PARTICIPANT INFORMATION SHEET

PROJECT TITLE: Autonomic dysfunction in Atrial Fibrillation: an autonomic characterisation study (AFAF Study)
HUMAN RESEARCH ETHICS COMMITTEE APPROVAL NUMBER: H-2018-***
PRINCIPAL INVESTIGATOR: Professor Prashanthan Sanders
STUDENT RESEARCHERS: Dr Varun Malik (Primary contact), Dr Mehrdad Emami & Dr Ricardo Mishima
STUDENT'S DEGREE: MBBS, BMedSci, FRACP. PhD Candidate.

Dear Participant,

You are invited to participate in the research project described below.

What is the project about?
This research project is about the effect of common heart disorders on the nerves of the heart.
We aim to identify whether the nerves in patients with these conditions respond differently to changes in body posture and blood pressure and whether these changes are responsible for the disease itself. We think this is very important because identifying the role of heart nerves in these disorders can hopefully provide better treatments for these disorders.

We are enrolling patients with Atrial Fibrillation (AF; abnormal heart beat) as well as patients without AF who have the risk factors for AF, those who already have a form of heart nerve problem or healthy adults aged 18-75.

We shall perform tests <u>in one visit</u> to measure the heart nerve responses to changes in the volume of blood in the heart:

Who is undertaking the project?
This project is being conducted by Dr Varun Malik a Cardiologist at The Centre of Heart Rhythm Disorders and the Cardiovascular Centre, 62 Beulah Road in Norwood. This research will form the basis for the degree of PhD at the University of Adelaide under the supervision of Professor Prashanthan Sanders and Dr Dennis Lau; who are senior Cardiologists with expertise in heart rhythm disorders.

Why am I being invited to participate?
You are being invited as you are either a patient with Atrial Fibrillation (AF).

You may also be a patient without AF (but at some risk of it), a patient with another form of heart nerve disorder or a healthy adult volunteer aged between 18-75 without any of the above problems or any heart disease. Patients with Parkinson's disease or thyroid disorders are not being studied.

What am I being invited to do?
You are being invited to participate in a study that will take two and a half hours at the Centre of Heart Rhythm Disorders site*; Cardiovascular Centre, 62 Beulah Road, Norwood.* As a part of the study you will also be asked to take a heart rate monitor home with you at home for 24-hour period after the test.

- You will be asked to abstain from coffee, tea, alcohol, caffeinated or energy drinks or chocolate (caffeine-free) for one day prior to the test and will be asked not to eat or drink (fast) for 4 hours prior to the test.
- Medications that could interact with the tests such as antiarrhythmic medication or blood pressure lowering drugs will be withheld for at least 3-5 days prior to the test. The exact medications and doses to miss will be decided upon for you individually and will be done in conjunction with your treating doctor; to ensure safety.
- We shall ask you some questions to ensure that you fit the study requirements and what your symptoms are in relation to your AF; such as whether you experience chest pain, breathlessness, tiredness (no personal information will be collected), This information will be in the form of a questionnaire.
- For monitoring; a small cuff will be placed on your finger to measure blood pressure and heart rate. This is painless. An electrical recording of your heart will be taken by 3 patches with electrodes placed on your chest (similar to having an ECG or holter test). Also, painless.
- An intravenous cannula (plastic tube) will be placed in a vein in the forearm for some blood tests that measure specifically the hormones in your blood stream that control your blood pressure. We shall use this to collect a small sample of blood (15 mL or 3 teaspoons) on insertion and then on two occasions during the test. This minor procedure (similar to a blood test) can cause some minor bruising and pain on insertion of the needle. Most patients can tolerate this very well but if the pain becomes unbearable we shall abandon this step.
- In this arm; we shall also place a very fine needle (smaller than the needle used for the blood test) into a small nerve in the arm (either behind the elbow or on the crease of the elbow). The insertion can cause some discomfort including some pain (during insertion of the needle) as well some numbness and tingling in the hands during the test. This is to measure the activity of the nerves in response to the changes of the blood volume to the heart. These symptoms settle when the needle is removed from the body and is considered very safe. It is highly unlikely to have any long term adverse effects (rarely the numbness and tingling could persist for a few weeks but this improves on its own). *NOTE: Although this procedure is safe and usually reasonably tolerated; this is an optional component and you may wish to participate in the rest of the protocol without participating in this component. Please let us know if this is the case.*
- We shall place an elastic wire across the other arm (painless) together with two cuffs (inflated by air) that are similar to blood pressure machine cuffs – one of these will be used to stop the blood flow to your hand and the other to gently stop blood flow from the veins back to the heart (there will be blood flow into the arm) for a maximum of one minute at a time. This can cause some minor tingling and numbness in the hand and recovers completely when the cuff is removed. This measurement is not associated with any side effects after the removal of the device.
- We will then lie you down with the lower half of your body enclosed in a clear perspex LBNP box (from the hips down to the legs). The purpose of this box is to 'draw' blood toward your legs and feet by gentle application of suction pressure. *This influences stretch receptors in the heart; which then send information to your brain about the volume of blood you have in your body, and your brain makes changes in your heart beat and to your arteries to keep your blood pressure constant.* There are no harmful side effects of LBNP. There is no associated pain. The test will take 40 minutes. We shall take 3 teaspoons of blood (15 mL) at the end of the test from the plastic tube in the arm. This repeat blood test is not painful as we shall obtain the sample from the tube already placed in the arm.
- We shall place a soft clip on your ear (tragus) to allow us to stimulate the heart nerve through the skin through an impulse generator during this test. This Is also painless (the nerve is stimulated at levels below that which we can feel).

- Whilst lying flat we shall place your legs on a tall cushion for 30 minutes to draw blood toward the heart. We shall measure your heart rate, blood pressure, nerve activity and blood flow in your arm as described above. We shall take more 3 teaspoons of blood (15 mL) at the end of the test from the plastic tube in the arm. This is not associated with discomfort.
- Finally, whilst sitting upright,
    a. We shall ask you to blow into a rubber tube at a steady rate for 15 seconds whilst we monitor you.
    b. Grip a rubber ball tightly for 1 minute and measure your blood pressure, heart rate, arm blood flow and nerve activity for 5 minutes after this.
    c. Place one of your hands in a bucket of icy-cold water for 5 minutes. This can be unpleasant and even cause some pain – but most people can tolerate this for 5 minutes. It is also completely safe. In some people, this can cause significant pain or even (rarely) may cause you to faint. In this unlikely event, we shall stop all testing, make sure that we treat you and allow you to recover fully and make sure you are well enough before you go home.

    There will be no additional blood tests taken (a total of three blood tests will be taken throughout the testing protocol).

    You will be able to then return home (and can drive immediately following the tests).

- You shall be given a heart rhythm monitor to wear for 24 hours after this test and will be asked to return it the following day. This can be worn at home and with any activity (showering, dressing, with physical activity and at work). There will be no restrictions placed on your daily activities.

In some cases, you may continue to visit the clinic for your ongoing treatment. We would like to repeat these tests at a future date. There are no obligations for your repeating this study. We shall simply ask if you would like to be contacted again. If you agree; this does not obligate you to accept the next invitation to participate after you have received your treatment. Participation in this study will not affect any treatment that you receive and is entirely voluntary. You will be given opportunity to decline to participate at any time –point but in particular after you have been shown the testing protocol on the day.

How much time will my involvement in the project take?

There will be one visit to the Cardiovascular Centre, 62 Beulah Road, Norwood that will last approximately 2.5 hours. We shall also request one brief visit (less than 5 minutes) to return equipment after a period of monitoring at home *the following day*. We would request the return of the equipment the *following day* and at a *maximum* of 48 hours from the date of the initial study so that we can use the monitor for other patients. We shall provide you with free of charge parking facilities for both the visit as well as for the return of equipment.

Are there any risks associated with participating in this project?

Some monitoring equipment (the fine needle used for the nerve activity recording in the elbow) and the blood test itself can cause some discomfort when placed through the skin. Once it is placed there should be no further pain. In the case of the nerve activity needle; some patients can feel numbness or tingling during the test. If this is causing you discomfort we shall remove the needle immediately. In rare

instances the needle can cause some numbness in the hands to persist for a few days (this resolves on its own without any treatment as is not associated with long term problems).

In addition to the discomfort from needles; there may be some discomfort from stopping blood flow to the hand (for a maximum of 1 minute at a time) as well as from the icy water. If this is causing you significant discomfort; we shall stop immediately.

Finally, you may experience some lightheadness or faint – it is very unlikely. If this occurs we shall stop the experiment and allow you to recover completely.

In conjunction with your treating cardiologist; we shall determine if it will be safe to stop *some* of your heart or blood pressure medications (those that can interfere with the test results) for a period of approximately 3-5 days. In this case, both the cardiologist and our team will assess your medication list and decide together with yourself if we can temporarily with-hold some medications to allow us to do the test. The main risk in doing so is that you may have symptoms such as *palpitations* from episodes of AF or symptoms of high blood pressure; *light-headedness or blurred vision*. Should you develop any of these symptoms or are concerned please contact the study investigator Dr Malik or any of the other investigators (details listed below). You may also prefer to contact your cardiologist directly. He or she will be aware of all of the medication changes required for the study.

What are the potential benefits of the research project?

There will be no direct benefit to you from participating in this study. However, we will have greater knowledge of how AF influences the control of blood pressure and how long those effects last. By participating in this study, you will contribute to the understanding of how our body's control of blood pressure changes with heart rhythm disorders and whether the nerves of the heart can potentially offer any future treatment strategies for all patients with your condition.

Can I withdraw from the project?
Participation in this project is completely voluntary. If you agree to participate, you can withdraw from the study at any time. A decision not to participate will not affect your ongoing treatment in any way which is separate to this study.

What will happen to my information?

Confidentiality and privacy: All participants will have an identification code that will be used instead of personal details in order to maintain privacy. Any personal details will be stored on one secured computer in the clinical practice. Access to this computer will be restricted to study co-ordinators (listed below). Your personal data will not be disseminated in any form.

Storage: All of your de-identified records from the experiments will be stored on one computer within the cardiology practice where you visit for your treatment. Access to this information will be restricted to the study co-ordinators alone. The computer will be otherwise in a locked room. Any paper records (questionnaires and consent forms) will be housed under lock and key within the medical practise. They will be kept for up to 5 years. Electronic records will be stored for a maximum of 10 years.

Publishing: The aggregate (summary) data (an average of all the patient's medical conditions as well as results from the tests will be presented by way of posters or at oral presentations, or reported in peer-reviewed medical journals and form part of a dissertation (thesis) to be presented to and examined by

The University of Adelaide as a component of Dr Varun Malik's candidature for the degree of PhD. No individual data will be reported and none of your personal details will be identified.

Sharing: We may utilise the information gathered in this study to guide further experiments as well as utilise some of the data collected in future research projects. In all subsequent studies; aggregate or summary data only will be used. We have no plans to share data in any online repository.

Your information will only be used as described in this participant information sheet and it will only be disclosed according to the consent provided, except as required by law.

Who do I contact if I have questions about the project?

If you have any questions or would like further information about this study, or if you experience a research-related injury or illness, please contact Dr Varun Malik on (08) 08 8313 9000 or (08) 7074 0000 (as the primary contact). You may also contact Dr Dominik linz on (08) 08 8313 9000, Dr Adrian Elliott on 08 8313 9000, Dr Dennis Lau or Professor Prashanthan Sanders on (08) 8222 2723. In case of emergency (for instance if you develop symptoms from withdrawing your medications) you may choose to contact Dr Malik during office hours and also after hours on (08) 7074 0000 or you can contact your treating cardiologist.

What if I have a complaint or any concerns?

The study has been approved by the Human Research Ethics Committee at the University of Adelaide (approval number H-2018-xxx). This research project will be conducted according to the NHMRC National Statement on Ethical Conduct in Human Research (2007). If you have questions or problems associated with the practical aspects of your participation in the project, or wish to raise a concern or complaint about the project, then you should consult the Principal Investigator. If you wish to speak with an independent person regarding concerns or a complaint, the University's policy on research involving human participants, or your rights as a participant, please contact the Human Research Ethics Committee's Secretariat on:

Phone: +61 8 8313 6028

Email: hrec@adelaide.edu.au

Post: Level 4, Rundle Mall Plaza, 50 Rundle Mall, ADELAIDE SA 5000

Any complaint or concern will be treated in confidence and fully investigated. You will be informed of the outcome.

If I want to participate, what do I do?

You are asked to contact Dr Varun Malik on (08) 08 8313 9000 to arrange a time to attend for the study and return the consent form (either by post or you can bring it with you on the day of the tests).
We thank you for taking the time to read this information sheet and should you decide to participate we thank you for your contribution.

Yours sincerely,

Dr Varun Malik, Dr Ricardo Mishima, Dr Mehrdad Emami, Dr Dominik Linz, Dr Adrian Elliott, Dr Dennis Lau, Dr Rajiv Mahajan, Professor Leonard Arnolda & Professor Prashanthan Sanders

Centre for Heart Rhythm Disorders
The University of Adelaide.