Central Virginia Veterans Affairs Health Care System (CVHCS)
Richmond Institutional Review Board
Consent Form

Template Version Date: (6/15/2021)

Title of Research Study: Vagal Nerve Stimulation as an Alternative Therapy for Premature Ventricular Contractions

Sponsor: CVHCS/Pauley Heart Pilot Program

Protocol Number: none

Investigator Name & Address: Dr. Jose Huizar, M.D., Richmond VA Medical Center,1201 Broad Rock Blvd, Rm 4A-100 (111J3), Richmond, VA 23249, Phone: 804-675-5151

KEY INFORMATION: Premature Ventricular Contractions (PVCs) are a type of irregular heartbeat. PVCs can cause palpitations, affect the quality of life, and very frequent PVCs may cause heart failure over time. Treatment for more frequent PVCs include medications and heart ablation (a catheter is passed through an artery or vein into the heart and uses radio waves to destroy cardiac tissue to stop the PVCs). Unfortunately, the medications may have side effects and ablation does not always work.

For people with less frequent PVCs, there are no clear treatment guidelines. It is not clear that treating people with less frequent PVCs will improve quality of life or decrease the risk of developing heart failure in the future.

We are asking you to take part in a research study to see if noninvasive vagal nerve stimulation will decrease PVCs better than medications. Stimulating the vagal nerve slows down the heart and may decrease PVCs. Noninvasive vagal nerve stimulation will be done by sending a small electrical current through a clip attached to your ear or by having you doing breathing exercises. These treatments are not approved by the Food and Drug Administration (FDA) for less frequent PVCs. This initial information is provided to help you decide whether to participate in the study.

If you take part in this study, you will receive all 3 treatments (medications, clip attached to ear, and breathing exercises), each for 2 weeks with a 1 to 2 week break between each treatment. While you are receiving each treatment, your heart rhythm will be monitored using a Zio Patch (a peel and stick device that is worn on your chest). Your participation in this study will last approximately three to four months, and you would be required to come to the VA at least 5 times in that period. Visits will include questions about your health and medications, a physical exam, electrocardiograms (EKGs, heart tracing) and questionnaires. Specific details about each study clinic visit are provided below in Section 3.

You may want to participate because it will help us learn if these noninvasive treatments decrease PVCs. You may not want to participate because of the potential risk of side effects from the treatments. You may choose not to enroll in the study and continue receiving routine care for your PVCs.

Additional detailed information is provided for your review in the sections below. Ask the research team questions until you feel you have enough information to make your decision to participate or not. Participating in this research study is completely voluntary. Your decision to participate or not will have no effect on any of the services, benefits, or rights that you are otherwise entitled.

The doctor in charge of this study is Dr. Jose Huizar and he can be reached at 804-675-5151. Other important contact information is listed below.

1. Whom should I contact for questions? (Contacts)

If you have any questions, concerns, or complaints regarding this study, unexpected reactions, or you are injured and/or become ill because of participation in this study please call at any time:

	Office	Off Hours
Dr. Jose Huizar	**(804) 675-5151**	**(804) 477-5429**
Dr. Pouria Shoureshi	**(804) 675-5151**	**(301) 310-5468**
Research Coordinators	**(804) 675- 5601 / 6730**	

If you are unable to reach any of the study staff listed and need immediate medical assistance, please call the Richmond VAMC operator at 800-784-8381 and ask for the Emergency Room physician to obtain advice or call the **Emergency Room directly at (804)-675-5527**. If you have any questions, concerns, or complaints about your rights as a research subject you may contact the **Richmond Institutional Review Board (IRB) at (804) 675-5676.** The IRB is responsible for reviewing research in humans and making sure that your safety and rights are protected.

2. What is this research study about? (Introduction)

You are being asked to take part in this research study because you have PVCs. PVCs are a type of irregular heartbeat. PVCs can cause palpitations, affect the quality of life, and very frequent PVCs may cause heart failure over time. The purpose of this research study is to see if noninvasive vagal nerve stimulation will decrease PVCs better than medications.

In this study, your PVCs will be treated with medications and 2 types of noninvasive vagal nerve stimulation. The order in which you receive the treatments will be determined by chance unless you are not on a beta-blocker. In that case we will perform the Medication Therapy last and start you on a usual care regime of beta-blockers. The three treatments are:

<u>Medication Therapy (MT)</u>

The standard treatment for PVCs is medication including beta-blockers (BB - cause your heart to beat more slowly and with less force) and calcium channel blockers (CCB - relaxes the heart and blood vessels and can slow the heart rate). If you are already taking one of these medications, they will be continued during the study. The dose may be adjusted by the study doctor. If you are not taking a BB, the study doctor will start you on one during the last two weeks of the study to determine if it decreases your PVCs. If it does this medication will be continued after the study. During the 2-week MT part of the study, you will wear a Zio Patch (a peel and stick device that is worn on your chest) to monitor your heart rhythm.

Lower-Level Tragus Stimulation (LLTS)
LLTS is done using Transcutaneous Electrical Nerve Stimulation (TENS), a small battery-operated device attached to a clip on the inner portion of your ear. TENS uses a mild electrical current to stimulate the vagal nerve and slow down your heartbeat. You will need to use the TENS device one hour twice a day (including right before bedtime) for two weeks. You will return the device after you complete this part of the study.

Heart Rate Variability Bio Feedback (HRV-BF)
HRV-BF requires that you load an app (Inner Balance) onto your smart phone. The study staff will show you how to use the app and give you written instructions. Using the app, you will be asked to do breathing exercises twice a day (including right before bedtime) for 2 weeks. You will attach a clip to your ear to monitor your heart rate during the sessions. Sessions will last up to 15 minutes. The app will guide your breathing based on your heart rate. You will return the earpiece and the app will be removed from your phone after you complete this part of the study.

For the LLTS and HRV-BF parts of the study, you will be asked to keep a daily log with the time the TENS or app were used, device settings and any comments related to each session. You will return the daily log to the study staff at the end of each 2-week session.

During each of the 2-week Baseline, MT, LLTS and HRV-BF parts of the study, you will wear a Zio Patch to monitor your heart rate and rhythm and check for PVCs. You will be required to return the Zio Patch device in the box provided at the end of the two weeks.

The study staff will review the results from the first 5 patients. If we do not see an effect after 14 days of MT, LLTS or HRV-BF, we may extend the study by 4-6 weeks for additional MT, LLTS or HRV-BF testing.

Approximately 20 Veterans will participate in this study. Your participation in this study will last approximately three to four months and may be extended to four to five months depending upon the first 5 veterans' effects during their first treatment arm. You would be required to come to the VA at least 5 times in that period. Each visit will last 2-3 hours

3. What is expected of me? (Procedures)

If you agree to participate, you will be asked to sign this consent form before any study procedures are done. The tests and procedures described below are being done for the purposes of this research.

This study consists of following parts:

- Screening Visit – To see if you are eligible to participate
- A Baseline 2-week Zio Patch Monitoring Period
- Wash-Out Period
- First Treatment Period
- Wash-Out Period
- Second Treatment Period
- Wash-Out Period
- Third Treatment Period
- Wash-Out Period
- End of Study Visit

Screening Visit

- You will be asked about your current health, and your past medical and surgical history.
- You will be asked about any medications (prescription or over the counter), vitamins, supplements, or natural remedies you are currently taking.
- Your vital signs (heart rate, breathing rate, blood pressure and temperature) will be measured.
- A physical exam will be done.
- The InTENSity 10 should not be used in people who have a pacemaker or a history of seizures. You will not be able to participate in this study if you have a pacemaker or a history of seizures.
- An electrocardiogram (ECG) will be done. An ECG is a non-invasive way to record the electrical activity of your heart.
- You will be asked to complete 2 questionnaires about your quality of life. These will take about 15 minutes to complete.
- A third questionnaire will ask about your well-being.

If you are eligible to participate in the study after the Screening Visit, you will be assigned randomly (by chance, like the flip of a coin) to receive one of the three treatments, unless you are not on a beta-blocker. In that case we will perform the Medication Therapy last and start you on a usual care regime of beta-blockers. You will know what treatment you are receiving.

Baseline Zio Patch Monitoring Period

- The study staff will place a Zio Patch device on your chest that you will wear for a 2-week baseline before starting treatment.

Wash-Out Period

- Evaluation Period of 1 to 2 weeks during which you will receive no-treatment and we will evaluate your burden of PVC.

Treatment Periods

- The first Treatment Period visit will be after you have worn the Zio for two weeks and the doctor confirms your PVC burden.
- At the beginning of each 2-week treatment period, the study staff will instruct you on: which medications to take for MT, or how to use the TENS device, or how to use the HVR-BR app. You will be given a daily log to fill out while wearing the Zio Patch.
- The study staff will also place a Zio Patch device on your chest that you will wear during each of the 2-week treatment periods (if this treatment period needs to be extended you will only wear the Zio Patch for the last two weeks of treatment.)
- At the end of each treatment period, you will mail in the Zio Patch in the box provided following the enclosed directions.
- There will be a 7-14 day wash out period before you will return to the study clinic, turn in your daily log, and/or return the TENS device, and/or have the app removed from your phone.
- Your medications will be reviewed.
- Vital signs will be measured, and a physical exam will be done.
- An ECG will be done.
- You will be asked to complete the same questionnaires you did at the prior Screening Visit.

Wash-Out Period

- Between the last Treatment and End of Study Visit there will be 1 to 2 weeks during which you will receive no-treatment.

End Of Study Visit

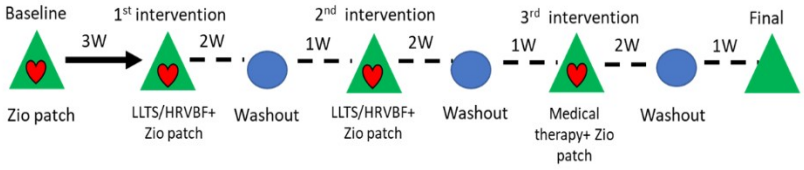
- Your medications will be reviewed.
- Vital signs will be measured, and a physical exam will be done.
- You will be asked to complete the same questionnaires you did at the prior Screening Visit.
- An ECG will be done.

Study timeline:

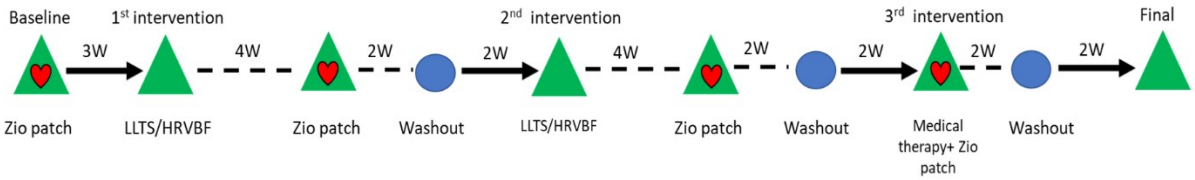
A: Shortest study timeline (12 weeks),

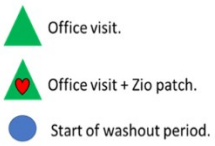
B : Longest study timeline (23 weeks)

2.A



2.B





4. **Will my data and/or samples be kept for use in the future? (Future use of data/samples)**
After the removal of identifiable information, your information and/or biospecimens collected as part of this research may be used for future scientific research without additional consent from you.

5. Will the research benefit me? (Benefits)
No benefit is guaranteed**.** However, the information we get from this study might help others with PVCs in the future.

6. What are my alternatives to being a research subject? (Alternative Therapy)
You do not have to participate in this study to receive treatment for your PVCs. You may choose to receive other treatments, including other investigational treatments. Your study doctor will discuss these and any other options with you before you sign this consent form.

7. What are my risks? (Risks, Inconveniences, Discomforts)
Participation in this study may involve risks that are unknown at this time. Your condition may stay the same, may improve or may worsen from study participation. You should let the study staff know about any changes in your health or any symptoms, side effects, complaints, illnesses, or injuries you may have while you are participating in this study.

Medication Risks: for beta-blockers **Serious side effects: Call Dr. Huizar at once if you have:**

- very slow heartbeats;

- a light-headed feeling, like you might pass out;
- shortness of breath (even with mild exertion), swelling, rapid weight gain; or
- cold feeling in your hands and feet.

Common side effects may include:

- dizziness;
- tired feeling;
- depression;
- confusion;
- memory problems;
- trouble sleeping/ nightmares;
- may make it harder for you to know when your blood sugar level is too low; or
- mild itching or rash.

LLTS Risks:
- Ear clip may cause redness or irritation
- May cause a burn if clip is left on too long or the intensity level is set too high
- May cause muscle twitching
- May cause unpleasant shocks if the clip is not applied correctly or your skin is wet
- May cause bradycardia (slow heart rate), low blood pressure, and dizziness

HRV-BF Risks:
- May cause bradycardia (slow heart rate), low blood pressure, and dizziness
- Hyperventilation (dizziness or lightheadedness, shortness of breath, dry mouth, numbness/ tingling in your arms or around your mouth)

Zio Patch Risks:
- Adhesive pads may cause redness, irritation, or itching

PVCs can be a serious condition with many complications whether or not you participate in this study.

All drugs have the potential to cause allergic reactions including the drugs used in this study. Allergic reactions may be mild to severe, and include the following symptoms: chills, fever, skin rash, hives, itching, watery eyes, swelling, headache, difficulty breathing, difficulty swallowing, severely low blood pressure, organ failure, and death. Serious allergic reactions require immediate medical attention.

8. Will I get paid? (Compensation)
You will be paid $100 for each of the scheduled in person visits. If you receive payments from McGuire Research Institute greater than $600 in a calendar year, it will be reported to the IRS along with your social security number. The information that you are providing for this research study may lead to new clinical or educational knowledge, tests, treatments, or products. These products could have some financial value. There are no plans to provide financial payment to you or your relatives if this occurs.

9. Will I have to pay? (Cost of Participation)
You will not have to pay, and your insurance will not be billed for treatments or procedures that are part of this study regardless of whether you are a Veteran or a non-Veteran. If you get a bill for research services, contact your study doctor or research nurse. Some Veterans are required to pay co-payments for medical care and services provided by the CVHCS. These co-payment requirements will continue to apply to medical care and services provided by the VA that are not part of the study.

10. Does pregnancy prevent me from participating? (Pregnancy)
Every effort will be made to have females enter this study, but pregnant women, women trying to become pregnant, and breastfeeding women will not be enrolled. Study treatment may involve risks to you, your unborn child, or a breast-fed baby. You should tell your study doctor immediately if you think you might have become pregnant. Do not wait until your next scheduled visit.

Medically accepted birth control is required to enter this study. This may include, but is not limited to, birth control pills, IUD's, condoms, diaphragms, implants, being surgically sterile, or being in a post-menopausal state. However, no birth control method eliminates the risk of pregnancy. If you are a female and if pregnancy occurs, you will be removed from this study. If you are a female of childbearing age, you must have a negative pregnancy test before entering the study.

11. What if I get injured? (Research Related Injury)
A research injury is any injury or illness caused by your participation in the study. In the event of a research injury, necessary medical treatment will be provided to assist your recovery from the injury. If you are a CVHCS study participant (Veteran or Non-Veteran), the CVHCS (not you or your insurance) will provide necessary medical treatment should you be injured by being in this study. You will be treated for the injury at no cost to you. This care may be provided by the CVHCS, or arrangements may be made for care at another facility.

In the event of injury resulting from your participation in this research study, you should contact your study team. If you want to speak to someone who is not a member of the study team to discuss problems, ask questions or voice concerns, you can call the Richmond IRB at (804) 675-5676.

This agreement does not include treatment for injury/illness that is not a result of the study. To help avoid injury, it is very important to follow all study directions. You are not giving up any of your legal rights by signing this form.

12. Who Will See My Information? (Confidentiality)
The study team will put information about your participation in this study in your medical record as it is important for other health care providers taking care of you to know of the study treatment you are receiving. The confidentiality of your research records will be maintained according to professional standards of confidentiality and Veterans Health

Administration (VHA) regulations. Records identifying you may be reviewed by the members of the research team, the Research and Development Committee and its sub-committees, accrediting agencies, officials from the VHA, the Office of Research Oversight, the VA Office of the Inspector General, CVHCS, McGuire Research Institute and its auditor, and other federal oversight agencies such as the Food and Drug Administration, Office for Human Research Protections, or as required by law.

The information collected about you while you are in the study such as your name, age and social security number will be protected. Study records will be kept in locked filing cabinets and on computers protected with passwords. Information published or presented about the results of this study will not identify you.

During the study, the results of some testing done for research purposes may not be made available to you and will not be placed in your medical record. The study doctor will share any clinically relevant results with you. You will not have access to your research-related health records while you are participating in this study.

The ways your study doctor will use your study-related health information and the people who may receive it are identified in a separate form entitled, Authorization for Use & Release of Individual Identifiable Health Information for Veterans Health Administration Research. You will be asked to sign that form to show that you give permission for these uses and sharing of your information. You do not have to sign the authorization form. However, if you do not sign, you will not be able to participate in the study.

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.

13. Do I have to participate in this study, or can I withdraw from the study? (Voluntary Participation and Withdrawal)

Participation in this study is voluntary and you may refuse to participate or withdraw from the study at any time without penalty or loss of benefits to which you are otherwise entitled. The study staff will answer any questions you may have about the study. You are free to withdraw your consent and stop participation at any time. If you decide to withdraw from this study, you should contact Dr. Huizar to discuss termination of your participation. It is important that you do this so that Dr. Huizar can withdraw you safely. Stopping will in no way change the quality of care you receive now or in the future at this institution or your right to participate in other studies.

Any data collected prior to withdrawal will continue to be used for the study by the investigator and samples collected cannot be withdrawn.

Any significant new findings that develop during the research study that may affect your decision to continue participating will be provided to you as soon as possible.

Your participation in this research study may be ended without your consent for the following reasons:

- If the study doctor believes, for any reason, that it is within your best interest.
- If you develop side effects that are considered dangerous.
- If you refuse to use the study devices or perform the breathing exercise.
- If you fail to return for follow-up as recommended by your study doctor
- If you fail to follow the study doctor's instructions.
- If you do not have the equipment needed to support Inner Balance app
- If you refuse to have tests that are needed to determine whether the study treatments are safe and effective.
- If you require treatment with drugs that are not allowed in this study.
- If you become pregnant.
- If other causes prevent continuation of the clinical research study.
- FDA, Richmond IRB may also end the study at any time.

14. Date of Consent Form Revision: July 12, 2023

Subject Name:_____ **Date:**_____

Title of Research Study: Vagal Nerve Stimulation as an Alternative Therapy for Premature Ventricular Contractions

Principal Investigator*:* Dr. Jose Huizar **CVHCS:** Richmond

RESEARCH SUBJECTS' RIGHTS: I have read or have had read to me all of the above.

Dr. **Huizar** (or an associate) has explained the study to me and answered all my questions. I have been told of the risks or discomforts and possible benefits of the study. I have been told of other choices of treatment available to me. I have been given the chance to ask questions and obtain answers.

I understand that I do not have to take part in this study, and my refusal to participate will involve no penalty or loss of rights to which I am entitled. I may withdraw from this study at any time without penalty or loss of VA or other benefits to which I am entitled. The results of this study may be published, but my records will not be revealed unless required by law. By signing below, I am agreeing to participate in this research study. I will receive a signed copy of this consent form.

_____ _____

Subject's Signature **Date**

_____ _____

Signature of Person Obtaining Informed Consent **Print name/Date**