Academic and Clinical Central Office for Research and Development

Participant Information Sheet for Patients

The TAKO MEMRI Study – Study 1 Manganese-Enhanced Magnetic Resonance Imaging in Takotsubo Cardiomyopathy

Sponsors: University of Edinburgh and NHS Lothian

Chief Investigator: Professor Dave Newby
University of Edinburgh
49 Little France Crescent
Edinburgh
EH16 4SB
0131 242 6515

You are being invited to take part in a research study. Before you decide whether or not to take part, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully. Talk to others about the study if you wish. Contact us if there is anything that is not clear, or if you would like more information. Take time to decide whether or not you wish to take part.

What is the purpose of the study?

Takotsubo cardiomyopathy or “broken heart syndrome” is often triggered by physical or emotional stress. For a short time, the heart does not pump efficiently and can become swollen. We see a rapid improvement in how the heart pumps a few weeks later and for many patients, this never happens again. We still do not fully understand why or how it happens.

Research studies performed at the University of Edinburgh have shown subtle changes in the heart muscle can persist in people who recover from takotsubo cardiomyopathy. This change can be detected by performing a specialised MRI scan.

In this study, we propose to ask people with a recent diagnosis of takotsubo cardiomyopathy to try some established heart treatments to see if this can improve how the heart muscle works. The medications given will be ones which we currently use in people with other types of heart problems.

Why have I been invited to take part?

You have been invited because you have recently been diagnosed with takotsubo cardiomyopathy within the past 3 months.

Do I have to take part?

No, it is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form, with at least 24 hours to decide. If you decide to take part, you are still allowed to withdraw at any time and without giving a reason. Deciding not to take part or withdrawing from the study will not affect the healthcare you receive or your legal rights.

What will happen if I take part?

Below is a flow chart showing what the study involves.

Visit 1
Consent, clinical history and examination.
Patient questionnaire, walking test and blood tests.
Heart tests: ECG, heart ultrasound and MRI scan.
Allocation to Bisoprolol, Valsartan or no medication.
3 hours.

↓

Patients allocated to Bisoprolol and Valsartan will need to return for two additional visits 1 week and 2 weeks after starting medication. This is to check their heart rate, blood pressure and blood tests and to have their medication dose adjusted (10 minutes). Once on the highest dose, patients will not require to attend for these fortnightly visits. Patients randomised to no medication will not need to attend for these visits.

↓

Visit 2 (4 weeks later)
Clinical history, examination, questionnaire and walking test.
Heart tests: ECG, heart ultrasound and MRI scan.
Adjustments to your medication and pill counting.
3 hours

↓

Visit 3 (3 months later)
Clinical history, examination, questionnaire, blood tests, walking test.
Heart tests: ECG, heart ultrasound and MRI scan.
Stopping your medication and pill counting.
3 hours

Preparation before the visits

You should avoid doing any strenuous exercise for 24 hours before the visit. Strenuous exercise may interfere with the results of some of the blood tests.

If, for any reason, you are feeling unwell before the scheduled visit, simply contact a member of the research time who will advise accordingly.

If you have been prescribed medication as part of the study we will ask you to bring empty pill packets with you so we can check if the correct medication has been taken.

Visit 1 – 3 hours:

- **Consent** (10 minutes): We will check if you are suitable for the study and you can discuss any questions with the doctor. If you are satisfied with the information we have provided and wish to take part, you will be asked to sign a consent form. We may ask you to sign a consent form at this visit or prior to this if we meet you whilst you are still in hospital. We will also ask that you consent to us informing your GP that you are taking part in the study. If you are pregnant or breast-feeding, you should not take part.
- **Medical history and physical examination (**about 15 -20 minutes): We will check that you can enter the study safely by reviewing any illnesses you may have or have had, any medicines you may have taken or are currently taking and look at your height, weight, blood pressure and heart rate. We will also ask questions regarding your family's health history. We will also ask some questions to make sure you do not have metal objects in your body to decide if you will be safe in the MRI machine.
- **Blood tests** (about 10 minutes): We will take up to four tablespoons of blood during the entire study for research purposes. You may require further blood tests out with this for safety and monitoring purposes, if you are prescribed a study drug. We will be checking your kidney function, liver function and full blood count to check you are safe to take part in the study. We will also be storing blood samples for future research purposes, although this is optional.
- **Patient questionnaire** (about 10 minutes): We will ask you to complete a questionnaire asking about current symptoms and quality of life.
- **ECG** (about 5 minutes): We will take a tracing of the electrical activity of your heart by attaching sticky pads to your chest.
- **Cannula** (about 10 minutes): A cannula is a small needle which we insert into a blood vessel (vein) in your arm. This allows us to give the manganese dye during the MRI scan.
- **Urine pregnancy test** (about 5 minutes): We will perform this in all female patients of childbearing potential. This is because the manganese contrast dye we give in the study can be harmful in pregnancy, meaning you cannot take part in the study if you are pregnant.
- **Echocardiogram** (about 20 minutes): This involves placing an ultrasound probe on the skin over your heart with some cold jelly to enable us to take ultrasound pictures of the heart. We usually ask you to lie on your left side for the test. It is a painless test and is similar to the baby scans pregnant women get.
- **6-minute walk test** (6 minutes): This involves asking you to walk on the flat for 6 minutes while we monitor your oxygen levels using a probe on your finger. You can ask to stop the test at any point.

- **MRI of the heart** (about 1 hour): Cardiac MRI is a safe test that uses magnets, radio waves and a computer to take both still and moving pictures of your heart and major blood vessels. The scanner is a large magnet shaped like a long "tunnel" that is open at both ends with a sliding table. You will be asked to remove your clothing and will be provided with a gown to wear. You will be given headphones to cover your ears as the scanner is noisy. You can speak with the doctors and radiographers throughout the entire scan. During the scan, you will need to lie still on your back as movement can blur the images. We will ask you to breathe in and out and hold your breath for several seconds for some of the scans. You will be given an agent which enhances the images of the heart through the cannula in your arm. This compound behaves like a dye that makes the images of your heart clearer and incorporates a natural mineral, manganese, that the body normally uses for other bodily functions. MRI scans are painless but involve the use of a strong magnetic field, so if you have any of the following, you would not be suitable for a scan, and would not be able to take part in this study:
    - permanent pacemaker or defibrillator
    - metal clips in blood vessels of the brain
    - injury to the eye involving fragments of metal
    - shrapnel injuries
    - other metal or electronic implants
    - pregnant or breast-feeding
    - permanent make up containing metal substances

You will also be asked to remove any metal objects (such as house keys) from your person. If you have dental implants, hair extensions, jewellery or hair accessories containing metal you will be asked to remove them.

- **Randomisation to medications** (about 10 minutes): Randomisation means you will be assigned by chance to one of three possible options: treatment with a drug called Bisoprolol, treatment with a drug called Valsartan or no medication. We currently use both Bisoprolol and Valsartan to treat people with high blood pressure or other heart conditions. If you are already on similar tablets for blood pressure or other conditions, we may have to consider changing some of your current medications before we can randomise you to the study medication. We would only change your medication if it was safe to do so. In certain cases, we may suggest an alternative medication.

Additional visits only for participants randomised to Bisoprolol and Valsartan (1 week and 2 weeks after starting on medication) – 10 minutes:
Patients started on Bisoprolol and Valsartan medication start on a low dose, after which the medication dose is gradually increased every week for two weeks. In order to increase the medication dose safely, we will need to check your heart rate, blood pressure and blood tests (to check the kidney function). This will involve two additional visits which will take approximately 10-20 minutes. You do not need to attend for these visits if you have been allocated to not take any medication. We will issue you with a prescription for the new dose of medication at this visit but please do not take the new dose of medication until we have contacted you with your blood

results. If blood tests remain abnormal in participants after subsequent visits, you may be invited for additional blood tests.

Visit 2 (4 weeks after visit 1) – 3 hours:

- **Medical history and physical examination (**about 15 -20 minutes)
- **Patient questionnaire** (about 10 minutes)
- **ECG** (about 5 minutes)
- **Cannula** (about 10 minutes)
- **Urine pregnancy test in women of childbearing potential** (about 5 minutes)
- **Echocardiogram** (about 20 minutes)
- **6-minute walk test** (6 minutes)
- **MRI of the heart with manganese** (about 1 hour)
- **Pill counting** (about 5 minutes) We will perform pill counting to assess treatment compliance and therefore you will be requested to bring empty drug bottles/ blister packs back with you at this visit.

Visit 3 (3 months after visit 2) – 3 hours:

- **Medical history and physical examination (**about 15 -20 minutes)
- **Patient questionnaire** (about 10 minutes)
- **ECG** (about 5 minutes)
- **Cannula and blood tests** (about 10 minutes)
- **Urine pregnancy test in women of childbearing potential** (about 5 minutes)
- **Echocardiogram** (about 20 minutes)
- **6-minute walk test** (6 minutes)
- **MRI of the heart with manganese** (about 1 hour)
- **Pill counting** (about 5 minutes)
- **Stop study medication if this has been prescribed. If Bisoprolol has been prescribed the dose will be reduced gradually before this is stopped completely. We will ask you to reduce the dose by 2.5mg each week and will ask for consent to inform your GP. The reason for this is that stopping Bisoprolol too quickly can cause side effects such as palpitations.**

What are the possible benefits of taking part in the study?

Your help and the information we obtain from this study may improve our understanding of takotsubo cardiomyopathy.

The results of this study may be used for the future commercial development of a new medicinal product, treatment or test. Your participation in this study will not entitle you to benefit financially from the commercial development of the product, treatment or test. If required, you will be reimbursed for travel expenses.

What are the possible disadvantages of taking part?

1. If you take part in this study, you will have 3 **MRI scans**. MRI is safe and does not involve any ionising radiation (X-rays).
- As the scanner consists of a powerful magnet, it may attract certain metallic objects. You must not have a scan if you have had metallic objects or medical devices (e.g. pacemaker) inserted into your body during an operation.
- The scan is noisy, and we provide headphones to protect your ears.
- The scan involves lying flat in a slightly confined space and a small number of people find this too claustrophobic. You will be given a chance to see the scanner to make sure that you are comfortable in it before the study starts. The doctor will be able to remove you from the scanner at any time and you will not need to finish the scan if it is too uncomfortable. You will be given a buzzer that you will be able to use at any time if you wish to stop the study.
- If you are pregnant or breast-feeding, you should not take part because the MRI and manganese used in this study may harm an unborn or nursing baby.

2. **Manganese contrast** is the compound which we are investigating with this study. It has been tested in clinical trials and has been approved as safe for use in humans. One or two of our subjects (out of over 300 people) have experienced a brief feeling of nausea. If this becomes a problem, we can treat this with an anti-sickness tablet if required. Other minor side-effects which are possible are mild discomfort around the injection site, a feeling of light-headedness, warmth or flushing. These are uncommon, and usually very transient but we can stop the study at any time if required. You will be closely monitored following the injection, with continual ECG and blood pressure readings throughout the MRI scan.

3. **Cannula** is a “plastic tube” in the arm which some people find uncomfortable and there can be bruising at the site of needle entry. Our staff are highly trained in cannula insertion and we will make sure you are as comfortable as possible.

4. **ECG** involves placing sticky pads on your chest can lead to skin irritation in rare cases.

5. **Medications** prescribed to you as part of the study may be associated with side effects. Although rare, we would encourage you to let us know or seek medical attention if you think you have experienced any side effects related to the study medication. If you develop a significant side effect/intolerance to the study medication prescribed then we may need to withdraw you from the study for safety reasons.
- Bisoprolol:
    - Not well tolerated in patients with severe asthma (e.g. requiring previous hospitalisation), low blood pressure or slow heart rate

    - Potential side effects: dizziness (caused by slow heart rate or low blood pressure), erectile dysfunction, rash, cold hands and feet
- Valsartan:
    - Not well tolerated in patients with low blood pressure or impaired kidney function
    - Potential side effects: dizziness (caused by low blood pressure), impaired kidney function (this would be picked up on blood tests and usually reverses on stopping the medication), oral swelling, rash, nausea, diarrhoea
    - If you develop a significant illness or diarrhoea/vomiting whilst on this medication which prevents you from eating and drinking as normal, you may need to stop taking the medication for a few days until you recover

Other unexpected risks:
You may have side effects that we do not expect or know to watch for now. Call the study team if you have any symptoms or problems. If you have any concerns which occur out of hours, or you are unable to contact the study team for any reason, you should attend your GP or your local Emergency Department.

Incidental Findings:
Although very unlikely, it is possible that some of the blood tests or scans you have as part of the study discover abnormal findings. If this does happen, we will discuss these with you and your GP as a priority to ensure that any findings are followed up with the appropriate healthcare specialists to ensure that you receive any appropriate tests or treatment.

What if there are any problems?

In the unlikely event that something goes wrong and you are harmed during the research and this is due to someone's negligence then you may have grounds for a legal action for compensation against NHS Lothian, but you may have to pay your legal costs. The normal National Health Service complaints mechanisms will still be available to you.

What will happen if I don't want to carry on with the study?

Taking part in this study is voluntary. You are free to withdraw from the study at any time. Your decision will not affect your ability to receive future medical care. However, if you are prescribed medication as part of the study this would need to be discontinued. If you choose to stop participating in the study, or unable to continue, we would like to still make use of your data with your permission. The researchers will still use information about you that was collected before you ended your participation, but no new data will be added after that point. If you decide to stop being in the study, we will ask you to inform Dr Jennifer Ramsay. You can find her contact details at the end of this leaflet.

Even if you do not change your mind, we may decide to take you out of the study if for example the study sponsor closes the study at any time for administrative or other reasons.

If you lose the capacity to consent during the study, you will be withdrawn from the study. Identifiable data or tissue already collected with consent would be retained and used in the study. No further data or tissue would be collected or any other research procedures carried out on or in relation to you.

What happens when the study is finished?

When the study finishes, the data will be analysed by the research team at the University of Edinburgh. Your data will be pseudonymised and will be identifiable via a study ID number which only the study doctors will have access to. The blood sample to measure your blood count, kidney function and some other basic assessments, will be immediately analyzed at the local laboratory in the Royal Infirmary of Edinburgh. After analysis, blood samples will not be referred to again by the study team and will be stored according to NHS Lothian regulations as part of your confidential medical record for a minimum period of 5 years. We will ask your consent to use your data and stored blood tests in future studies. Furthermore, the images taken of your heart will again be identifiable via a study ID number which only the study doctors will have access to. If there are any future studies which uses your data, stored blood samples or cardiac images, these will be used by one of our research collaborators with your consent.

The research may lead to the development of a commercial product or new technologies. There are no plans to pay you if this occurs.

We will also have a discussion with you at the end of the study regarding your medication. If we have changed your medication at the start of the study then we may restart this medication once the study is finished. We will inform your GP which medication should be stopped or continued at the end of the study.

Will my taking part be kept confidential?

All the information we collect during the course of the research will be kept confidential and there are strict laws which safeguard your privacy at every stage.

The study information will be recorded in your medical notes. Personal data, which may be sensitive, e.g. ethnic origin, health, date of birth, will be collected only for research purposes in connection with this study. Some information will also be recorded on data forms that will be sent to a data processing office and entered onto a computer. All of your data collected for the study would be looked at for auditing and monitoring by authorised persons from the sponsor, the University of Edinburgh, to make sure that it is being carried out correctly. The sponsor may disclose information to regulatory authorities for auditing purposes. All investigators have a duty of confidentiality to you as a research participant and nothing that could reveal

your identity would be disclosed outside the research study site. The data from the study will be recorded pseudonymously and processed electronically where applicable you would not be identifiable from this.

All data, images of your heart and blood samples collected will be identified by a code number and your identity will remain unknown. All information, which is collected about you that leaves the clinic, will have your name and address removed so that you cannot be recognized by it. Your study doctor is responsible for keeping a code list which makes it possible to link your assigned number to your name. This will be kept in a safe place to ensure that in case of an emergency you can be identified and contacted. The code list will be kept for up to 5 years after study completion.

How will we use information about you?

We will need to use information from your medical records and provided to us by you for this research project.

We will collect your Community Health Index (CHI) number or NHS number. Note that the CHI is a population register, used in Scotland for health care purposes. The CHI number uniquely identifies a person on the index and is personal identifiable information. Your CHI number or NHS number is being collected to allow us to check your medical record, safely prescribe medications and to report test results appropriately.

Other personal identifiable information collected will include your initials/ name / date of birth / ethnicity / address / post code/ telephone number / e-mail address. People will use this information to do the research or to check your records to make sure that the research is being done properly.

People who do not need to know who you are will not be able to see your name or contact details. Your data will have a code number assigned instead.

We will keep all information about you safe and secure in the Clinical Research Facility in the Royal Infirmary of Edinburgh.

All your study data will be protected in accordance with the local Data Protection regulations. You have the right to access and to ask for the correction of the information collected about you during the study. If you decide to stop taking part in the study, no new data will be collected and you may ask for your previously retained identifiable samples to be destroyed, to prevent further analysis. However, we may contact you to obtain some information about your health in case there is an ongoing adverse event posing you a potential health safety risk after the decision to stop taking part.

All information and data which are collected about you that leaves the hospital clinic will be identified by a study participant identification code and will not contain your personal identifiable information. This is called “pseudonymisation”. This is to ensure that your identity will remain unknown to anyone outside of the normal hospital clinic. If you need any further information about your data and how it is used, please contact the study doctor Dr Jennifer Ramsay on 07980916309.

What are your choices about how your information is used?

You can stop being part of the study at any time, without giving a reason, but we will keep information about you that we already have.

If you choose to stop taking part in the study, we would like to continue collecting information about your health from your medical records. If you do not want this to happen, tell us and we will stop.

We need to manage your records in specific ways for the research to be reliable. This means that we won’t be able to let you see or change the data we hold about you.

Where can you find out more about how you information is used?

You can find out more about how we use your information:

- At www.hra.nhs.uk/information-about-patients/
- Our leaflet available at www.hra.nhs.uk/patientdataandresearch
- By asking one of the research team
- By sending an email to jennifer.ramsay4@nhslothian.scot.nhs.uk
- By phoning us on 07980916309

What will happen to the results of the study?

This study will be written up and published in international medical literature. It may also be presented at medical conferences.

You will not be identifiable in any published or presented results.

If you would like an update on how the study is going or a summary of the study when it is finished, please contact Dr Jennifer Ramsay, GMC number 7489965.

Who is organising and funding the research?

This study has been organised by Prof. David Newby and Dr Jennifer Ramsay and sponsored by the University of Edinburgh and NHS Lothian. It is funded by the British Heart Foundation.

Who has reviewed the study?

The North of Scotland Research Ethics Committee 1.

Researcher and Contact Details

Dr Jennifer Ramsay
Chancellor's Building
Royal Infirmary of Edinburgh
49 Little France Crescent
EH16 4SB

Independent Contact Details

If you would like to discuss this study with someone independent of the study please contact:

Dr Alan Japp
Consultant Cardiologist
Edinburgh Royal Infirmary
Alan.japp@nhs.scot

Complaints

If you wish to make a complaint about the study, please contact NHS Lothian:

Patient Experience Team – NHS Lothian
Mainpoint
102 Westport
Edinburgh
EH3 9DN

By telephone
0131 536 3370 (open Mon-Fri, 9am to 2pm)

By email
LOTH.Feedback@nhs.scot

Participant ID:

CONSENT FORM FOR TAKO MEMRI

Please **initial** box

I confirm that I have read and understand the information sheet (Version ….. Date……) for the above study. I have had the opportunity to consider the information, ask questions and have had these questions answered satisfactorily.	☐
I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason and without my medical care and/or legal rights being affected.	☐
I give permission for the research team to access my medical records for the purposes of this research study.	☐
I understand that relevant sections of my medical notes and data collected during the study may be looked at by individuals from the Sponsor (University of Edinburgh and NHS Lothian), from the NHS organisation or other regulatory authorities where it is relevant to my taking part in this research. I give permission for these individuals to have access to my data and medical records.	☐
I give permission for my personal information (including name, address, age, date of birth, telephone Number, email address and consent form) to be passed to the Clinical Research Facility for administration of the study.	☐

	Please **initial** box
I give permission for my Community Health Index (CHI) number or hospital number to be collected and retained on NHS servers.	☐
I understand that the results of this study may be used for future commercial development of products/tests/treatments and I will not benefit financially from this.	☐
I agree to my General Practitioner being informed of my participation in the study.	☐
I agree to take part in the above study	☐

	Yes	No
I agree to my anonymised data and tissue being used in ethically approved future studies. (optional)	☐	☐
I agree to my anonymised blood samples to be sent to other academic institutions within the UK (optional)	☐	☐

…… …… ……

Name of person giving consent	Date	Signature
.....	.....	.....
Name of person taking consent	Date	Signature

1x original – into Site File; 1x copy – to Participant; 1x copy – into medical record