

**PARTICIPANT INFORMATION AND CONSENT FORM (PICF)**

Site: The Alfred Hospital

**Project Title: Investigator Led Study of IV Milrinone in Heart Failure with Preserved Ejection Fraction (HFpEF).**

**Protocol Name: MilHFpEF-IV-02**

**Project Sponsor: Alfred Health**

**Principal Researcher**: A/Prof Justin Mariani

**HREC number:**  HREC/52907/Alfred-2019

Local Project/Reference Number: Project 306/19

This Participant Information and Consent Form is 13 pages long. Please make sure you have read all the pages.

1. Introduction

You are invited to take part in this research project because you suffer from shortness of breath which is suspected to be due to a heart condition called heart failure with preserved ejection fraction (“HFPEF”). This condition refers to your heart being too stiff and unable to relax properly when it needs to fill with blood. This problem causes a pressure build-up in your heart, which in turn causes a pressure build-up in the blood vessels of the lungs. Your doctor may also have referred you specifically to have the pressure in your heart measured.

This Participant Information and Consent Form informs you about the research project. It explains the tests and treatments involved. Knowing what is involved will help you decide if you want to continue to take part in the research.

Please read this information carefully. Ask questions about anything that you don’t understand or want to know more about. Before deciding whether or not to continue taking part, you might want to talk about it with a relative, friend or your local doctor.

Participation in this research is voluntary. If you don’t wish to take part, you don’t have to. You will receive the best possible care whether you take part or not.

If you decide you want to take part in the research project, you will be asked to sign the consent section. By signing it you are telling us that you:

• understand what you have read;

• consent to take part in the research project;

*•* consent to the use of your personal and health information as described.

You will be given a copy of this Participant Information and Consent Form to keep.

1. What is the purpose of this research?

The heart is a muscle that pumps blood around the body. The heart’s pumping cycle has two phases. First, the heart muscle contracts (squeezes) and pumps blood out into the body (called systole). Secondly, the heart muscle relaxes and fills with blood (called diastole).

Heart failure is a condition where the heart’s pumping cycle does not function as it should. There are two types of heart failure (with about half of patients with the condition falling into each group):one where the pump/contraction function of the heart is reduced, which is called systolic heart failure; in the other type, the heart does not fully relax, so it does not fill properly with blood. This is called diastolic heart failure or “heart failure with normal pump function”. The official medical term is “heart failure with preserved ejection fraction”, and is abbreviated as HFPEF. At the moment, there are no established medical therapies for HFPEF.

Our research has shown that people with HFPEF develop breathlessness very quickly during physical activity because the heart muscle cannot relax normally. In this study we want to test the effect of lower doses of a drug called Milrinone, delivered intravenously (into the vein), on the pressure in the heart during exercise in HFPEF patients.

The use of intravenous Milrinone in this study is considered experimental. Intravenous Milrinone has not been approved for use by the Therapeutics Goods Administration (TGA) in Australia for patients with diastolic heart failure, but is approved for patients with systolic heart failure. Because of its actions on the heart we hope that it may be helpful in patients with diastolic heart failure.

We have done research in the past with the use of intravenous (IV) Milrinone in patients with diastolic heart failure, although at higher doses. We are now extending this research to study the effect of lower doses of IV Milrinone on diastolic heart failure or HFPEF.

This study is being conducted at The Alfred Hospital led by A/Prof Justin Mariani. Data from this study may be shared with Cardiora Pty Ltd, a company that has interest in developing another form of Milrinone for HFPEF.

If knowledge acquired through this research leads to discoveries that are of commercial value to Cardiora Pty Ltd, or the study doctors or their institutions, there will be no financial benefit to you or your family from these discoveries. Professor David Kaye, an associate investigator in this study, is the founder of Cardiora Pty Ltd and a named inventor on a published patent for the use of Milrinone in patients with HFpEF.

3. What does participation in this research involve?

Before you begin the study, you will be given detailed information about the study medicine, the study, and any other relevant information by research staff. You are encouraged to ask questions until you are sure that you fully understand the nature and requirements of the study.

The doctor in charge of this study is A/Prof Justin Mariani. Before you decide if you want to be a part of this study, we want you to know the purpose of the study, how it may help you, any risks to you, what other choices you may have, and what is expected of you.

There are no additional costs associated with participating in this research project, nor will you be paid. All medication, tests and medical care required as part of the research project will be provided to you free of charge.

If you decide to be assessed for inclusion in the study, you will be asked to visit The Alfred Hospital for an initial assessment visit (screening visit). Before any procedures are undertaken, you will be asked to sign a consent form. The original of the consent form will be kept at the Alfred Hospital and you will get the copy to keep. You are still free to withdraw from the study at any time and without giving a reason. This will not affect the medical care you receive. You will then have some tests to check that the study is suitable for you.

For female patients of child bearing age, as the effects of the study drug on pregnant women and the unborn foetus are unknown, we will perform a serum pregnancy test to ensure that you are not pregnant during the course of the study.

The screening visit may take approximately 1 hour. When results of the examinations performed at this visit are available, the study staff will confirm whether the trial is suitable for you.

You will be participating in a double-blind, randomised, controlled research study.

Sometimes we do not know which treatment is best for treating a condition. To find out we need to compare different treatments. We put people into groups and give each group a different treatment. The results are compared to see if one is better. To try to make sure the groups are the same, each participant is put into a group by chance: this is called a “randomised” study.

Neither you nor your treating doctor will know if you received the treatment (intravenous milrinone) or control (placebo), until the completion of the research study. This is called a “double-blind” study, “controlled” by the use of placebo (no treatment).

This double-blind, randomised, controlled study approach is required to enable researchers and doctors to compare different treatment arms, to investigate if a low dose of milrinone has the potential to treat HFPEF more effectively than placebo.

If you are deemed eligible to participate in the trial, you will be assigned at random to receive either intravenous milrinone or placebo. The placebo medication in this instance will be normal saline (salt water) and does not contain any active ingredients. 6 out of 8 patients will receive active ingredient, (75% chance) with 2 out of 8 paticipants receiving placebo (non active treatment)..

This research project has been designed to make sure the researchers interpret the results in a fair and appropriate way.

**Screening visit**

After reading this information sheet, if you agree to participate in the study, you will be asked to sign the attached consent form. You will be asked about your previous medical problems, your current health and any medications you may be taking. You will undergo a physical examination (including height and weight). This will include vital signs (i.e. blood pressure, heart rate, respiratory rate and temperature) sitting and standing, and a tracing of your heart rhythm (electrocardiogram, ECG), as well as an ultrasound of your heart, an echocardiogram (“echo”).

An ECG is a simple medical test that detects heart abnormalities by measuring the electrical activity of the heart as it contracts. You will need to remove the clothing from the upper part of your body so that sticky dots can be attached to your chest, arms and legs. These sticky dots are then attached to leads to become electrodes that detect the electrical currents generated by the heart, which are measured and recorded by the ECG machine. This procedure will take approximately 5 minutes to complete.

A blood test will be taken to measure the level of your kidney function and of heart-related proteins in your blood. If you are a woman of child-bearing age, we will perform a serum pregnancy test to ensure that you are not pregnant.

**On study**

**Study day**

After the screening procedures are completed, you will be notified regarding your eligibility to participate in the trial. If you are eligible to participate in the trial, you will be asked to return to The Alfred Hospital.

On the study day, you will be evaluated again by the study doctor. A physical exam will be performed, an ECG and blood test will be taken. Following this, you will be required to undergo an exercise right heart catheterisation study. The exercise heart catheterisation study is a common test used to diagnose HFPEF. You may have had this procedure conducted previously.

After using local anaesthetic on the skin, a small tube (called a catheter) is placed through a needle in the left or right vein in your arm. If the veins in your arm are too small we may need to use the vein on the side of your neck. Under X-ray guidance, the tube is directed toward the chambers of the right side of the heart, to the main artery feeding your lungs. Moving the tube to different parts of the body is painless and you will generally be unaware of its location. Another small tube is placed into an artery (blood vessel) of your wrist/arm to measure the arterial pressure and to obtain blood samples.

These procedures are commonly performed both clinically and in research studies. They are performed under local anaesthetic and every effort is made to minimise discomfort. We will first measure the pressures within the heart and the lung arteries at rest. You will then be asked to pedal a bicycle whilst lying down. When you start to feel short of breath we will repeat the pressure measurements and you will stop the exercise. Once you have regained your breath we will give you the milrinone or placebo over 10 minutes. After a further 10 minutes we will repeat the measurements at rest and during the same exercise. Arterial and mixed venous blood gas samples will be taken at rest and peak exercise from the catheter in your arm to minimise your discomfort. You will receive a total of 20 minutes of this infusion.

This procedure will take approximately 30 minutes and you will need to wait a further 2 hours before you are able to go home.

This concludes your participation in this trial. You will not be paid for your participation in this trial. *However, you will be reimbursed for any travel costs incurred, up to a maximum of $50.*

**5. Other relevant information about the research project**

This is a study that will be conducted in Australia 8 participants will be enrolled in this research study.

**6. Do I have to take part in this research project?**

Participation in any research project is voluntary. If you do not wish to take part, you are not obliged to. If you decide to take part and later change your mind, you are free to withdraw from the project at any stage. If you do decide to take part, you will be given this Participant Information and Consent Form to sign and you will be given a copy to keep.

Your decision whether to take part or not to take part, or to take part and then withdraw, will not affect your routine treatment, your relationship with those treating you or your relationship with The Alfred Hospital.

Before you make your decision, a member of the research team will be available so that you can ask any questions you have about the research project. You can ask for any information you want. Sign the consent form only after you have had a chance to ask your questions and have received satisfactory answers.

**7. What are the alternatives to participation?**

You do not have to take part in the trial to receive treatment at this site and if you decide not to take part it will not change the level of care you receive. The alternative to being a volunteer in this study is to remain on your usual care for your condition. Your study doctor will discuss these options with you before you decide whether or not to take part in this research project. You can also discuss the options with your local doctor.

8. What are the possible benefits of taking part?

There will be no clear benefit to you from your participation in this research. However, your participation will allow better characterisation of HFPEF, which could, in turn, result in better therapies for this disease in the future.

9. What are the possible risks and disadvantages of taking part?

Medical treatments often cause side effects or complications. You may have none, some or all of the effects listed below, and they may be mild, moderate or severe. However, the occurrence of severe complications or side effects is unlikely.

If you have any of these side effects, or are worried about them, talk with your doctor. Your doctor will also be looking out for side effects. There may also be side effects that the researchers do not expect or do not know about and that may be serious. Tell your study doctor immediately about any new or unusual symptoms that you get.

**Blood test:** Having blood taken may cause some discomfort or bruising. Sometimes, the blood vessel may swell, or blood may clot in the blood vessel, or the spot from which tissue is taken could become inflamed. Rarely, there could be a minor infection or bleeding. If this happens, it can be easily treated.

**Milrinone IV –** Milrinone is a common therapy given to heart failure patients. The drug has an “inodilator” effect, which means it enhances the pumping ability of the heart as well as helping widen the blood vessels. This helps to alleviate the backed-up pressure of the heart.

The side effects of Milrinone include: abnormal heart rhythm, kidney damage, loss of electrolytes in your blood, drop in blood pressure, headache, liver damage, chest pain, and bronchospasm (very rare).

**Right heart catheterisation** is a routinely performed diagnostic procedure in patients with cardiac diseases. The catheter will be inserted into an arm vein after application of local anaesthesia. The side effect most frequently observed with this procedure is bleeding or bruising at the puncture site. The risk of occurrence of a serious, and potentially life threatening, complication is very low (<1 in 1000) and we have a long record of safety with these procedures. Potential (reported) complications include temporary disturbance of the heart rhythm, cardiac perforation and pulmonary artery perforation.

During the catheterisation study we will use an X-ray system to guide the placement of the catheter, which improves the safety of the procedure. The use of radiation is associated with a certain risk (mainly the occurrence of cancer). Due to possible adverse effects on the unborn child, pregnant women are excluded from the study.

**Radiation Risks**

This research study involves exposure to a very small amount of radiation. As part of everyday living, everyone is exposed to naturally occurring background radiation and receives a dose of about 2 millisieverts (mSv) each year. The effective dose from this study is about 1 mSv.

Have you been involved in any other research studies that involve radiation? If so, please tell us. Please keep information contained within the Patient Information and Consent Form about your exposure to radiation in this study, including the radiation dose. You will be required to provide this information to researchers of any future research projects involving exposure to radiation.

The effects of the study drug on the unborn child and on the newborn baby are not known. Because of this, we will perform a serum pregnancy test to ensure that you are not pregnant at the screening visit. If you do become pregnant whilst participating in the research project, you should advise your study doctor immediately. Your study doctor will withdraw you from the research project and advise on further medical attention should this be necessary. You must not continue in the research if you become pregnant.

If you are male, you should not father a child or donate sperm for at least 1 month after the last dose of study medication. You should advise your study doctor if you father a child while participating in the research project. Your study doctor will advise on medical attention for your partner should this be necessary.

The use of effective contraception during the course of the research, and for 1 month after completion of the research project, is strongly advised. You should discuss methods of effective contraception with your study doctor.

**10. What will happen to my test samples?**

Collection of blood samples is part of the study. We will collect approximately 20 ml (one tablespoon) of blood. Blood tests performed include a full blood count, NT-BNP (which is a marker used for heart failure), kidney and liver functions tests. These are done to ensure your safety during the study. These samples will be analysed at The Alfred Pathology labs, and these samples will be destroyed following confirmation of the tests results (usually within 7 days).

A separate sample will be used to analyse the level of Milrinone in your blood. This sample will be stored in a freezer until the end of the study and sent for analysis to a laboratory in Adelaide, Australia. Once the analysis is complete the sample will be destroyed. The consent for the use of the stored blood sample is specific for this research only.

11. What if new information arises during this research project?

During the research project, new information about the risks and benefits of the project may become known to the researchers. If this occurs, you will be told about this new information. This new information may mean that you can no longer participate in this research. If this occurs, the person(s) supervising the research will stop your participation. In all cases, you will be offered all available care to suit your needs and medical condition.

**12. Can I have other treatments during this research project?**

Whilst you are participating in this research project, you may not be able to take some or all of the medications or treatments you have been taking for your condition or for other reasons. It is important to tell your doctor and the research staff about any treatments or medications you may be taking, including over-the-counter medications, vitamins or herbal remedies, acupuncture or other alternative treatments. You should also tell your doctor about any changes to these during your participation in the research. Your study doctor should also explain to you which treatments or medications need to be stopped for the time you are involved in the research project.

**13. What if I withdraw from this research project?**

If you decide to withdraw from this project, please notify a member of the research team before you withdraw. This notice will allow that person or the research supervisor to inform you if there are any health risks or special requirements linked to withdrawing.

If you do withdraw your consent during the research project, the study doctor and relevant study staff will not collect additional personal information from you, although personal information already collected will be retained to ensure that the results of the research project can be measured properly and to comply with law. You should be aware that data collected by the sponsor up to the time you withdraw will form part of the research project results. If you do not want them to do this, you must tell them before you join the research project.

14. Could this research project be stopped unexpectedly?

This research project may be stopped for a variety of reasons. These may include reasons such as:

* unacceptable side effects,
* the drug being shown not to be effective,
* the drug proves to be effective and does not require any further testing,
* decisions made by local regulatory/health authorities.

**15. What happens when the research project ends?**

At the end of the study, you will **not** be able to continue taking the study medication. Your research doctor will discuss your continuing medical supervision and care after the study has finished.

16. What will happen to information about me?

By signing the consent form you consent to the study doctor and relevant research staff collecting and using personal information about you for the research project. Any information obtained in connection with this research project that can identify you will remain confidential. Your information will only be used for the purpose of this research project and it will only be disclosed with your permission, except as required by law.

In accordance with relevant Australian *and/or* Victorian privacy and other relevant laws, you have the right to request access to your information collected and stored by the research team. You also have the right to request that any information with which you disagree be corrected. Please contact the study team member named at the end of this document if you would like to access your information.

Any information gathered during this research study that can identify you will remain confidential and will only be used for the purpose of this research study. In accordance with applicable laws, every effort will be made to keep all information about you private. The information gathered will be stored in a re-identifiable (“coded”) format with a study number. There is, however, a screening log kept by the study staff to connect the study number to the patient’s true identity, in order to perform data verification. The re-identifiable information will only be shared with your permission, except as required by law. At the end of this study it is possible that the information collected for all patients, including you, may be presented at a local or international scientific conference or published in a scientific journal. This will be done in a de-identified manner, where your personal details will not be published nor revealed in any way.

All information will be presented in such a way that neither you nor any other patient may be identified. By signing the consent form you give permission for your re-identifiable data to be used in this way.

Your health records and any information obtained during the study can be inspected by the Australian Therapeutic Goods Administration (TGA) - a regulatory agency for clinical trials in Australia – for the purpose of source data verification and procedures. Similarly, the data might be inspected by the Food and Drug Administration (FDA) of the United States of America (USA), and other national drug regulatory authorities. By signing the attached consent form, you authorise release of, or access to, this confidential information to the relevant study personnel and regulatory authorities as noted above.

Information about you will not be sent to overseas parties.

All study data for this trial will be kept indefinitely upon completion of the trial. Only members of the study team will have access to the data, which will be either securely locked in a storeroom or be protected by an electronic password.

Information about you may be obtained from your health records held at this and other health services for the purpose of this research. By signing the consent form you agree to the study team accessing your health records if they are relevant to your participation in this research project.

Information about your participation in this research project may be recorded in your health records.

It is anticipated that the results of this research project will be published and/or presented in a variety of forums. In any publication and/or presentation, information will be provided in such a way that you cannot be identified, except with your permission. The study results will be presented at national and international meetings. We will put the results of the study on The Alfred Heart Centre website ( [www.alfredheartcentre.org.au](http://www.alfredheartcentre.org.au)).

17. Complaints and compensation

In the event that you suffer an injury or a complication as a result of this research project, you should contact the study team as soon as possible and you will be assisted with arranging appropriate medication treatment. If you are eligible for Medicare, you can receive any medical treatment required to treat the injury or complication, free of charge, as a public patient in any Australian public hospital.

* The other avenue that may be available to you for seeking compensation if you suffer an injury as a result of your participation in this research project is through the court

**18. Who is organising and funding the research?**

This research project is an investigator led study organised by A/Prof Justin Mariani and Prof David Kaye.

No member of the research team will receive a personal financial benefit from your involvement in this research project.

19. Who has reviewed the research project?

All research in Australia involving humans is reviewed by an independent group of people called a Human Research Ethics Committee (HREC). The ethical aspects of this research project have been approved by the Alfred Hospital Ethics Committee.

This project will be carried out according to the *National Statement on Ethical Conduct in Human Research* (*2007*) produced by the National Health and Medical Research Council of Australia. This statement has been developed to protect the interests of people who agree to participate in human research studies.

20. Further Information or Any Problems

The person you may need to contact will depend on the nature of your query. If you want any further information concerning this project or if you have any medical problems which may be related to your involvement in the project (for example, any side effects), you can contact the principal study doctor or any of the following people:

Name: A/Prof Justin Mariani

Role: Principal Investigator

Telephone: 03 9076 3263

**Clinical contact person**

|  |  |
| --- | --- |
| Name | Eliza Dean |
| Position | Research Nurse |
| Telephone | 9076 2948/90763040 |
| Email | hfresearch@alfred.org.au |

If you have any complaints about any aspect of the project, the way it is being conducted or any questions about being a research participant in general, then you may contact:

|  |  |
| --- | --- |
| Reviewing HREC name | Alfred Hospital Ethics Committee |
| Telephone | 03 9076 3619 |
| Email | research@alfred.org.au |

**Reviewing HREC approving this research** **and HREC Executive Officer details:**

You will need to tell Alfred Health HREC the following HREC project number: 306/19.

**Research Governance Officer details:**

|  |  |
| --- | --- |
| Name | Office of Ethics and Research Governance |
| Position | Complaints Officer |
| Telephone | 0390763619 |
| Email | research@alfred.org.au |



**Participant Consent Form**

|  |  |  |
| --- | --- | --- |
| **Title** | **Investigator Led Study of IV Milrinone in Heart Failure with Preserved Ejection Fraction (HFpEF).** |  |
| **Protocol Number** | **MilHFpEF-IV-02** |  |
| Project Sponsor: | Alfred Health |  |
| **Principal Investigator**  **Local Project Number**  **HREC number** | A/Prof Justin Mariani  306/19  HREC/52907/Alfred-2019 |  |
| **Site Name** | The Alfred Hospital |  |

**Declaration by Participant**

I have read the Participant Information Sheet or someone has read it to me in a language that I understand.

I understand the purposes, procedures and risks of the research described in the project.

I give permission for my doctors, other health professionals, hospitals or laboratories outside this hospital to release information to *The Alfred Hospital* concerning my disease and treatment for the purposes of this project. I understand that such information will remain confidential.

I have had an opportunity to ask questions and I am satisfied with the answers I have received.

I freely agree to participate in this research project as described and understand that I am free to withdraw at any time during the study without affecting my future health care.

I understand that I will be given a signed copy of this document to keep.

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|  | | | | | | |
|  | Name of Participant (please print) | |  |  |  |  |
|  | | | | | | |
|  | Signature |  | | Date |  |  |
|  | | | | | | |

**Declaration by Study Doctor/Senior Researcher†**

I have given a verbal explanation of the research project, its procedures and risks and I believe that the participant has understood that explanation.

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|  | | | | | | |
|  | Name of Study Doctor/  Senior Researcher† (please print) | |  | | |  |
|  | | | | | |  |
|  | Signature |  | | Date |  |  |
|  | | | | | | |

† A senior member of the research team must provide the explanation of, and information concerning, the research project.

Note: All parties signing the consent section must date their own signature.



**Form for Withdrawal of Participation**

|  |  |
| --- | --- |
| **Title** | **Investigator Led Study of IV Milrinone in Heart Failure with Preserved Ejection Fraction (HFpEF)** |
| **Protocol Number** | **MilHFpEF-IV-02** |
| **Project Sponsor:** | Alfred Health |
| **Principal Investigator**  **Local Project Number**  **HREC number** | A/Prof Justin Mariani  306/19  HREC/52907/Alfred-2019 |
| **Site Name** | The Alfred Hospital |

**Declaration by Participant**

I wish to withdraw from participation in the above research project and understand that such withdrawal will not affect my routine treatment, my relationship with those treating me or my relationship with The Alfred Hospital.

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|  | | | | | | |
|  | Name of Participant (please print) | |  |  |  |  |
|  | | | | | | |
|  | Signature |  | | Date |  |  |
|  | | | | | | |

*In the event that the participant’s decision to withdraw is communicated verbally, the Study Doctor/Senior Researcher will need to provide a description of the circumstances below.*

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**Declaration by Study Doctor/Senior Researcher†**

I have given a verbal explanation of the implications of withdrawal from the research project and I believe that the participant has understood that explanation.

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| --- | --- | --- | --- | --- | --- | --- |
|  | | | | | | |
|  | Name of Study Doctor/  Senior Researcher† (please print) | |  | | |  |
|  | | | | | |  |
|  | Signature |  | | Date |  |  |
|  | | | | | | |

† A senior member of the research team must provide the explanation of and information concerning withdrawal from the research project.

Note: All parties signing the consent section must date their own signature.