PARTICIPANT INFORMATION SHEET

Clinical Study of UMOD NKCC2 interaction on salt-sensitivity in hypertension

Prof Sandosh Padmanabhan, Prof David Webb, Prof Tom MacDonald

Invitation to Participate

You are being invited to take part in a research project. Before you decide, it is important for you to understand why the research is being done and what it will involve.

- Section one tells you the purpose of research and what will happen if you take part.
- Section two gives you more detailed information.

Please ask 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 and discuss with family or friends if you would like to. Thank you for reading this leaflet

SECTION ONE: Study Information

What is the purpose of the study?

Hypertension (high blood pressure) is the leading risk factor for the development of cardiovascular disease (CVD) including heart attack, heart failure, stroke, and kidney disease.

Drug therapy is the most common form of treatment and there are five main classes of drugs used to reduce blood pressure and reduce the risk of heart attacks and strokes. Currently the choice of initial drug(s) is based upon a person's age and ethnic background. Despite the availability of numerous blood pressure lowering drugs, only about half the patients prescribed a particular drug will respond to it and only 1 in 3 people with hypertension have their blood pressure controlled to target (<140/90 mmHg).

There is research evidence that a single letter change in the DNA makeup (genetic code) of an individual can influence the level of a protein called uromodulin present in the urine. Whilst this has no major impact on health, slightly higher levels of the protein may make the individual more responsive to a specific type of blood pressure lowering drug (water tablets) called loop diuretics.

This research project aims to test if patients with uncontrolled blood pressure may respond better to a blood pressure lowering drug, Torasemide, based on a single letter change in their DNA. Torasemide is a loop diuretic (water pill) which is approved, in the UK, for the treatment of high blood pressure, but not commonly used. We aim to develop a test to predict if patients with specific genetic markers will respond or not, to loop diuretics.

We aim to enrol 240 participants into the research study who have blood pressure which is not controlled on one or more blood pressure lowering medications.

Why have I been invited?

You have been invited because you have been identified from information from UK Biobank, SHARE register, GoDARTS study, your GP surgery or your local blood pressure clinic as having high blood pressure and you are taking one or more blood pressure lowering medications.

If you have been invited via UK Biobank or SHARE then you may have been chosen because you are known to have a particular DNA letter change or you may have been chosen because you are known to have high blood pressure. You will still have your DNA tested by the study team as detailed below.

Who is doing the research?

The research is being done by doctors who are high blood pressure specialists at three Scottish university hospitals: Prof Sandosh Padmanabhan (University of Glasgow), Prof David Webb (University of Edinburgh) and Prof Tom MacDonald (University of Dundee).

Do I have to take part?

No. Your participation is entirely voluntary. Your decision to participate or not will not affect you or your medical care. If you decide not to take part, you do not need to tell us why. If you do decide to participate, you are free to withdraw your consent, without telling us why, and to discontinue participation at any time without prejudice. This will not affect your medical care.

What will happen to me if I take part in the UMOD study?

The study will be in two parts.

Part one of the study will involve some tests to check if you are suitable to take part.

In part two of the study you will undergo some further tests and take the study medication for 16 weeks. These tests are detailed in section 2 of this information sheet. You will be assessed by the team at various points during the 16 weeks and at the end you will repeat the tests again.

SECTION 2: Study procedures

What do I have to do?

Firstly, you will register your interest about the study either by accessing the study website (www.bhfumod.co.uk) or by paper consent provided by your study nurse (inset local nurse telephone number and/or email).

Part 1 of the study

If you are interested in participating the first step would be to register on the study website (www.bhfumod.co.uk) and complete your initial consent and personal details. If you have any

question about screening or participation please contact the study team in Glasgow on 0141 232 7600.

Or you can complete your initial consent in paper form at your study centre and provide your study nurse with your details. During this screening visit you can ask any questions you may have about screening and participation in the study.

You will have some tests to check if you are suitable to take part in the study. The first of these tests is checking your blood pressure at home (referred to as home blood pressure monitoring or HBPM). For this, you will be sent a home blood pressure monitor. (or you can collect from your local GP surgery or blood pressure clinic). The home blood pressure monitor is an electronic device similar to that used in the GP surgery, or clinic, and has clear instructions with it on how you can measure your blood pressure. You will either enter the readings on the website or telephone/email your study nurse with the readings. You are welcome to keep the blood pressure machine after the study if you are eligible to participate in part two the study. If you are not able to participate in part two of the study, we kindly ask that you return the home blood pressure monitor or by post in the envelope provided.

The second test involves checking your DNA to ensure you have the correct letter type that is required for the study. For this you will be sent a salivary kit and clear instructions. When we have sent the DNA kit one of our research team will follow up with a phone call to check you have received this, are happy with the instruction or if you want to ask any questions. You will be provided a stamped addressed envelope to return the saliva sample to the Glasgow team for DNA testing. We shall test the DNA then a member of the study team will contact you, by your preferred method (telephone, email) to arrange a suitable appointment at the study centre to discuss part two.

If your blood pressure monitoring and/or DNA analysis determine that you are not able to participate in the study, we will write to you to let you know and thank you for your interest in our research.

Part 2 of the study

For those eligible to participate, at your first study visit you will have an opportunity to ask the research team any questions you may have about the study. The research team will then ask you to complete the main consent form for the study and ask questions about your medical history. Your doctor may also wish to perform a clinical examination (listen to your heart and lungs) and/or carry out an ECG, looking at your heart's rate, rhythm and electrical activity. During the visit you will also have various other measurements (height, weight) and tests (bloods, urine and blood pressure).

If you meet the study entry requirements you will then be given the study drug which is Torasemide (5mg once per day) to take each day in addition to your usual medications. We recommend that you take this in the morning although you can take it at another time if this is more convenient. If you forget to take a tablet then take it as soon as you remember. However, it if it is nearly time for the next dose then skip the missed dose. Do not take a double dose to make up for a forgotten dose. If you are already on a drug similar to Torasemide, we will ask you to stop this for two weeks before starting Torasemide.

The UMOD study requires participants to take Torasemide for 16 weeks and during this time we would like to see you at your local study centre. We would make suitable appointments to see you

for 4-5 study visits, and would reimburse you for your travel expenses (up to a total of £40 in total for the duration of the study).

Prior to or during some study visits you will have your blood pressure monitored by ambulatory monitoring or home blood pressure. An ambulatory monitor is a blood pressure device/cuff which you wear for 24 hours and it automatically records every half hour during the day and every hour at night. Home blood pressure is the same as part 1 of the study. At the end of the study, your GP will continue to manage your blood pressure and you may keep the home blood pressure monitor.

What are the possible benefits of taking part?

There is little personal benefit to you however you will have your blood pressure monitored and reviewed by a specialist team. The information obtained will be extremely useful in shaping how patients with high blood pressure are treated in the future and used to improve medical knowledge.

Are there any risks involved?

There may be minor bruising at the site from which the blood sample is taken, some people feel faint or light-headed when having blood taken. If you have had a blood sample taken before then the procedure will be very similar. Ambulatory blood pressure monitors can be uncomfortable but is similar to having your blood pressure taken in the GP surgery; ambulatory blood pressure monitoring gives us lots of valuable information and more measurements than having your blood pressure monitored at the GP surgery.

What is the drug that is being used and what are the possible side effects of treatment?

Torasemide has been approved in the UK for treatment of high blood pressure and other conditions. It works by making you pass more urine so you may need to go to the toilet more often. However like all medicines Torasemide may cause other unwanted side-effects although not everyone gets them. The most common side effects that may affect up to 1 in 10 people are changes to the amounts of water, salt or minerals in your body. The signs of this may be headache, dizziness, particularly when standing up, and muscle twitching. If you feel dizzy you should not drive or use any tools or machinery. Other common side effects include loss of appetite, feeling sick or being sick. Other very rare side effects (affects less than 1 in 10 000) are allergic skin reactions, which can be serious, and sensitivity of the skin to sunlight or other sources of light such as sun-beds. Please speak to the study doctor if you think you have developed these or any other side effects.

You will be provided with an Alert Card which you should carry with you at all times while you are participating in the study. Please show the Alert Card to any Health Care Professional including doctor, nurse or pharmacist, who is caring for you.

Certain medicines, including a group of antibiotics called cephalosporins, should not be taken at the same time as Torasemide. With your permission we will write to your GP and advise that this be considered by your GP before they are used during the study. If these antibiotics are required we recommend that you stop the study medicine and let the study team know.

Can I become pregnant or breast feed during the study?

Torasemide, if taken during pregnancy might affect an unborn baby. Therefore, you must not take part in the study if you are breast feeding, pregnant, planning on becoming pregnant or are not using a reliable method of contraception. If appropriate we will advise you about contraception before you decided whether to take part in the study. A pregnancy test will be performed in women of child-bearing potential before starting treatment and at the end of treatment. If you do become pregnant during the study you should tell the study team immediately

Can I withdraw from the study?

Yes, you can withdraw from the study, at any time, without having to tell us why. This would not affect the standard of care you receive or your future treatment.

What happens at the end of the study?

Your participation in the study will end after 16-18 weeks. At the end of the study you will be assessed by a doctor from the study team who will discuss ongoing treatment options for your high blood pressure. Your GP will continue to manage your high blood pressure and will be provided with a letter at the end of the study period. Whilst Torasemide is approved for use in the UK for treatment of hypertension it may not be available after completion of the study and approval for prescribing would be required on a case by case basis. Other medicines though that have a similar action are available without restriction and may be an option for ongoing treatment.

What will happen to my blood, DNA and urine samples at the end of the study?

We would like to use your anonymised clinical information collected in this study and keep any left-over blood, DNA and urine samples for use in other studies related to high blood pressure or cardiovascular disease in the future. This means that you cannot be identified from any of the information or samples retained and that the samples can be used for other tests in other research studies undertaken by the investigators of the BHFUMOD study. Any additional tests or studies carried out using your samples will be authorised by the research ethics committee and NHS research and development department prior to the testing being carried out.

We will ask for your consent to use and retain this information. If you do not wish your information and samples to be retained for this purpose then you do not have to consent to this, your participation in the current BHFUMOD study will not be affected.

Will my GP be informed that I am taking part in the study?

With your agreement, we will inform your GP by letter.

What if there is a problem or if something goes wrong?

Any complaint will be addressed. If you wish advice from a doctor who is independent and not part of this study, please contact Dr Craig Harrow who is another blood pressure/stroke specialist at the Queen Elizabeth University Hospital and University of Glasgow, 0141 2111000 (switchboard).

In the event that something does go wrong there are no special compensation arrangements. If you are harmed and this is due to someone's negligence then you may have grounds for legal action against NHS Greater Glasgow and Clyde but you may have to pay for your legal costs. The normal National Health Service complaints mechanism will still be available: http://www.nhsggc.org.uk/get-in-touch-get-involved/complaints/

Will my taking part in the study be kept confidential?

All personal information collected about you during the study will be kept strictly confidential. You will be assigned a unique study number which will be used to identify your samples so that all analyses will be carried out anonymously. Personal data will be stored only in paper form (consent form) and study data will be kept separate from the paper forms on a password protected computer. If you consent to take part in the study, the investigators will look at your medical records where this relates to your participation. Members of the Ethics Committees, Regulatory Authorities and representatives of the Sponsor, NHS Greater Glasgow and Clyde may also review your medical records, where this relates to your taking part in the study, to ensure the proper conduct of the study. Your records will not be used for any other purpose or be disclosed to anyone else without your permissionAny report or publication of research will not contain any information from which participants can be identified.

What will happen to the results?

Results will be used to try to improve services for patients with high blood pressure. Anonymised results will be published in medical journals and presented at medical conferences.

Who is funding this study?

This research study is being funded by a research grant from the British Heart Foundation (CS/16/1/31878) led by Professor Sandosh Padmanabhan.

Who has reviewed the study?

Members of the West of Scotland Research Ethics Committee 5 have reviewed the study (16/WS/0160).

Contact for further information

For further information about this study, or any information you may have about it please contact the Glasgow study team, 0141 2327600 (Glasgow Clinical Research Facility). This leaflet if for you to keep and if you agree to take part in the study a copy of the signed consent form will be given to you to keep.

If you would like independent advice regarding this study you can contact Dr Craig Harrow who is a stroke and blood pressure specialist who is not involved in this study (0141 2112000, Queen Elizabeth University Hospital switchboard).

Finally thank you for taking the time to read this information leaflet and considering taking part in the study; please contact us with any further questions/queries**.**