**A randomized controlled clinical trial to assess the effect of dapagliflozin on renal and cardiovascular outcomes in patients with severe chronic kidney disease
(The RENAL LIFECYCLE Trial)**

**Participant Information Sheet/Consent Form**

Interventional Study – Adult providing own consent

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| **Australia Project Sponsor** | The George Institute for Global Health | **Global Project Sponsor** | University Medical Center Groningen |
| **Global Chief Investigator** | Professor Ronald Gansevoort | **Australian Chief Investigators** | Professor Sunil Badve and Associate Professor Clare Arnott |
| **Local Principal Investigator** | *[Insert PI Name]* | **Site/Hospital Name**  | *[Insert Site name ]* |

You are invited to take part in a research study called The RENAL LIFECYCLE Trial. You are being asked to participate because you have been diagnosed with severe chronic kidney disease.

**Why are we doing this study?**

People with severe chronic kidney disease are at a risk of developing chronic kidney disease complications including kidney and heart failure. Research has shown that it may be possible to reduce the risk of these complications by using a medication called sodium glucose co-transporter 2 (SGLT2) inhibitor, which act in your kidneys to lower sugar levels in your blood. The aim of the RENAL LIFECYCLE Trial is to see whether the SGLT2 inhibitor, dapagliflozin, can slow the loss of kidney function and heart failure in patients with chronic kidney disease, including dialysis and kidney transplant patients.

**What does the study involve?**

* If you agree to take part in this study, the study team will invite you to attend a screening visit to check whether you are eligible to participate and if you are, you will be asked to sign the study Consent Form.
* You will then be randomised to the study. This means that you will be placed into one of two groups (dapagliflozin or placebo) using chance (like tossing a coin).

From your randomisation visit, you will be required to take dapagliflozin or placebo (depending on the group you are placed in) once a day, for the duration of the study (about 4 years). After the randomisation visit, you will be followed-up at two weeks, three months, six months and six monthly thereafter: all visits are face-to-face at your hospital and can often be combined with your normal hospital visits. Most visits will take a maximum of one hour. An overview of the study visits is outlined in the image below:

You are also invited to undergo an optional MRI (magnetic resonance imaging) and an echocardiogram of your heart, to see the effect of the medication on your heart. The MRI will be taken at a scanning centre located within an hour’s drive of your hospital. This scanning center has been selected and engaged by the Sponsor to perform these tests. The echocardiogram will be completed in your hospital during your study visit. You are also invited to complete an optional cognitive function test to see the effect of the medication on your thinking and movement speed. This test is completed at your hospital during your study visit.

Please note you can leave the study at any time if you or your doctor/medical specialist want you to. Your choice will not affect the care you get from your doctors and nurses.

**What are the risks?**

All medical treatments involve some risk of harm. The common known risks of dapagliflozin include genital yeast infection (thrush), passing more urine, headache and backpain. Uncommon, rare and very rare side effects include dehydration, diabetes ketoacidosis (the body produces excess blood acids, called ketones) and necrotising fasciitis (soft tissue infection of the genitals). If you get put in the placebo group, the chance of heart failure or kidney failure might be higher. You will be monitored closely by your study doctor to minimise this risk. There are more details about the risks in the following document.

**How will my confidentiality be protected?**

All information collected from you will be treated confidentially and stored securely. In any study reports or publications your identity will remain confidential.

# Table of Contents

[Table of Contents 2](#_Toc160008442)

[1 Introduction 3](#_Toc160008443)

[2 What is the purpose of this research? 3](#_Toc160008444)

[3 What does participation in this research involve? 4](#_Toc160008445)

[4 What do I have to do? 7](#_Toc160008446)

[5 Will I be paid? 8](#_Toc160008447)

[6 What are the possible benefits of taking part? 8](#_Toc160008448)

[7 What are the possible risks and disadvantages of taking part? 8](#_Toc160008449)

[8 What will happen to my test samples? 10](#_Toc160008450)

[9 What if new information arises during this research study? 10](#_Toc160008451)

[10 Can I have other treatments during this research study? 10](#_Toc160008452)

[11 Do I have to take part in this research study? 10](#_Toc160008453)

[12 What are the alternatives to participation? 11](#_Toc160008454)

[13 Can I withdraw from the study? 11](#_Toc160008455)

[14 Could the study be stopped unexpectedly? 11](#_Toc160008456)

[15 What happens when the research study ends? 11](#_Toc160008457)

[16 Confidentiality/Privacy 12](#_Toc160008458)

[17 What happens with the results? 12](#_Toc160008459)

[18 Compensation for injuries or complications 12](#_Toc160008460)

[19 Who is organising and funding the research? 13](#_Toc160008461)

[20 COVID-19 13](#_Toc160008462)

[21 Further information and who to contact 13](#_Toc160008463)

# Introduction

You are invited to take part in a research study called The RENAL LIFECYCLE Trial. You are being asked to participate because you have been diagnosed with severe chronic kidney disease. The research study is testing a new treatment for reducing the occurrence of kidney and heart failure in people with severe chronic kidney disease, including dialysis and kidney transplant patients. The treatment is called dapagliflozin (Forxiga®), a medication usually used in people with diabetes. This medication is known as a sodium glucose co-transporter 2 (SGLT2) inhibitor.

This Participant Information Sheet/Consent Form tells you about the research study. It explains the tests and treatments involved. Knowing what is involved will help you decide if you want the participant to take part in the research.

Please read this information carefully. Ask questions about anything that you don’t understand or want to know more about. Before deciding whether or not to take part, you might want to talk about it with a relative, friend or your usual doctor.

Participation in this research is voluntary. If you do not wish to take part, you don’t have to. You will receive the best possible care whether or not you take part.

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

* Understand what you have read
* Consent to taking part in the research study
* Consent to having 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 Participant Information Sheet and Consent Form to keep.

# What is the purpose of this research?

Chronic kidney disease is a common illness, affecting 10% of the adult population worldwide. The most common causes of chronic kidney disease are diabetes, hypertension, and chronic glomerulonephritis(the long-term inflammation and scarring of the glomeruli, which are tiny blood vessels in the kidney that filter blood and produce urine). People living with chronic kidney disease are at high risk of serious complications such as kidney failure and heart failure.

Current treatment of chronic kidney disease includes blood pressure control as well as blood sugar control in people who also have type 2 diabetes. This helps to reduce the risk of developing chronic kidney disease complications. These treatments have been successful, but there remains a high number of people with chronic kidney disease who develop kidney failure and heart failure. Research has shown that it may be possible to reduce the risk of these complications by using an additional medication for people who develop severe chronic kidney disease, called a sodium glucose co-transporter 2 (SGLT2) inhibitor.

SGLT2 inhibitors act in your kidneys, causing you to lose more sugar into your urine, which lowers the sugar level in your blood. They may also reduce your chance of developing a serious kidney or heart problem.

Research conducted in people with chronic kidney disease often excluded people with poor renal function (i.e., estimated glomerular filtration rate [eGFR] less than 25ml/min/1.73m2, dialysis patients and renal transplant recipients). People with poor renal function are at higher risk of kidney failure, heart failure and death. New research has shown that SGLT2 inhibitors may be effective in preventing kidney failure, heart failure and death in people with severe chronic kidney disease, including dialysis and renal transplant patients.

The RENAL LIFECYCLE trial is testing whether the SGLT2 inhibitor, dapagliflozin, can slow the loss of kidney function and heart failure in patients with severe chronic kidney disease, including dialysis and kidney transplant patients. We are also investigating the safety and how well you tolerate this drug.

Dapagliflozin is approved in Australia to treat type 2 diabetes, symptomatic heart failure with reduced ejection fraction (when your heart pump function is impaired) and in patients with chronic kidney disease (stage 2, 3, or 4) who are at risk of disease progression. However, it is not currently approved to treat people with severe chronic kidney disease who have an eGFR less than 25mL/min/1.73m2. Therefore, this study is an experimental treatment for dapagliflozin. This means that it must be tested to see if it is an effective treatment for people with severe chronic kidney disease, including dialysis and kidney transplant patients. This study will be conducted under the Therapeutic Goods Administration (TGA) Clinical Trials Notification (CTN) Scheme. This allows the investigators to use this product for medical research purposes once the research has been assessed and approved by an authorised Human Research Ethics Committee (HREC).

This study is being conducted at 10-15 hospitals across Australia and in multiple sites across Europe. Approximately 1500 participants will be recruited for this study from Australia, The Netherlands, Germany, and Belgium. In Australia, we expect 250 participants will join the study.

This research has been initiated by Professor Ronald Gansevoort at the University Medical Center, Groningen (UMCG) in the Netherlands in collaboration with a team of doctors and researchers based at national and international healthcare facilities and universities. In Australia, this research is being conducted by Professor Sunil Badve and Associate Professor Clare Arnott at the George Institute for Global Health, an affiliate of the University of New South Wales, Australia.

This research has been funded in Australia by a National Health and Medical Research Council (NHMRC) 2021 Medical Research Future Fund (MRFF) International Clinical Trial Collaborations (ICTC 21-1 Application 2015414).

# What does participation in this research involve?

If you decide to participate in this study, you will be participating in a randomised controlled trial. Sometimes we do not know which treatment is best for treating a condition. To find out we need to compare different treatments. We put people into groups and give each group a different treatment. The results are compared to see if one is better. To try to make sure the groups are the same, each participant is put into a group by chance (i.e., random).

This is a double-blind study. This means that you and the study doctor will not know which treatment you are receiving. However, in certain circumstances the study doctor can find out which treatment you are receiving. You will have an equal chance of receiving either the study medication (i.e., dapagliflozin) or a placebo. A placebo is a medication with no active ingredients. It looks like the real thing but is not. Each group will continue to receive standard care regardless of their treatment arm.

The study medication will be provided to you free of charge.

After the randomisation visit, you will be followed-up at two weeks, three months, six months and six monthly thereafter: all visits are face-to-face at your hospital and can often be combined with your normal hospital visits. Your participation in the study will last about 48 months (i.e., 4 years). However, the exact duration of the study may be shorter or longer than the intended 48 months, depending on, among other things, how quickly the total number of required participants can be included. Most visits will take a maximum of one hour.

The consent form (attached to this information sheet) must be signed before any study procedures or visits take place.

All study visits will take place at your hospital, with a member of the study team.

## Visit 1 – Screening Visit (-2 weeks)

If a study hospital staff team member thinks that this study may be suitable for you to take part in, you will be invited to attend a screening visit.

After you have signed the informed consent form the following screening tests will then be performed to check your suitability for the trial:

* You will be asked questions about your lifestyle, medical history, any medications you are taking.
* Measurement of blood pressure, heart rate, height, and weight.
* You will be asked to complete blood and urine tests.
* Blood or urine pregnancy test for people of child-bearing potential.

We may need more information from your general practitioner/medical specialist. We will only do this if it is in connection with your own safety. Examples of when we ask for more information are when your medication use is not completely clear or when we need more information about surgeries and/or treatment methods you have had in the past. We will inform you before we contact your general practitioner and/or treating medical specialist.

If the results of the screening tests indicate that the study is not suitable for you, you may be eligible to repeat the screening tests after one month at the study doctor’s judgment. If you are eligible to rescreen you will need to sign a new consent form and you will receive a new participant ID. If you meet all entry criteria, you can proceed to the randomisation visit.

If the results of the screening tests indicate that the study is not suitable for you, you will not be able to take part. If this is the case, the study coordinator will discuss this with you and arrange for your regular health care to continue.

## Assessments completed at each study visit

* Review of your health since the last visit and if there have been any changes to your medications.
* Measurement of blood pressure, heart rate, and weight.
* You will be asked to complete a blood test.

## In addition, the following assessments will be completed at:

## Visit 2 – Randomisation Visit – Day 0

* You will be asked to complete a urine test.
* You will be asked to complete two questionnaires to assess your quality of life and your general health.
* You will have the option to complete two scans – a cardiac MRI and/or echocardiogram.
* You will have the option to complete a cognitive function test.

## Visit 3 – Week 2

* How many pills of the study medication you have taken since your last visit and if you have experienced any side effects. You will be asked to return any unused study medication including empty containers.

## Visit 4 – Month 3

* How many pills of the study medication you have taken since your last visit and if you have experienced any side effects. You will be asked to return any unused study medication including empty containers.
* You will be asked to complete a urine test.

## Visit 5 – Month 6

* How many pills of the study medication you have taken since your last visit and if you have experienced any side effects. You will be asked to return any unused study medication including empty containers.
* You will be asked to complete a urine test.
* You will be asked to complete two questionnaires to assess your quality of life and your general health.
* You will have the option to complete one scan – an echocardiogram.
* You will have the option to complete a cognitive function test.

## Visit 6 Onwards – 6-Monthly Visits

* How many pills of the study medication you have taken since your last visit and if you have experienced any side effects. You will be asked to return any unused study medication including empty containers.
* You will be asked to complete a urine test.
* You will be asked to complete two questionnaires to assess your quality of life and your general health every 12 months.
* You will have the option to complete two scans – a cardiac MRI and/or echocardiogram at your 12-month visit.
* You will have the option to complete a cognitive function test every 12 months.

## End of Study or Early End of Treatment Visit

* You will be asked to complete a urine test.
* You will be asked to complete two questionnaires to assess your quality of life and your general health.
* You will have the option to complete a cognitive function test.

## Information About Your Blood Tests and Urine Tests Throughout the Study

* Blood tests:
	+ You will be asked to fast (to not eat or drink anything apart from water for 8 hours) before the blood tests.
	+ At your screening, 2 weeks, 3 months, 6 months and 6 monthly thereafter visits - The blood tests will involve collection of 20 mL (or 4 teaspoons) of blood to measure your kidney function.
	+ At your randomisation and end of study/early end of treatment visits - The blood tests will involve collection of 20 mL (or 4 teaspoons) of blood and will measure your kidney function, blood sugar, cholesterol, calcium and phosphorus.
	+ At your randomisation, 3 month and end of study/early end of treatment visits – you will have the option to provide an additional 20mL (or 4 teaspoons) of blood for storage, this is so additional tests can be done after the study.
* Urine tests:
	+ The urine test will involve collection of 40-50 mL of urine and will measure your kidney health.
	+ Urine collection takes place in the morning of the study visit.
	+ At the randomisation, 3 months, 6 months and 6 monthly thereafter visits - Participants on dialysis will need to collect urine for 24 hours.
	+ At your randomisation, 3 month and end of study/early end of treatment visits – you will have the option to provide an additional 40-50mL of urine for storage, this is so additional tests can be done after the study.

## Unscheduled Visit

If you decide to stop participating at any stage throughout the study before the final study visit, or need to come in for any reason, you will be asked to return to your hospital for a visit. The Early End of Treatment Visit procedures described above will be completed during this visit.

## Important Information About Your Study Medication

The dose of study medication you receive at this visit and throughout the study will be the standard dose that is approved for the treatment of chronic kidney disease in Australia, but you will not know if you are taking the study medication or a placebo. You will take one pill of study medication per day. The study medication should be stored at room temperature and away from light, excess heat, and moisture (not in the bathroom). The study medication should be taken once a day in the morning with a little water (around the same time every day between 7 and 9 o’clock in the morning). It doesn’t matter if you take the drug before or after breakfast.

**If you forget to take your study medication** and it has been less than 6 hours since you usually take it, take your study medication immediately. If it has been more than 6 hours, take your next dose of study medication at the usual time the following day. Do not take a double dose to make up for the dose that you missed.

**If you require a planned surgery,** it is necessary that you temporarily stop taking your study medication at least three days before your surgery. If you require an emergency surgery, the surgery can proceed and your doctors will monitor you closely after the surgery for any side effects. Your study medication can be re-started once you are eating and drinking as usual or as instructed by your doctors.

If you are unwell and attend a healthcare facility e.g., GP Practice or Hospital Emergency Department, please show them your RENAL LIFECYCLE Wallet Card, as this will explain that you are taking part in a clinical trial and may be taking Dapagliflozin or placebo.

## Optional Assessments

### Cardiac MRI Scan

You are also invited to undergo a MRI (magnetic resonance imaging) scan of your heart. The study researchers are looking at the effect of the study medication on your heart. These scans will be taken at a scanning centre located within an hour’s drive of your hospital. This scanning center has been selected and engaged by the Sponsor to administer these tests. If you agree to participate, your identifying information (e.g. name and contact details) will be forwarded to the MRI provider for the purpose of booking your appointment.

An MRI scanner is a machine that uses electromagnetic radiation (radio waves) in a strong magnetic field to take clear pictures of the inside of the body. Electromagnetic radiation is not the same as ionising radiation used, for example, in X-rays. The pictures taken by the machine are called MRI scans.

You will be weighed before being asked to lie on a table inside the MRI scanner. You’ll be asked to lie in a comfortable position and stay still for around 15 minutes. The scanner will create images of your heart. The scanner is very noisy, you may be given some earphones to reduce the noise. Some people may experience symptoms of claustrophobia from lying in a confined space. If you do experience discomfort at any time during the scan, you will be able to alert staff by pressing on a call button provided to them.

There are no proven long-term risks related to MRI scans as used in this research study. MRI is considered to be safe when performed at a centre with appropriate procedures. However, the magnetic attraction for some metal objects can pose a safety risk, so it is important that metal objects are not taken into the scanner room.

You will be thoroughly examined to make sure there is no reason to not have the scan. You must tell study staff if you have metal implanted in your body, such as a pacemaker or metal pins.

The scans we are taking are for research purposes. They are not intended to be used like scans taken for a full clinical examination. The scans will not be used to help diagnose, treat or manage a particular condition. A specialist will look at your MRI scans for features relevant to the research study. On rare occasions, the specialist may find an unusual feature that could have a significant risk to your health. If this happens, we will contact you to talk about the findings. We cannot guarantee that we will find any/all unusual features.

If required, you may be reimbursed for any additional travel or parking expenses associated with the cardiac MRI visits .

### Echocardiogram

You are also invited to undergo an echocardiogram of your heart. The study researchers are looking at the effect of the study medication on your heart. This test will be completed in your hospital during your study visit. An echocardiogram is a painless test looking at the electrical signals of your heart. Electrodes will be stuck to various parts of your chest to measure your heart rate and normality of your heartbeat. This assessment will take around 15 mins.

If you opt into doing the echocardiogram, you will also be asked to complete a questionnaire on your heart health, this should take around 5-10 minutes.

### Cognitive function

You are also invited to complete a cognitive function test. The study researchers are looking at the effect of the study medication on your thinking and movement speed. This test will be completed in your hospital during your study visit. The test is completed on a mobile phone or tablet and takes 90 seconds.

# What do I have to do?

If you decide to participate:

* You need to attend the scheduled visits and cooperate with the study procedures as described in Section 3 above.
* You must tell your study coordinator if you have participated in another research study in the past year or are currently in another research study. While participating in this study, you should not take part in another research study without approval from your doctor.
* You must carry the participant card of the study with you, for example in your wallet. The card states that you are participating in this study and whom to warn in the event of an emergency. Show this card when you visit a (other) physician.
* You need to inform the study coordinator about any health problems, accidents or medical interventions that happen while you are in the study, even if you think it is not important.
* You need to inform the study coordinator if you have been taking or not taking your study medication.
* You need to inform the study coordinator if you start any new medication or stop any medication that you are already taking. This includes prescribed or over the counter products.
* You must remember to bring your unused study medication and all empty containers to each of your study visits and explain if there is any lost or missing study medication.
* You need to inform the study coordinator if you decide not to continue in the study. You don’t have to give a reason for your decision.
* There are no lifestyle restrictions (e.g., physical restrictions, participation in sport) or dietary restrictions in this study.

# Will I be paid?

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

# What are the possible benefits of taking part?

We cannot guarantee or promise that you will receive any benefits from taking part in this study; however, possible benefits may include a reduction in the risk of heart complications and slowing the progression of kidney disease. Some people may also benefit from the information learned in this study. This research may help to develop a new therapy for others with similar conditions.

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

Medical treatments often cause side effects. You may have none, some, or all 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 GP/ treating medical specialist or the study coordinator. Your GP/treating medical specialist and the study coordinator will also be looking out for side effects. It is very important that you tell your GP/treating medical specialist and the study coordinator about your full medical history and about all the medications you are taking as some medical conditions and medications may mean it is not suitable for you to take the study medication.

There may be side effects that the researchers do not expect or do not know about and that may be serious. Tell your GP/treating medical specialist and the study coordinator immediately about any new or unusual symptoms that you get.

If you experience stomach upset, including vomiting or diarrhoea or an infection, and/or you are unable to eat, let your study coordinator know as soon as possible as it may be necessary to temporarily stop taking your study medication until you are feeling better.

If you require an admission to hospital or surgical procedure/operation, or a scan with intravenous contrast (e.g., CT scan), let your and study coordinator know as soon as possible as it may be necessary to temporarily stop taking your study medication (please see section ‘Important Information About Your Study Medication’ in this Participant Information Sheet and Consent Form for further information).

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, you may need to stop your treatment. Your GP/treating medical specialist will discuss the best way of managing any side effects with you.

The risks associated with dapagliflozin are well known.

*For Diabetic Participants –* Dapagliflozin does not normally cause hypoglycaemia (low blood sugar) although hypoglycaemia may occur when dapagliflozin is taken with other medications to lower blood sugar levels e.g., sulfonylurea or insulin. Symptoms of hypoglycaemia may appear suddenly and include feeling weak and/or shaky, light-headedness, dizziness, inability to concentrate, a fast or pounding heartbeat, sweating and hunger. If you experience these symptoms, it is important to raise your blood sugar levels by eating 5 to 7 jellybeans, 3 teaspoons of sugar or honey, or drinking half a can of full sugar soft drink. You should also inform your GP/medical specialist and study coordinator as soon as possible.

**Dapagliflozin**

* *Common side effects (occur in between 1 in 10 and 1 in 100 people)*
	+ Genital yeast infection (thrush): symptoms include genital burning, redness, pain, and discharge.
	+ Passing more urine than usual or need to urinate more often
	+ Headache
	+ Back pain

The side effects listed above are usually mild and short-lived.

* *Uncommon side effects (occur in between 1 in 100 and 1 in 1,000 people)*
	+ Dehydration: symptoms include unusual thirst, light-headedness, or dizziness upon standing, and fainting or loss of consciousness. If you experience these symptoms, contact your GP and the study coordinator as soon as possible.
* *Rare side effects (occur in between 1 in 1,000 and 1 in 10,000 people)*
	+ Diabetes ketoacidosis (also known as DKA) is a rare but very serious possible side effect of dapagliflozin. Symptoms include vomiting, abdominal/stomach pain, excessive thirst, deep and fast breathing, confusion, unusual sleepiness or tiredness, sweet smelling breath, rapid weight loss. If you experience these symptoms, stop taking your study medication immediately and attend your nearest emergency department. You should also inform your GP and the study coordinator as soon as possible.
* *Very rare side effects (occurs in less than 1 in 10,000 people)*
	+ Necrotising fasciitis of the perineum or Fournier’s gangrene is a very rare, serious soft tissue infection of the genitals or the area between the genitals and the anus. Symptoms include pain or tenderness, itching, swelling in the genital or back passage area, fever or generally feeling unwell. If you experience these symptoms, stop taking your study medication immediately and attend your nearest emergency department. You should also inform your GP and the study coordinator as soon as possible.

Some side effects may occur that usually do not need medical attention. These side effects may go away during treatment as your body adjusts to the medicine. Also, your GP may be able to tell you about ways to prevent or reduce some of these side effects.

**Pregnancy Risk**

The effects of dapagliflozin could harm an unborn child. It is not safe to take this medicine during the second and third trimester of pregnancy. Because of this, it is important that research participants are not pregnant or breast-feeding and do not become pregnant during the research study. You must not participate in the research if you are pregnant or trying to become pregnant, or breast-feeding. If you are person of childbearing potential there is a possibility, you will be required to undergo a pregnancy test prior to commencing the research study.

Participants of childbearing potential are strongly advised to use effective contraception during the research and for a period of three months after completion of the research study. You should discuss methods of effective contraception with your study doctor.

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

**Blood Tests**

Having a blood sample taken may cause some discomfort, bruising, minor infection, or bleeding. If this happens, it can be easily treated.

# What will happen to my test samples?

Blood and urine samples will be collected at your hospital by the study coordinator for standard safety evaluations and will be tested at your hospital laboratory. These samples will be labelled with your name and date of birth, as they would be if you were not in a research study and linked to your medical record as per any standard blood and urine test. Your test results will be entered into the study database by the study coordinator in a de-identified form meaning they will not contain your name, only your study participant number. Access to your information will be strictly controlled and only authorised research staff members will have access. Following this, these samples will be securely destroyed after testing, according to the hospital laboratory’s standard procedures. All hospital laboratories will be accredited organisations to perform human blood and urine testing.

Some Australian hospitals are participating in the donation of additional blood and urine samples for future analysis. If your hospital is participating, your study coordinator will discuss this with you. Your donation of these additional samples is optional. You can still participate in the study and not provide additional samples.

If you choose to participate you will be asked to provide additional consent, to indicate whether you agree to the collection and storage of your blood and urine samples. The purpose of collecting these samples is to explore if there are associations with severe chronic kidney disease, effects of the study medication, clinical outcomes, and toxicity. These samples will be collected by your hospital pathology services, spun/prepared using standard operating procedures and stored in the freezer facility of the local pathology department at your hospital in Australia. Samples will then be transferred to the University Medical Center Groningen, Netherlands and stored for a maximum of 25 years, after which they will be destroyed. These additional samples will be labelled with your study participant number, visit number and date. The list linking your study participant number to your name will be stored at a secure place in the hospital. Only participant numbers will be used, to process your additional blood and urine samples. Access to your information will be strictly controlled and only authorised research staff members will have access.

# What if new information arises during this research study?

Sometimes during a research study, new information becomes available about the treatment that is being studied that may affect your willingness to continue in the study. If this happens, your study team will tell you about it in a timely manner and discuss with you whether you want to continue in the research study. If you decide to withdraw, your GP/treating medical specialist will arrange for your regular health care to continue. If you decide to continue in the research study, you will be asked to sign an updated consent form.

On receiving new information, your GP/treating medical specialist might consider it to be in your best interests to withdraw you from the research study. 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 study?

Whilst you are participating in this research study, your GP/treating medical specialist will continue to manage your clinical care and medications as per usual practice.

It is important to tell your GP/treating medical specialist and the study coordinator about any treatments or medications you may be taking, including over-the-counter medications, vitamins or herbal remedies, acupuncture, or other alternative treatments. You should also tell your GP/treating medical specialist and the study coordinator about any changes to these during your participation in the study. Your GP/treating medical specialist should also explain which of your treatments or medications need to be stopped for the time you are involved in the study.

It may also be necessary for you to take medication during or after the research study to address side effects or symptoms that you may have. You may need to pay for these medications and so it is important that you ask your doctor about this possibility.

# Do I have to take part in this research study?

Participation in any research study 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 study at any stage.

If you do decide to take part, you will be given this Participant Information Sheet and Consent Form to sign and you will be given a copy to keep.

Your decision whether 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 your hospital.

# What are the alternatives to participation?

You do not have to take part in this research study to receive treatment at your hospital. You may continue your usual care for your severe chronic kidney disease without being in this research study or you may be able to take part in another research study. Your study hospital staff team member will discuss these options, including their possible benefits and risks, with you before you decide whether to take part in this research study. You can also discuss the options with your general practitioner (GP), treating medical specialist and other treating healthcare professionals.

# Can I withdraw from the study?

If you decide to withdraw from the study, please notify a member of the study team beforehand. This notice will allow the study coordinator or your GP/treating medical specialist to ask you your reason for withdrawing and discuss any health risks or special requirements linked to withdrawing.

You may withdraw from taking the study medication or withdraw your consent to participate in the study. If you do withdraw your consent during the study, you will be asked to complete one final visit. If you decide to withdraw, you will have the option to allow study staff at the end of the study to contact you, your GP/treating medical specialist, or another party (this includes publicly available sources) to obtain information about your health status.

If you do decide to withdraw, study staff will not collect additional personal information from you, although personal information already collected will be retained to ensure that the results of the research study can be measured properly and to comply with law. You should be aware that data collected by the sponsor up to the time you withdraw will form part of the study results. Please let us know at the time when you withdraw what you would like us to do with the information we have collected up to that point.

# Could the study be stopped unexpectedly?

Your participation in the study may be stopped without your consent at any time. The reasons may include:

* You have side effects from study treatment and further study treatment is not in your best interest;
* Your medical condition changes and further study treatment is not in your best interest;
* You do not attend clinic visits and cooperate in the study procedures as described in Section 3 of this Participant Information Sheet;
* Study procedures are not followed, and continued study participation is not in your best interest;
* A decision by health authorities in Australia or overseas; or
* The study is cancelled by the trial global sponsor, UMCG or the local sponsor, The George Institute for Global Health.

This research study may be stopped unexpectedly for a variety of reasons. These may include reasons such as:

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

Decisions made in the commercial interests of the sponsor or by regulatory/health authorities.

# What happens when the research study ends?

The study medication, dapagliflozin, is not yet proven for use in people with poor renal function (eGFR less than 25ml/min/1.73m2). Therefore, you will not be able to continue to receive dapagliflozin indefinitely. When the study ends, your GP/treating medical specialist will discuss treatment choices with you.

You have a right to receive feedback about the overall results of this study. You can tell us that you wish to receive feedback by ticking the relevant box on the Participant Consent Form. A study team member will provide you with a summary of the results of the study. The study team member can also tell you which treatment you received.

#  Confidentiality/Privacy

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

Study monitors, auditors, representatives of regulatory authorities and ethics committee may also be granted direct access to your original medical records for verification of trial procedures and/or data.

All electronic information collected will be entered directly into a secure web-based database hosted by the global sponsor in The Netherlands - University Medical Center, Groningen. All electronic information will be deidentified to protect your confidentiality and computer records will be password-protected. Information collected from you using paper-based measures will be deidentified and stored securely at your hospital (with later transfer at the end of the study to The George Institute for Global Health for secure storage), and only approved research personnel will have access to this information. For those who complete the cardiac MRI sub-study, electronic images will be transferred directly to The George Institute for Global Health for storage on our password and firewall protected server in a deidentified form. All deidentified electronic images will then be securely transferred to Mycardium AI in the United Kingdom for data analysis. All electronic and paper-based trial documentation will be kept and securely archived for 25 years. After this time, it will be securely destroyed.

You will be asked to provide your consent for the research team to share or use the information collected from you in future, ethics-approved research that:

* Will be specific to the aims of this research; and/or
* Will be used in any future research.

Your information will only be shared in a format that will not identify you.

# What happens with the results?

All information collected from you for this study will be stored electronically in a database maintained by UMCG. It is intended for the results of this study to be presented or published at medical conferences and in scientific journals.

In any publication, information will be provided in such a way that you cannot be identified. Results of the study will be provided to you, if you wish. By signing the consent form, you agree to your data being included in the results published for this study.

A description of this clinical trial will be available on [www.clinicaltrials.gov](http://www.clinicaltrials.gov). This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website anytime.

#  Compensation for injuries or complications

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

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

# Who is organising and funding the research?

The study is being funded in Australia by a NHMRC 2021 MRFF International Clinical Trial Collaboration Grant. The study medication is being provided in-kind by the pharmaceutical company AstraZeneca who make dapagliflozin. AstraZeneca has had no role in the design and conduct of the study, and will not be involved in interpretation of results and publication of data.

You will not benefit financially from your involvement in this research study even if, for example, knowledge acquired from analysis of your samples prove to be of commercial value to the UMCG and/or The George Institute for Global Health.

In addition, if knowledge acquired through this research leads to discoveries that are of commercial value to the UMCG, The George Institute for Global Health or the study hospitals there will be no financial benefit to you or your family from these discoveries.

No member of the research team will receive a personal financial benefit from your involvement in this research study (other than their ordinary wages).

# COVID-19

Considering the COVID-19 pandemic, The George Institute for Global Health would like to alert participants that all sites will be working to the national guidelines which may involve confirming participants’ health status prior to their scheduled visit and rescheduling visits if you are sick with the flu or COVID-19. At your visit, the site will request your COVID-19 status.

# Further information and who to contact

When you have read this information, the study doctor and/or study coordinator will discuss it with you further and answer any questions you may have. If you would like to know more at any stage, please feel free to contact:

|  |  |
| --- | --- |
| **Site Principal Investigator:**  |  |
|  | *[Insert site-specific details]* |
| **Complaints:** |  |
|  | *[Insert site-specific procedures]* |

## Ethics Approval

All research involving humans is reviewed by an independent group of people called a Human Research Ethics Committee (HREC) or Institutional Review Board (IRB). This study has been approved by the Ethics Review Committee (RPAH Zone) of the Sydney Local Health District. Any person with concerns or complaints about the conduct of this study should contact the Executive Officer on 02 9515 6766 and quote protocol number X22-0201.

The conduct of this study at the [*name of hospital*] has been authorised by the [*name of Local Health District*]. Any person with concerns or complaints about the conduct of this study may also contact the Research Governance Officer [*or other officer*] on [*telephone number*] and quote protocol number [*insert local protocol number*].

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

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

**Consent Form**

Interventional Study – Adult providing own consent

|  |  |
| --- | --- |
| **Title** | A randomized controlled clinical trial to assess the effect of dapagliflozin on renal and cardiovascular outcomes in patients with severe chronic kidney disease |
| **Short Title** | The RENAL LIFECYCLE trial |
| **Global Study Sponsor**  | University Medical Center Groningen |
| **Australia Study Sponsor**  | The George Institute for Global Health |
| **Global Chief Investigator**  | Professor Ronald Gansevoort |
| **Australian Chief Investigators** | Professor Sunil Badve and Associate Professor Clare Arnott |
| **Local Principal Investigator** | *[Insert PI Name]* |
| **Location** | *[Location]* |

**Declaration by Participant**

I, \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

 *[Print full name]*

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

1. I have been made aware by \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ (“the researcher”) of the procedures involved in the study, time involved, including any known or expected inconvenience, risks, discomfort or potential side-effects and of their implications as far as they are currently known.
2. I understand that the researcher will conduct this study in a manner conforming to ethical and scientific principles set out by the National Health and Medical Research Council (NHMRC) of Australia and the Good Clinical Research Practice Guidelines of the Therapeutic Goods Administration.

1. I acknowledge that I have been given time to consider the information and to seek other advice.
2. I acknowledge that refusal to take part in this study will not affect the usual treatment of my condition.
3. I acknowledge that I am volunteering to take part in this study and I may withdraw at any time.
4. I understand that any blood and urine samples collected will only be used for this research study, as described in the relevant section of the Participant Information Sheet.
5. I acknowledge that this research has been approved by: the Sydney Local Health District Human Research Ethics Committee.
6. I acknowledge that any regulatory authorities may have access to my medical records concerning my disease and treatment for the purposes of this study. However, I understand my identity will not be disclosed to anyone else or in publications or presentations.
7. I give permission for my doctors, other health professionals, hospitals, or laboratories outside this hospital site to release information to my GP, hospital and the study coordinator concerning my disease and treatment for the purposes of this study. I understand that such information will remain confidential.
8. I understand that I may be contacted after the end of this study to be invited to participate further for assessment of my health and wellbeing in the longer term.
9. I understand that I will be given a signed copy of this document and the Participant Information sheet to keep.
10. I would like to receive a copy of the study results when they become available.
My email address is:\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

|  |  |
| --- | --- |
| **Additional Consent**  | **Yes or No** |
|  |  |
| 1. I consent to my coded data being used for future research.
 |  |
|  |  |
| 1. I consent to the collection and storage of additional blood and urine samples to use it for future research
 |  |
|  |  |
| 1. I consent to being approached after this study is finished to ask whether I want to participate in a follow-up study
 |  |
|  |  |
| 1. I consent to the researcher’s notifying me which treatment I have had after all participants have completed the study and this information becomes available

My email address is: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ |  |
|  |  |
| 1. I consent to the use of my email address for digitally completing the questionnaires

My email address is: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ |  |
|  |  |
| 1. I consent to participate in the **Cardiac MRI sub-study**. I understand that I may withdraw participation from the sub-study at any time without any affect on my participation in the main study.

*An MRI scan at baseline and 12 months.* |  |
|  |  |
| **For participants on peritoneal dialysis only**1. I consent to participate in the **Echocardiogram sub-study**. I understand that I may withdraw participation from the sub-study at any time without any affect on my participation in the main study.

*An echocardiogram and questionnaire at baseline, 6 months and 12 months.* |  |
|  |  |
| 1. I consent to participate in the **Cognitive sub-study**. I understand that I may withdraw participation from the sub-study at any time without any affect on my participation in the main study.

*A cognitive function test at baseline, 6 months, 12 months and once every 12 months thereafter until end of study or early end of treatment.*  |  |

|  |  |  |
| --- | --- | --- |
| **Name of Participant** |  |  |
|  |  *(please print – First name / Family name)* |  |
| **Signature** |  | **Date** |  |  |
|  |  |  |  |  |

**Declaration by Witness**

I have witnessed and certify the Participant’s verbal consent to voluntarily agree to participate in this research study.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Signature of Impartial Witness** |  | **Date** |  |  |
| *(to be completed only if the participant cannot read the participant information sheet)* |  |
| **Printed name of Impartial Witness** |  | **Relationship to the Participant** |  |  |
| The Participant’s confirmation is attested by the above signature of an Impartial Witness |  |

**Declaration by Study Staff Member†**

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

|  |  |  |
| --- | --- | --- |
| **Name of Study Staff Member Delegated to Conduct Consent** |  |  |
|  |  *(please print – First name / Family name)* |  |
| **Signature** |  | **Date** |  |  |
|  |  |  |  |  |

†A senior member of research team must provide the explanation of, and information concerning, the research study. The staff member conducting consent must be delegated to do so on the study delegation log.

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