Meets 2018 Common Rule Requirements

Uniformed Services University
CONSENT TO PARTICIPATE IN RESEARCH
Title: Comparative cohort study of post-acute COVid-19 infection with a nested, randomized controlled trial of IVAbradine for those with postural orthostatic tachycardia syndrome (COVIVA) **Principal Investigator:** COL David Saunders, MD, MPH

You may be eligible to take part in this research study. This form gives you important information about the study.

Please take time to carefully review this information. You should talk to the researchers about the research study and ask them any questions you have. You may also wish to talk to others (for example, your friends, family, or your personal physician) about your potential participation in this research study. You do not have to take part in this study. Participation is voluntary. You may also leave the research study at any time without penalty.

1. KEY INFORMATION:

Some COVID-19 survivors continue to experience symptoms after 12 weeks of the beginning of the disease, and this condition has been called "Long Haul COVID-19" (LHC). These symptoms include dizziness, tachycardia (a heart rate over 100 beats per minute), palpitations, confusion, and fatigue, and can greatly lower an individual's quality of life.

Postural Orthostatic Tachycardia Syndrome (POTS) is a condition with remarkable similarities to the LHC symptoms, especially tachycardia, confusion, and fatigue. POTS frequently strikes otherwise healthy individuals following viral illness or trauma, and can pose concerns and challenges to daily activities. Recent reports suggest many LHC patients meet diagnostic criteria for POTS. However, the actual prevalence of those meeting the diagnostic criteria for POTS is still unknown.

The purpose of this study is to identify the proportion of LHC patients with symptoms of postural orthostatic tachycardia syndrome (POTS) who actually have a corresponding diagnosis of POTS and determine the benefits of ivabradine treatment.

In this study, we will perform genetic testing to identify risk factors for LHC and POTS. Any changes that may impact your healthcare management will be clinically confirmed at no cost to you. If you are in the nested POTS RCT, you may also receive information regarding genetic changes that may affect how drugs are processed in your body. Further details are found in Section 5.

Ivabradine is an FDA approved drug that is currently used to treat tachycardia, or a heart

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rate over 100 beats per minute, in patients with heart failure. For participation in this study, you will be asked to take the study medication (2.5 mg to 7.5 mg) or placebo twice daily for 3 months and this may be extended up to 12 months. Ivabradine may cause fetal toxicity when administered to a pregnant woman based on findings in animal studies. If you are ABLE TO BECOME PREGNANT and you want to take part in this study, you should know that Ivabradine might be harmful. You should not get pregnant or breastfeed while in this study.

Your decision to participate or not participate in this study will not affect your future care in the military healthcare system (if you are an MHS beneficiary), or your relationship with your health care provider. If you are no an MHS beneficiary, you will need to have appropriate medical insurance and a primary doctor who you can follow up with if needed. For more information on medical insurance and clinical trial participation, see https://www.cancer.gov/aboutcancer/treatment/clinical-trials/paying/insurance. Note that this study does not involve cancer, but the information at the referenced website is useful for anyone who is participating in a clinical trial to understand.

If you decide to take part in this research study, you will be asked to sign this document and receive a copy to take home. Before you sign this document, be sure you understand what the research study is about, including the risks and possible benefits to you.

Please tell the researchers if you are taking part in another research study.

2. WHAT IS THE PURPOSE AND DURATION OF THIS RESEARCH AND WHO WILL TAKE PART?

This study has two cohorts: Cohort 1 (referred to as the 'overall cohort' throughout this form) consists of approximately 200 participants who have a diagnosis of LHC as well as a 'comparator group' of approximately 50 participants who have previously tested positive for COVID-19 but did not have LHC; and Cohort 2 consists of participants with symptoms of POTS and will be enrolled in the Postural Orthostatic Tachycardia Syndrome (POTS) Randomized Controlled Trial (RCT) and is referred to as the 'POTS RCT' throughout this form. You are being asked to take part in this research study because you have been previously diagnosed with COVID-19 with or without LHC and with or without POTS.

The purpose of this research study is to learn about the rate of Postural Orthostatic Tachycardia Syndrome (POTS) in people with long COVID-19 symptoms. The study will also determine the benefit of ivabradine for treating a fast heart rate (known as tachycardia), which is an important symptom of POTS. This study will also evaluate and track risk factors and outcomes among participants with LHC.

If you meet the study's inclusion criteria, you be enrolled into the **overall cohort.** This part of the study may include people who have had COVID-19 both with and without symptoms

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of LHC. After screening and enrollment, we will assess whether or not you have POTS using wearable monitoring devices. If you are found to have POTS or another condition known as inappropriate sinus tachycardia (IST), you will be invited to participate in the **POTS RCT**. The POTS RCT study will test whether the drug ivabradine helps to reduce your heart rate and improve symptoms. This consent form establishes consent for both parts of the study. If you are found to be eligible for the nested POTS RCT, you may be randomly assigned to one of two study groups: one that will receive ivabradine and one that will receive a placebo (further explained in section 4.2).

All study visits will take place on the Naval Support Activity–Bethesda base at the Uniformed Services University (USU) Translational Medicine Unit (TMU) or at an off-site clinic . There will be about 250 people taking part in the overall LHC cohort study at USU for a period of 2 years. The duration of participation per visit is about two hours per session.

During your participation, you will have up to 8 visits with the study team. After your enrollment you will need to return to the Translational Medicine Unit or off-site facility at 1 and 2 weeks and then at 1, 3, 6 and 12 months. If you are not found to have POTS (and therefore have been enrolled in the overall cohort), you will only need to return at 1, 3, 6 and 12 months. The number and frequency of visits may vary based on whether you are in the overall LHC cohort or randomized into the nested POTS RCT.

3. SCREENING PROCESS TO QUALIFY FOR PARTICIPATION IN THIS STUDY

Before you can take part in this study, you will need to have some tests and provide some information so that the Investigators can confirm that you qualify for the study. This is called the "Screening Process". These tests may have been done or this information collected as a part of your regular medical care in the past. However, we will collect this information again as part of the study to ensure you meet study criteria and can safely join the study. The screening process will start with discussion and signing of informed consent (this form).

If you decide to participate, you will have a medical history and physical exam, COVID-19 antibody test result, electrocardiogram (EKG), baseline breathing test, mental health assessments, and blood tests. Vital signs and metabolic blood testing will be performed in the lying down and standing positions. You will be asked to sign a medical records release which will be sent to your primary care doctors. The records requested will be focused on your history of COVID-19 including how severe your illness was, what you were treated with, if you were admitted to the hospital, and if you suffered any complications from treatment. The investigators will review this information, along with your medical history and review any medications you are taking including over-the-counter supplements. If you are not a Military Health System beneficiary, you will be asked to provide proof of current medical insurance coverage.

You may take part in the LHC overall cohort study if you:

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1. Are between 18-80 years old
2. Have a history of documented COVID-19 infection of any severity to include a positive COVID-19 PCR, or antibody test
3. *For the Long-Haul COVID-19 cohort* – meet criteria for 'long-haul' COVID-19 (LHC) with symptoms related to COVID-19 infection lasting more than 12 weeks following acute illness
4. *For the non-Long Haul COVID-19 comparison group* – do not meet criteria for LHC, ie, no ongoing symptoms related to COVID-19 infection >12 weeks following acute illness
5. Are able and willing to provide informed consent and can participate for the study duration
6. Are willing to participate in a nested sub-study of ivabradine if you qualify for that study
7. Have current medical insurance coverage and a primary healthcare provider or team

You may be eligible to take part in the POTS RCT if you:

1. Satisfy the inclusion criteria for the LHC cohort study stated above
2. Have an increase in supine to standing heart rate >20 beats per minute with a drop in systolic blood pressure less than 20 mm Hg or a drop in diastolic blood pressure less than 10 mm Hg OR Have a 24-hour average heart rate of ≥90 beats per minute in sinus rhythm
3. For females of childbearing age – willing to use a highly effective form of contraceptive with
   <1% failure rate or practice abstinence for the duration of the study

You may not participate in the LHC cohort study or the POTS RCT if you:

1. Have a resting heart rate of less than 60 beats per minute
2. Have heart conditions known as atrial fibrillation or supraventricular tachycardia
3. Documented pre-existing POTS or inappropriate sinus tachycardia prior to contracting COVID-19
4. Have an allergic reaction or known contraindications to the drug Ivabradine which include
   Acute decompensated heart failure
   a. Clinically significant hypotension
   b. Heart conditions known as sick sinus syndrome, sinoatrial block or 3rd degree AV block, unless you have a functioning demand pacemaker already placed
   c. Clinically significant bradycardia (slow heart rate)
   d. Severe liver impairment
   e. Pacemaker dependence where your heart rate is maintained only by your pacemaker
   f. Take drugs which inhibit or induce a liver metabolism enzyme cytochrome P450 3A4. The Investigator will advise you whether this applies based on which essential medications or food supplements you are currently taking.
5. Are a pregnant or lactating woman or are of childbearing potential and unwilling to use effective contraceptives or practice abstinence

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6. Have impaired gastrointestinal absorption that would prevent you from using drugs by mouth
7. Taking any of the following drugs unless you and your doctor agree they are safe to discontinue and you have stopped taking them for at least one week: a. beta-blockers calcium- channel blockers
   b. cholinesterase inhibitors (pyridostigmine),
   c. vasoconstrictors (midodrine, octreotide, droxidopa, stimulants)
   d. sympatholytics (clonidine, methyldopa)
   e. blood volume enhancers (fludrocortisone, desmopressin, salt supplementation)
   f. oral ketoconazole (contraindicated)
8. Are currently experiencing acute suicidality

After you have completed your initial assessment at the screening visit, the Investigators will assess whether it is safe and appropriate for you to participate in the study. There may be questions regarding whether the exclusion criteria above apply to you. If this happens and you wish to participate in the study, the Investigators may (with your permission) contact your health care provider(s) to further clarify whether or not it is safe for you to participate in the study.

4. WHAT WILL HAPPEN IF YOU DECIDE TO BE IN THIS RESEARCH?

You will have a discussion with a study investigator, or their designee, about the reasons for this study and what the study will involve, have an opportunity to ask your questions, and then sign a consent form (this form).

4.1 If you are enrolled in the overall LHC cohort, you will have a brief follow-up medical exam by a study physician, fill out surveys about your quality of life, mood, physical symptoms, and thinking, and complete a few tasks on a tablet device, and complete an audio-recorded mental health interview assessment, to assess your psychological well-being. You will also have metabolic, immune system and genetic blood testing to better understand your risk factors for COVID-19, LHC, POTS and related conditions, and the drugs used in the study. You will be provided with a non-invasive monitoring device to check your heart function and vital signs at enrollment. You will wear the device continuously as much as possible for 1 week along with completion of a detailed symptom diary focused on your heart. You will return to the TMU for a second screening visit to have the monitoring data reviewed by study investigators to see if you meet criteria to participate in the **POTS RCT**. If your heart monitoring does not show POTS or an inappropriate heart rate (IST), you will not participate in the nested RCT part of the study but will remain in the LHC **overall cohort**. If you do not have POTS, or other medically significant findings during the monitoring period, you will have a follow-up visit by phone with the study team. If you do not have POTS but do have other medically significant findings, you may be asked to return to the study center to discuss the findings with a study doctor and referred back to your primary care provider. You will continue to be followed for

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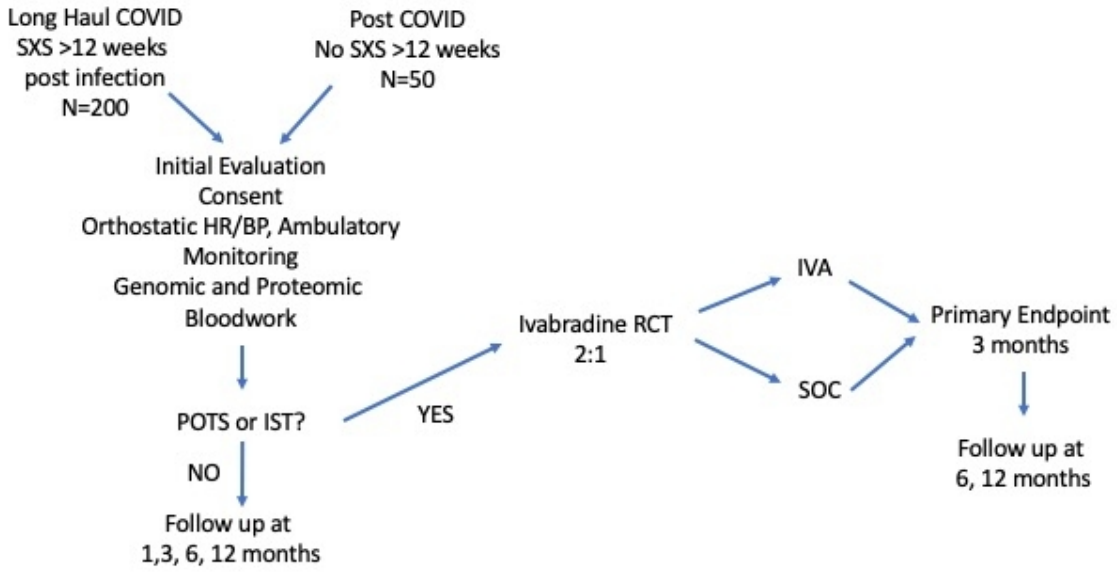
periodic assessments at months 1, 3, 6 and 1 year. See the Figure 1, Study Design, for further explanation of assignment to the LHC overall cohort and the nested POTS RCT.

Figure 1: Study Design



You will be asked to participate in the nested POTS RCT if after at least 1 week of wearing the monitoring device you have:

1. A heart rate of more than 90 beats per minute while in the standing position and/or;
2. An increase in heart rate when moving from the lying to a standing position of more than 20 beats per minute and/or;
3. An average heart rate of more than 90 beats per minute over a 24-hour period and
4. If you are a woman of childbearing potential – are willing to use a highly effective birth control with <1% failure rate or practice abstinence for the duration of the study

For participation in this study, you will be asked to take the study medication (2.5 mg to 7.5 mg) or placebo twice daily for 3 months and this may be extended up to 12 months. **If you are found eligible to participate in the nested POTS RCT,** you will be randomly assigned to one of two groups. Randomization means you will have a chance of being assigned to either the ivabradine treatment group or the placebo (non-active pill) group. You will have a one in three chance of being in the placebo group. A placebo is an inactive, harmless substance that looks like the research study medication but contains no medication.

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4.2a You will not know whether you are receiving the research study medication or a placebo.

4.2b You will be followed for 3 months to determine the effect of Ivabradine. After 3 months, placebo participants will be offered Ivabradine treatment and followed along with treated participants for an additional 9 months for safety.

4.2c If you have been treated with ivabradine without clear benefit when you reach the three month mark, you will be informed of the results to date and counseled by an Investigator on continuing the medication. You will be followed for an additional 9 months for safety.

4.2d Nested POTS RCT participants will return at week 1, 2, month 1, 3, 6 and 12 to have repeated measures of seated and standing vital signs, review of ambulatory vital signs, symptom diary and heart function (for one week before the month 1, 3 and final visits), blood tests, adverse events and medication review. Participants not enrolled to the RCT (the overall cohort with LHC or non-LHC without POTS) will return at months 1, 3, 6 and 12 for repeat blood tests, adverse events, and medication review. All participants will have a follow-up medical exam, surveys, and tablet-based tasks at 1, 3, 6 and 12 months. In addition, all participants will have blood tests for safety, a breathing test, and will complete the mental health interview assessment at 3 and 12 months.

Be aware that all results from this research study will not be directly placed in any medical record by research staff. Significant results that could influence your healthcare will be provided to participants share with your primary healthcare provider. See Section 5 for details.

5. WHAT ARE THE RISKS OR DISCOMFORTS FROM BEING IN THIS RESEARCH?

There is a very minimal risk of physical discomfort from participation in this study for the overall cohort participants without POTS (both of LHC and non-LHC). There is a minimal risk related to blood draw. You may have a bruise or be sore at the site where blood is drawn. There is also a slight possibility of infection at the site where the blood is drawn. In addition, discomfort may also occur while wearing monitoring devices. Monitoring may be uncomfortable to wear and/or reveal a previously undiagnosed cardiac or medical condition. Participants will be informed of any clinically significant and actionable abnormality and subsequently referred to their primary providers for appropriate additional evaluation in such instances.

Possible risks may also include discomfort due to providing information about sensitive topics during the clinical interviews and when completing certain questionnaires. You may also experience some frustration while completing tasks on

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the tablet device. If during the clinical interview it becomes apparent that you are experiencing thoughts about suicide, the interviewer or appropriately trained member of the study staff will ask you to share more information to evaluate your safety. If there are ongoing concerns about your safety, we will refer you for a psychological consultation and outside psychological treatment as recommended. If you are in need of an urgent evaluation (e.g., actively suicidal with a plan to carry out such actions), an on call healthcare professional will be contacted for an immediate consultation and appropriate intervention as necessary (potentially including an escort to a local emergency room).

If at any point in the study the investigators become aware of a treatment that may be more effective or appropriate for your needs and/or symptoms, we will provide relevant information and referrals for you to take to your primary care physician.

Genetic Analysis

In this study, we will use a test that looks at most of your genes or DNA. Any changes that may impact your healthcare management will be clinically confirmed at no cost to you. If you are in the nested POTS RCT, you may also receive information regarding genetic changes that may affect how drugs are processed in your body. If we find a gene change that we believe to be medically useful, we will contact you to discuss this. It would be recommended that you receive clinical confirmation if this change is found and this clinical testing would require an additional consent process. If we find and confirm a gene change that we believe to be medically useful, the genetics service will contact you to schedule an additional genetic counseling appointment. This meeting with a genetic counselor will consist of individually tailored counseling regarding the significance of any returnable results to your future health. As part of this counseling, you may be referred to your Primary Care Doctor for further follow up and medical evaluation. Costs may be associated with the recommended follow-up and medical management and should be discussed with your Primary Care Physician.

If no genetic results are returned to you then there were no clinically actionable results that were found based on current American College of Medical Genetics (ACMG) guidelines. This research testing does not replace clinically indicated genetic testing. If you have a personal or family history of a hereditary condition, you should discuss this with your doctor and/or a clinical genetic counselor. Although efforts are made to protect the privacy and confidentiality of your research study records, if you choose to take part in this research study, there is some risk that someone could get access to the personal information in your medical records or other research information that the study team has stored about you.

Genetic Information Non-Discrimination Act (GINA)

This federal law generally makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information and family history. This law generally will protect you in the following ways:

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1. Health insurance companies and group health plans may not request your genetic information arising from this research.

2. Health insurance companies and group health plans may not use your genetic information when making decisions regarding your eligibility or premiums.

3. Employers with 15 or more employees may not use your genetic information coming from this research when making a decision to hire, promote, or fire you or when setting the terms of your employment.

4. All health insurance companies and group health plans and all employers with 15 or more employees must follow this law.

5. GINA's health insurance protections do not apply to members of the military who receive their healthcare through TRICARE, for veterans who receive their healthcare through the Veterans' Administration, and for federal employees enrolled in the Federal Employee Health Benefits Plan. While GINA's employment protections do not apply to military members and federal employees, presently an Executive Order protects federal employees from genetic discrimination in employment, and the military has its own policies in place that may protect against genetic discrimination. GINA's protections should apply for a military member once he or she leaves the service and enters the private sector.

Be aware that this new federal law does not protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance.
Another potential risk of this study is the compromise of subject confidentiality. However, the investigators will make every effort to protect subject confidentiality through secure data management and de-identification/ coding as detailed in the description of our database system in section “Other Measures to Minimize Risks of Harm” on this form.

Other Abnormal Findings

While in the study, activities will be completed as outlined in section 5 of this form. Any results from these activities that are clinically relevant and clinically actionable will be given to you.
Significant abnormal findings will be included in a letter provided to the volunteer to provide to their physician.

Ivabradine Risks

Participants with these conditions will be excluded from the nested POTS RCT. Study participation will be halted for those who develop any of the below during the course of the RCT:

- Acute decompensated heart failure
- Clinically significant hypotension (low blood pressure)
- Sick sinus syndrome, sinoatrial block or 3rd degree AV block, unless a functioning demand pacemaker is present
- Clinically significant bradycardia (abnormally slow heart action)

- Severe hepatic (liver) impairment
- Heart rate maintained exclusively by the pacemaker
  - Taking strong cytochrome CYP3A4 inhibitors
  - The drug is not recommended for those with 2nd degree AV block, and will not be used

The risks of Ivabradine use include development of atrial fibrillation (an irregular heartbeat) and symptomatic bradycardia (slow heartbeat). Other adverse events reported with >1% frequency have included high blood pressure and seeing lights or halos around objects.

Rare adverse events reported during post-marketing approval have included:

- Syncope (temporary loss of consciousness caused by a fall in blood pressure)
- Low blood pressure, torsade de pointes (a form of rapid heart rate)
- Ventricular fibrillation (a dangerous type of irregular heartbeat), ventricular tachycardia (a fast, abnormal heart rate that starts in your heart's lower chambers, called the ventricles)
- Angioedema (skin swelling that is similar to hives, but the swelling is under the skin instead of on the surface)
- Erythema (superficial reddening of the skin, usually in patches, as a result of injury or irritation causing dilatation of the blood capillaries)
- Rash
- Pruritus (severe itching of the skin)
- Urticaria (a rash of round, red welts on the skin that itch intensely)
- Vertigo (a spinning sensation even when not moving)
- Double vision and visual impairment

All participants enrolled to the nested POTS RCT will be monitored for these conditions. To ensure correct use of ivabradine, doses will be adjusted based on your response. You should notify study team of side effects that occur in between study visits.

Blood Draw

Total blood draw volume for participants completing the study will be 320mL or 21.3 tablespoons with an additional 219.5 mL (14.6 tablespoons) for those in the nested POTS RCT (total 539.5 mL or 36 tablespoons). Drawing these amounts of blood is safe and should not affect your health.

Other Measures to Minimize Risks of Harm (Precautions, safeguards):

Coded data will be maintained electronically through a secure database system (known as REDCap) maintained on a Department of Defense (DoD) server. The Principal Investigator and research team will monitor the conduct of this study, and confidentiality of the data collected for this study. All information gathered about you during the course of the study will be identified with a study code number as an additional safeguard in order to protect your identity and confidentiality. This process is further explained in Section 15 below.

Research-related injury

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Ivabradine is an FDA approved drug being used to treat rapid heart rate associated with heart failure. Although there have been other studies showing it helps patients with POTS, FDA has not approved it for use in this specific condition. Care for research related injury, in the rare event that it would occur would be provided consistent with Department of Defense Instruction 6025.23 1570 (26 Sept 2020). See Section 21 for full details.

Ivabradine may cause fetal toxicity when administered to a pregnant woman based on findings in animal studies. If you are ABLE TO BECOME PREGNANT and you want to take part in this study, you should know that Ivabradine might be harmful to (1) an unborn child if you are pregnant; or (2) an infant if you are breast-feeding. You will take a urine pregnancy test and the test result must be negative before you can participate in this study. If the urine test is inconclusive, we will do a blood test. Volunteers with a positive pregnancy test will not be allowed to continue participating in the study. You should not get pregnant or breastfeed while in this study. The only completely reliable methods of birth control with a <1% failure rate are not having sex or surgical removal of the uterus and other birth control methods that have less than 1% failure rate according to the CDC: copper IUD (0.8%), hormone-releasing IUD (0.1-0.4%) and hormone-releasing implant (0.1%). Other methods, such as the use of condoms, a diaphragm or cervical cap, birth control pills, IUD, or sperm killing products are not totally effective in preventing pregnancy.

If you become pregnant or feel you might be pregnant, contact your personal physician and the principal investigator of this study listed in the Contact Information section at the end of this document. There may also be other risks of taking part in this study that we do not yet know about.

6. WHAT ARE THE POSSIBLE BENEFITS FROM THIS RESEARCH?

Ivabradine may prove to have benefit in those with POTS, and is the primary objective of the nested POTS RCT. However, there is no guarantee that you will benefit from being in this research.

The data obtained from this research study may help improve diagnosis and management of LHC in the future and improve medical treatment.

7. WHAT ARE THE ALTERNATIVES TO TAKING PART IN THIS RESEARCH?

There may be other options for treatment of LHC and POTS. You should talk with your personal physician about your options. Choosing not to take part in this research study is also an option. The medication involved in this research study may also be available through your personal physician without taking part in this study.

8. IS THERE COMPENSATION FOR YOUR PARTICIPATION IN THIS RESEARCH?

If you are in the nested POTS RCT, you will receive $100 after each completed visit once beginning at randomization (week 1, week 2, months 1, 3, 6 and 12).
To be compensated for participation in this study, you may be asked to complete and sign a

Receipt of Compensation Form along with a W-9; you may receive a 1099-MISC at the end of the year and you may need to report this compensation as income when filing your tax return with the IRS.

Volunteers who are government employees including active duty military will require permission from their supervisor prior to enrollment, and will only be seen in an off-duty status.

9. ARE THERE COSTS FOR PARTICIPATING IN THIS RESEARCH?

No, there are no costs to you for taking part in this research study.

10. PRINCIPAL INVESTIGATOR (responsible for scientific and technical direction):

David Saunders, MD, MPH
Colonel, Medical Corps, US Army
+1 (301) 318-6024
clinical.research.unit.53-ggg@usuhs.edu

11. STUDY SPONSOR (the organizations or persons who oversee the study and are responsible for analyzing the study data):

The Defense Health Agency is the Funder for the study**.** However, the study is being conducted as Investigator-initiated research. Results are not intended for submission to the FDA under this protocol. As the funder of this research, the Department of Defense may have access to your research data in accordance with Department of Defense Instruction DoDI 3216.02

12. SOURCE OF FUNDING:

Defense Health Agency

13. LOCATION OF THE RESEARCH:

Translational Medicine Unit, Department of Medicine
Uniformed Services University, Building 17, Suite 2A
4301 Jones Bridge Road, Bethesda, MD 20814-4712

Study visits may take place at other locations on campus or at an off-site satellite clinical location as space permits. You will be informed of these changes. Lab testing may be performed in some cases at contracted laboratory facilities.

14. DISCLOSURE OF FINANCIAL INTERESTS AND OTHER PERSONAL ARRANGEMENTS:

Neither the research study team, USU, Defense Health Agency nor Department of Defense have any financial, commercial nor other conflicts of interest related to this research study.

15. WHO WILL SEE MY INFORMATION (PRIVACY) AND HOW WILL IT BE PROTECTED (CONFIDENTIALITY)?

Records of your participation in this research study may only be disclosed in accordance with state and federal law, including the Federal Privacy Act, 5 U.S.C.552a, and its implementing regulations. DD Form 2005, Privacy Act Statement - Military Health Records, contains the Privacy Act Statement for the records. A copy of DD Form 2005 can be given to you upon request, or you can read on-line at:
https://www.esd.whs.mil/Portals/54/Documents/DD/forms/dd/dd2005.pdf

Procedures to protect the confidentiality of the data in this study include but are not limited to: Any paper forms that have information that could identify you with will be in a locked cabinet in a locked facility located at the USU Translational Medicine Unit. Any electronically-stored personal information will be maintained on a password protected folder on a USU server that is password and access card protected. Blood samples will not contain any personally identifying information. Instead they will be labelled with a study code number. Audio-recorded clinical interviews assessing psychological well-being also will be electronically labelled with a study code number. All information that could be used to identify you will remain strictly confidential and in the custody of the study team.

Researchers will make every effort to protect your privacy and confidentiality; however, there are risks of breach of information security and information loss.

If applicable, 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. The study entry will include a summary of results once available but will not contain individual results or any manner of identifying information. You can search this website at any time.
Complete confidentiality cannot be guaranteed for military personnel, because of the nature of military service.

Previously undisclosed information derived from the study regarding your health may be required to be reported to appropriate medical or command authorities to ensure the proper execution of the military mission, including evaluation of fitness for duty.

Information gained from your participation in this research study may be published in the medical literature, discussed for educational purposes, and used generally to further science. You will not be personally identified when your information is shared in these ways; all information will de-identified.

Examples of persons who may access your personal health information (PHI) for the purpose of quality assurance and/or oversight include representatives of the DoD Higher Level Review, the Henry M. Jackson Foundation for the Advancement of Military Medicine (HJF), The Metis Foundation, the Food and Drug Administration (FDA), the Department of Health and Human Services (DHHS) Office for Human Research Protections, and the DHHS Office for Civil

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Rights. These records may be looked at by staff from the Uniformed Services University of the Health Sciences (USU) Institutional Review Board (IRB). This disclosure is unlikely to occur, but in that case, your health information would no longer be protected by the HIPAA Privacy Rule. In addition to the research study team members, the following people and/or organization(s) will be allowed to disclose, use, and receive your information, but they may only use and disclose the information to the other parties on this list, to you or as permitted by law: Any organization participating in an approved research-related data or information exchange in connection with this study.

- Your returnable genetic results, findings and related recommendations provided to you by the study team will be provided to you to disclose to your primary care physician.
- The genetic data that is returned to you because of medical significance will be shared with you and you can share with your primary physician, at your discretion.
- Any laboratories, individuals, and organizations that use your coded samples and health information in connection with this study.
- Any federal, state, or local governmental agency that regulates the study, such as the U.S. Food and Drug Administration (FDA).
- U.S. Department of Health & Human Services (DHHS), and Office for Human Research Protections (OHRP) or other government agencies in this or other countries.
- Controlled-access public research data repositories required for broad data sharing, including NIH-designated data repositories such as the Genomic Data Commons (GDC), Proteomic Data Commons (PDC) and The Cancer Imaging Archive (TCIA).
- The designated Protocol Review and Monitoring Committees, Institutional Review Boards (IRB), Privacy Boards, Data and Safety Monitoring Board and their related staff that have oversight responsibilities for this study.

The organizations and people listed above may employ or pay various consultants and companies to help them understand, analyze and conduct this study. All of these people may not be known now, but if you would like to have more specific information about this at any time during the study, you may ask the study doctor and your questions will be answered.

If all information that does or could identify you is removed from your records, the remaining information will no longer be subject to this authorization and may be used or shared for other purposes. Fully de-identified data collected through the research study may be submitted to publicly accessible databases. These data will be available for general research purposes without additional IRB approval.

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16. LONG TERM USE OF DATA

The investigators have requested to save selected data collected from your participation in this research study for possible use in future research. If future use of research data is undertaken, only de-identified information will be used or shared. You have a number of options with regard to this request. If the stored data has an identifying link (coded) you can request to be contacted and sign a separate consent form to allow the use or available of this data in another study. You may also choose either to not allow any further use of your data, allow use of only de-identified data, or give consent now for the use of your identifiable data to be used in future studies. This future research may be in the same area as the original study or it may be for a different kind of study. You will be provided choices at the end of this consent form to allow or deny use in future research studies.

Any future research using your retained data will require a research protocol for the proposed study approved by an Institutional Review Board (IRB) (a committee responsible for protecting research participants) or other authorized official responsible for protecting human subjects of research. The data protections for privacy and confidentiality described in this consent form will apply to any future use of your stored data.

Future Use of Biologic Specimens: The investigators in this study are asking for your permission to store your samples described above for future use in other research studies. The specifics of any potential future research studies are unknown at this time, and none are currently planned. Future use studies may be in the areas of infectious or cardiovascular diseases, or in other unrelated fields. If you opt to permit future use, your samples would be stored with only the following information: study ID and collection date. This is not considered to be identifying information and cannot be traced back to you as the donor or study participant.

The storage (bank) area is maintained at the USU Translational Medicine Unit. The Principal Investigator is responsible for the storage bank (see contact information above). Future research requesting portions of your samples from the bank must have the approval of the TMU and also must have a qualified investigator with a research protocol for their newly proposed research study approved by an Institutional Review Board (IRB) (a committee responsible for protecting research participants). It is possible these other researchers will request approval from an IRB to contact you in the future if you opt in for future use of specimens.

Some future research studies may include genetic testing of your samples stored at the bank. Since storage (banking) of biologic specimens for future genetic testing is still undergoing development, the benefits and risks of genetic testing are not fully known at this time. It is believed that the risks are very low. Using new technology, information about your DNA structure (genetic information) gained from your banked samples can be used to indicate risk for developing certain diseases. This genetic information is unique to you and may indicate changes in your future health status or life expectancy, or that of your children and other relatives. These discoveries could be stressful and cause psychological difficulties or family problems. It is also possible that during future research, people of your ethnic background may be found to be at more risk for certain diseases.

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Release of personally identifiable genetic information may pose a possible risk of discrimination or increased difficulty in obtaining certain types of insurance for you and your family members. The Genetic Information Nondiscrimination Act of 2008 (Pub. L. 110-233) also known as "GINA" is a federal law that prohibits discrimination in health insurance coverage and employment based on genetic information. GINA is described above in Section 5. GINA does not apply to employers with fewer than 15 employees. GINA's protections in employment do not extend to the US military. Nor do they apply to health insurance through the TRICARE military health system, the Indian Health Service, the Veterans Health Administration, or the Federal Employees Health Benefits Program. Lastly, the law does not cover long term care insurance, life insurance or disability insurance.

Potential risk would occur if the confidentiality of your data is breached. Because of the consequences of a breach of confidentiality, every effort will be made by the study team to protect your privacy. The TMU storage procedures to protect your data confidentiality include:

a. Your specimens will be coded – no personally identifying information will be included.

b. Your samples may be stored indefinitely at the bank, or until no samples remain. Generally, you will not be provided with the results of the future studies using your samples from this bank. This is typically the case because the research results at that early point will not have a clear meaning for or direct clinical benefit to you.

c. You may request that your specimen be withdrawn from the bank at any time if you decide you no longer want to participate. This can be done by notifying the PI listed above.

d. Your biospecimens (even if identifiers are removed) may be used for research that could eventually lead indirectly to commercial profit. However, there is no intent from this study for commercial profit of any kind. You would not share in commercial profit if it were to occur. The Investigators and study team are either US government employees or non-profit contractor personnel.

We plan to continue studying your sample for years to come. If we find information after your death that might be important to the health of your family, we will try to reach one or more contacts to let them know that this information is available to share with your family.

The contact I would like to share this information with is:_____who can be reached at_____.

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17. USE OF INFORMATION AND SPECIMENS

During this research study, you could be asked to provide the following types of samples (biological specimens): coded blood **or urine** samples - any identifiers may be removed. Deidentified information or biospecimens may or may not be used or shared for future research.

The research may include whole genome sequencing (i.e., sequencing of a human germline or somatic specimen with the intent to generate the genome or exome sequence of that specimen).

While this study is on-going, your samples will be handled in accordance with this study's protocol and applicable regulations at the following laboratory: **USU American Genome Center/Center for Military Precision Health**.

When this study is over, your samples will be disposed of in the following manner: **Samples will have all individually identifying information removed upon study completion**. Following the removal of all identifying information, samples that will not be used in future research will be discarded according to Occupational Safety and Health Administration (OSHA) standards including DNA deactivation with bleach, then discarded into biomedical waste to be incinerated/autoclaved.

The information and/or specimens obtained from you for this study might be used for future studies. We may remove anything that might identify you from the study records, data and/or specimens. If we do so, study information and/or specimens may then be used for future research studies or given to another scientific investigator without getting additional permission from you. It is also possible that in the future we may want to use or share study information that might identify you. If we do, a review board will decide whether or not we need to get additional permissions from you.

18. INCIDENTAL FINDINGS

There is a possibility that while reviewing your test results we may see an abnormality that we did not expect to see in this study. This is what is called an "incidental finding." This applies to

both general health findings and genetic testing (see Section 4 for further information on genetic testing). The genetic incidental finding that is medically significant will be provided to you to be shared with your primary physician, at your discretion. General health findings could include results from laboratory testing, electrocardiograms, wearable monitoring devices, and other monitoring undertaken in the study.

We will let you know if we see such an incidental finding that is clinically relevant and clinically actionable. Depending on the type of incidental finding, we may contact you by phone. In the case of a significant finding affecting your health, the researcher will inform you right away. Depending on the type of finding, we may also give information about this incidental finding to your primary doctor who may then refer you to appropriate providers for further evaluation.

- An incidental finding may cause you to feel anxious

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- Since an incidental finding could become part of your medical record, you could face greater difficulty in getting health or life insurance

The costs for any care that will be needed to diagnose or treat an incidental finding would not be paid for by this research study with the exception of clinical confirmatory genetic testing. These costs would be your responsibility. If you are a DoD beneficiary, you will have access to care through standard Military Health System and TRICARE procedures.

19. VOLUNTARY PARTICIPATION

The decision to take part in this research study is completely voluntary on your part which means you do not have to take part if you do not want to. You may also leave the research study at any time. If you choose not to take part in this research study or if you leave the study before it is finished, there will be no penalty or loss of benefits to which you are otherwise entitled.

You will be informed if significant new findings develop during the course of this research study that may relate to your decision to continue participation.

20. WHAT HAPPENS IF I WITHDRAW FROM THIS RESEARCH?

If you choose to withdraw, you must tell the study investigator as soon as possible by phone, email, or mail. If you do not follow these procedures, this may compromise the integrity of your data collected under this research study. It is possible that the validity of the study results may also be compromised.

If you are receiving treatment as part of this research study and subsequently withdraw, you will no longer be eligible for such research-related treatment. Contact your personal physician to discuss medical treatment for your condition. By leaving this study at any time, you in no way risk losing your right to medical care and there will be no penalty to you. You will not lose any of your benefits to which you are otherwise entitled. Unless you specify otherwise, any research samples and information that have been collected will be kept and used by the study investigators as originally intended under the study protocol.

Please note that taking back your consent to take part in this research does not take back your HIPAA Authorization to use or reveal your protected health information. To take back your authorization, please send a letter to the Principal Investigator as discussed above. The Principal Investigator of this research study may stop you from taking part in this research study at any time if it is in your best interest for health reasons or otherwise; if you can't complete the research study procedures; or if you no longer qualify to take part.

The sponsor or funder of this research study may terminate the research study and/or your participation in this research study for safety reasons. There is no guarantee that the drug you will receive during this research study will continue to be available to you through the military health system and/or your medical insurance. If you have questions about this, you should talk with your regular healthcare provider.

21. WHAT HAPPENS IF YOU ARE INJURED AS A RESULT OF THIS RESEARCH?

If you think that you have a research-related injury, notify the Principal Investigator immediately using the contact information in the section below.

In the unlikely event that you are injured because of your participation in this research and you are a DoD healthcare beneficiary (e.g., active duty military, dependent of active duty military, retiree), you are authorized space-available medical care for your injury within the DoD healthcare system, as long as you remain a DoD healthcare beneficiary. This care includes, but is not limited to, free medical care at DoD hospitals or DoD clinics.

If you are injured because of your participation in this research and you are not a DoD healthcare beneficiary, you are authorized space-available medical care for your injury at a DoD hospital or DoD clinic as appropriate; medical care charges for care at a DoD hospital or a DoD clinic will be waived for your research-related injury. If you obtain care for research-related injuries outside of a DoD or DoD-referred hospital or clinic, you will not be reimbursed for those medical expenses.

For DoD healthcare beneficiaries and non-DoD healthcare beneficiaries: Transportation to and from hospitals or clinics will not be provided or paid for by DoD. Unless you are covered by TRICARE, no DoD reimbursement is available if you incur medical expenses to treat research related injuries. No additional compensation is available for research-related injuries beyond the provision of healthcare. You are not waiving any legal rights by signing this consent form.

22. CONTACT INFORMATION:

Principal Investigator (PI)

The Principal Investigator or a member of the research staff will be available to answer any questions throughout this study.
Principal Investigator: COL David Saunders, MD
Phone: +1 (301) 318-6024
Email: clinical.research.unit.53-ggg@usuhs.edu
Mailing Address: Translational Medicine Unit, Department of Medicine, Uniformed Services University, 4301 Jones Bridge Road, Bethesda, MD 20814

USU Human Research Protection Program (HRPP) Office

The Human Research Protection Program Office Point of Contact and/or Human Protections Administrator (HPA) will be available to answer questions or discuss concerns you may have about this research study.
Human Protections Administrator/HRPP POC: Dr. Petrice Longenecker Phone (301) 295-9534

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Institutional Review Board (IRB) Office

If you have any questions about your rights as a research participant or if you have concerns or complaints about the research study, please contact the IRB Office at: (301) 295-9534
Uniformed Services University, 4301 Jones Bridge Road, Bethesda, MD 20814
IF THERE IS ANY PORTION OF THIS DOCUMENT THAT YOU DO NOT UNDERSTAND, ASK THE INVESTIGATOR BEFORE SIGNING. YOU MAY CONSULT WITH YOUR PERSONAL PHYSICIAN OR LEGAL ADVISOR, IF YOU WISH.

A signed and dated copy of this document will be given to you.

Please initial the sentence that reflects your choice:
_____I authorize storage of data collected as part of this study for use in future research.
_____I do not authorize storage of data collected as part of this study for use in future research.

Please initial the sentence that reflects your choice:
_____I authorize storage of my biological study specimens for use in future research.
_____I do not authorize storage of my biological study specimens for use in future research.

IF THERE IS ANY PORTION OF THIS DOCUMENT THAT YOU DO NOT UNDERSTAND, ASK THE INVESTIGATOR BEFORE SIGNING. YOU MAY CONSULT WITH YOUR PERSONAL PHYSICIAN OR LEGAL ADVISOR, IF YOU WISH.

A signed and dated copy of this document will be given to you. Please indicate your preferred method of contact regarding this study:

_____Phone call _____Postal service _____Email _____Any of these methods

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ATTESTATION OF PARTICIPANT

I,_____, attest that I have a Primary Care Physician, adequate health insurance and meet the study criteria of 'access to healthcare' for purposes of returning positive results of genetic testing.

_____
Participant Initials

SIGNATURE OF PARTICIPANT

By signing below, I agree that I have been provided time to read the information describing the research study in the consent form. The content and meaning of this information has been explained to me. I have been provided with the opportunity to ask questions. I voluntarily consent to participate in this study.

By signing this form, I have not given up any of my legal rights as a research participant.

_____
Printed Name of Participant

_____ _____
Signature of Participant Date

Your signature below indicates you are legally authorized to act on behalf of the participant, and have read this document. You will receive a copy of this document.

SIGNATURE OF INDIVIDUAL ADMINISTERING CONSENT (Can only be signed by an investigator or staff approved to administer consent)

_____

Printed Name of Administering Individual

_____ _____
Signature of Administering Individual Date

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