

Participant Information Sheet/Consent Form

Title RECALL-Pilot REducing Cognitive decline and dementiA by Lowering
bLood pressure PILOT

N/A

Study Sponsor The George Institute for Global Health

Principal Investigator Professor Craig Anderson

1. Introduction

You are invited to take part in a research project called the RECALL Pilot study. This study is to test whether it is possible for us to run a blood pressure lowering study remotely, that is without you needing to visit a clinic. In the future we are keen to run a longer term remote study to measure whether blood pressure lowering helps to prevent decline in thinking skills, such as memory or planning, known as mild cognitive impairment and/or dementia but first we need to test whether it is possible to run a study remotely.

The treatment in this study involves taking a one pill per day called GMRx2. GMRx2 is a combination of three commonly used blood pressure lowering medications, all at a low dose. It is in tablet form.

This study includes 300 participants and will run for several months. Your part in the study will be for approximately 60-days.

This study is being coordinated by The George Institute for Global Health, an affiliate of the University of New South Wales, Australia. It has also been endorsed by Dementia Australia.

This Participant Information Sheet and Consent Form tells you about the research project. It explains the tests and treatments that are involved. Knowing what is involved will help you decide if you want to take part in the research. Please read this information carefully. You can contact our study team to 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 doctor.

Participation in this research is voluntary. If you don't wish to take part, you don't have to. You will continue to receive your usual care from your usual GP for the duration of the study.

Sometimes during the course of a study, new information becomes available about the treatment that is being used. While you are participating in this study, you will be kept informed of any significant new findings which may affect your willingness to continue in the study.

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

- understand what you have read,
- consent to take part in the research project,
- consent to have the tests and treatments that are described in this information sheet,
- consent for the use of your personal and health information as described in the information sheet and,

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

2. What is the purpose of this research?

This research study is to see if it is feasible to run blood pressure lowering studies and to collect information on thinking skills remotely (i.e. so that participants do not have to come into the clinic).

The treatment in this study involves taking a one pill per day called GMRx2. GMRx2 is a combination of three commonly used blood pressure lowering medications, all at a low dose. These three medications are: telmisartan 20mg, amlodipine 2.5mg, and indapamide 1.25mg. The treatment of high blood pressure usually starts with one (or more) of the drugs being used in this study. George Medicines have no financial or commercial interest in the study.

Medications, drugs and medical devices have to be approved for use by the Therapeutic Goods Administration (TGA) in Australia and the Australian Federal Government before they can be sold or prescribed by a doctor. GMRx2 (as a single pill) is not an approved medication, but the three separate medications within GMRx2 are approved for the treatment of people with hypertension. This study will be conducted under the 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).

3. What does participation in this research involve?

The average length of time you will be involved is 60-days. Your involvement will be almost entirely from home (i.e. you will only be required to attend a pathology centre twice for required blood tests). The medication will be posted out to you. You will need to complete all of the baseline and follow-up testing at home on your computer/laptop/tablet/smartphone. You will need to have access to a

computer/laptop/tablet/smartphone that is connected to the internet to complete all of the test procedures required for this study.

Signing the consent form does not guarantee your enrolment into the study - it allows the study team to assess your suitability to participate. The information collected about you in the 'Screening, baseline assessment and initial enrolment' period will be used to see if you are suitable to participate. Your GP practice may be contacted to provide medical information to study investigators.

1) Screening, baseline assessment and initial enrolment

You will be asked to complete the consent forms, baseline materials (consent forms and 2 brief questionnaires), and to provide a measurement of your blood pressure from a GP, pharmacy, or using a home monitor. We will ask you for information about you, for example your age, sex, your health and medications, and your contact details. You will need to have a valid email address to be in this study, as all communications will be sent by email. You will also be asked to provide the details of a 'study buddy' contact (e.g. spouse, carer, relative or close friend) who we will be able to contact if we need more information about you (e.g. if we cannot contact you). Your study buddy will need to provide consent for us to contact them, and you will need to ask them to complete the online consent form (the link for this will be sent to you once you enrol). We will also require the details of your GP or medical centre. You will need to complete all of this information online.

We suggest that you have all of your medication boxes/containers in front of you when completing the screening information, as you will be asked to enter information about some of your medications to help ensure both your eligibility and that we can provide you with adequate care.

As part of the screening phase, we will also be asking you to complete baseline tests of cognition using the Creyos online testing portal (find out more: <http://www.creyos.com>).

Completion of these initial forms and tests will take approximately 60 minutes.

After completing this, if you are eligible for the next phase, you will be dispensed the study medications for a 60-day period.

Starting the study

The study will run for approximately 60 days. In this phase you will receive a half dose of the study medication (GMRx2) for 30-days, followed by the full dose for a further 30-days. These will be posted out to you in 2 clearly labelled bottles – one for the half dose, and one for the full dose. You will need to take 1 tablet a day, with or without food. It can be taken with your other medications and should be taken at about the same time every day. You will receive specific instructions about taking your study medication. If you miss a dose and it is within 6 hours of the usual time you take your medicine, then take it immediately. If it's more than 6 hours, continue taking your medicine the following day at the usual time with the usual dose of one tablet. We will be needing to know how many pills you have left overall, so please do not throw out any pills until you are told to do so.

There will be a helpline that you, your study buddy, your doctor, or another treating medical professional can ring at any time throughout the study if you have any issues with the study (e.g. completing any of the tests or questionnaires, accessing the study webpage) or the medication (e.g. questions about the dosage or the medication, side effects). We will have study staff as well as trained pharmacy and medical staff available to answer your questions and support you whilst you participate in the study.

Creyos testing:

You will be asked to complete a short subset of 3 tests from the Creyos website at specific times during the study (e.g. when you enrol to participate, when the study medication is posted out to you, and at the end of the study). You should use a desktop or laptop/tablet to complete these (not a smart phone) as they have a bigger screen. You will do this at home by clicking on the link we provide to you – this link is personalised for you. These tests will take approximately 10-20 minutes of your time. These tests are intended to give us a snapshot of your thinking skills, they are not diagnostic. If you are concerned about your thinking skills you should visit your GP for a clinical assessment.

Blood tests:

All participants who are eligible for the study will be asked to get a blood test at the beginning and end of the study. This is to collect information about kidney-function which will be used to add to existing data/knowledge from prior research studies on GMRx2. Blood collection forms will be sent to you with the study medication for two blood tests.

Blood pressure monitoring:

If you are eligible for the study, you will also be given the option to participate in a blood pressure monitoring component. For this part, you will be provided with a blood pressure monitor, and required to take your blood pressure at home, 3 times in the morning and 3 times in the evening on 2 consecutive days in a sitting position after sitting quietly for a few minutes. You will be asked to do this at 3 timepoints in the study (start, middle, end). Specific instructions will be provided to you. You will also be asked to complete an online questionnaire providing details of the dates and time you measure your blood pressure, and the date you start taking your study medication.

You will need a smartphone to be involved in this part of the study, as the blood pressure monitor uses an app to collect readings that must be downloaded to a smartphone.

Participation in this part of the study is optional – you can participate in the rest of the study without participating in this blood pressure monitoring component.

During the study (week 4)

All participants will be required to complete online questionnaires and the Creyos tests at the beginning, during, and at the end of the study. These will involve online cognitive testing described above and brief online questionnaires about your health. We will send you a reminder via email when these are to be completed – this will take approximately 10-30 minutes of your time.

Possible additional testing:

If your online cognitive testing records an unusual result, for example, if it records a large amount of missing data or a score that is lower than expected we will ask you to do the test again to check if there was a problem with the test. If your second test also shows a score that is lower than expected we will ask you to complete a telehealth assessment with a trained researcher to carry out some standard assessments of your thinking skills. If these assessments are lower than expected for your age we will advise you to contact your GP and all the information from our assessments will be provided to them to carry out a clinical assessment as your primary care provider. Your GP will also be provided with up to date resources on cognitive skills and blood pressure by our team. Please note, this study cannot provide a medical diagnosis. If your GP thinks you need a medical assessment they can provide this as can any specialists you are referred to.

If you have had any unplanned hospitalisations, new conditions that were severe enough to need prompt health service treatment, and **any** accidents or falls that required prompt treatment by a medical practitioner, we ask that you please report them to us, through an **SAE form** sent via a link to this form to your email or contact us via email at RECALL@georgeinstitute.org.au or call the study team on (02) 8052 4438.

If you would like us to resend this form or don't know whether to report something to us, please contact us on RECALL@georgeinstitute.org.au or call the study team on (02) 8052 4438.

4. What are the alternatives to participation?

Participation in this research study is voluntary. There are other treatments available to manage your blood pressure. You can discuss these options with your general practitioner or medical specialist before you decide whether or not to take part in this research study.

5. Are there any benefits?

This study aims to generate further medical knowledge and to determine whether it is possible for remote studies to collect data on blood pressure and thinking skills. We will use this information to help us design a future longer-term remote blood pressure lowering study to understand if blood pressure lowering will help prevent Mild Cognitive Impairment and/or dementia or provide other health benefits. Participation in this study may not directly benefit you. You will have a chance to monitor your cognitive and memory skills, as well as your blood pressure by being in the study.

6. Are there any risks?

All medical treatments involve some risk of injury or side-effects. In addition, there may be risks associated with this study that are presently unknown or unforeseeable. The risks associated with the study medication being used are well-known and are outlined below. You will be provided with an information card with your medication that states you are participating in this study, and details of the study medication, purpose of the study, and the helpline phone number. You can provide this to your treating doctor/healthcare professional if needed.

You should not eat grapefruit or Seville oranges nor drink grapefruit juice while you are on study treatment. Check to see if fruit juices or soft drinks contain these juices, as these may affect the levels of study drug in the blood.

This medicinal product contains a drug substance, which may give a positive reaction in doping tests. There is a possibility that lowering your blood pressure may lead to an increased risk of dizziness or faintness and a consequent fall.

Study Medication

The possible side-effects of the study medication (i.e. GMRx2) is the same as if you were to take a low dose of any of the medications separately. However, it is expected that at low doses, such as in this study, any side-effects are unlikely to be severe and to resolve quickly once the medication is stopped. The known side-effects that may be experienced when a person takes the full dose of the medications being used in the study are listed below:

Common side-effects – occur in 1 to 10 of every 100 patients:

- nausea, diarrhoea, dizziness, muscle pain, low blood pressure, swelling in your lower legs or hands, increased uric acid levels.

Uncommon side-effects – occur in 1 to 10 in every 1000 patients:

- sleepiness, pins and needles sensation in the body, insomnia, back pain, blurred vision
- low appetite, low blood sugar (symptoms of hunger, sweating, shakiness and/or weakness)
- allergies (such as skin rash, itching, hives, swelling and/or shortness of breath)

Rare and very rare side-effects – occur in less than 1 in 1000 patients:

- weight loss, fever, heart irregularities (sensation of fluttering in the chest, racing or slow heart rate, shortness of breath and/or dizziness), weakness, coughing, sensitivity to light.

Telmisartan and indapamide, two of the three blood pressure lowering medications, may contain the additives lactose or sorbitol. People with the following rare hereditary conditions should not take this medicine:

- galactose intolerance (inability to break down the sugar galactose),

- Lapp lactase deficiency (missing or low levels of the enzyme lactase)
- glucose-galactose malabsorption (poor absorption of the sugars glucose and galactose)
- fructose intolerance (inability to break down fructose, a sugar found in fruits and vegetables).

Taking telmisartan made with lactose is not likely to affect persons with lactose intolerance.

Blood Collection

The risks of a blood test include pain, a bruise at the point where the blood is taken, redness and swelling of the vein, infection and rarely fainting.

7. Compensation for injuries or complications

If you suffer any injuries or complications as a result of this study, you should contact your doctor 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.

8. Will taking part in this study cost me anything, and will I be paid?

Participation in this study will not cost you anything except for your time. You will not be paid for your involvement.

9. What will happen to my test samples?

The blood tests are used to determine whether the medications have caused any unwanted side-effects. However, none of the samples will be stored or used for future research. All samples will be sent to the pathology provider's local laboratory for analysis and then discarded.

10. What should I do if I experience dehydration due to nausea and vomiting because of taking the trial medication?

Please seek immediate medical attention and stop the trial medicine if you have any signs or symptoms of dehydration – fatigue, dizziness, excessive thirst and dry mouth, infrequent urination, dark-coloured urine or feeling lightheaded upon standing.

11. Can I have other treatments during this research project?

You may continue to take your usual treatment while participating in this study. However, you should not start the study with very high blood pressure that warrants ongoing treatment. Should you need treatment for high blood pressure during the study, or develop severe hypertension during the study,

specific blood pressure medication may be recommended by your GP. It is important that you let us know if your GP prescribes any additional medication for you or changes the dose/frequency of your current medication whilst you are participating in this study. We will provide a letter that you can give to your GP that explains what the study is for and what medication is included. You and/or your GP will also be able to ring the study helpline to do this; we will also ask you about this in each follow-up questionnaire.

12. Could this research study be stopped unexpectedly?

The study may be stopped unexpectedly for a variety of reasons, for example:

- unacceptable side-effects or a decision made by local regulatory health authorities.

13. What if I wish to withdraw from this research project?

You are free to withdraw at any point without giving a reason at any time. If you do decide to withdraw please let us know that you are withdrawing.

If you wish to no longer take the study medication (or you need to cease to take the study medication for medical reasons), you will be asked to continue to complete the online questionnaires and cognitive testing for the duration of the study, to help us follow up on your progress and wellbeing. You can refuse to do this, and fully withdraw from the study if you wish. If you decide to leave the study, the researchers would like to keep the health information about you that has been collected. This is to help them make sure that the results of the research can be measured properly. If you decide to withdraw and do not wish for the health information that you have already provided to be used, please notify the study staff.

14. What happens when the research project ends?

The medication provided during this study will not be available at study completion. All three components of the medication are available individually. You will be referred back to your specialist/GP for ongoing management.

As this study is focused on long-term health outcomes that may extend beyond the time that you are actively involved, by signing the consent form, you agree to us contacting you in the future.

15. 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 information transferred electronically will be deidentified to protect your confidentiality and computer records will be password-protected. Trial documentation will be kept and securely archived for 15 years.

Although research studies are established with a primary purpose, it is often helpful for scientists to share the information they get from studies in order to learn more about how health is affected and treatment works more or less in particular types of patients from different parts of the world. Combining information from different studies in one place helps them learn even more about the health and wellbeing of people and how best to use new treatments. The collection of information is sometimes called a databank. We may wish to store the coded data from this study into one or more of such databanks, where together with data from other studies, can be used to extend knowledge. This work may or may not be directly undertaken by research personnel associated with this study but in most cases is undertaken by staff who work for research institutes or universities. Information will be contributed to such databanks in a way that you cannot be identified. The location of such databanks is likely to be at The George Institute or at similar academic research institutes or at universities that The George Institute collaborates with in Australia and in other countries. It is not possible to determine how long the study data will be stored in any databanks. By signing the consent form, you agree to your de-identified results being pooled into other databanks. This does not include results from any blood samples collected.

16. CREYOS cognitive tests

As part of this study, you will be completing online cognitive tests. These tests are developed, hosted and administered through a third party, Creyos. Your study portal will provide you with a direct link to the Creyos testing platform. Creyos are based in Canada. By completing the testing in Creyos as part of this study, you are agreeing to only use the Creyos testing platform for the purposes of this study, to follow the instructions provided, to only complete the Creyos tests required in the study, and to only complete these tests when the study team ask you to complete them.

17. What happens with the results?

All information collected from you for this study will be stored electronically in a database maintained by The George Institute for Global Health, an affiliate of the University of New South Wales in Australia. 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. By signing the consent form, you agree to your de-identified data being included in the results published for this study.

Further information

If you would like to ask any further questions on the study, please contact us at:

recall@georgeinstitute.org.au or call the study team on (02) 8052 4438.

You could also discuss this study with your GP. If you would like information on the study and/or the study medication to discuss with your GP, this is available for you to download on the study website:

www.RECALL.org.au

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 [X23-0101].

The conduct of this study has been authorised by the Sydney Local Health District. Any person with concerns or complaints about the conduct of this study may also contact the Research Governance Officer on 02 9515 6766 and quote protocol number [X23-0101].

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 online consent form– the link is provided in a separate email that has been sent to you. This information sheet is for you to keep.

Study Sponsor The George Institute for Global Health

Participant

I, _____
[name]

of _____
[address]

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

1. I am aware 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.
3. I acknowledge that I have been given time to consider the information and to seek other advice.
4. I acknowledge that refusal to take part in this study will not affect the usual treatment of my condition.
5. I acknowledge that I am volunteering to take part in this study and I may withdraw at any time. I understand that if I withdraw from the study, the information I have provided to date will be used in the study.
6. I acknowledge that if I withdraw my consent to take the study medication, or for medical reasons can no longer take the study medication, I will be asked to continue to complete the online follow up questionnaires and tests till the end of the study. I understand I can refuse to do this, and withdraw fully from the study.
7. I understand that any blood samples collected will only be used for this research project, as described in the relevant section of the Participant Information Sheet.

8. I understand that the researchers may contact my GP practice if they need any further information about me, for the purpose of the study.
9. I understand that the researchers may contact my study buddy if researchers have attempted to contact me and have been unsuccessful.
10. I acknowledge that this research has been approved by: the Sydney Local Health District Human Research Ethics Committee.
11. I agree that I will use only use the Creyos online tests for the purpose of this study, and that I have read and understood the restrictions stated by Creyos in Section 16 of this Participation Information Sheet.
12. I understand that I will be emailed a signed copy of this document and the Participant Information sheet to keep.
13. I understand that I may be contacted after this study to discuss my experiences of the study and to provide feedback to the research team.
14. I understand that I will need to contact my 'Study Buddy' to get them to complete the online 'Study buddy' consent form to allow the researchers to contact them if they need any additional information on my health and wellbeing, during or immediately following the study.
15. I would like to receive a copy of the study results when they become available. My email address is: _____

Yes, I agree to above:

Your name _____

(please print – First name / Family name)

Signature _____

Date _____