UNIVERSITY of MARYLAND
THE FOUNDING CAMPUS

RESEARCH CONSENT FORM

Protocol Title: Early Elimination of Premature Ventricular Contractions in Heart Failure (EVAC-HF)

Study No.: HP-00046178

Principal Investigator: Timm Dickfeld, MD, PhD
(410)328-7801

Your participation in this study is completely voluntary and you may withdraw at any time. You can ask questions at any time

PURPOSE OF STUDY:
Your doctor has determined that you have a high number of extra heart beats (more than 20% of your normal heart beats) coming from the bottom chambers of your heart. These extra beats are called premature ventricular contractions or PVCs. You also have some heart muscle weakness and it is possible that these extra heart beats (PVCs) are causing this weakness of the heart muscle.
The purpose of this study is to investigate if eliminating at least 80% of these PVCs can improve the function of the heart and prevent worsening heart failure better than taking standard medication.

This study that will be conducted at multiple hospitals inside and outside of the US and will be coordinated from the University of Maryland Medical Center in Baltimore, MD, USA. The study plans to enroll 56 patients worldwide. Here at University of Maryland Medical Center we plan to enroll up to 11 participants. Patients that consent to participate in this study will be followed for 2 years.

INFORMATION ABOUT PVC'S AND PVC ABLATIONS:
Premature ventricular contractions (PVC) are a very common irregular heart beat (arrhythmias) even in patients without heart disease. Frequent PVCs are thought to occur in about 1–4% of the general population. Many patients with PVCs complain about skipping of their heart (palpitations), shortness of breath and feeling tired. In some patients PVCs may also result in weakening of the heart muscle (heart failure), which might be reversible with suppression of the PVCs.

A common way to get rid of PVCs is an ablation procedure during which a small area of heart muscle that creates the PVCs is cauterized, so that it can no longer cause PVCs. This has been performed for many years and is an overall safe and effective procedure to eliminate PVCs. In the ablation, a catheter with an

electrode at its tip is guided with moving X-rays (fluoroscopy) displayed on a video screen to the exact site inside the heart where cells give off the electrical signals that stimulate the abnormal heart rhythm. Radiofrequency energy (similar to microwave heat) is transmitted from the catheter tip to the area. This destroys carefully selected heart muscle cells in a very small area (about 1/5 of an inch) and can stop the area from creating the extra impulses that cause the extra heartbeats. Additionally, some medications have the ability to suppress PVCs (antiarrhythmic medications). PVC ablation and antiarrhythmic medications have both been used to treat patients with PVC's and a reduced heart function. The heart function is referred to as ejection fraction (measured by cardiac ultrasound (echocardiogram). In this study it will be required that your ejection fraction will be less than less than or equal to 45% (with 55% or more being normal).
Fluoroscopy used in these procedures are considered standard of care at this institution. You will not receive any additional radiation dose by participating in this research.

PROCEDURES

To qualify for this study you are required to have both frequent extra heart beats and a weakening of the heart muscle. The frequent heart beats may be a cause for your heart failure and your study participation will help determine if suppressing those beats with an ablation and possibly antiarrhythmic medication is helpful in treating this condition.

If you decide to participate in this study you will be one of 56 subjects in this multi-center study. Your participation is completely voluntary.

If you agree to take part in this study, we will gather information about your current and past health. A complete history will be taken which will include information such as age, sex, race, medical history, a list of your medications, and how well you function on a day to day basis. Your doctors will look at a Holter monitor that reports your heart rhythm for 24 hours to assess the amount of PVC's you are having. They will also look at the results of your cardiac ultrasound (echocardiogram) to assess your heart function. These 2 tests will decide if you are a good candidate for this study. In addition if you have had a cardiac MRI your doctor may be utilizing that information. All these diagnostic tests are considered to be standard of care for patients with frequent PVC's.

If you are enrolled in the study the treatment you get will be chosen by chance, like flipping a coin. Neither you nor the study doctor will chose what treatment you get. You will have a 50/50 chance in being given each treatment. You will either continue on the best currently available medical treatment for a weak heart muscle (as determined by your doctor) or will undergo a PVC catheter ablation (with a possible second ablation or antiarrhythmic medication, if the first ablation was not a success).

If you are randomized to the ablation the procedure will be scheduled. The ablation is done in these cases as a standard clinical procedure. The goal of the ablation is to reduce the amount of PVC's by 80%. If after your ablation you still have more than 20% of the PVC's left over your physician and you will decide if you will undergo a second ablation procedure or if you will take antiarrhythmic medication. The catheter used for the ablation is not specifically approved by the FDA for PVC ablations but is commonly used for this and other types of ablations. If the second ablation can also not reduce the PVC's by 80% your doctor will prescribe antiarrhythmic medication for treatment.

All patients in the study will continue to take the best possible medications for the heart muscle weakness. If you are randomized to not undergo the ablation you will be monitored and at the end of 6 months of participation you may choose to have the PVC ablation.

Procedures performed as standard clinical care for patients with frequent PVCs and weak heart muscle:

1) The 24 hour Holter monitor is a portable monitor that you can wear at home. You cannot shower or bathe with this on, but you can do anything else you normally do. Your doctor will routinely assess how many PVCs you are having at baseline and if they improve with therapy. The Holter result that your doctor ordered at baseline will be used to see if you may be a candidate for this study. Your doctor will also determine the effect of treatment on the number of PVCs you have after six months. Additionally, patients undergoing an ablation procedure will have a 24 hour Holter monitor after procedure to confirm success.

2) Similarly, your doctor will assess the strength of the heart muscle intermittently using cardiac ultrasound (echocardiogram). The results of a routine echocardiogram will be used to assess if you are a candidate for this study. To assess if the heart function changed with the treatment your doctor will repeat an ultrasound after 6 months. If your doctor feels that your heart function may have changed in between he/she may also chose to get another ultrasound at any time point to make sure that your clinical situation is stable

3) Your doctor may also perform an MRI (magnetic resonance imaging) of the heart to see if you have any scar inside the heart muscle. The MRI machine looks like a "big donut" with the patient in the center. Using magnetic fields it is a very good test to assess abnormalities of the heart muscle and is done on a routine basis. Your doctor may check your kidney function first to make sure that you are a good candidate for contrast material. You may also sign a separate consent form for the MRI. If you have an ICD or a pacemaker or have trouble in narrow spaces (claustrophobia) your doctors may decide not to perform an MRI.

4) Patients assigned to catheter ablation of the PVCs will be scheduled for the procedure at a time of your convenience. The procedure will take place at the University of Maryland Medical Center and will be done identically as any standard of care PVC ablation. You will sign a separate consent form for this procedure, which will explain all the risks and benefits of the ablation procedure.

As part of the study the following procedures are done for research purposes only:

1) A small amount of blood will be drawn (approximately 4 teaspoons) from your vein. The blood will be used to test markers of heart failure before and after treatment. This will be done at the first visit and then again at the 6 month visit.

Blood taken from your veins will be kept frozen for 10 years in the investigator's lab and will not have your name or other personal information. Results will not be told to you or your healthcare provider. The test tube will be labeled with a unique code number only. The investigators Timm Dickfeld, MD and Shawn Robinson, MD, (University of Maryland) will have access to this code, as well as research staff directly involved in the study at the University of Maryland.

I give permission to draw and store my blood up to 10 years and include my blood sample in future genetic and blood based analysis:

YES_____ _____

NO_____ _____

Initial Date

In the future, as new research provides more information about the relationships of heart failure to frequent PVCs, we may want to test your blood samples for the presence of different markers. Samples of your blood will only be stored at the University of Maryland. These samples may be shipped to other labs to perform specialized tests and will not contain any of your personal information. If at any time you decide that you do not want your blood stored any longer, you can call the Principal Investigator, Dr, Timm Dickfeld at 410-328-6056.

2) A six minute walk test measures the maximum distance you can walk in a period of 6 minutes. The test can be done within any hallway and requires no more than a simple stopwatch. This will be done at the first visit and then again at the 6 month visit.

3) A Heart failure questionnaire to assess your quality of life and possible symptoms from heart muscle weakness will be performed at the initial and six month visit.

4) We may contact you and your doctor approximately one and two years after the study started to see how you are doing. This may also include reviewing your medical records and imaging studies that you had in the meanwhile.

5) At the completion of this study you will be notified of any findings that are published.

STUDY SCHEDULE

	Enrollment/ Randomization	First Ablation	Second ablation	6 month follow up	1 yr Follow Up	2 Yr Follow Up
Blood work	yes			yes		
Review of current meds	yes	yes	yes	yes	yes	yes
Echocardiogram	yes			yes		
Holter monitor	yes			yes		
EKG	yes			yes		
NYHA Classification	yes			yes	yes	yes
Review of symptoms	yes	yes	yes	yes	yes	yes
6 Minute Walk	yes			yes		
KC and Minnesota questionairre	yes			yes		

POTENTIAL RISKS/DISCOMFORTS:

1. Ablation procedure risks

There are risks associated with the EP test and ablation procedure, these risks will be discussed with you by your doctor. General risks include an allergic reaction to the local anesthetic, low blood pressure, perforation or rupture of a blood vessel, hemorrhage (bleeding) and/or bruising (hematoma/swelling) at

the site of the catheter placement, development of a false pouch in the vessel wall (pseudo aneurysm), inflammation of the inner (endocarditis) or outer (pericarditis) lining of the heart, heart valves, and/or lungs (pleurisy), or damage to the heart valves and or their supporting structures (ruptured chordae tendinae), fluid in the lungs (pulmonary edema), coughing up blood from the lungs, blood clots in the vein, artery, or cavity of the heart (thrombus), an opening between body structures (left atrial/esophageal fistula), air or dislodgement of a blood clot resulting in a stroke or embolism, and/or obstruction of the vein and/or artery.

Bleeding from the site of catheter placement may go away without treatment, may require the application of pressure to the site, or (extremely rare) may require surgical intervention in the groin and/or heart. Accumulation of blood in the lining of the vessel wall or development of a false pouch may be painful. If it is small it may go away with no treatment, or may require manual compression at the groin, or ultrasound guided compression (like the echocardiogram). Rarely, surgical repair may be necessary. Return to normal activities would be delayed about a week. All they risks rarely occur but can be severe.

A clot may form on one of the catheters, on the surface of the heart at the site of the ablation, or at another site in the heart or in a blood vessel. The clot could become dislodged and travel through the blood stream and block an artery. This could produce a stroke, heart attack, or injury to another organ. Though this is a very rare occurrence it can be life threatening.

Other conditions which could develop include a local or generalized infection; perforation (tear or hole) of the heart with bleeding into the pericardial sac that surrounds the heart (tamponade), fluid accumulation around the heart (effusion), low blood pressure, permanent or temporary nerve damage to the heart or diaphragm that may affect breathing (phrenic nerve), abnormal heart rhythms, chest pain, or heart attack. It is also possible that the heart could stop beating (cardiac arrest), or that you could stop breathing (respiratory arrest), or that you could die. Bleeding into the lining around the heart may go away without treatment, may require placement of a tube into the lining around the heart, or (although extremely rare) require surgical correction. The radiation from the x-ray, which is used to guide the catheters' positions, may cause damage to the skin or other organ systems. Standard of care safety measures are maintained to minimize these risks but they can be life threatening.

During the procedure you will receive a type of x-ray called fluoroscopy to help the doctors guide the catheters in the heart. The radiation from the x-ray, which is used to guide the catheters' positions, may cause damage to your skin or other organs. Your radiation dose will be monitored during the procedure(s). The amount of fluoroscopy used in this procedure is the same as any other PVC ablation and standard of care safety precautions and assessments are maintained.

The radiation may slightly increase the risk of a fatal malignancy (1 in 1,000) or the chance that a child of yours may develop a genetic (birth) defect (1 in 2 million). This risk will be unlikely due to the standard of care for women of child bearing potential will require a negative pregnancy test.

You will be offered sedation throughout the procedure. Some of the known effects associated with sedation include allergic reactions, respiratory difficulties, low blood pressure, cardiac arrest (death) and nausea and/or vomiting. It is possible that aspiration (inhaling matter into the lungs) may occur. Standard of care safety measures will be utilized to minimize the possibility of these risks.
Insertion of the catheter (small tube) into the artery to monitor blood pressure may result in dislodgement of a blood clot and/or impairment of blood flow and oxygen to the tissue from the artery. The risks

associated with drawing blood include discomfort/pain, bruising, bleeding and infection which is minimized with standard of care being utilized

The risks and discomfort associated with all ablation procedures potentially include damage to an area of your heart in close proximity to the site that is being ablated. During the ablation procedure you may experience chest discomfort or a sensation of burning in the chest. Insertion and/or removal of the catheters may cause you to experience lightheadedness/fainting, loss of blood pressure, heart rate slowing, nausea, and anxiety for a brief time (known as a Vasovagal reaction). All these risks are minimized with standard of care monitoring and emergency response standards are available.
If your doctor feels that the procedure requires mapping or ablation that is better approached from the outside of the heart, injury to abdominal organs, the heart, or nerves in the chest can occur.

The risks for this procedure are the same as for any PVC ablation procedure. You will sign a separate consent for this procedure being done in the electrophysiology lab.
These risks can be severe but all efforts are made to minimize these risks and rarely occur.

2) Risk of worsening heart failure- There is the possibility that with medication and/or ablation your heart failure symptoms may not improve of worsen. It will be important that you report any worsening of symptoms so your doctor may treat accordingly.

3) Standard of Care Holter Monitor and Echocardiogram Risks:
There are no known significant risks associated with these tests. There is a slight possibility of skin redness or irritation due to the placement of the ECG electrodes, which should disappear within several hours of removing the electrodes.

4) Blood drawing can cause pain, bruising, lightheadedness and, on rare occasion, infection. These risks are minimal and rare. This is done no differently than a typical blood drawing at your doctor's office.

5) There are risks of loss of confidentiality to patients that participate in this trial; however all necessary precautions will be taken to assure your confidentiality is maintained and breach of confidentiality rarely occurs by maintaining research guidelines. Your information will be kept in secure locations. In any publication or presentation of research results, your identity will not be disclosed. Medical records that may identify you may, however, be reviewed by authorized individuals part of our research team, hospital auditors, regulatory authorities and Institutional Review Board members. Disclosure of your medical records to these authorized individuals may be protected by federal privacy rules and regulations. By signing this document, you consent to such inspections or reviews and to the copying of your records if required by one of these parties.

6) Pregnant females are excluded from participation in this trial because they are not eligible for catheter ablation due to radiation risks to the developing fetus. All females with child bearing potential that want to participate will need to do a pregnancy test the morning of the ablation procedure, and the test must be negative to have an ablation.
There may be risks in this study which are not yet known.

POTENTIAL BENEFITS

You may or may not benefit by taking part in this study. There is no guarantee that you will receive direct benefit from your participation in this study.

Your participation may help investigators recognize a potentially unique and new effective treatment strategy. If assigned to the catheter ablation group, effective therapy may include benefits such as improved pumping function of the heart (ejection fraction), reduced symptoms of heart failure, and decreased symptoms related to PVCs.

ALTERNATIVES TO PARTICIPATION

Your alternative is to not take part. If you choose not to take part, your healthcare at University of Maryland Medical Center will not be affected.

The alternative to this study is to attempt to control the amount of PVC's by adjusting your current medications or adding new medications or to proceed with a PVC ablation. This would be decided by you and your physician.

COSTS TO PARTICIPANTS

There are no additional costs to you as a consequence of your participation in this study. You and your insurance company will be billed for all tests and procedures that are considered standard of care for patients with PVC's and related heart failure; this includes the 24 Holter monitor, echocardiograms, MRI if obtained, hospitalization or ablation procedure.

PAYMENT TO PARTICIPANTS

You will not be paid to participate in this study

CONFIDENTIALITY and ACCESS to RECORDS

- ☐ This study will involve confidential information. Only the research staff will have access to the information, it will be coded and all your personal information such as name and date of birth will be removed, and all the data will be stored in a locked office and maintained in a password protected electronic database.
- ☐ Your name will not be used in reports or publications.
- ☐ Efforts will be made to limit your personal information, including research study and medical records, to people who have a need to review this information. We cannot promise complete secrecy. Organizations that may inspect and copy your information include the IRB and other representatives of this organization, or the FDA (Food and Drug Administration).
- ☐ The monitors, auditors, the IRB, the Food and Drug Administration will be granted direct access to your medical records for verification of the research procedures and date. By signing this document you are authorizing this access.

The data from the study may be published. However, you will not be identified by name. People designated from the institutions where the study is being conducted and people from the sponsor will be

allowed to inspect sections of your medical and research records related to the study. Everyone using study information will work to keep your personal information confidential. Your personal information will not be given out unless required by law.

RIGHT TO WITHDRAW

Your participation in this study is voluntary. You do not have to take part in this research. You are free to withdraw your consent at anytime. This includes having any of your previously collected blood samples removed and destroyed at your request. Refusal to take part or to stop taking part in the study will involve no penalty or loss of benefits to which you are otherwise entitled at the University of Maryland Medical Center. If you decide to stop taking part it is requested you provide a written notification, if you have questions, concerns, or complaints, or if you need to report a medical injury related to the research, please contact the investigator Timm Dickfeld, MD at 410-328-6056.
If you withdraw from this study, already collected data may not be removed from the database.
You will be told of any significant new findings which develop during the study and may affect your willingness to participate in the study.

CAN I BE REMOVED FROM THE RESEARCH?

The person in charge of the research study or the sponsor can remove you from the research study without your approval. Possible reasons for removal include failure to attend follow up appointment. The primary investigator can also end the research study early. The study doctor will tell you about this and you will have the chance to ask questions if this were to happen.

UNIVERSITY STATEMENT CONCERNING RESEARCH RISKS

The University of Maryland Medical Center is committed to providing participants in its research the rights due them under State and federal law. You give up none of your legal rights by signing this consent form or by participating in the research project. This research has been reviewed and approved by the Institutional Review Board (IRB). Please call the Institutional Review Board (IRB) if you have questions about your rights as a research subject.

Participating in research may result in an injury, as explained above. If you suffer an injury directly related to your participation in this project, University of Maryland Medical Center and/or one of its affiliated institutions or health care groups will help you obtain medical treatment for the specific injury and provide referrals to other health care facilities, as appropriate. University of Maryland Medical Center and/or its affiliated institutions or health care groups will not provide you with financial compensation or reimbursement for the cost of care provided to treat a research-related injury or for other expenses arising from a research-related injury. The institution or group providing medical treatment will charge your insurance carrier, you, or any other party responsible for your treatment costs. If you incur uninsured medical costs, they are your responsibility. Uninsured medical costs to treat research related

injuries not caused by drug or device under study are your responsibility. The study staff can give you more information about this if you have a study injury.

By signing this Consent Form, you are not giving up any legal rights. If this research project is conducted in a negligent manner and you are injured as a direct result, you may be able to recover the costs of care and other damages from the individuals or organizations responsible for your injury.

If you have questions, concerns, complaints, or believe you have been harmed through participation in this research study as a result of researcher negligence, you can contact members of the IRB or the Human Research Protections Office (HRPO) to ask questions, discuss problems or concerns, obtain information, or offer input about your rights as a research participant. The contact information for the IRB and the HRPO is:

University of Maryland School of Medicine
Human Research Protections Office
BioPark I
800 W. Baltimore Street, Suite 100
Baltimore, MD 21201
410-706-5037

Signing this consent form indicates that you have read this consent form (or have had it read to you), that your questions have been answered to your satisfaction, and that you voluntarily agree to participate in this research study. You will receive a copy of this signed consent form.

If you agree to participate in this study, please sign your name below.

_____
Participant's Signature

Date:_____

_____
Investigator or Designee Obtaining Consent Signature

Date:_____