm that the oral interpretation occurred.)

Name of Witness (Print)	Signature	Date Signed

CEDARS-SINAI MEDICAL CENTER

APPENDIX: EXPERIMENTAL SUBJECT'S BILL OF RIGHTS

In accordance with California Health and Safety Code 24172, any person who is required to consent to participate as a subject in a research study involving a medical experiment or who is requested to consent on behalf of another has the right to:

1. Be informed of the nature and purpose of the experiment.

2. Be given an explanation of the procedures to be followed in the medical experiment, and any drug or device to be utilized.

3. Be given a description of any attendant discomforts and risks to the subject reasonably to be expected from the experiment.

4. Be given an explanation of any benefits to the subject reasonably to be expected from the experiment, if applicable.

5. Be given a disclosure of any appropriate alternative procedures, drugs or devices that might be advantageous to the subject, and their relative risks and benefits.

6. Be informed of the avenues of medical treatment, if any, available to the subject after the experiment if complications should arise.

7. Be given an opportunity to ask any questions concerning the experiment or the procedure involved.

8. Be instructed that consent to participate in the medical experiment may be withdrawn at any time and the subject may discontinue participation in the medical experiment without prejudice.

9. Be given a copy of any signed and dated written consent form used in relation to the experiment.

10. Be given the opportunity to decide to consent or not to consent to a medical experiment without the intervention of any element of force, fraud, deceit, duress, coercion, or undue influence on the subject's decision.

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AUTHORIZATION FOR USE AND DISCLOSURE OF IDENTIFIABLE HEALTH INFORMATION FOR RESEARCH

• USE AND DISCLOSURE OF HEALTH INFORMATION

If you agree to this Authorization, you give permission to the research team at Cedars-Sinai Medical Center ("CSMC") to use or disclose your identifiable health information ("private information") for the research study titled "**STANDARD-DOSE APIXABAN AFTER VERY LOW-DOSE THROMBOLYSIS FOR ACUTE INTERMEDIATE-HIGH RISK ACUTE PULMONARY EMBOLISM** "(SAFE-LYSE)" which is described in the Consent Form for Research ("Consent Form") to which this Authorization is attached. In particular, you authorize the research team acting under the direction of the Principal Investigator to review your medical records and collect your private information from the following sources:

- ☑ Laboratory tests
- ☑ Pathology reports
- ☑ Imaging reports (e.g., x-rays or scans)
- ☐ Photographs or videos of your image
- ☑ Doctor/clinic records
- ☑ Hospital/medical records
- ☐ Mental health records
- ☐ Billing records
- ☑ Other tests or other types of medical information: Cath lab reports

• WHO WILL HAVE ACCESS TO YOUR PRIVATE INFORMATION?

Your private information will be used by and/or shared with the CSMC investigators listed in Section A of the Consent Form and their research staff.

In addition to the research team, if applicable, the following parties may receive your private information and inspect your records:

- The reviewing Institutional Review Boards and CSMC offices with authority to oversee research compliance.
- U.S. government agencies, such as the Food and Drug Administration and the Department of Health and Human Services.
- Researchers at other organizations who are participating in this research study.
- The Study Sponsor and its business partners, for matters related to research study oversight, data analysis and use of research results in product development.

- Representatives from regulatory agencies in other countries may join in the review of your research records, including research-related medical reports and information, with the Sponsor and/or the FDA.

CSMC is required by law to protect your private information. However, the recipients described above may re-disclose (or share) your information with other parties unless such sharing is prohibited by law.

- **WHEN WILL MY AUTHORIZATION EXPIRE?**

By signing this document, you authorize the use and sharing of your private information until the end of the research study.

- **REVOKING AUTHORIZATION**

You may change your mind and revoke (take back) this Authorization at any time. Even if you revoke this Authorization, the research team may still use or disclose private information they already have obtained about you as necessary to maintain the integrity or reliability of the current research. To revoke this Authorization, you must write to the Principal Investigator of the research study. The mailing address is: 8700 Beverly Blvd., Los Angeles, CA 90048 (Attn: Dr. Victor Tapson).

- **NOTICE OF RIGHTS AND OTHER INFORMATION**

You do not have to agree to this Authorization, but if you do not agree, you may not participate in the research study. CSMC may not condition (withhold or refuse) treating you on whether you agree to this Authorization.

If you agree to this Authorization, please sign on the appropriate signature line. You will receive a copy of this Authorization.

APPENDIX: FLOWCHART OF PROCEDURES – Medicare Coverage Analysis (MCA) Review

LEGEND
R = Research item/procedure done only for research purposes and covered by the study
SS = Standard of care item/procedure that is part of regular care, but covered by the study
S = Standard of care item/procedure that is part of regular care and billed to the patient/insurance

Procedures	**Baseline up to 48 hours pre-study medication**	**Day 0**	**Day 1**	**Day 2**	**Day 3 & Day 7**	**Day 30 ± 15 days (Clinic Visit)**	**Day 90 ± 15 days (Phone Contact)**	**Day 180 ± 15 days (Clinic Visit)**	**Day 270 ± 15 days (Phone Contact)**	**Day 365 ± 15 days (Clinic Visit)**	**ET[1]**
Informed consent	R										
Inclusion/Exclusion	R										
Randomization		R									
Heparin anticoagulation therapy[2]	S	S	S								
Pregnancy test (if applicable)	S										
Medical and demographic history	S										
Physical exam	S		S			S		S		S	S
Vital signs including pulse ox	S	S	S	S		S		S		S	S
Chest contrast-enhanced computed tomographic angiogram (chest CTA)	S		R								

Procedures	**Baseline up to 48 hours pre-study medication**	**Day 0**	**Day 1**	**Day 2**	**Day 3 & Day 7**	**Day 30 ± 15 days (Clinic Visit)**	**Day 90 ± 15 days (Phone Contact)**	**Day 180 ± 15 days (Clinic Visit)**	**Day 270 ± 15 days (Phone Contact)**	**Day 365 ± 15 days (Clinic Visit)**	**ET[1]**
Echocardiogram	S		S			S		S			S
Ultrasound of lower extremities to rule out DVT	S										
ECG	S										
Hemoglobin, hematocrit, platelet count	S	S	S	S		S					
BUN, creatinine	S	S	S			S					
Liver Function Tests	S					S					
aPTT, PT and INR	S	S									
Troponin I (or Troponin T)	S										
BNP	S										
sPESI	R		R								
Quality of life questionnaires (PROMIS PF-6 and Pulmonary Embolism Quality of Life (PEmb-QOL)						R		R		R	R
Administration of tPA/placebo		R									

Procedures	**Baseline up to 48 hours pre-study medication**	**Day 0**	**Day 1**	**Day 2**	**Day 3 & Day 7**	**Day 30 ± 15 days (Clinic Visit)**	**Day 90 ± 15 days (Phone Contact)**	**Day 180 ± 15 days (Clinic Visit)**	**Day 270 ± 15 days (Phone Contact)**	**Day 365 ± 15 days (Clinic Visit)**	**ET[1]**
Administration of apixaban[3]			SS	SS	SS	SS	SS	SS	SS		
6 Minute Walk and Borg Dyspnea scale						S		S		S	S
Remote health checks (phone and email)							R		R		
Review of medications and adverse events, bleeding events and VTE events	R	R	R	R	R[4]	R	R	R	R	R	R

Footnotes:

[1]Early Termination: Obtain if subject withdraws early

[2]Heparin duration up to clinician discretion but patient must be on for at least 24 hours after infusion of study drug.

[3]Could start as early as 24 hours post treatment, contingent upon clinician discretion.

[4]72-hour assessment of AE will be conducted either in person or if discharged via telephone call. Day 7 follow up will be telephone call.

APPENDIX: Detailed Description of Common Medical Procedures Performed for Research Purposes and Associated Risks

The procedures listed below are often performed as part of routine care for a person with your condition. They are being repeated, or performed more frequently as part of this research. However, the risks associated with each procedure should be comparable to what you would experience even if you were undergoing the procedure outside this research study.

Study Procedure	Related Risks
Blood draw: A needle is placed in the vein in your arm to draw blood	Blood drawing may cause some pain and has a small risk of bleeding, bruising, or infection at the puncture site. There is also a small risk of fainting.
Electrocardiogram (ECG): abbreviated as EKG or ECG – is a test that measures the electrical activity of the heartbeat using electrodes (disposable adhesive discs placed on the skin).	There's no pain or risk associated with having an electrocardiogram. When the disposable adhesive discs are removed from your skin, there may be some minor skin discomfort or irritation. You may experience temporary discomfort (pulling on the skin/skin hair) during removal of the patches. This hair may be shaved for patch placement.
Physical Exam: Includes height, weight, vital signs (heart rate and blood pressure)	There are no physical risks associated with these procedures.
Concomitant Medications: You will be asked about your previous and current medications that you take.	There are no physical risks associated with these procedures.
Medical History Review: You will be asked about your medical and surgical history with attention to risk factors for thromboembolism and bleeding.	There are no physical risks associated with this procedure.
6-Minute Walk Test (6MWT): You will be asked to walk for 6 minutes along a designated pathway (a track in the hospital hallway) while being observed by study personnel. You will be observed before, during and after the 6-minute walk by study personnel. Your heart rate and blood pressure will be recorded before and after the test. We will also measure the distance that you are able to walk during the 6 minutes. After the test, you will also be asked a few questions. The test and assessments will take about 10-15 minutes, but no more than 30 minutes total.	There is a rare possibility of fainting, while you perform the 6 Minute walk test. Please note that all medical procedures will be done in the presence of the study Investigator and research team in order to minimize the occurrence of such untoward events.
An ultrasound called transthoracic echocardiogram (TTE): This is performed by placing a probe across the surface of your chest; it is used to examine and provide images of the heart.	If you participate in this study, when you have the echocardiogram (ultrasound) a solution may be injected into your vein to help the doctor see the pictures of your heart more clearly. There are two types of solutions that may be used and they are

	DEFINITY® and OPTISON™. If you have an allergy to eggs or if you have had a reaction to blood or blood products, or albumin in the past, you may have an allergic reaction to OPTISON™. It is important to let the doctor know of any allergies or reactions you may have had in the past. Please inform the doctor of any history of liver disease or respiratory difficulties/disease. DEFINITY®, the other solution, may cause a change in the rhythm of your heart. Please inform the doctor if you believe you are pregnant or if you have a congenital heart defect (heart problem you were born with).
Pregnancy Test: If you are a woman who is able to become pregnant, blood samples will also be used to do a pregnancy test	If your test is positive, you will be told and at that point you should discuss options available with your primary physician.
Questionnaires: You will be asked to complete questionnaires. We will ask you questions to evaluate your quality of life. We think it should take about 10 minutes to complete the questionnaire. Questionnaires will ask you to respond to questions about pain you are experiencing, other medical symptoms and how it affects the activities of daily living and your emotions.	If you feel uncomfortable or embarrassed answering any question, you may skip it. The questionnaire will be labeled with a unique study number that will link your identity so that only the research team can recognize you.
Demographic Information: You will be asked about your age, gender, race, ethnicity	There are no physical risks associated with these procedures.