VUMC Institutional Review Board
Informed Consent Document for Research

Study Title:	A randomized controlled trial of ryR2 inhibition with dantrolene and susceptibility to ventricular arrhythmias in patients with structural heart disease
Version Date:	12/13/23
PI:	William G. Stevenson, MD

Name of participant: _____ Age: _____

The following is given to you to tell you about this research study. Please read this form with care and ask any questions you may have about this study. Your questions will be answered. Also, you will be given a copy of this consent form.

Key Information:
The first section of this document contains some key points that the research team thought you would find important. The study is described in more detail after this section. If you do not understand something, please ask someone.

Key information about this study:

You are being asked to take part in this research study because you have an abnormal heart rhythm and will be having a procedure called an "ablation" to treat your ventricular tachycardia (VT) or premature ventricular contractions (PVCs). This may be because medications to treat your abnormal heart rhythms have not been effective. We are testing a medication called dantrolene to find out whether it can be a new treatment for ventricular tachycardia. This medication is approved by the Food and Drug Administration (FDA) for a rare form of muscle spasms, but it hasn't been tested and is not approved for the treatment of ventricular tachycardia. The potential benefit from this study is that we may learn more about how ventricular tachycardia occurs in the heart and how to prevent it from happening. Your ablation will be performed the same whether or not you are in this study. If you agree to this study, you will be given a one-time dose of dantrolene or placebo after your ablation is completed. You will be asleep and monitored by your doctors and the operating room staff the entire time you will be given the medication. We will study its effect on your heart's electrical system and pumping, muscle strength, and breathing. This study will not require any further visits from you once you leave the hospital; however, we may ask to draw blood from you while you are in the hospital if you choose to participate.

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Detailed Information:
The rest of this document includes detailed information about this study (in addition to the information listed above).

You are being asked to take part in this research study because you have an abnormal heart rhythm. You and your heart doctor have decided to perform a procedure called "ablation" to treat your ventricular tachycardia or premature ventricular contractions. This may be because medications to treat your heart rhythm have not been effective. We are testing a medication called dantrolene to find out whether it can be a new treatment for ventricular tachycardia. This medication is approved by the Food and Drug Administration (FDA) for a rare form of muscle spasms, but it hasn't been tested and is not approved for the treatment of ventricular tachycardia. There will be 84 people taking part in this study.

Your blood samples and information about you may be made available to others to use for research. To protect your privacy, we will not release your name or other information that can identify you. You will not receive any benefit as a result of the tests done on your samples. These tests may help us learn more about the causes, risks, treatments, or how to prevent this and other health problems. Your samples may be used to make new products or tests. These may have value and may be developed and owned by the study staff, Vanderbilt University, and/or others. If this happens, there are no plans to provide money to you.

You do not have to be in this research study. You may choose not to be in this study and get other treatments without changing your healthcare, services, or other rights. You can stop being in this study at any time. If we learn something new that may affect the risks or benefits of this study, you will be told so that you can decide whether or not you still want to be in this study. Your medical record will contain a note saying you are in a research study and may contain some research information about you. Anyone you authorize to receive your medical record will also get this information.

Participation in this study will not affect your ablation procedure. This is an investigational study and there are no alternative treatments.

Side effects and risks that you can expect if you take part in this study:

The research study will be performed while you are asleep for your ablation procedure, so you will not feel any potential discomfort related to pacing or arrhythmias.

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Arrhythmia induction study:
Uncommon risks (≤10%) of the research related to measuring your heart's electrical system, pumping function, and trying to induce arrhythmias are the same risks as those for the ablation procedure , including, but not limited to, bruising or bleeding at the catheter site, infection, blood clots (including stroke), new arrhythmias, slow heart rate, and very rarely, death.

Dantrolene:
There are risks related to dantrolene. It is used clinically for other disorders and has been tested in studies of healthy volunteers. Side effects are temporary, and you are less likely to experience side-effects because you will be asleep when dantrolene is given. In addition, your anesthesiologist will be monitoring you throughout the procedure. However, some residual side-effects are possible. Common (>10%) reported side-effects include flushing, excessive sleepiness, and mild difficulty speaking. Uncommon side effects (≤10%) include nausea and mild difficulty swallowing , pain in the extremities, skins rash and shortness of breath. Rare side-effects include vomiting, headache, blurry vision, mild muscle weakness, dizziness, mild fast heart rate, pain at I.V site, mild heart conduction delay and allergic reaction/anaphylaxis.

Risks that are not known:

Because this treatment is investigational, meaning non-FDA approved, there may be risks that we do not know about at this time.

Good effects that might result from this study:

A) The benefit to science and humankind that might result from this study is that we may learn more about how ventricular tachycardia occurs in the heart and how to prevent it from happening. Findings from this study may lead to dantrolene, or a similar medication, being developed as a new treatment for ventricular tachycardia.

B) You may personally receive no direct benefit by participating in this study.

Procedures to be followed:

During your procedure, you will be given a dose of dantrolene through an I.V. , or if you are part of the placebo group you will be given no medication. Then we will measure its effect on your heart's electrical system and pumping function using the tools that are used for your ablation. This will be performed

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after your doctor has finished the ablation, so the ablation procedure will be performed the same regardless of whether or not you participate in the study.

While you are waiting to go to the procedure room, we will measure your hand strength using a tool that you squeeze. We will also measure the strength of your breathing using a special inhaler. These tests take a couple minutes.

The day of the ablation will proceed normally. You will undergo standard preparations for a ventricular tachycardia ablation. As part of the ablation procedure, your doctor will place I.V's in the blood vessels in your leg. The I.V's will be used for placing the tools used for the procedure, drawing blood, and measuring your blood pressure. Some of the tools used are small pacing wires to study your heart's electrical system and induce arrhythmias like ventricular tachycardia. Another tool is used to measure your heart's pumping function. You will also have a mask over your nose and mouth that will provide oxygen and be used to measure your breathing. The research study will be performed after the ablation portion of your procedure is completed. At that time, a one-time dose of dantrolene or placebo will be given I.V, which takes 3-minutes. Immediately after that, we will study your heart's electrical system and pumping function to measure the changes caused by dantrolene. This will include attempts to induce arrhythmias, which we think will be decreased by dantrolene. However, if ventricular tachycardia is induced, your doctor may decide that you need more ablation. This will be decided by your doctors and not the research team. We will collect blood as part of this study to measure dantrolene levels. 2 tablespoons of blood will be collected during your ablation procedure using the I.V's that were placed in your leg. After the procedure we will collect blood up to seven more times depending on how long you stay in the hospital. The total amount of blood collected after the procedure is less than 2 tablespoons. The blood will usually be collected at the same time your doctor is collecting blood for their lab tests. If extra sticks are needed for research, you may refuse this and still be allowed to participate in the study. At two and 24 hours after the procedure, we will repeat the measurements of your hand grip using the tool you squeeze and your breathing strength using the inhaler. This is to test whether your strength is back to where you were before the procedure. You will spend the night in the hospital after the ablation. This is done for all patients who undergo ventricular tachycardia ablation, regardless of whether you participate in this study. You will be on strict bedrest until the morning after the procedure. Nurses or study staff will assist you the first time you get out of bed and walk after the procedure. Your doctors will see you that morning and let you go home if they think you are ready.

Payments for your time spent taking part in this study or expenses:

None

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Costs to you if you take part in this study:

If you agree to take part in this research study, you and/or your insurance will not have to pay for the tests and treatments that are being done only for research. However, you are still responsible for paying for the usual care you would normally receive for the treatment of your illness. This includes treatments and tests you would need even if you were not in this study. These costs will be billed to you and/ or your insurance. You have the right to ask what it may cost you to take part in this study. If you would like assistance, financial counseling is available through the Vanderbilt Financial Assistance Program. The study staff can help you contact this program. You have the right to contact your insurance company to discuss the costs of your routine care (non-research) further before choosing to be in the study. You may choose not to be in this study if your insurance does not pay for your routine care (non-research) costs and your doctor will discuss other treatment plans with you.

Payment in case you are injured because of this research study:

If it is determined by Vanderbilt and the Investigator that an injury occurred as a direct result of the tests or treatments that are done for research, then you and/or your insurance will not have to pay for the cost of immediate medical care provided **at Vanderbilt** to treat the injury.

There are no plans for Vanderbilt to pay for any injury caused by the usual care you would normally receive for treating your illness or the costs of any additional care. There are no plans for Vanderbilt to give you money for the injury.

Who to call for any questions or in case you are injured:

If you should have any questions about this research study or if you feel you have been hurt by being a part of this study, please feel free to contact study coordinator, Diane Crawford, RN at 615-936-6069 or if you cannot reach the research staff, please call Dr. William Stevenson or Dr. Ben Shoemaker at 615-322-2318.

For additional information about giving consent or your rights as a person in this study, to discuss problems, concerns, and questions, or to offer input, please feel free to call the VUMC Institutional Review Board Office at (615) 322-2918 or toll free at (866) 224-8273.

Reasons why the study doctor may take you out of this study:

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If your ablation procedure is not completed for any reason, you will be withdrawn. The doctor may take you out of this study if you ask to be taken out of the study. You may also be withdrawn if your clinical condition changes prior to the ablation and you are no longer eligible. You may also be taken out of this study for other reasons. You will be told why if this happens.

What will happen if you decide to stop being in this study?

If you decide to stop being part of the study, you should tell your study doctor. Deciding to not be part of the study will not change your regular medical care in any way.

Clinical Trials Registry:

A description of this clinical trial will be available on 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 Web site at any time.

Confidentiality:

Your study records and data will be stored in a secure database. The database will reside in a password protected secure web site supported by Vanderbilt. Only study personnel will have access to the database. Information in the database that will identify you will only be available to study personnel. Your biological samples will be stored with a barcode. This barcode will not include any identifying information. Only study staff will have access to these barcodes. A list will be kept by study staff that will be able to link your barcode to your identifying information. Only study staff will have access to your identifying information. Vanderbilt may share your information, without identifiers, to others or use it for other research projects not listed in this form. Vanderbilt, Dr. Stevenson, Dr. Shoemaker, and their staff will comply with any and all laws regarding the privacy of such information. There are no plans to pay you for the use or transfer of this deidentified information.

Privacy:
Any samples and information about you may be made available to others to use for research. To protect your privacy, we will not release your name. You will not receive any benefit as a result of the tests done

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on your samples. These tests may help us, or other researchers learn more about the causes, risks, treatments, or how to prevent this and other health problems.

Your samples may be used to make new products or tests. These may have value and may be developed and owned by the study staff, Vanderbilt University, Vanderbilt University Medical Center, and/or others. If this happens, there are no plans to provide money to you.

Study Results:

As part of the study, Dr. William Stevenson, Dr. Shoemaker and his study team may share the results of your study and/or non-study linked bloodwork, as well as parts of your medical record, to the groups named below. These groups may include people from the Federal Government Office for Human Research Protections, the Vanderbilt University Institutional Review Board, and the National Institutes of Health. Federal privacy rules may not apply to these groups; they have their own rules and codes to assure that all efforts, within reason, will be made to keep your PHI private.

The study results will be kept in your research record for at least six years after the study is finished. At that time, the research data that has not been put in your medical record will be kept for an unknown length of time. Any research data that has been put into your medical record will be kept for an unknown length of time.

Authorization to Use/Disclose Protected Health Information
What information is being collected, used, or shared?

To do this research, we will need to collect, use, and share your private health information. By signing this document, you agree that your health care providers (including both Vanderbilt University Medical Center and others) may release your private health information to us, and that we may use any and all of your information that the study team believes it needs to conduct the study. Your private information may include things learned from the procedures described in this consent form, as well as information from your medical record (which may include information such as HIV status, drug, alcohol or STD treatment, genetic test results, or mental health treatment).

Who will see, use or share the information?
The people who may request, receive or use your private health information include the researchers and their staff. Additionally, we may share your information with other people at Vanderbilt, for example if needed for your clinical care or study oversight. By signing this form, you give permission to the research team to share your information with others outside of Vanderbilt University Medical

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Center. This may include the sponsor of the study and its agents or contractors, outside providers, study safety monitors, government agencies, other sites in the study, data managers and other agents and contractors used by the study team. We try to make sure that everyone who sees your information keeps it confidential, but we cannot guarantee that your information will not be shared with others. If your information is disclosed by your health care providers or the research team to others, federal and state confidentiality laws may no longer protect it.

Do you have to sign this Authorization?

You do not have to sign this Authorization, but if you do not, you may not join the study.

How long will your information be used or shared?

Your Authorization for the collection, use, and sharing of your information does not expire. Additionally, you agree that your information may be used for similar or related future research studies.

What if you change your mind?

You may change your mind and cancel this Authorization at any time. If you cancel, you must contact the Principal Investigator in writing to let them know by using the contact information provided in this consent form. Your cancellation will not affect information already collected in the study, or information that has already been shared with others before you cancelled your authorization.

You have the right to see and copy the PHI we gather on you for as long as the study doctor or research site holds this data. To ensure the scientific quality of the research study, you will not be able to review some of your research data until after the research study is finished.

If you decide not to take part in this research study, it will not affect your treatment, payment or enrollment in any health plans or affect your ability to get benefits. You will get a copy of this form after it is signed.

STATEMENT BY PERSON AGREEING TO BE IN THIS STUDY

I have read this consent form and the research study has been explained to me verbally. All my questions have been answered, and I freely and voluntarily choose to take part in this study.

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Date _____ Signature of patient/volunteer _____

Consent obtained by:

Date _____ Signature _____

Time: _____ Printed Name and Title _____

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Consent for Genetic Research

The purpose of this study is to look at genes (DNA) and how they affect health and disease. Genes are the instruction manual for your body. The genes you get from your parents decide what you look like and how your body behaves. They can also tell us a person's risk for certain diseases and how they will respond to treatment.

You are being asked to give a blood sample for genetic research. What we learn about you from this sample is not put in your health record. Your test results will not be shared with you or your doctor. No one else (like a relative, boss, or insurance company) will be given your test results.

A single blood sample will be taken at the same time blood is being taken for the main part of the study. This will not take any additional time or require additional needle sticks.

One risk of giving samples for this research may be the release of your name that could link you to the stored samples and/or the results of the tests run on your samples. This may cause problems with insurance or getting a job.

To prevent this, these samples will be given a code. Only the study staff will know the code. The name that belongs to the code will be kept in a locked file or in a computer with a password. Only Drs. Stevenson and Shoemaker and members of their study team will have access to your name.

Health insurance companies and group health plans may not use your genetic information when making decisions regarding your eligibility or premiums. Employers with 15 or more employees may not use your genetic information that comes from this research when planning to hire, promote, or fire you or when setting the terms of your employment.

Your sample will be used to make DNA that will be kept for an unknown length of time (maybe years) for future research. The sample will be destroyed when it is no longer needed.

Your samples may be used to make new products, tests or findings. These may have value and may be developed and owned by the study staff, Vanderbilt University, Vanderbilt University Medical Center, and/or others. If this happens, there are no plans to provide money to you.

Your samples and information about you may be shared with others to use for research. To protect your privacy, we will not release your name.

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You will not receive any benefit as a result of the tests done on your samples. These tests may help us learn more about the causes, risks, treatments, or how to prevent this and other health problems.

Giving samples for research is your free choice and you may be in the study even if you do not want your samples used or stored for gene research.

At any time, you may ask to have your sample destroyed. You should contact Dr. Ben Shoemaker at 2525 West End Avenue Suite 300-A Nashville, TN 37203/ # 615-322-2318 to have your sample destroyed and no longer used for research. We will not be able to destroy research data that has already been gathered using your sample. Also, if your identity was removed from the samples, we will not be able to locate and destroy them.

There will be no costs to you for any of the tests done on your samples. You will not be paid for the use of your samples.

Please check Yes or No to the questions below:

My blood/tissue sample may be used for gene research in this study.

☐ Yes ☐ No

My blood/tissue sample may be stored/shared for future gene research in atrial fibrillation.

☐ Yes ☐ No

My blood/tissue sample may be stored/shared for future gene research for other health problems (such as cancer, heart disease, etc).