Participant Information Sheet

Study title

Study of metabolomics as a precision medicine tool (MetCYP).

Study Researcher

Chief Investigator – Professor Ewan Pearson
Principal Investigator – Dr. Mads Kjolby

We would like to invite you to take part in this research study

Before you decide whether or not to participate, we need to be sure that you understand firstly why we are doing the study and secondly what it would involve if you agreed to take part. We are therefore providing you with this information. Please take time to read it carefully, ask any questions, and, if you want, discuss it with others. We will do our best to explain and provide any further information you may ask for now or later. You do not have to make an immediate decision – you will have a minimum of 48 hours to decide.

This study is being sponsored by the University of Dundee. It is being funded by The Wellcome Trust. The study has been organised by Professor Ewan Pearson (Chief Investigator) and Dr Mads Kjolby (Principal Investigator).

What is the aim of this study?

Thank you for showing an interest in taking part in MetCYP. The invitation letter and summary study flyer you received told you briefly about the study.

There are several types of CYP enzymes in the liver, and they are involved in the metabolism (break down) of drugs. We are interested in a CYP enzyme called CYP2C9. We know approximately 4 in 100 people genetically have a rare form of CYP2C9 that reduces the function of the enzyme. You have been invited as you joined SHARE and you may have the genetic traits we are interested in.

People who carry the relatively rare form of CYP2C9 will be otherwise well but will not break down some prescribed drugs very effectively. This would result in an increased risk of side effects if they are prescribed some specific drugs. There are a number of drugs that are broken down by CYP2C9, including the common diabetes drugs called sulphonylureas (e.g. Gliclazide, Glipizide, Tolbutamide). In current practise of prescribing drugs, we do not measure CYP2C9 function, as this is not easily done, requiring a day long test with many blood samples.

Using a technique called metabolomics where multiple metabolites or markers are measured in the blood, we have recently discovered that certain markers ("metabolites") in the blood can potentially tell us how well CYP2C9 is working with a single blood test. In this study we wish to test whether a single blood sample with measurements of metabolites can replace the more extensive methods with several blood samples.

If the simpler test is valid, it can be used as a screening tool before starting medication and can help predict which drugs would be better for the individual with diabetes or other conditions.

What does this study involve?

The study will last about 2 -3 weeks in total, including the 3 visits outlined below. The time between study visits where the tolbutamide challenge is conducted (day 2 and 3 in table below), is a minimum of 1 week. A total of 24 people will be participating in the study.

During the study, you'll visit our research site 3 times - it's the Clinical Research Centre at Ninewells Hospital in Dundee. Your first visit will last about an hour. Your other 2 visits will last about 7 hours each. If you take any regular medications these will not change between visits. We also kindly ask that you do not drink alcohol 24 hours prior to each of the study visits as it may affect the results of the research tests.

The figure below outlines the 3 study visits; lunch will be provided after the tests in visits 2 and 3. You will have a comfortable hospital bed to lie on as well as TV and internet access.

Screening Visit	Tolbutamide challenge + Fluconazol	Tolbutamide challenge + Placebo
About an hour • Review study information • Sign a consent form • Check your medical history • Single blood test to check you are eligible	**About 7 hours** • You will fast from 9pm the night before and you will take 1 tablet of research medication • Arrive at clinical Research Centre at 8am • A drip will be placed in the back of your hand • You will take 1 tablet tolbutamide • You will empty your bladder • Blood samples will be taken at specified time intervals • Urine will be collected for 2x12 hours. • Lunch at the end of the test	**About 7 hours** • You will fast from 9pm the night before and you will take 1 tablet of research medication • Arrive at clinical Research Centre at 8am • A drip will be placed in the back of your hand • You will take 1 tablet tolbutamide • You will empty your bladder • Blood samples will be taken at specified time intervals • Urine will be collected for 2x12 hours. • Lunch at the end of the test

Will you take blood samples as part of this study?

Yes, this study involves taking blood samples. The blood test in visit one allows the team to check that you are safe to take part in the study. The blood tests in visits 2 and 3 are to check the pattern of the levels of tolbutamide in your blood. The study will involve taking around 300 ml of blood in total, this is less than a pint of blood. A pint of blood would be the volume you would give if you were to donate blood once.

All your blood samples from this study will be safely stored in special freezers. If you decide to participate in this study, once you have signed the consent form, you will be allocated a unique study ID. All your study tests will be stored under the study ID and will not use your name. Only members of our research team will be able to identify you from your study ID.

Visit One – Screening & Baseline Visit
About an hour.

We'll go over the study again with you; you will have plenty of time in this visit to ask any questions you may have. Then we'll take a few details about your health and what medications you're on. If you're happy to go ahead, we'll ask you to sign a consent form. We will then arrange your other two study visits with you at times that are convenient for you.

We'll take about 10ml of blood to check your levels of red blood cells, kidney-, liver function, and a pregnancy test. We'll also measure blood glucose. We'll check these results to make sure you can take part in the study. If your blood tests are not normal for any reason, we'll discuss this with you, and tell your GP if you consent. This may stop you taking part in the study.

We will supply you with 2 tablets of research medication (placebo/fluconazole), which is labelled "Research Medication #XXXX" and "Study Day 1" and "Study Day 2". #XXXX refers to your study ID. The order of fluconazole or placebo will be random (i.e. like flipping a coin) and you and the investigator will be blinded to which you will be taking on each day. This means, that neither you nor the study team knows the order of which tablet you have had on either of the two study days. We will, however, be able to decode the order of tablets ("fluconazole and placebo" or "placebo and fluconazole") after the study is completed.

Visits Two & Three
Around 7 hours
Visit Two and Three – tolbutamide challenge after placebo or fluconazole

If you consent and you would like, we can contact you the day before to remind you of participation and pretreatment.

You'll come to the research centre first thing in the morning (8:00 am.), having fasted overnight from 9pm the night before and have taken 1 tablet of research medication (placebo or fluconazole). You should have a snack just before your start to fast at 9pm. We encourage you to drink plenty of plain water while fasting.

We'll put a drip into your arm, this is known as a "cannula". Where we put the cannula depends on where your best vein is in your elbow or on your hand. A cannula is a fine plastic tube about 2cm long that is put into your vein using a needle. The needle is removed to leave the plastic tube in the vein. It might be a bit sore when the needle first goes in, like a small "pin prick". Sometimes it can take more than one attempt to put the cannula in so that it is safe and effective. The cannula won't hurt afterwards, if it does, please alert a member of the team. We will put a dressing on it to keep it in position. The drip in this test is to take blood samples from, so no need

for more needles. We will make every effort to make sure that you are comfortable and can move your arms and hands around as normally as possible.

We will take some blood samples at the start of this test to check your sugar, hormone and metabolite levels. We will also take a sample to analyse for a particular gene you possess (detailed later in this information sheet). You will then be given a glass of water (300ml, just less than a can of coke). Along with the water you will have 1 tolbutamide tablet. We are giving you the tolbutamide to test the function of your liver enzymes (CYP2C9).

Once you have had the tolbutamide tablet, we will monitor your blood levels for 6 hours by taking blood from the cannula we have inserted. You will be required to be at the hospital for approximately 7 hours for the blood sampling and initial urine collection. The urine collection will be continued after you leave the hospital, and can be done from your home. We will collect your urine in two periods from the beginning of the experiment and 12 hours. The following 12 hrs we will collect urine as well. In total, urine will be collected for 24 hours in a row at each of the two study visits. The urine collection will be completed in your home in the two containers we supply to you. The urine does not need refrigeration. We will arrange to pick up the urine from your home. At the end of the blood tests at each of these two visits, we will remove the cannula safely and hygienically. You are welcome to stay and relax before you travel home.

Contraceptive advice

If you are a woman of child bearing potential and are sexually active you must be willing to have pregnancy testing prior to study entry. Both tolbutamide and fluconazole are safe to use when pregnant. If you are pregnant you will not be able to take part in the study.

You must be willing to use a form of a medically approved birth control method:

- Combined Oral Contraceptive Pill
- Placement of an intrauterine device – 'coil'
- Barrier methods of contraception: male condom only
- Established use of oral, injected, transdermal or implanted hormonal methods of contraception
- Male partner sterilisation

If you are a sexually active man with female partner of child bearing potential, you will be required to use a form of medically approved birth control method as listed above.

What are the possible benefits of taking part?

You will get no clinical benefit from the tests performed during your 3 visits to the centre. On two of your visits, you'll be given a tolbutamide and a tablet to be taken the night before containing either fluconazole or placebo. Tolbutamide will be given at a very low dose. It's important you understand that we are giving you tolbutamide not to treat you, but for our research to gauge how well your CYP2C9 enzyme is working. You'll only get it twice as part of the research study. Fluconazole inhibits CYP2C9 function, and slows the metabolism of tolbutamide

down. We expect inhibition of CYP2C9 will alter the metabolites in your blood and also tolbutamide metabolism. This is to validate metabolomics (measuring your blood metabolites) as a method to determine CYP2C9 function independently of genetics.

However, your taking part will help our research. With the results from this study, we hope to improve our understanding of how best to use some drug treatments, including a common diabetes treatment. This may benefit you in the future, but not right away.

As a token of our appreciation and compensation for your time to take part in the study, the team would like to offer you vouchers of your choice for either Amazon or Tesco. You will receive a £25 for your time and attendance at the screening visit, and £75 for each of the two test visits (£175 in total).

The team realise that you will be travelling for appointments, therefore all reasonable travel expenses (e.g. petrol money, train and public transport fares, short distance taxis) will be reimbursed. Long distance taxi fares will not be reimbursed.

What are the possible disadvantages and risks of taking part?

Our team's priority is to make sure you are comfortable and safe throughout the study. You'll have a comfortable hospital bed to lie on, as well as TV and internet access. It's in your and the team's best interest to make sure you know all about any risks involved.

It is our duty to inform you of the risks involved before you decide whether to take part in this study. We will go over everything again in detail with you at the first visit, and if you would like to proceed with the study, we will ask you to sign a consent form.

You will not be able to get information on your samples or genetic information (e.g. CYP2C9 status).

Tolbutamide Medicine

Tolbutamide is a medicine commonly used to treat type 2 diabetes. Tolbutamide has been part of National and International guidelines for how we manage type 2 diabetes for some time, so we know it is safe to use.

The main risk of tolbutamide medicine is that it may make your blood sugar levels fall. In this study, we are using a single dose of tolbutamide which is equivalent to the lowest starting dose when treating diabetes patients. We'll monitor your blood sugar levels every 60 minutes during the study to make sure that we keep you safe. Tolbutamide have been used in similar studies and is rarely associated with any change in blood sugar. If your sugar level does drop too low, we will give you something sugary to eat or drink. If you have driven to the research centre, we will make sure that you are safe to drive before you leave.

Fluconazole Medicine

Fluconazole is an antifungal drug normally used for treatment of fungal infections in mouth, nail and skin. Fluconazole has been used for many years, and the side-effects known to be associated with longer term use of fluconazole include: mildly elevated liver enzymes if used for long periods of time (approx. 1 in every 10-100 people), diarrhoea (approx. 1in every 10-100 people), rash (approx. 1 in 10-100 people), hypersensitivity (approx. 1 in 80 people). You will only receive a single dose in the study and side effects are not expected.
The only medication you will have at your home is two tablets of "Research Medication" (see page 2), where one tablet contains 200 mg fluconazole and the other, placebo. Overdose is not possible in adults but the drug may interact with other medication. If the medication is ingested by mistake by another adult or child please contact us as soon as possible (contact information on page 10).

Regular medication

If you do use medication regularly, this can be taken as usual, with the exception of any morning medication on study visits (day 2 and 3). For medication to be taken in the morning, we will ask you to postpone to 9:00 am on the study visit days after we have initiated the study on that day.

Cannulas

As mentioned, the tests involve you having cannulas inserted. Sometimes if a cannula moves, or is not lying in the vein properly, the cannula will need to be removed and, if you're happy, re-inserted in another vein.

As a cannula involves making a break in the skin, there is always a risk that infection can get in. Our team will ensure that your skin is cleaned thoroughly before the cannula is inserted, it will be kept as clean as possible during the study. To ensure your safety, the cannula will be looked after in accordance with strict guidelines set out by NHS Tayside. If despite cleanliness infection occurs around the cannula site, you may require a course of antibiotics from your doctor, the research team will make a note of this. Our team will make every effort to ensure that your cannulas are kept as clean as possible.

Do I have to take part?

It is up to you to decide. Participation in this study is entirely voluntary and you are free to refuse to take part or to withdraw from the study at any time without having to give a reason and without this affecting your future medical care or your relationship with medical or nursing staff looking after you.
If you decide to/or have to withdraw from the study for any reason, with your permission, the data collected up until the point you withdraw will be used in the study analysis.
However, you can decide to withdraw your consent for the study at any time. If you decide to withdraw consent, then we will destroy all data and samples we have collected from you, they will not be used in the analysis.

What will be done with my blood samples?

We will store the blood samples for 5 years. We will share the samples with Metabolon (USA), who will analyse them for metabolites. Only study ID, and not personal details, will be shared. We will share samples with other

researchers and commercial companies for research purposes relating to this project, and for future related research projects.

Will my personal information be kept confidential?

Identifiable information about you and your collected study data will be stored locally and designated members of the research team will have access to this information.

For data management purposes, your anonymised coded study data will also be securely stored on a password-protected database(s) in the University of Dundee. Specified members of the data management team will also have access to your identifiable information.

Your data will be archived securely for at least five years after the end of study, after which it will be destroyed. Identifiable information about you will not be published or otherwise shared. Your anonymous study data may be shared with other researchers in the UK/EU/other.

If you opt out from participating in future research, the data and any remaining biological material (blood or urine) generated from this study will be destroyed 5 years after end of study.

General Data Protection Regulation for Healthcare and Research

How will we use information about you?

We will need to use information from your medical records for this research project.
This information will include your initials, name and contact details. 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 instead. We will keep all information about you safe and secure. To measure metabolites, and breakdown products of tolbutamide in your blood samples, we will send the samples to USA and Denmark, respectively. The only information that will be sent with samples are your anonymised StudyID number, which cannot be linked to your personal information. Thus, no person identifiable data will be sent outside UK. The collaborators must follow our rules about keeping your information safe and the destruction of your samples.
Once we have finished the study, we will keep some of the data so we can check the results. We will write our reports in a way that no-one can work out that you took part in the study.

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.
- 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.

- If you agree to take part in this study, you will have the option to take part in future research using your data saved from this study. Biological samples will be stored in the Tayside Biorepository.

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

You can find out more about how we use your information

- at www.hra.nhs.uk/information-about-patients/
- by asking one of the research team
- by sending an email to dataprotection@dundee.ac.uk, or
- by ringing us on +44 (0) 1382 383900.
- **www.hra.nhs.uk/patientdataandresearch**

Patient Advise and Support Service

The decision as to participate in the study or not, is entirely up to you. We are available for questions and further information, or you may want information from a person who is not part of the study. We have enclosed contact information from Patient Advice and Support Service in Scotland (https://www.cas.org.uk/pass) telephone at 0800 917 2127, or contact Dr. Anna Barnett, at Ninewells Hospital, a.l.z.barnett@dundee.ac.uk, for independent advice.

What if something goes wrong?

If you have any concerns about your participation in the study, you have the right to raise your concern with a researcher involved in conducting the study or a doctor involved in your care.

If you have a complaint about your participation in the study, you should first talk to a researcher involved in the study. However, you have the right to raise a formal complaint. You can make a complaint to a senior member of the research team or to the Complaints Officer for NHS Tayside.

Complaints and Feedback Team
NHS Tayside
Ninewells Hospital
Dundee DD1 9SY
Freephone: 0800 027 5507
Email: TAY.feedback@nhs.scot

In the event that you think you have suffered harm as a result of your participation in the study there are no automatic financial compensation arrangements. However, you may have the right to make a claim for compensation. Where you wish to make a claim, you should consider seeking independent legal advice, but you may have to pay for your legal costs.

Insurance

The University of Dundee is sponsoring the study. The University of Dundee maintains a policy of public liability insurance which provides legal liability cover in respect of damages, costs and expenses arising out of claims.

Tayside Health Board is a member of the NHS Scotland Clinical Negligence and Other Risks Insurance Scheme (CNORIS) which provides legal liability cover of NHS Tayside in relation to the study.

As the study involves University of Dundee staff undertaking clinical research on NHS Tayside patients, such staff hold honorary contracts with Tayside Health Board which means they will have cover under Tayside's membership of the CNORIS scheme.

UK travel insurers should not ask about, or take into account, participation in a clinical trial when underwriting a travel insurance application. Beyond the health condition (or conditions) that you have, participation in a trial does not affect your ability to get travel insurance.

Your data will remain confidential unless we, the Sponsor, are legally required to disclose information by Court order or by statute.

Who has reviewed this study?

The West Midlands – Solihull Research Ethics Committee, which has responsibility for scrutinising all proposals for medical research on humans, has examined the proposal and has raised no objections from the point of view on research ethics. It is a requirement that your records in this research, together with any relevant medical records, be made available for scrutiny by monitors by University of Dundee/Tayside Medical Science Centre and NHS Tayside, whose role is to check that research is properly conducted and the interest of those taking part are adequately protected.

What happens next?

We thank you for expressing your interest for further information with regards to the study. We will contact you via phone after you have had a couple of days to review the information. If you are interested to participate, we will to arrange for you to come for visit 1. At this visit we will go through the study with you in person and give you time to ask any questions you may have. We will check your medical history and the blood tests outlined in "Visit 1" in this information sheet to make sure you are safe to participate. If you are happy to proceed, we will ask you to sign a consent form. We will then arrange the other study visits to suit you.
At the end of the entire study you may get a copy of the scientific publication if you wish so.

COVID-19 and trial participation

To protect you, all study activities will adhere to Scottish Government guidance and local NHS Tayside infection control procedures with relation to COVID-19. 48 hours prior to study, a member of study team will contact you to complete a COVID-19 questionnaire with regards to screening for symptoms and/or contacts you may have

had who had a COVID-19 infection. We will ask you to check your temperature 48 hours prior to the study visit, and on study visit days, you will have your temperature checked by a member of the study team. If you develop a temperature or your COVID-19 questionnaire suggests you are at high risk of infection we will reschedule the study visit and ask that you follow the government guidelines regarding self-isolation an COVID testing.

Contact details for further information.
If you have any further questions or you would like to arrange to speak with the study doctor please contact us using the details below.

For further contact please contact:

Dr Mads Kjolby

Principle Investigator

Professor Ewan Pearson

Chief Investigator

Ninewells Hospital and Medical School

Dundee DD1 9SY

Tel: 01382 383387 (external)

Email: mkjoelby001@dundee.ac.uk E.Z.Pearson@dundee.ac.uk

Thanks for taking time to read this information and for considering participating in this study.
If you would like more information or want to ask questions about the study, please contact the study team using the contact details above. You can contact us Monday – Friday between 09:00-17:00.