Evaluation of Conventional Ablation With or Without Focal Impulse and Rotor Modulation to Eliminate Human AF (RECONFIRM)

Informed Consent Form

NCT02456233

April 16, 2024

Are you participating in any other research studies? _____ Yes _____No

PURPOSE OF RESEARCH

You are undergoing a clinically indicated ablation, and are invited to participate in a research study to compare two methods of treatment (ablation) for your heart rhythm disorder (atrial fibrillation). The first method is to eliminate triggers of your disorder, the traditional approach of pulmonary vein isolation (PVI). This works in many patients, so that some experts feel that no more is necessary. The second method is to perform PVI but to eliminate "substrate" or rotors and focal sources (FIRM) identified by analyzing ECG signals from inside your heart. The advantage of this approach is that additional targets are ablated including in the right atrium, but some experts feel that additional targets are not needed and the right atrial targets are unimportant. **In this trial**, we will compare whether PVI alone, which often passes through rotor sites in the left atrium, or PVI + FIRM, which may include ablation of right atrial rotors, is more effective. This study is a randomized trial. That is, nobody will decide which approach to use in you, but this will be allocated by chance just before the procedure. You will have an equal chance of getting PVI or PVI+FIRM, both of which are considered to be acceptable therapy. This randomized design is a routine type of study, and this one is sponsored by the National Institutes of Health of the United States.

You were selected as a possible participant in this study because you have atrial fibrillation (AF), even though we have tried medications (anti-arrhythmic drugs). The PVI limb of the study will usually take 3-4 hours, and the FIRM limb will add 30-40 minutes to this time. This includes 5-10 minutes of extra radiation (additional fluoroscopic exposure). After your treatment, we will follow-up with you for at least the next 2 years to see if you have any symptoms (i.e., rapid beats) or recurrence of heart rhythm disorder, in which case we will ask you whether you would like to repeat the ablation. With your permission, we might ask you in the future to enroll in extra studies related to this one.

If you decide to terminate your participation in this study, you should notify Sanjiv Narayan, MD (Co-Protocol Director) at [redacted].

Stanford University expects to enroll 120 research study participants who have atrial fibrillation. If enrollment for this study is slow, we will recruit from additional sites in the United States.

VOLUNTARY PARTICIPATION

Your participation in this study is entirely voluntary. Your decision not to participate will not have any negative effect on you or your medical care. You can decide to participate now, but withdraw your consent later and stop being in the study without any loss of benefits or medical care to which you are entitled.

DURATION OF STUDY INVOLVEMENT

This research study is expected to take approximately two years. After your electrophysiology study and ablation, we will collect data from your regular clinical follow-up appointments in the Stanford Arrhythmia Service.

PROCEDURES

If you choose to participate, Paul Wang, MD, Sanjiv Narayan MD and their research study staff will do the following:

After your consent, you will be asked to complete a quality of life questionnaire. This can be done at any time prior to your procedure.

For your standard care, as recommended by your doctor, we will perform an electrophysiology study (EPS) and ablation. In this, we will insert thin, sterile wires (catheters) through your blood vessels to record signals from inside your heart while we stimulate (pace) it. Your standard clinical procedure will also apply energy to stop (ablate) your rhythm disorder. The total time for this standard clinical procedure is usually 4-5 hours.

<u>Women of Childbearing Potential</u>
You are about to undergo a clinical electrophysiologic study and ablation. If you are a woman who is able to become pregnant, it is expected that you will use an effective method of birth control to prevent exposing a fetus to a potentially dangerous agent with unknown risk. If you are pregnant or currently breast feeding, we will not enroll you in this study, to avoid any additional procedural or radiation time. You understand that if you are pregnant, if you become pregnant, or if you are breast-feeding during this study, you or your child may be exposed to various risk, including exposure to radiation.

To confirm to the extent medically possible that you are not pregnant, you agree to have a pregnancy test done before beginning this research study.

You must agree to avoid sexual intercourse or use a birth control method judged to be effective by the investigator and which will not interfere with the proposed investigation. You must accept the risk that pregnancy could still result despite the responsible use of reliable method of birth control. You agree to notify the investigator as soon as possible of any failure of proper use of your birth control method, or if you become pregnant, either of which may result in your being withdrawn from the study.

You will not need a CT scan purely for this research, although it may have been obtained already for your clinical care. Data from this CT scan may be used by the research team to learn more about your heart rhythm disorder.

For your standard care, we may also use special catheters that are FDA approved and often used for your clinical ablation. Primarily we will use a mapping catheter that expands into a basket (called a basket catheter). We may also use medications (isoproterenol, esmolol and/or atropine) that are also FDA approved and that alter your heart rhythm disorder so that we can understand it better and design better treatment.

RESEARCH

1) For research purposes, you will be assigned by chance ("randomized") to one of the following treatments, both of which are very reasonable to many in our field. If you are not willing to have either one of those treatments, you should tell us immediately, and we will treat you with the method that you are willing to have (not as part of this clinical trial). An independent committee (not including Dr. Narayan) are evaluating these options. If the results of either form of treatment are lower than those of the other, the trial will be stopped. The two treatment options are:

a) **Pulmonary vein isolation (PVI).** This involves performing a standardized ablation procedure in any patient – to use FDA approved circular catheters to find and eliminate triggers that start AF, often within the pulmonary veins. PVI typically treats the left atrium. We will only ablate at safe regions. The total case time is 3-4 hours. PVI has a 50-65% chance of eliminating your AF after 1 procedure at 1 year, with a somewhat higher success rate after 2 or more procedures. PVI involves an average of 40-60 minutes of energy delivery to your heart, depending on how complicated your AF appears to be during the case.

b) Pulmonary Vein isolation (PVI) AND FIRM ablation (Focal Impulse and Rotor Modulation). FIRM is a new approach developed by our group, using FDA approved basket catheters to find electrical circuits that may actually keep your AF going ("rotors" or "focal impulses"). FIRM typically treats both atria, since you and most patients likely have an average of 2-3 rotors/focal impulses in unpredictable locations. We will then add PVI. We will only treat (ablate) safe regions. The total case time will be 30-40 minutes longer than PVI alone. This is one of the first randomized trials of FIRM, which is why we are doing the trial. FIRM+PVI has a 50-70% chance of eliminating your AF after 1 procedure at 1 year. FIRM + PVI involves an average of 50-60 minutes of energy delivery to your heart, depending on how complicated your AF appears to be during the case.

II) For research purposes, we will follow-up with you in clinic after your procedure, and ask your primary care doctor to see if you have any symptoms (such as rapid beats) over the next 2 years. These visits will usually be at 1, 3, 6, 9, 12 and 24 months. You will be asked to complete a quality of life questionnaire at all of these visits except month 1. We may also contact you by telephone to complete this questionnaire if you do not come to the clinic visits. If you have a recurrence of AF, we will ask you whether you would like to repeat the ablation. If so, we will ask you to remain in the study so we can continue to collect information from you.

PARTICIPANT RESPONSIBILITIES

As a participant, your responsibilities include:

- Follow the instructions of the Protocol Director and study staff.
- Keep your study appointments. If it is necessary to miss an appointment, please contact the Protocol Director or research study staff to reschedule as soon as you know you will miss the appointment.
- Tell the Protocol Director or research study staff about any side effects, doctor visits, or hospitalizations that you may have.
- Tell the Protocol Director or research staff if you believe you might be pregnant.
- Ask questions as you think of them.
- Tell the Protocol Director or research staff if you change your mind about staying in the study.

WITHDRAWAL FROM STUDY

If you first agree to participate and then you change your mind, you are free to withdraw your consent and discontinue your participation at any time. Your decision will not affect your ability to receive medical care for your disease and you will not lose any benefits to which you would otherwise be entitled.

If you decide to withdraw your consent to participate in this study, you should notify Sanjiv Narayan, MD at [redacted]. Your clinically-indicated electrophysiology study and ablation procedure and any other treatment and follow-up will continue as directed by your doctor.

The Protocol Director may also withdraw you from the study without your consent for one or more of the following reasons:

- Failure to follow the instructions of the Protocol Director and study staff.
- The Protocol Director decides that continuing your participation could be harmful to you.
- Pregnancy
- You need treatment not allowed in the study.
- The study is cancelled.
- Other administrative reasons.
- Unanticipated circumstances.

POSSIBLE RISKS, DISCOMFORTS, AND INCONVENIENCES

There are risks, discomforts, and inconveniences associated with any research study. These deserve careful thought. You should talk with the Protocol Director if you have any questions.

a) If you are randomized to the PVI + FIRM arm, you will be exposed to an additional 5-10 minutes of fluoroscopy (at 1.8 mSv/min, this is approximately 9-18 mSv radiation exposure). This is in addition to the fluoroscopy you will be exposed to from your clinically indicated electrophysiology study (EPS) and ablation.

For atrial fibrillation ablation, the total amount of radiation for a PVI procedure is approximately 40-60 minutes, and with FIRM ablation (5-10 additional minutes of radiation), it will be a total of 50-70 minutes (90-126

mSv at 1.8 mSv/min). Thus, this study involves additional exposure to radiation that adds 5-10 additional minutes, or about 18 mSv, which is approximately equal to 36% of the limit that radiation workers (for example, a hospital x-ray technician) are allowed to receive in one year. This amount of radiation involves minimal risk and is necessary to obtain the research information desired.

The Protocol Director of this study, Dr. Sanjiv Narayan, has determined and verified that most of the x-rays and imaging scans prescribed for this study would typically be performed as part of the standard medical care required to adequately monitor your current illness. If you are especially concerned with radiation exposure, or you have had a lot of x-rays or imaging scans already, you should discuss this with Dr. Narayan or your regular doctor.

b) As a result of participating in this study you may be under general anesthesia for an additional 30-40 minutes. The risks from this sedation are small but difficult to measure. We will monitor your vital signs and parameter during this and all times, and immediately stop the research if any parameter becomes abnormal.

c) During the study, the FIRM+PVI limb will require us to record for up to an additional 30-40 minutes from your heart. Any clinical procedure in the left heart carries a small risk of stroke, estimated as < 0.5%. We will minimize this risk by thinning your blood with a blood-thinning medication that is needed for your clinically-indicated EP study and ablation anyway. Thus, this time will add additional risk for stroke, but this risk is felt to be very small (<0.1% just for recording).

d) If you are randomized to the PVI+FIRM group, you will require additional anticoagulation (blood thinning medications) for the 30-40 minutes of the research. Anticoagulation may cause bleeding. However, you will be receiving anticoagulation for your clinical procedure anyway, at the identical dose that is required for this research. Because anticoagulation is always monitored every 15 minutes, the risk of bleeding from this additional time is minimal (<1%).

e) If you are randomized to the PVI+FIRM group, we may use medications (isoproterenol, esmolol, atropine) that are fully approved and often used in patients, but may not always be used if the research were not being performed. These medications and doses are FDA approved, and short

lived. Isoproterenol increases heart rate and reduces blood pressure (both of which resolve when the drug is stopped). If you have existing angina or a recent heart attack, isoproterenol may cause a heart attack. Esmolol is a beta-blocker, similar to those used in outpatients for blood pressure control. This may reduce your blood pressure, but we will not use this if you have marginal or low blood pressures. Atropine is an anti-vagal drug that will speed up the heart, and is often used clinically. In summary, the risk of side effects from these medications is low, based on decades of use in other patients.

f) There is a small risk of stroke (under 0.5%), a small risk of heart attack (under 0.5%), a small risk of tearing your heart (approximately 1%), and a small risk of death (typically quoted at 0.1%)

g) There is a risk of loss of confidentiality of your patient data or research results. However, we will take every reasonable precaution to prevent the loss of confidentiality of your information. All information collected during the study will be kept in a locked file. Any publications using information collected during the study will not include your name or any information that can identify you.

Unforeseeable Risks

Although this study does not involve any experimental treatments or equipment, there may be some unknown risks that are currently unforeseeable. You will be informed of any significant new findings that may affect your wanting to continue.

POTENTIAL BENEFITS

We cannot and do not guarantee or promise that you will receive any benefits from this study. It is possible that FIRM ablation will be more successful and/or faster than conventional PVI, although it is also possible that FIRM ablation may be less successful and/or that this study will take up to 30-40 minutes more time than PVI. The investigators, however, will learn more about what causes your heart rhythm disorder, and this may help to design better treatments in the future.

ALTERNATIVES

The alternative to the research method is simply to refuse to participate in the research protocol. Your clinically-indicated electrophysiology study and ablation procedure and any other treatment or follow-up will not be affected in any way by your decision to take part in this research.

PARTICIPANT'S RIGHTS

You should not feel obligated to agree to participate. Your questions should be answered clearly and to your satisfaction. If you decide not to participate, tell the Protocol Director.

You will be told of any important new information that is learned during the course of this research study, which might affect your condition or your willingness to continue participation in this study.

ClinicalTrials.gov

A description of this clinical trial will be available on *http://www.ClinicalTrials.gov*, as required by U.S. Law. 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.

CONFIDENTIALITY

The results of this research study may be presented at scientific or medical meetings or published in scientific journals. Your identity and/or your personal health information will not be disclosed except as authorized by you or as required by law**.** However, there is always some risk that even de-identified information might be re-identified.

Patient information may be provided to Federal and other regulatory agencies as required. The FDA, the National Institutes of Health (the sponsor of this study) and the Stanford Institutions Review Board may inspect research records and learn your identity.

This research is covered by a Certificate of Confidentiality from the National Institutes of Health. The researchers with this Certificate may not disclose or use information, documents, or biospecimens that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other action, suit, or proceeding, or be used as evidence, for example, if there is a court subpoena, unless you have consented for this use. Information, documents, or biospecimens protected by this Certificate cannot be disclosed to anyone else who is not connected with the research except, if there is a federal, state, or local law that requires disclosure (such as to report child abuse or communicable diseases but not for federal, state, or local civil, criminal, administrative, legislative, or other proceedings, see below); if you have consented to the disclosure, including for your medical treatment; or if it is used for other scientific research, as allowed by federal regulations protecting research subjects.

Authorization To Use Your Health Information For Research Purposes

Because information about you and your health is personal and private, it generally cannot be used in this research study without your written authorization. If you sign this form, it will provide that authorization. The form is intended to inform you about how your health information will be used or disclosed in the study. Your information will only be used in accordance with this authorization form and the informed consent form and as required or allowed by law. Please read it carefully before signing it.

What is the purpose of this research study and how will my health information be utilized in the study?

The purpose of this study is to compare two methods of treatment (ablation) for your heart rhythm disorder (atrial fibrillation). The first method is the conventional approach of pulmonary vein isolation (PVI). The second method is to perform PVI but also to eliminate "substrate" or rotors and focal sources (FIRM) identified by analyzing ECG signals from within your heart. By agreeing to participate in this study, study personnel will be allowed access to your physician and hospital records related to the diagnosis, treatment and follow-up of your heart rhythm disorder. This information may also be shared

with the government (FDA) and regulatory agencies as required by law. You will not be identified in any reports or publications in scientific journals on this study. The records will be kept confidential to the extent provided by federal, state and local law. Further confidentiality and privacy information appears in the section about 'HIPAA', later on in this document.

Publication of study results

The results of the study may be published in a medical book or journal, or presented at meetings for educational purposes, but your identity will not be disclosed.

Do I have to sign this authorization form?

You do not have to sign this authorization form. But if you do not, you will not be able to participate in this research study. Signing the form is not a condition for receiving any medical care outside the study.

If I sign, can I revoke it or withdraw from the research later?

If you decide to participate, you are free to withdraw your authorization regarding the use and disclosure of your health information (and to discontinue any other participation in the study) at any time. After any revocation, your health information will no longer be used or disclosed in the study, except to the extent that the law allows us to continue using your information (e.g., necessary to maintain integrity of research). If you wish to revoke your authorization for the research use or disclosure of your health information in this study, you must write to: Sanjiv Narayan, MD, PhD; Stanford Medicine; 300 Pasteur Drive; Stanford CA 94305.

What Personal Information Will Be Obtained, Used or Disclosed?

Your health information related to this study, may be used or disclosed in connection with this research study, including, but not limited to:

- Personal information, such as your name, patient identification number, birth date and social security number;
- Medical and health records that are relevant to the Research Study, such as your medical history, physical examination records, x-rays, MRIs, and test results;
- All health information collected during the research study.

Who May Use or Disclose the Information?
The following parties are authorized to use and/or disclose your health information in connection with this research study:

- The Protocol Director (Paul Wang, MD) and Co-Protocol Director (Sanjiv Narayan, MD)
- The Stanford University Administrative Panel on Human Subjects in Medical Research and any other unit of Stanford University as necessary
- Research Staff

Who May Receive or Use the Information?
The parties listed in the preceding paragraph may disclose your health information to the following persons and organizations for their use in connection with this research study:

- The Office for Human Research Protections in the U.S. Department of Health and Human Services
- National Institutes of Health
- The Food and Drug Administration
- Stanford Data Safety Monitoring Board

Your information may be re-disclosed by the recipients described above, if they are not required by law to protect the privacy of the information.

When will my authorization expire?
Your authorization for the use and/or disclosure of your health information will end on February 28, 2030 or when the research project ends, whichever is earlier.

Will access to my medical record be limited during the study?
To maintain the integrity of this research study, you may not have access to any health information developed as part of this study until it is completed. At that point, you would have access to such health information if it was used to make a medical or billing decision about you (e.g., if included in your official medical record).

_____ _____
Signature of Adult Participant Date

_____
Printed Name of Adult Participant

FINANCIAL CONSIDERATIONS

Payment
You will not be paid to participate in this research study.

Costs
If you participate in this study, the study will pay for those services, supplies, procedures, and care associated with the study that are not a part of your routine medical care. However, there may be additional costs to you. These include basic expenses like transportation and the personal time it will take to come to the study visits. You and/or your health insurance must pay for services, supplies, procedures, and care that are required during this study for routine medical care. **You will also be responsible for any co-payments and/or deductibles as required by your insurance.** Participation in this study is not a substitute for health insurance.

Sponsor
The National Institutes of Health is providing financial support and/or material for this study.

Financial Interests

Dr. Narayan is a paid consultant to Abbott, the company whose products may be used in this study.

COMPENSATION for Research-Related Injury

All forms of medical diagnosis and treatment – whether routine or experimental – involve some risk of injury. In spite of all precautions, you might develop medical complications from participating in this study. If such complications arise, the Protocol Director and the research study staff will assist you in obtaining appropriate medical treatment. In the event that you have an injury or illness that is directly caused by your participation in this study, reimbursement for all related costs of care first will be sought from your insurer, managed care plan, or other benefits program. **You will be responsible for any associated co-payments or deductibles as required by your insurance.**

If costs of care related to such an injury are not covered by your insurer, managed care plan or other benefits program, you may be responsible for these costs. If you are unable to pay for such costs, the Protocol Director will assist you in applying for supplemental benefits and explain how to apply for patient financial assistance from the hospital.

You do not waive any liability rights for personal injury by signing this form.

CONTACT INFORMATION

Questions, Concerns, or Complaints: If you have any questions, concerns or complaints about this research study, its procedures, risks and benefits, or alternative courses of treatment, you should ask the Co-Protocol Director, Dr. Sanjiv Narayan. You may contact him now or later at [redacted].

Injury Notification: If you feel you have been hurt by being a part of this study, please contact the Co-Protocol Director, Dr. Sanjiv Narayan, at [redacted].

Independent Contact: If you are not satisfied with how this study is being conducted, or if you have any concerns, complaints, or general questions about the research or your rights as a participant, please contact the Stanford Institutional Review Board (IRB) to speak to someone independent of the

research team at (650)-723-5244 or toll free at 1-866-680-2906. You can also write to the Stanford IRB, Stanford University, 3000 El Camino Real, Five Palo Alto Square, 4th Floor, Palo Alto, CA 94306.

EXPERIMENTAL SUBJECT'S BILL OF RIGHTS

As a research participant you have the following rights. These rights include but are not limited to the participant's right to:

- be informed of the nature and purpose of the experiment;
- be given an explanation of the procedures to be followed in the medical experiment, and any drug or device to be utilized;
- be given a description of any attendant discomforts and risks reasonably to be expected;
- be given an explanation of any benefits to the subject reasonably to be expected, if applicable;
- be given a disclosure of any appropriate alternatives, drugs or devices that might be advantageous to the subject, their relative risks and benefits;
- be informed of the avenues of medical treatment, if any available to the subject after the experiment if complications should arise;
- be given an opportunity to ask questions concerning the experiment or the procedures involved;
- be instructed that consent to participate in the medical experiment may be withdrawn at any time and the subject may discontinue participation without prejudice;
- be given a copy of the signed and dated consent form; and
- 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.

May we contact you about future studies that may be of interest to you?
____ Yes ____ No

Signing your name means you agree to be in this study and that you were given a copy of this signed and dated consent form.

_____ _____
Signature of Adult Participant Date

_____
Printed Name of Adult Participant

_____ _____
Signature of Person Obtaining Consent Date

_____
Printed Name of Person Obtaining Consent