

**Royal Perth Hospital**

**PARTICIPANT INFORMATION SHEET**

***Project Title:*** *Assessment of extra-renal effects of SGLT2-inhibitors in anuric haemodialysis patients using microneurography*

***Chief Principal Investigator:*** *Dr Srivathsan Thiruvengadam*

***Principal Investigator:*** *Dr Awf Abdulrahman Shaban*

You are invited to take part in this research because you have been diagnosed with end stage renal failure and are undergoing hemodialysis as part of your treatment. This research aims to assess whether empagliflozin, a medication ***approved for treatment of type 2 diabetes***, decreases the activity of the Sympathetic Nervous System (SNS); the part of the nervous system responsible for the fight or flight response. Note, Empagliflozin is ***not currently approved*** in Australia as a medication ***to decrease the activity of the SNS***. Therefore, use of empagliflozin in this study is experimental.

This information sheet explains the study and describes what will be involved should you decide to participate. Please read the information carefully and ask any questions you might have. You may also wish to discuss the study with a relative, friend or your GP.

**BACKGROUND AND PURPOSE**

In a recent, large study the medication empagliflozin used to treat type 2 diabetes was shown not only to improve blood sugar levels but to reduce the relative risk of death resulting from cardiovascular causes (heart attack and heart failure). While it is understood that empagliflozin lowers blood sugar levels by increasing the amount of sugar that is removed from the body via the urine, it also has effects on other organs such as the brain, heart and liver which may play a part in reducing SNS activity and improving cardiovascular risk. These effects were shown in diabetic and non-diabetic patients. This project therefore focuses on the ‘basic science’ or understanding another mechanism of action of Empagliflozin.

Over-activated Sympathetic system is linked to many disease states including diabetes, heart failure and obesity. Emerging evidence suggests that empagliflozin may also reduce the activity of the SNS, possibly explaining the finding of improved cardiovascular outcomes in diabetic patients in the recent trial. It is currently unclear regarding the significance of empagliflozin’s effect on organs outside of the kidney. By testing the impact of empagliflozin on patients with end stage renal failure who do not produce urine (anuric), it will be possible to estimate these extra-renal effects as without significant urine production there will be no increase in glucose loss from the kidney. This study has therefore been designed to assess the effectiveness of empagliflozin in reducing sympathetic nerve activity (blood pressure, weight, blood sugar levels, etc) in 20 individuals with end stage renal failure who are anuric. The Therapeutic Goods Administration (TGA) recommends that Empagliflozin is not used in people with severe renal impairment (eGFR <30). This study aims to provide more data on the safety of this medication in this population, in addition to other expected benefits.

Dobney hypertension Centre and East Metropolitan Health Service will provide in kind support for the study This study is designed by Dr Srivathsan Thiruvengadam and Dr Awf Abdulrahman Shaban of the Nephrology Department.

**WHAT PARTICIPATION IN THE STUDY INVOLVES**

If you agree to participate, we will ask you to sign the consent form at the end of this document. No study assessments or procedures will be performed prior to your written consent. If you decide to participate in this study your study doctor will inform your local doctor, with your permission. After signing the consent form, you will be asked to undergo tests as described below. This is considered as a **screening visit**; and will be done while you are having your regular dialysis. The screening visit will include medical history, clinical examination and vital signs, electrocardiogram, and pregnancy test if applicable.

Pathology will be done as part of standard of care on dialysis days.

The total duration of participation in this project is approximately 6 weeks. This will comprise:

* x1 baseline visit
* x2 follow-up visit at 3 and 6 weeks
* All visits will be on non-dialysis days and be conducted at Royal Perth Hospital Research Foundation building.

This study follows a ‘prospective cohort design’ with diabetic and non-diabetic arms. This means that you will receive empagliflozin 25mg/daily for six weeks, starting on the day of the initial baseline visit.

**Screening Visit**

Screening visit will be done while you are having your regular dialysis.

* Your personal information, medical history, medication use, and current health status will be recorded.
* A physical examination will be conducted by a study doctor (e.g., the doctor will listen to your heart and lungs).
* Your physical measures: height, weight, hip, neck and waist circumference etc. will be recorded.
* A fasting blood sample will be drawn as part of standard of care to exclude any relevant medical condition

You will be asked to attend Royal Perth Hospital Research Foundation building. having fasted for 12 hours.

* Seated office Blood Pressure (BP) and Heart Rate (HR) will be recorded in both of your arms. Three or more consecutive measurements will be taken in the arm with highest BP after a 5-minute rest period. Standing blood pressure measurements will also be recorded.
* If you are a woman of childbearing potential, you will be provided with a pregnancy test to ensure you are not pregnant prior to inclusion in the study.
* An electrocardiogram (ECG) test will be performed to assess the electrical activity of your heart. Small gel stickers will be placed on your chest, arms and legs, attached via a series of cables to the ECG device which will record your heart’s activity over a short period of time (less than 1 minute).
* *Central BP:* Central BP measurements will be obtained using an automated arm blood pressure cuff, programmed to inflate on four occasions over a period of ten minutes. This will be done via ambulatory home BP monitor that will last for 24 hours and collected back from participant on next dialysis session.
* *Nerve recording (Microneurography)*: Two tiny, sterile electrodes (less than 1/2 mm in diameter) will be inserted into your leg. One of the electrodes will serve as a reference that will only need to pass through the skin while the other will be carefully aimed at a large nerve that passes near the surface of the skin just behind the knee. When the electrode is placed close to or in the nerve you will be able to hear and see on a monitor the activity of your ‘excitatory’ or sympathetic nervous system. This procedure is called microneurography. It has been safely practiced since the 1970’s and is in use around Australia. The electrodes will be removed within a minute once the recording is finished. This will be done while you are lying in semi-sitting position.
* *Heart Rate Variability (HRV)*. During the nerve recording we will monitor your blood pressure (using a small cuff placed around your finger), the activity of your heart (ECG, by placing 3 ECG stickers on your chest) and your breathing rate (using a respiratory belt placed around your chest).
* *Empagliflozin administration:* You will be given the first dose of empagliflozin 25mg as a tablet, and you will be monitored for 90 minutes after taking this tablet. After this monitoring period, microneurography will be repeated a 2nd time as explained above. Empagliflozin 25mg is to be taken daily for 6 weeks following the initial dose and will be ceased after the follow-up visit. If you forget to take the morning dose it can be taken at any time that day up till 8 pm. If forgotten for the whole day DO NOT take 2 doses the next morning. Please note date of missed dose.

We will ask you to perform a series of tests during the nerve recording which will assess the response of your excitatory system to each test. They will include:

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* *Handgrip Test (HGT)*

Using a small handheld device that measures force you will be asked to sustain a handgrip of 30% of your maximum voluntary contraction for 3 minutes.

* *Mental Stress Test (MST)*

You will be asked to do serial subtractions as fast as possible for 3 minutes.

* *Cold Pressor Test (CPT)*

Your hand will be submerged in ice-cold water for 1-2 minutes. You will be encouraged to keep your hand submerged for the 2-minute period however you are free to remove your hand from the water whenever you feel necessary. This test is not painful but may be uncomfortable.

**Follow-up Visits (approx. 3 hours)**

You will be asked to attend Royal Perth Hospital Research Foundation building, where you will be asked to undergo the following:

* *Central BP, as previously described*
* *Nerve recording (Microneurography), as previously described*
* *Heart Rate Variability (HRV), as previously described*

**POSSIBLE SIDE EFFECTS AND RISKS**

Medical treatments often cause side effects. You may have none, some or all of the effects listed below, 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 will also be looking out for side effects.

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

Based on our previous experience with the types of procedures used in this study, the likelihood of severe side effects is considered low. Nevertheless, you may want to consider taking any risk in the absence of direct benefits for your own health. The most serious one, but very rare one, is **ketoacidosis**. It occurs when the body starts breaking down fat at a very high rate. The liver processes the fat into a fuel called ketones, which causes the blood to become acidic. **This side effect can be avoided if you avoid taking the medication while fasting, vomiting, or sick (sick day rules).** We provide further details and estimated rates of risk for individual procedures below which are based on our own experience and review of the literature:

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| **Potential Risk** | **% likelihood occurrence** |
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| **MICRONEUROGRAPHY** *If you experience any discomfort or have any concerns following the nerve recording procedure please contact Winthrop Professor Markus Schlaich on (08) 9224 0382.*  |
| Mild discomfort or pain at the site where the microelectrode is inserted | < 1 in 4 or 25% |
| Temporary paraesthesia (abnormal sensation of the skin such as numbness, tingling, tickling, prickling, or burning) in the lower leg where microneurography has been performed | <1 in 33 or 3% |
| **HRV TEST** |
| Pain due to the blood pressure cuff or electrical monitor wrapping around your arm or fingers | < 1 in 20 or 5% |
| Bruising from the blood pressure cuff | < 1 in 20 or 5% |
| Skin reaction from the adhesive used to attach electrodes to skin | < 1 in 50 or 2% |
| **COLD PRESSOR TEST** |
| Pain associated with having hand in cold water for 1-2 minutes | < 1 in 5 or 20% |
| Raynaud phenomenon in susceptible subjects (temporary pain, tingling, numbness) | < 1 in 20 or 5% |
| **CENTRAL BP MEASUREMENTS** |
| Discomfort / Pain due to the blood pressure cuff wrapping around your arm or leg | < 1 in 20 or 5% |
| Bruising from the blood pressure cuff | < 1 in 50 or 2% |
| **USE OF EMPAGLIFLOZIN 25MG/DAILY** |
| Genital burning, redness, pain or discharge associated with a genital yeast infection  | < 1 in 5 or 20% |
| Increase in frequency and/or volume of urination | < 1 in 5 or 20% |
| Symptoms of low blood sugar including sweating, weakness, hunger, dizziness, trembling etc. | < 1 in 50 or 2% |
| Ketoacidosis | < 1 in 25 or 4% |
| However, side effects related to Empagliflozin are less likely to happen in this study cohort with anuria (less than 100 ml of urine per day) |

**Pregnant Women:**

The effects of Empagliflozin and the adrenaline/noradrenaline spillover and renal blood flow measurements on the unborn child and on the newborn baby are not known. Because of this, it is important that research project participants are not pregnant or breast-feeding and do not become pregnant during the course of the research project. You must not participate in the research if you are pregnant or trying to become pregnant, or breast-feeding. If you are female and childbearing is a possibility, you will be required to undergo a pregnancy test prior to commencing the research project.

If you do become pregnant whilst participating in the research project, you should advise your study doctor immediately. Your study doctor will withdraw you from the research project and advise on further medical attention should this be necessary. You must not continue in the research if you become pregnant.

**POSSIBLE BENEFITS**

Potential benefits to you may include a reduction in weight and/or blood pressure levels which could result in a reduction of the risks of heart attack and stroke. We cannot guarantee that you will receive any benefits from your participation in this study. Information gained from this study may benefit others in the future.

**PRIVACY AND CONFIDENTIALITY**

The information gathered about you by the investigator or obtained during this study will be held by the investigator in strict confidence as far as the law allows. All the people who handle your information will comply with the Commonwealth Privacy Act 1988. If the results of the trial are published in a medical journal, as is intended, no reader will be able to identify individual patients.

**WHAT IF SOMETHING GOES WRONG?**

In the event that you suffer an expected or unexpected side effect or medical accident during this study that arises from your participation, you will be offered all full and necessary treatment by Royal Perth Hospital. Participation in this project does not alter any right to compensation that you may have under statute or common law.

**COSTS TO PARTICIPATION**

There is no cost to you to participate in this study. You will not receive any payment for participating in this study. All tests and medical care required as part of the study project will be provided to you free of charge.

As you need to fast for 12 hours prior to your Baseline visit, a meal will be served at the end of this visit. Reasonable expenses associated with participation in this project will be reimbursed i.e. travel, parking, etc.

**VOLUNTARY PARTICIPATION AND WITHDRAWAL**

Participation in this study is entirely voluntary. You do not have to participate if you do not want to and your decision to participate or not will in no way affect your current or future care at Royal Perth Hospital. You are also free to withdraw from the study at any time without reason or justification. Data collected up until the time of withdrawal will continue to be used in the study.

**CONTACTS FOR FURTHER INFORMATION**

If you have any questions about this study, please contact the Principal Investigator Dr Awf Abdulrahman Shaban on (08) 9224 2244 at the Royal Perth Hospital.

This study has been approved by the Royal Perth Hospital (RPH) Human Research Ethics Committee. If you have any concerns about the conduct of the study or your rights as a research participant, please contact the East Metropolitan Health Service (EMHS) Research Ethics & Governance Unit on (08) 9224 2260 or email EMHS.REG@health.wa.gov.au and quote the ethics approval number RGS0000003840.



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**CONSENT FORM**

***Project Title:*** *Assessment of extra-renal effects of SGLT2-inhibitors in anuric haemodialysis patients using microneurography*

***Chief Principal Investigator:*** *Dr Srivathsan Thiruvengadam*

***Principal Investigator:*** *Dr Awf Abdulrahman Shaban*

I, …………………………………………... agree to participate in the above study.

I have been provided with a copy of the Participant Information Sheet explaining the study which I have read and understood.

I have been given the opportunity to ask questions about the study by the Investigator and any questions have been answered to my satisfaction.

I understand that I may withdraw from the study at any time without affecting any future medical treatment, or the treatment of the condition which is the subject of the study.

I am aware that all research data collected will only be used for the purpose of this study and will be kept confidential as far as the law allows and that my participation will not be disclosed without my consent.

I understand that I will be given a signed copy of this document to keep.

Signed …………………………………………... Date ……………………

Signature …………………………………………... Date ……………………

of person obtaining consent

Name ……………………………………….

of person obtaining consent



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**FORM FOR WITHDRAWAL OF PARTICIPATION**

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**Declaration by Participant**

I wish to withdraw from participation in the above research project and understand that such withdrawal will not affect my routine treatment, my relationship with those treating me or my relationship with **[insert site name]**. I understand that data collected up until the time of withdrawal will continue to be used in the study.

Name of Participant \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

(please print)

Signature \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ Date \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

In the event that the participant’s decision to withdraw is communicated verbally, the Study Doctor/Senior Researcher must describe the circumstances:

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**Declaration by Study Doctor/Senior Researcher†**

I have given a verbal explanation of the implications of withdrawal from the research project and I believe that the participant has understood that explanation.

Name of Study Doctor/Senior Researcher \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

(please print)

Signature \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ Date \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

†A senior member of the research team must provide the explanation of and information concerning withdrawal from the research project.