easternhealth

Participant Information Sheet/Consent Form

Title	The Metformin Aneurysm Trial
Short Title	MAT
Protocol Number	5.0
Protocol Date	24th September 2020
Study Sponsor	James Cook University
Principal Investigator	Associate Professor Anthony Dear
Site	Eastern Health – Box Hill Hospital

1. Introduction

You are invited to take part in a research study called the Metformin Aneurysm Trial (MAT). This study aims to determine whether metformin, a commonly prescribed medication for diabetes, is an effective treatment for people with abdominal aortic aneurysm (AAA). More specifically, this study will look at whether metformin prevents the need for surgical repair of AAAs and death due to AAA rupture (bursting). The reason you have been invited to take part in this study is because you have been diagnosed with an AAA (the ballooning and weakening of a major blood vessel in your abdomen), and you do not have diabetes.

This study will be conducted by a group of international researchers and will involve 1,954 participants in Australia, New Zealand, Sweden and the United Kingdom. The total duration of the study for all participants will be for an average of 3.5 years.

This study received the main source of funding from the National Health and Medical Research Council (NHMRC) of Australia, and is coordinated internationally by the Queensland Research Centre for Peripheral Vascular Disease (QRC-PVD) at James Cook University, Australia, and The George Institute for Global Health of the University of New South Wales, Australia.

This Participant Information Sheet and Consent Form tells you about the research study. It explains the tests and treatments that are involved. Knowing what is involved will help you decide if you want to take part in this study. Please read this information carefully. Ask questions about anything that you do not understand or want to know more about. Before deciding whether or not to take part, you might want to talk about it with a relative, friend or your local doctor.

Participation in this study is voluntary. If you do not wish to take part, you do not have to. You will receive the best possible care whether or not you decide to take part. Whatever your decision, please be assured that it will not affect your medical treatment, or your relationship with the staff who are caring for you. Sometimes during the course of a study, new information becomes available about the treatment that is being studied. While you are participating in this study, you will be kept informed of any significant new findings which may affect your willingness to continue in the study.

If you decide you want to take part in this study, you will be asked to sign the consent section of this form. By signing this form, you are telling us that you:

• Understand what you have read,

• Consent to take part in the research study,

• Consent to have the tests and treatments that are described in this information sheet, and

• Consent to the use of your personal and health information as described in the information sheet.

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

2. What is the purpose of this study?

The purpose of this study is to investigate whether treatment with metformin is better at reducing the need for AAA surgery and reducing the risk of death due to AAA rupture when compared with placebo medication. The study also aims to investigate the effect of metformin on AAA growth, major adverse cardiovascular events (for example, heart attack or stroke), health-related quality of life, and the requirement for other peripheral vascular surgical procedures.

Metformin is used to control blood sugar levels in people with Type 2 diabetes mellitus, particularly in those who are overweight. It is used when diet and exercise are not enough to control high levels of blood sugar. Several studies suggest that metformin might also reduce AAA growth. By reducing AAA growth, metformin may reduce the need for surgery and, more importantly, the risk of death due to AAA rupture.

AAA is a common problem in older adults, affecting approximately 5% of men and 1% of women aged over 60 years. The main concern with AAA is the risk of rupture which can be life threatening. At present, the only treatment available for AAA is surgical repair. However, AAA surgery has several risks, so it is only usually recommended for patients with large AAAs (≥55mm), which have a higher risk of rupture. Most AAAs gradually increase in size over time to the point where surgery is recommended. There is no known effective medication for AAAs. Therefore, there is a need to identify medications that might stop AAAs from growing, to avoid the need for surgery and reduce the risk of AAA rupture. This study will test whether or not metformin prevents the need for AAA surgery and reduces the risk of AAA rupture in participants with AAAs measuring ≥39mm in diameter. If the results of this study are positive, they would be relevant to some tens of millions of people worldwide who currently receive no treatment for their AAA.

3. What does participation in this study involve?

Signing the consent form does not guarantee your enrolment in the study; rather it allows us to commence discussions and investigations to assess your suitability to participate. The information collected about you at the screening appointment and during the run-in will determine if you are suitable to continue in the study. If we deem you suitable to continue in the study, you will be randomly allocated to receive either metformin extended-released (XR) or placebo medication. We anticipate that this study will take approximately 3.5 years to complete, however it may take longer than this. All participants will need to keep taking their study medication until the study has finished. If it takes longer than 3.5 years to complete this study, then you will have to take your study medication for more than 3.5 years. During this time, you will be followed-up by telephone every three months, with the option to attend a face-to-face visit annually if feasible for you and the study centre.

Screening/Run-in

At the screening visit/phone call, a trained member of the study team, usually a doctor, nurse or study coordinator, will ask you a series of questions about your medical history and current medications. You will also be asked to complete two questionnaires related to your quality of life. You may be asked to undergo a blood test so that we can test for diabetes and measure your kidney function. If you have had these tests within the last six months, we will obtain these results instead.

Finally, your most recent AAA ultrasound images and report will be obtained to measure the diameter of your AAA. If you have not had an ultrasound scan within the last six months, you will be asked to undergo ultrasound imaging.

At the end of the screening appointment, if you are suitable to continue, you will be dispensed study medication (i.e. metformin XR or placebo) that will last for six weeks. You will not be told which study medication you have been given, but your study doctor will know this information. You will be provided with instructions to take your medication - one 500mg tablet once daily for weeks 1 and 2, followed by two 500mg tablets (1000mg) once daily for weeks 3 and 4, and finally three 500mg tablets (1500mg) once daily for weeks 5 and 6. A member of the study team will contact you by telephone every two weeks to assist in achieving the 1500mg dose, to determine how well you are tolerating the study medication and to report any adverse events. Your general practitioner will be informed about your participation in the run-in phase of the study.

Randomisation

A member of the study team will review all the information collected. Your study doctor, nurse or study coordinator will confirm that you are eligible to continue in the study. If you are eligible and you wish to take part in the study, you will then be randomised (like 'tossing a coin') to receive study treatment. You will have a 50% chance of receiving either of the following study medications:

Metformin extended release (XR) *or* placebo medication

Placebo medication is a tablet without any specific activity. It is a substance that does not contain active treatment. Sometimes we do not know which treatment is best for treating a condition. To find out, we need to compare different treatments with placebo. We put people into groups and give each group a different treatment. The results are compared to see if one is better. To try and make sure the groups are the same, each participant is put into a group by chance (randomised). MAT is called a double-blind study. This means that neither you nor your study doctor will know which treatment you are receiving. However, if necessary and in certain circumstances, your study doctor can readily find out which treatment you are receiving.

A member of the study team will provide you with a six month supply of your allocated study medication. You will be instructed to take three tablets of study medication, once daily with food. It is advised to take the study medication with your evening meal to reduce any gastrointestinal discomfort. You will receive specific instructions about taking your study medication. Your general practitioner will be informed about your participation in the main phase of the study.

Three-monthly Follow-up telephone calls

Every three months, you will be required to answer some questions about your health. You will be asked about your adherence to the study medication, the number of tablets remaining in the study medication kit and any side effects that you may have had. Every six months you will be provided with your next supply of study medication.

Annual Follow-up/Final Follow-up

You will be given the option to attend a face-to-face follow-up appointment annually and at the final follow-up appointment, if feasible for you and the study centre. In addition to the procedures described for the three-monthly follow-up, you will be asked to complete two questionnaires related to your quality of life. You will be asked about any changes to your other medications. We will request

copies of any AAA ultrasound images and reports you have had since the last visit so we can record the diameter of your AAA. If you have undergone any additional imaging, for example CT or MRI, we will also collect copies of these images and reports. You may be asked to undergo a blood test so that we can measure your kidney function. If you have had these tests within the last three months, we will obtain these results instead. You will be required to continue taking the study medication until the study ends, even if your AAA is repaired during the study period. This is so we can investigate the effect of the study medication on other outcomes including the incidence of major adverse cardiovascular events (for example, heart attack or stroke), health-related quality of life, and requirement for other peripheral vascular surgical procedures.

4. What are the alternatives to participation?

Participation in this research study is voluntary. There are no medications currently available to manage your AAA. If you decide not to participate, you will continue to visit your general practitioner and/or specialist as you would normally for surveillance of your AAA.

5. Can I have other treatments during this research study?

You may continue to take your regular medications, vitamins and supplements while participating in this study. While taking part in this study we ask that you do not participate in any other medication studies as this may impact the results of our study. If you start taking non-study metformin for any reason during the course of this study, please inform the study team immediately.

6. What are the possible benefits?

The information that we obtain from this study may help to improve the management of patients with AAA, however, participation in this study may not directly benefit you.

7. What are the possible risks?

All medical treatments involve some risk of injury or side-effects. In addition, there may be risks associated with this study that are presently unknown or unforeseeable. A member of the study team will carefully record any problems or side-effects you have, and these will be relayed to the principal researcher to ensure you are kept as safe as possible. The risks associated with metformin are well-known and are outlined below.

<u>Study medication</u>

The known side effects that may be experienced when a person takes metformin are listed below.

Very common side effects – occur in more than 1 in 10 patients:

> Mild gastrointestinal symptoms (such as diarrhea, nausea, vomiting, abdominal pain and loss of appetite) especially during the initial treatment period. These symptoms are generally short-lived and disappear after the first few weeks. Taking metformin with meals can help reduce these symptoms.

Common side-effects – occur in about 3 in 100 patients:

- Taste disturbance

Very rare – occur in less than 1 in 10,000 patients:

- Skin reactions (such as redness of the skin, itching and hives)

- Lactic acidosis. This serious condition can occur due to build-up of lactic acid in the blood. No clinical trials of metformin among people without diabetes have had a single case of lactic acidosis to date. In this study participants are thoroughly screened to ensure they are not at risk of lactic acidosis, however it is important to understand the following symptoms of lactic acidosis:
    - Nausea, vomiting, stomach pain
    - Trouble breathing
    - Feeling weak, tired or generally unwell
    - Unusual muscle pain
    - Sleepiness
    - Dizziness or lightheadedness
    - Shivering, feeling extremely cold
    - Slow heart beat

If you experience any of these go to the emergency department at your nearest hospital.

Blood collection

The risks of a blood test include pain, a bruise at the point where the blood is taken, redness and swelling of the vein, infection and rarely fainting.

8. Compensation for injuries or complications

If you suffer any injuries or complications as a result of this study, you should contact your doctor as soon as possible, who will assist you in arranging appropriate medical treatment. If you are eligible for public healthcare, you can receive any medical treatment required to treat the injury or complication, free of charge, as a public patient in any public hospital.

In addition, you may have the right to take legal action to obtain compensation for any injuries or complications resulting from the study. Compensation may be available if your injury or complication is sufficiently serious and is caused by unsafe drugs, or by negligence of one of the parties involved in the study (for example, the researcher). You do not give up any legal rights to compensation by participating in this study.

9. Will taking part in this study cost me anything, and will I be paid?

Participation in this study will not cost you anything, and you will not be paid.

10. What if I wish to withdraw from this research study?

If you decide to withdraw from the study, please notify a member of the study team right away. If you withdraw consent for further treatment, data will continue to be collected unless you specify otherwise. If you decide to leave the study, the researchers would like to keep the health information

about you that has been collected. This is to help them make sure that the results of the study can be measured properly. If you decide to withdraw and do not wish for your health information that has already been collected to be used, please notify a member of the study team.

11. What happens when the research study ends?

The medication provided during this study will not be available after the study has ended. You will be referred back to your general practitioner/specialist for the management of your AAA.

After the study has finished and you are no longer taking study medication, we would like to continue to collect health information about you from your hospital. This will help us to find out the very long-term effects of metformin on AAA. By signing the consent form, you agree to allow the study team to continue receiving your electronic health information from hospital, state or national health information service branches and hospital admissions registries. This data will be collected for up to five years after the study has ended. You will not be contacted during this time.

12. Confidentiality / Privacy

Any identifiable information that is collected about you in connection with this study will remain confidential and will be disclosed only with your permission, or except as required by law. Only the study researchers, monitors, representatives of regulatory authorities and ethics committee may have direct access to it. Access is required to check the accuracy of the information collected and to ensure that this trial is being carried out according to local requirements and/or regulatory guidelines.

Study monitors, auditors, representatives of regulatory authorities and ethics committee may also be granted direct access to your original medical records for verification of trial procedures and/or data.Computer records will be password-protected. Trial documentation will be kept and securely archived for 15 years.

Some of the information in this study may be collected from and of you by trained researchers appointed by James Cook University who will work from a remote location in collaboration with study staff at your site. By signing this consent form, you are agreeing for you and your next of kin's contact details to be stored in a secure password protected database that is accessible only by staff at this study site and by designated researchers who may contact you for your screening/run-in, randomisation and follow-up appointments. This database will also be used to store copies of your consent form, blood test results, AAA medical imaging reports and images. These documents will be identifiable. Study monitors will be granted access to these documents for data verification. This database will be separate from the database containing your study data. This database will be hosted by The George Institute for Global Health on a server based in Sydney, Australia.

Your study data will be stored electronically in a database created by The George Institute for Global Health. Only staff at this study site and designated researchers will have access to this database. All data will be coded to protect your confidentiality. This database will be hosted by IBM Corp on a server based in the United States of America.

The databases containing your personal information and your study data will not be linked in any way so that confidentiality and de-identification of the information collected about you for the purpose of the study will be maintained. We take your privacy very seriously and ensure that the databases meet the standards of all relevant privacy laws in Australia and overseas.

Any imaging that is performed of your aneurysm will be securely transferred to the QRC-PVD at James Cook University for central reading.

Information about you may be obtained from your health records held at this site and other health services for the purpose of this study. 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 study.

If relevant, information about your participation in this study may be recorded in your health records held at the Box Hill Hospital. For example, a copy of your signed consent form may be uploaded into your hospital or medical centre file if deemed necessary and appropriate when accessing your information from this site.

If similar studies are conducted by other research groups, then we would like to analyse all the available study data together to obtain the most reliable evidence on the effectiveness of metformin for AAA. This would involve securely transferring de-identified data to other established research groups for analysis. The receiving institution would have to demonstrate a high level of data security, and sign a contract agreeing that no data would be shared with third parties.

13. What happens with the results?

It is intended for the results of this study to be presented or published at medical conferences and in scientific journals. In any publication, information will be provided in such a way that you cannot be identified. Results of the study will be provided to you, if you wish. By signing the consent form, you agree to your data being included in the results published for this study.

Further information and who to contact

When you have read this information, the Principal Investigator or other designated study staff member will discuss it with you further and answer any questions you may have. If you would like to know more at any stage, please feel free to contact:

Site Principal Investigator: Associate Professor Anthony Dear

P: 03 9091 8873
E:anthony.dear@monash.edu

Site Coordinator: Andriana Chronopoulos

P: 03 9094 9510

E: andriana.chronopoulos@monash.edu

Regional Coordinating Centre: Queensland Research Centre for Peripheral Vascular Disease
P: 07 4781 5715

E:QRCPVD@jcu.edu.au

Ethics approval

All research involving humans is reviewed by an independent group of people called a Human Research Ethics Committee (HREC). This study has been approved by The Townsville Hospital and Health Service HREC. Any person with concerns or complaints about the conduct of this study should contact the Executive Officer on 07 4433 1440.

The conduct of this study at the Box Hill Hospital has been authorised by the Eastern Health Office of Research and Ethics. Any person with concerns or complaints about the conduct of this study may also contact the Research Governance Officer on 03 9895 3100.

This study will be carried out in accordance with the *National Statement on Ethical Conduct in Human Research (2007, updated 2018).* This statement has been developed to protect the interests of people who agree to participate in human research studies.

Thank you for taking the time to consider this study. If you wish to take part in it, please sign the attached consent form. This information sheet is for you to keep.

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CONSENT TO PARTICIPATE IN RESEACH

Title	The Metformin Aneurysm Trial
Short Title	MAT
Protocol Number	5.0
Protocol Date	24th September 2020
Study Sponsor	James Cook University
Principal Investigator	Associate Professor Anthony Dear
Site	Eastern Health – Box Hill Hospital

Declaration by Participant

I, _____

[Name]

of _____

[Address]

have read and understood the Information for Participants on the above named research study.

1. I have been made aware of the procedures involved in the study, time involved, including any known or unexpected inconvenience, risks, discomfort or potential side-effects and of their implications as far as they are currently known.
2. I understand that the researcher will conduct this study in a manner conforming to ethical and scientific principles set out by the National Health and Medical Research Council (NHMRC) of Australia and the Good Clinical Research Practice Guidelines of the Therapeutic Goods Association.
3. I acknowledge that I have been given time to consider the information and to seek other advice.
4. I acknowledge that refusal to take part in this study will not affect the usual treatment of my condition.
5. I acknowledge that I am volunteering to take part in this study and I may withdraw at any time.
6. I acknowledge that this study has been approved by: The Townsville Hospital Human Research Ethics Committee.
7. I acknowledge that any regulatory authorities may have access to my medical records concerning my disease and treatment for the purposes of this study. However, I understand that my identity will not be disclosed to anyone else in publications or presentations.

8. I understand that I will be given a signed copy of this document and the Participant Information Sheet to keep.

Name of Participant (please print)	
Signature	Date (dd/mmm/yyyy)

Declaration by Witness (to be completed only if the participant cannot read the participant information sheet)

I have witnessed and certify the Participant's verbal consent for him/her to voluntarily agree to participate in this research study.

Name of Impartial Witness (please print)	Relationship to the Participant
Signature	Date (dd/mmm/yyyy)

Declaration by Study Doctor/Senior Researcher≠

Name of Study Doctor/Senior Researcher≠ (please print)	
Signature	Date (dd/mmm/yyyy)

≠A senior member of the study team must provide the explanation of, and information concerning, the research study.

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