MEtfo**R**m**I**n for **T**reating Peripheral Artery Disease-Related Walking Impairment **(MERIT)**

Study Information Booklet for Participants & Consent Form

Interventional Study – *Adult providing own consent*

Protocol Number	2.3
Protocol Date	1st August 2019
Chief Principal Investigator	**Professor Jonathan Golledge,** James Cook University, College of Medicine and Dentistry, Townsville.
Site Principal Investigator	Professor Jonathan Golledge
Site Study Coordinator	Mrs Lisan Mulvey
Location	The Townsville Hospital

Part A: What does my participation involve?

Introduction

As you have been diagnosed with **peripheral artery disease (PAD)**, you are invited to participate in a study called Metformin for Treating Peripheral Artery Disease-Related Walking Impairment (MERIT). Peripheral artery disease is the **blockage and narrowing of blood vessels in your legs** which causes reduced blood flow in your lower limbs making it difficult and painful for you to walk.

This study information booklet contains important information and explains to you as openly and clearly as possible the requirements and activities involved in the study.

Please read this information carefully and ask questions if you do not understand anything or want more information. We also recommend you talk to a relative, friend or your local doctor about the study before making a decision.

Participation in this study is voluntary. If you don't wish to take part, you don't have to and it will have no impact on the medical treatment you are currently receiving.

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

• Understand what you have read

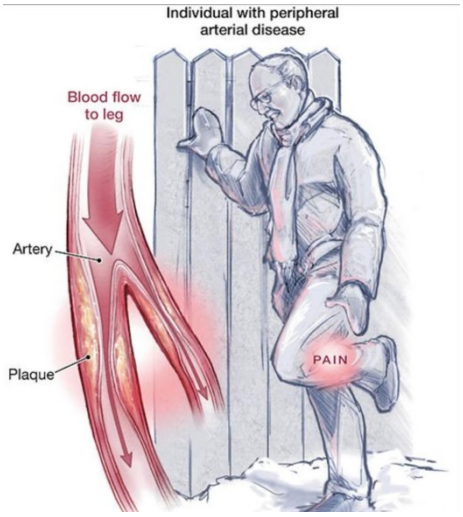
• Consent to take part in the research project

• Consent to have the tests and treatments that are described

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

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

About Peripheral Artery Disease (PAD) & Metformin



PAD is the blockage and narrowing of arteries in the legs leading to a reduction in blood supply to the lower limbs. The **common symptom of PAD is pain in the lower limbs during walking**. This is called **Intermittent Claudication** (IC). Intermittent claudication reduces the ability to undertake physical activity and reduces health related quality of life. **Over time this reduced walking ability and worsening of PAD leads to a downward cycle of chronic poor health, increased risk of amputations and high healthcare costs.**

The prevalence of PAD is rising yet there are no effective treatments to manage the disease. Surgical approaches are currently the most widely used method to restore arterial blood supply. Surgical options are not only expensive, but hold a greater risk of serious complications due to long term durability of the artery being compromised. A recent study by our group showed that patients who underwent surgical treatment for PAD had higher rates of repeat surgical procedures and amputations then those that didn't.

The current medical management of PAD do not effectively treat the symptoms of impaired walking. Walking is recommended for people who suffer IC to improve leg pain symptoms and reduce the risk of cardiovascular incidents. However, this solution is not favored by sufferers of IC due to pain experienced during exercise and regular supervised exercise programs are deemed too expensive to be offered by the Australian health care system.

There is a need for an effective drug treatment to improve related walking impairment for people with PAD.

A number of research studies suggests **metformin** may improve PAD related walking impairment. Metformin is currently approved by the Australian Therapeutics Goods Administration (TGA) for the management of Diabetes, type 2. Metformin has been shown to be well tolerated and safe making it an ideal drug to trial in a range of populations who do not have diabetes. The evidence suggests metformin may have favorable effects on PAD such as:

- Promoting new blood vessel development
- Improves blood vessel wall ability to respond to stimulus (and withdrawal of stimulus)
- Improving muscle function and metabolism
- Improving pain sensitivity

These favorable effects combined, are hypothesized to improve walking ability in people with PAD.

About the Study

The aim of this study is to determine if taking metformin up to three times per day over approximately 6 months will improve walking ability in people with PAD.

This study aims to recruit 116 people with PAD across a number of sites in Queensland. Approximately half of these participants will be randomly allocated to take metformin and the other half to take a placebo. All participants will be asked to take up to one 500mg capsules three times per day with food.

Did you know: The **placebo** is used as a control in studies to test whether the drug is effective. We call these studies 'placebo controlled trials'. The placebo (or control) plays an important role in testing new medication!

This study will measure the change in walking distance after 6 months of taking the drug. Walking distance will be measured using a 6 minute walk test assessment. The study will also measure the change in:

- Physical activity levels over 7 days using an activity monitor
- Markers in the blood related to peripheral artery disease
- Health related quality of life, and
- Lower limb blood supply

This study has been initiated by Professor Jonathan Golledge at the Queensland Research Centre for Peripheral Vascular Disease, James Cook University and the Townsville Hospital, Townsville. This research is being conducted at multiple sites and include The Townsville Hospital, QLD; Princess Alexandra Hospital, Woolloongabba, James Cook University, Townsville, QLD; The Royal Brisbane and Women's Hospital, Herston, QLD and The Prince Charles Hospital, Chermside West, QLD.

What does participation in this research involve?

Visits to the Study Centre:

If you decide to take part in this research trial you will be asked to make a minimum of four (4) visits to the study centre **The Townsville Hospital.** Some site may be able to offer parking facilities or reimbursement for parking fees at the study center.

Follow-up Phone Calls:

You will also be contacted by phone on eight (8) occasions. The first six (6) weekly phone calls are to assist you in increasing the dose of the study drug. The remaining two (2) phone calls will follow-up on your wellbeing during the study.

Take a study drug up to three (3) times per day:

This study asks you to take up to three (3) 500mg capsules daily. To minimize potential side effects (see page 8) you will start taking one capsule per day after breakfast. Over the first six weeks on the study you will be instructed to gradually increase the dose until you reach a maximum tolerated dose which is up to one capsule taken three times per day after meals. The timeline on the next page provides details on what you can expect during the course of this study.

Overall participant timeline:

Week	Type of Involvement	Details of Involvement	How much Study Drug to take
n/a	Obtain Consent	Prior to your involvement in the study it is important that you understand what is required of you and what participation involves.	n/a
-1	Commencing Screening Visit **Visit 1**	• **Screening interview and physical assessments** You will be asked by the study coordinator to confirm information on your age, health and smoking status. Your height, weight, waist, hip circumference, blood pressure and heart rate will be measured. This is done to provide baseline information will be collected from you prior to commencing the study drug. • **Ankle Brachial Pressure Index (ABPI)** Blood pressure will be taken from your ankle to test the blood flow to your feet. • **6 minute walk test** You will be asked to walk as far as you can, up and down a 25 meter track, for 6 minutes until you feel pain or cannot continue. • **Fitted with an ActiGraph activity monitor** You will be fitted with a small watch device on your wrist (match box size), which will monitor your activity levels. This device will be worn for 7 days and will be removed on your second visit to the study centre. • **Blood test and collection** A pathology request form will be provided for blood testing and collection. The blood test will measure your fasting blood glucose and kidney function. The blood collection will be used to assess circulating blood markers that have been associated with peripheral vascular disease.	n/a
0	Final Screening Visit **Visit 2**	• **Removal of ActiGraph activity monitor** At this visit the activity monitor will be removed and returned. • **Two (2) Questionnaires** You will be asked to complete 2 questionnaires about your general health and wellbeing and the impact intermittent claudication has had on your life. At the end of this visit it will be determined if you are suitable participant for this study. If you are deemed suitable, you will be supplied with the study drug required for the remainder of the study. Over the next six (6) weeks you will be contacted weekly and provided with instructions on how many capsules to take and when. At the end of the study you will be asked to return the empty bottles and unused drug on your visit at week 30.	n/a

<table>
<tr><th>Week</th><th>Type of Involvement</th><th>Details of Involvement</th><th>How much Study Drug to take</th></tr>
<tr><td>1</td><td>Phone call 1</td><td rowspan="6">You will receive weekly phone calls from the study coordinator to ask you:

• If you have taken the study drug as instructed and if the dose has been tolerated.
• If you had been experiencing any side effects to the medication such as gastrointestinal upset
• If you had experienced any changes to your health

Based on your answers, the coordinator will instruct you if you need to change the number of capsules to take each day.</td><td rowspan="2">One (1) capsule per day:
• after breakfast</td></tr>
<tr><td>2</td><td>Phone call 2</td></tr>
<tr><td>3</td><td>Phone call 3</td><td rowspan="2">Up to two (2) capsules per day:
• one capsule after breakfast
• one capsule after dinner.</td></tr>
<tr><td>4</td><td>Phone call 4</td></tr>
<tr><td>5</td><td>Phone call 5</td><td>Up to three (3) capsules per day:
• one capsule after breakfast
• one capsule after lunch
• one capsule after dinner</td></tr>
<tr><td>6</td><td>Phone call 6</td></tr>
<tr><td>7-9</td><td></td><td></td><td rowspan="5">Up to three (3) capsules per day:
• one capsule after breakfast
• one capsule after lunch
• one capsule after dinner</td></tr>
<tr><td>10</td><td>Phone call 7</td><td>You will receive a phone call from the coordinator to ask you about:
• If you have tolerated the number of capsules you have been taking each day.
• If you have experienced any changes to your health</td></tr>
<tr><td>11-19</td><td></td><td></td></tr>
<tr><td>20</td><td>Phone call 8</td><td>You will receive a phone call from the coordinator to ask you about:
• If you have tolerated the number of capsules you have been taking each day.
• If you have experienced any changes to your health</td></tr>
<tr><td>21-29</td><td></td><td></td></tr>
<tr><td>30</td><td>End of Study
Visit 3</td><td>• Repeat Assessments
You will undergo the same test and assessments to those carried out in your first screening visit at week -1.
o Physical assessment, ABPI, 6 minute walk test
o Fitted with an activity monitor
o Blood test and Collection
• Return Unused Study Medication & Bottles
You will be asked to return all empty bottles and unused medication.</td><td></td></tr>
<tr><td>30+1</td><td>End of Study
Visit 4</td><td>• Removal of ActiGraph activity monitor
• Two (2) Questionnaires</td><td>n/a</td></tr>
</table>

What do I have to do?

By agreeing to take part in this study, **you agree to take part in all the research activities in this booklet and take the study drug as directed unless told to stop by the coordinator or senior member of the research team**.

Your participation in this study will not prevent or restrict you from taking your normal medication, participating in any normal activities of daily living or attending other appointments.

While taking part in this study **it is advisable that you do not participate in any other drug studies** due to the potential impact it may have in this study.

Other relevant information about the research study

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

You will be reimbursed for your time and travel costs associated with the research study visit. Travel costs will be limited to parking or community flyer transport and reimbursement for your time will be to the amount of $100. This will be provided in the form of gift vouchers that will be given in three instalments, $25 after successfully attending screening visit, $25 after successful randomization and $50 upon the completion of the study.

Do I have to take part in this study?

Participation in any research project is voluntary. If you do not wish to take part, you do not have 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.

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

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 Townsville Hospital.**

If you decide to withdraw from this trial, please notify a member of the research team before you withdraw and you will be sent a study withdrawal form to complete. The data collected from you up to the date of withdrawal will be stored and used according to the research protocol unless you ask for your samples and data be destroyed.

What are the alternatives to participation?

You do not have to take part in this research project to receive treatment at **The Townsville Hospital.** If you decided not to participate, you will continue to visit your GP and/or vascular surgeon as you would normally. Please note, **participation in this study does not replace your usual care** received from your GP and/or vascular surgeon. You are encouraged to continue seeing your doctors as normal while participating in this study.

What are the **possible benefits** to taking part?

We cannot guarantee or promise that you will receive any benefits from this research; however, possible benefits may provide individual, community and research benefits.

Possible benefits to you

- Additional health and physical assessments that may not be carried out in your usual care.
- Access to a potential therapy for PAD-related walking impairment that is not currently indicated for people with PAD without Diabetes, type 2.
- Improved walking ability such as increase time walking before pain begins and reaches maximum pain.

Benefits to the community

- If this study is successful it may provide a potential new drug to treat PAD-impaired walking and benefit people who may suffer this condition in the future.

Benefits to QRC-PVD

- Your participation will assist us in achieving our research outcomes.
- This study, if successful may support further research in this area.
- Your participation will contribute to an increased understanding of PAD by our group and the world.

What are the **possible risks and disadvantages** of taking part?

Side Effects of Metformin

According to multiple studies Metformin is a well-tolerated and safe medication for people who do not have type 2 diabetes. The Metformin consumer information booklet is attached to this information booklet for your reference. The following side effects of Metformin are **generally**

Information about Drug Side Effects

In general, medical treatments often cause side effects. You may have none, some or all of the effects listed, and they may be mild, moderate or severe. If you have any of these side effects, or are worried about them, talk with your study doctor. Your study doctor and coordinator will also be looking for possible side effects.

There may be side effects that the researchers do not expect or do not know about which may be serious. Tell your study doctor immediately about any new or unusual symptoms you have.

Many side effects go away shortly after treatment ends. However, sometimes side effects can be serious, long lasting or permanent. If a severe side effect or reaction occurs, your study doctor may need to stop your treatment. Your study doctor will discuss the best way of managing any side effects with you.

mild and disappear after the first few weeks:

- Feeling sick (nausea)
- Vomiting
- Diarrhea
- Stomach Pain
- Taste Disturbance
- Loss of Appetite

- Skin reactions such as redness of the skin, inching or an itchy rash

Do not be alarmed by the list of side effects as you may not experience any of them. **It is recommended that you take metformin at meal times to reduce nausea and diarrhea.** If you experience any of these side effects, please notify the study coordinator.

A more serious, however very rare, side effect of taking metformin is lactic acidosis which is a buildup of lactic acid in your blood. 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 you are encouraged to go to the emergency department at your nearest hospital.

Other Risks or disadvantages taking part in this study

- There is a chance that you will not be allocated metformin and instead allocated the placebo. This means you may not experience personal benefit we expect from metformin. We will not know which group you have been allocated to but both groups are equally important. The information from the placebo group is compared to the information from metformin group to measure the effectiveness in the treatment of PAD.

- You may experience discomfort during blood collection however this is very temporary and does not exceed what you would expect from an ordinary blood test.

- The 6 minute walk test may provoke intermittent claudication. This discomfort/pain is not long lasting and will subside when you stop walking. Intermittent claudication does not cause damage to your body and will not worsen your PAD.

- You are required to undergo a variety of assessments and tests. There is a possibility the results of these tests may uncover a medical condition that you were unaware of. If this does occur, you and your regular GP will be informed.

What will happen to my blood samples?

The purpose of the blood test is to ensure you have adequate kidney function to eliminate the study drug from your body and to confirm do not have type 2 diabetes. The blood test will also provide information relating to lipid profiles (cholesterol, triglycerides etc) and CRP (indicator of inflammation) which are surrogate markers of cardiovascular events. The purpose of the blood collection is to assess certain markers in your blood which related to PAD and how these might change as a result of the study drug.

Your blood samples will be transferred to James Cook University laboratories where they will be stored and analysed at the end of the study. Before storage, your samples will be de-identified and replaced with the study ID number which is allocated to you at the commencement of the study.

Once the study has concluded, with your consent, any remaining blood sample will be kept and potentially used for other related research purposes. The consent for keeping these samples will be given on a separate consent form and is not included in the consent for this MERIT study. This consent is not a condition for participating in this study.

What if new information arises during this research project?

Sometimes during the course of a research project, new information becomes available about the treatment. If this happens, your study doctor will advise you and discuss whether you want to continue your participation. If you decide to withdraw, your study doctor will make arrangements for your regular health care to continue. If you decide to continue in the research project you will be asked to sign an updated consent form.

Your study doctor may also consider it to be in your best interests to withdraw you from the research project. If this happens, they will explain the reasons and arrange for your regular health care to continue.

Can I have other treatments during this research project?

While you are participating in this research project you are encouraged to continue to take your regular medications, vitamins and supplements. You should tell the study coordinator if you have any changes in your medication during the study.

While taking part in this study we ask that you do not participate in any other drug studies due to the potential impact on this study.

What if I withdraw from the research project?

If you decide to withdraw from the project, please notify the study coordinator before you withdraw. This notice will allow the coordinator to discuss your decision and provide appropriate withdrawal form.

If you do withdraw your consent during the research project, the study coordinator and relevant research staff will not collect any additional information from you. Information already collected will be retained to ensure the results of the research project can be measured accurately and to comply with law. Research data from your participation up until the time you withdraw will form part of the research project results.

Could this research project be stopped unexpectedly?

This research project may be stopped unexpectedly for a variety of reasons such as:

- Unacceptable side effects
- The drug being shown not to be effective
- The drug being shown to work and not need further testing

What happens when this research project ends?

Once the study ends, you will be encouraged to continue seeing your regular doctor as normal.

Once your involvement ends, there may be other participants being recruited or receiving treatment. This means that the study may not be finalised for months or years after your participation has ended. Once all participants have completed the study, the results will be analysis as a group and used in medical publications. Your individual results will not be published, only group results will be published. Therefore, it will not be possible to provide you with individualised

results, however, you will be notified by letter what the overall results show along with a copy of the published research article.

PART 2: How is the research project being conducted

What will happen to information about me?

By signing the consent form you consent that the study team is able to use your personal information for the research project. Any information obtained in connection with this study which can identify you will remain confidential. All documents, either physically or electronic will be stored securely at James Cook University where only authorized persons have access. Data containing personal information will be entered onto a secure database where only authorized persons have access to the information. Approved researchers with limited access to the databases will only see data relating to the study ID, not personal information. Data, samples and information provided to those outside the direct study team, such as statisticians, laboratory staff, steering committee and safety advisory panels, will be de-identified and coded with the study ID.

Your de-identified information will also be provided to an online platform hosted in the United Kingdom by Sealed Envelope Ltd, a copy contracted by the research group to perform the randomisations. Sealed Envelope custom designed the randomization system for our research needs. The information provided to Sealed Envelope includes your study number, first and last initial, date of birth, gender, coded site name, and basic assessment details. Your data will be held securely by Sealed Envelope in accordance with applicable United Kingdom and Australian privacy laws.

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.

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 health records from other health services if they are relevant to your participation in this research project.

If relevant, information about your participation in this research may be recorded in your health records. For example, a copy of your signed consent form may be uploaded into your hospital or medical center file if deemed necessary and appropriate when accessing your information from this facility.

In accordance with Australian and Queensland privacy and other relevant laws, you have the right to request access to personal information collected and stored by the research team. You also have the right to request any information which you disagree with be corrected. Please contact the study coordinator if you would like to access your information.

Complaints and Compensation

If you suffer any injuries or complications 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 medical 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.

Who is organizing and funding the research?

The study is being lead by Professor Jonathan Golledge, Director of the Queensland Research Centre for Peripheral Vascular Disease, James Cook University, Townsville, QLD, Australia.

There are no conflicts of interest (commercially or financially) for Professor Golledge and other principal investigators in this study. This study is not commercially sponsored. This study is an investigator led and sponsored study.

Further information and who to contact

Your Local Contact Person

Name	**Mrs Lisan Mulvey**
Position	**Trial Coordinator**
Telephone	**(07) 4433 1739**
Email	**Lisan.yip@jcu.edu.au**

In case of an **emergency or complaint** about this study please contact:

Name	Professor Jonathan Golledge
Position	Chief Principal Investigator
Telephone	0403840401
Email	jonathan.golledge@jcu.edu.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 approving this research and HREC Contact details

Reviewing HREC Name	The Townsville Hospital and Health Service Human Research Ethics Committee
Position	HREC Coordinator
Telephone	(07) 4433 1440
Email	TSV-Ethics-Committee@health.qld.gov.au

Local Research Governance Office (RGO) Contact details

	Townsville Research Education, Support and Administration (TRESA) Unit
Name	THHS Research Governance Officer
Position	
Telephone	07 4433 1351
Email	TSV-RGO@health.qld.gov.au

Consent Form - Adult providing own consent

Title	**MEtfoRmIn for Treating Peripheral Artery Disease-Related Walking Impairment**
Short Title	MERIT
Protocol Number	2.3
Chief Principal Investigator	Professor Jonathan Golledge
Site Principal Investigator	Professor Jonathan Golledge
Site Coordinator	Mrs Lisan Mulvey
Location	The Townsville Hospital

Declaration by Participant

- I have read the Participant Information Booklet 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 consent to the storage and use of blood samples taken from me for use, as described in the relevant section of the Participant Information Booklet for this specific research project
- I understand I may be approached and asked to consent to the information collected about me and my remaining samples (if any) being stored and used in other research projects after this study has completed. I understand this is optional and whatever I decide will not impact my participation in this study.
- I give permission for my doctors, other health professionals, hospitals or laboratories outside this hospital to release information to James Cook University and The Townsville Hospital concerning my disease and treatment for the purposes of this project. I understand that such information will remain confidential.
- I understand that, if I decide to discontinue the study treatment, I may be asked to attend follow-up visits to allow collection of information regarding my health status. Alternatively, a member of the research team may request my permission to obtain access to my medical records for collection of follow-up information for the purposes of research and analysis.

- 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.

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

Declaration by Member of the Research Team

Please tick: ☐ Trial Coordinator - ☐ Investigator - ☐ Healthcare Staff* - ☐ Other:

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

Name of Team Member (please print)	
Signature	Date

*Healthcare staff include doctors, nurses, health professionals and administration personnel who have been trained to consent participants into this study.

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