Participant Information Sheet/Consent Form

Title	Action To promote brain HEalth iN Adults (ATHENA) trial: pilot feasibility study
Short Title	ATHENA
Protocol Number	X20-0284
Study Sponsor	The George Institute for Global Health
Coordinating Principal Investigator	Professor Craig Anderson

1. Introduction

You are invited to take part in a pilot feasibility study for a trial called ATHENA. This is because you have slightly raised blood pressure and your memory or thinking skills may not be as good as they were in the past. ATHENA is designed to test if a new type of blood pressure pill – the 'Triple Pill' – could be used over the long-term to help prevent memory problems, and perhaps even dementia. This pilot feasibility study aims to find out whether we can run ATHENA without the need for face-to-face contact. You have reached part three of the screening phase of the study because you have been deemed eligible due to your memory problems, blood pressure and other factors.

The study will involve approximately 50 people in New South Wales, Australia. The aim is to check whether the study visits can be conducted over the phone and via videoconference. We will also find out how well the Triple Pill is tolerated. This includes looking out for any side-effects over a 6-week period.

This study is funded through a Program Grant from the National Health and Medical Research Council (NHMRC) of Australia. It is being run by The George Institute for Global Health.

This Information Sheet and Consent Form tells you about the research. It explains what tests and treatments are required , so that you can decide if you want to take part. Please read this 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 local doctor.

Joining this research is voluntary. If you don't wish to take part at this stage, you don't have to. You will receive the best possible care whether or not you decide to take part. Whatever your decision, please be assured that it will not affect your medical treatment, or your relationship with the staff who are caring for you.

Sometimes during the course of a study, new information becomes available about the study treatment. If this happens, we will let you know, in case you want to stop your involvement.

If you decide you want to take part in the study, 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 study
- consent to have the blood and memory tests, and take the study tablets that are described in this information sheet
- consent for the use of your personal and health information as described in the information sheet
- consent to your contact details being provided to a courier service to facilitate the delivery of the study drug and blood pressure machine to you

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

2. What is the purpose of this research?

The purpose of the study is to find out whether we can run ATHENA without the need for face-to-face visits. We are also testing whether the Triple Pill is well tolerated and safe for people like you. During the study, we will monitor your blood pressure, and also check for any side-effects.

The Triple Pill contains three different types of blood pressure lowering pills that are combined to form a single pill, or capsule. We are using three well established and approved blood pressure pills called telmisartan, amlodipine and indapamide. The doses used are all lower than usual (telmisartan 20mg, amlodipine 2.5mg, and indapamide 1.25mg).

High blood pressure throughout life is a known risk for dementia. This risk is likely to be most important for those aged between 50 and 70 years (mid-life). High blood pressure damages the blood vessels in the brain that is likely to make any dementia worse. High blood pressure also causes small undetected strokes. The World Health Organisation (WHO) dementia risk reduction guidelines published in 2019 gave strong recommendations for people to have their blood pressure lowered. But we don't know if this is true for people like you with only slightly raised blood pressure. Recent research from the United States (SPRINT-MIND study) has suggested that this approach may be effective. In this large blood pressure lowering study, there was a small reduction (15%) in memory problems in participants, when their systolic (the high reading on a blood pressure machine) blood pressure was reduced (from 140 to 121). Results from other studies have suggested a small reduction in new dementia cases (12% reduction) if blood pressure is reduced by 10mmHg systolic. As there are no available medications that can prevent dementia, reducing dementia risk factors, like high blood pressure, is a promising approach. To be successful, blood pressure lowering treatment would need to be very safe and be taken for many years. This is why we are planning this study, to prepare for a much larger trial in the future. We now believe that the brain develops signs of dementia over a very long time, perhaps 20-30 years before typical diagnosis (80-90 years of age; the Australian average for dementia). Risk reduction in mid-life (50-70 years) is likely to be the best chance of making a difference. Raised blood pressure is common in your age group, affecting two in five people.

The pilot feasibility study for ATHENA will include people aged 50-70 years, with moderately raised home blood pressure in the range from >120/75 and <135/85mmHg.

3. What does participation in this research involve?

You have already completed parts one and two of the pilot feasibility study to show you are suitable for this stage of the study. Part three will last for 6 weeks. After signing the Consent Form, you will undergo a detailed assessment of brain function via videoconference using the Zoom platform. If you

continue to be suitable for the study, we will mail out the study drug to your home address and invite you for two more online visits in four and six weeks' time.

You will continue to monitor your blood pressure daily as you did in part two of the study with the blood pressure machine that you were previously provided with. The blood pressure machine has been approved by the Therapeutic Goods Administration (TGA).

Visit 1: Videoconference: consent and eligibility review

At this visit, a trained member of the study team, usually a nurse or research coordinator, will ask you a series of questions about your medical history and current medications. They will also review your blood results and determine if you are eligible for the study. If you are eligible, you will be sent a link to complete two online questionnaires .

This videoconference call will take approximately 45 minutes.

Visit 2: Videoconference: memory tests

At this visit, a neuropsychologist will conduct some tests of your memory. You will also be required to complete additional online tests called the Cogstate Brief Battery. We will send the link for this after the call as you are required to complete the Cogstate tests independently. The videoconference will be recorded.

This videoconference call will take approximately 45 minutes. (breaks can be taken)

After this call, if you are still eligible and agree to continue in the study, you will be randomised (like 'tossing a coin') to receive study treatment and be mailed study medication that will last for four weeks. The pharmacy of Syntro Health will be supplying study medication and will be provided your contact details if you provide consent to this study, in order to facilitate the delivery of the study medication. You will have a 50% chance of receiving either the Triple Pill or placebo. This study design is important to test the safety and tolerability of the Triple Pill.

The placebo is a tablet without any specific activity. To try to make sure the people given the Triple Pill are the same as the people given the placebo, each person is put into the group by chance (randomised). This is a double-blind study; this means that neither you nor the researcher know which treatment you are receiving. This design helps improve the quality of the study. If necessary and in certain circumstances, the study doctor can readily find out which treatment you are receiving.

You will be provided with instructions to take your study medication – **one capsule**, **once daily** at approximately **the same time in the morning** for four weeks, with or without food. If you miss a dose, and it is within six hours of the usual time you take your medicine, then take it immediately. If it's more than six hours, continue taking your medicine the following day at the usual time with the usual dose of one capsule. Please do not take any study medication after four weeks and return any remaining medication to the study courier after six weeks.

Visit 3: Telephone call: 1 week post randomisation

We will call you a week after you have been taking the study medication to talk to you about how you are feeling and if there are any issues.

Visit 4: Videoconference call: 4 weeks follow-up

During this call, we will ask some questions about your health and study medication and complete some more memory tests. We will ask you if you've missed any doses of the study medication and check if you have had any side-effects. The videoconference will be recorded. We will ask you to mail us back any remaining tablets (we will provide the courier bag). You will be sent a blood test form to

be done at your local pathology laboratory within a week. Collection of a blood sample (normally taken from a vein of your arm) is required for testing of biochemistry, renal and liver functions, as well as your electrolytes. It will involve taking approximately 10 ml of blood for the tests which is around 2 teaspoons.

This videoconference will take approximately 45-60 minutes. (breaks can be taken)

Visit 5: Videoconference call: 6 weeks follow-up

During this call, we will check how you have been and whether there have been any side-effects. The videoconference will be recorded. We will send you and your general practitioner (GP) the results of your brain tests, with an explanation of what they mean, as well as the results of your blood tests and your blood pressure recordings. We will ask you to mail us back the blood pressure machine (we will provide the courier bag).

This videoconference will take approximately 15-30 minutes.

Between visits 1-5: self-blood pressure and heart rate monitoring

We will ask you to record your blood pressure and heart rate twice a week during the four-week treatment period and for two weeks after stopping the study medication.

4. What are the alternatives to participation?

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

5. Are there any benefits?

This study aims to find out if we can complete a blood pressure trial for memory problems using new methods. If successful we plan to do a much larger trial for people with mild memory problems. Your participation may not directly benefit you.

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 are well-known and are outlined below.

Study medication

The possible side-effects of the Triple Pill are the same as if you were to take each 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 rapidly once the medication is stopped. The known side-effects most often seen when taking the full dose of the medications being used in the study are:

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

- nausea, diarrhoea, dizziness, muscle pain, low blood pressure

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

- sleepiness, pins and needle 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
- a small risk of postural hypotension and falls
- a small risk of electrolyte abnormalities

Telmisartan and indapamide, two of the three BP-lowering medications, 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. If you are eligible for Medicare, you can receive this for your injury or complication free of charge as a public patient in any public hospital.

In the event of loss or injury, the parties involved in this study agree to be bound by the *Medicines Australia Guidelines for Compensation for Injury Resulting from Participation in an Industry-Sponsored Clinical Trial*. A copy of these guidelines can be provided to you by the Research Coordinator.

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

Participation in this study will not cost you anything. You will not be paid for being in the study but will be reimbursed for travel to your local pathology centre for blood tests. The cost of the tests will be covered by the study.

9. What will happen to my test samples?

The collection of blood during this research study is an important part of the study. The tests are used to check it is safe for you to join the study, and also check that there have been no side-effects. None of the samples will be stored or used for future research.

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

You may continue to take your usual treatments whilst in this study. However, you should not start the study if you have very high blood pressure that needs ongoing treatment. Should you need treatment for your blood pressure during the study, or develop severe hypertension during the study, we would recommend telmisartan in a dose of 40mg as a suitable add-on. If you usually take over the counter medications, please discuss these with the study team.

11. 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.

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

If you decide to withdraw from the study, please notify a member of the research team right away and inform them of any medical problems you experienced or medications you have taken since the last study contact. This will allow the research team to further discuss any health risks or special requirements linked to withdrawing.

If you withdraw consent for further treatment, data will continue to be collected unless you specify otherwise. 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 your health information that has already been collected to be used, please notify the study team.

13. What happens when the research project ends?

The medications provided during this study will not be available at the end of the study. You will be referred back to your specialist/physician for the management of any high blood pressure, and this may include prescription of individual components of the medications being used in the Triple Pill.

Sometimes studies are extended so that researchers can find out more about long-term health outcomes. It is possible that the follow-up period for this study will be extended. By signing the consent form, you agree to be contacted by the researchers in the future to be invited to participate in an extension phase of the study.

14. Confidentiality / Privacy

Any identifiable information that is collected about you in 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.

All data collected will be entered electronically and stored on a research database called REDCap. This is a secure, web-based database application, hosted and backed up to The George Institute for Global Health servers on a daily basis. The data will be analysed by the researchers at the George

Institute. The files will be retained for 15 years from the day the study is completed. Once this retention expires, the files will be disposed of using a confidential waste disposal service.

The videoconferences will be conducted using the Zoom platform. They will be recorded, and the data stored on The George Institute for Global Health secure servers for a period of 15 years after which they will be deleted.

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 coded to protect your confidentiality and computer records will be password protected. Trial documentation will be kept and securely archived for 15 years.

Some of the information in this study may be collected by trained researchers appointed by The George Institute who will work independently from those managing the study. By signing this consent form, you are agreeing for your contact details to be stored in a secure password protected database that is accessible only by the staff at this study site and by the designated independent researchers who may contact you to find out whether you have had any serious events, such as stroke or whether you have been admitted to hospital, during the study. This database will be separate from the database containing your study data, and these will not be linked in any way so that confidentiality and de-identification of the information collected about you for the purpose of the study will be maintained.

If you are eligible, we will send you a blood pressure machine (OMRON) with instructions for use. If applicable you will also be asked if you are willing to download the blood pressure measurements using an app called OMRON connect on to your personal smart phone. The study staff can help you to set this up. OMRON connect is a standalone application which means that all your personal data will be stored on your phone only. All data will be encrypted to ensure your personal data cannot easily be accessed by unauthorised parties. Should you choose to download the app there will also be an option to use the OMRON cloud to store your data, instead of on your phone. The OMRON cloud is a private server that is hosted by OMRON in Singapore. To protect your privacy, you will be given a unique username and password. Alternatively, you can just record your blood pressure readings manually on a chart and send to us via email or provide over the phone.

15. 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 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. 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.

Further information

When you have read this information, the Principal Investigator and/or Research 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:

Study Doctor/Study Coordinator:

16. Permission to use your data for future research projects

Your de-identified data may be shared with other local or international collaborators and used for future research purposes, however, Human Research Ethics Committee (HREC) approval will be sought to prior to any future use of the data. You can indicate your agreement to this on the Consent Form.

Complaints:

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 X20-0284.

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.

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 TO PARTICIPATE IN RESEARCH

Title	**A**ction **T**o promote brain **HE**alth i**N** **A**dults (ATHENA) trial: pilot feasibility study
Short Title	ATHENA
Protocol Number	X20-0284
Project Sponsor	The George Institute for Global Health
Coordinating Investigator	Professor Craig Anderson

I, _____

[name]

of _____

[address]

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.
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.

6. 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.

7. I understand that my video conferences will be recorded.

8. I acknowledge that this research has been approved by: the Sydney Local Health District Human Research Ethics Committee.

9. I understand that my participation in this study will allow the researchers and regulatory authorities to have access to my medical records concerning my disease and treatment for the purposes of this project. I understand that the study team will communicate with my GP. However, I understand my identity will not be disclosed to anyone else or in publications or presentations.

10. 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.

11. I understand that I will be given a signed copy of this document and the Participant Information Sheet to keep either via electronic download, email or via post.

12. I consent to my contact details being provided to a courier service to facilitate the delivery of the study medication and blood pressure machine to me.

13. I acknowledge that my de-identified data may be shared with other local or international collaborators and used for future research purposes, and I agree to this: ☐ Yes ☐ No

Name of Participant _____

(please print – First name / Family name)

Signature _____ Date _____

Declaration by Witness

I have witnessed and certify the Participant's verbal consent for he/she to voluntarily agree to participate in this research study.

Signature of Impartial Witness	Date (day/month/year)

(to be completed only if the participant cannot read the patient 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 Doctor/Senior Researcher†

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

Name of Study Doctor/
Senior Researcher†

(please print – First name / Family name)

Signature Date

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

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