Participant Information Sheet/Consent Form

Title	A Randomized, Double-Blind, Parallel-Group, Placebo-Controlled, 60 Week, Phase II Clinical Trial of Three Re-Purposed Medications in Moderate Severity Parkinson's Disease
Protocol Number	APM001
Project Sponsor	The University of Sydney. The Australian Parkinson's Mission
Principal Investigator	
Associate Investigator(s) *(if required by institution)*	[Associate Investigator(s)]
Location *(where CPI/PI will recruit)*	[Site name]

1 Introduction

You are invited to take part in this research project. This is because you have Parkinson's Disease. The research project is testing three new treatments for Parkinson's Disease. The medicines are Alogliptin, Albuterol and Nilvadipine.

This Participant Information Sheet/Consent Form tells you about the research project. It explains the tests and treatments involved. Knowing what is involved will help you decide if you want 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 local doctor.

Participation in this research is voluntary. If you don't 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 project, 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 take part in the research project
- Consent to have the tests and treatments that are described
- Consent to the use of your personal and health information as described
- Consent to have your biological samples taken and stored for future Parkinson's Disease research.

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

2 What is the purpose of this research?

Parkinson's disease is a progressive neurologic disorder that mainly produces abnormal limb movements (motor symptoms). Current treatments for Parkinson's disease help reduce the disability of the abnormal movements, but do not slow or stop the underlying loss of brain cells. This research project is investigating whether three treatments (study medications) currently used for the treatment of other diseases are effective in treating Parkinson's Disease.

Alogliptin is approved in Australia to treat patients with Type 2 Diabetes Mellitus. Nilvadipine is approved in Europe and Japan to treat patients with high blood pressure. Albuterol (also known as salbutamol) is approved in Australia for patients with Asthma and Chronic Obstructive Pulmonary Disorder.

Alogliptin, Nilvadipine and Albuterol are experimental treatments for Parkinson's Disease in Australia. This means that they are not approved by the Therapeutic Goods Administration (TGA) in Australia as treatments for Parkinson's Disease. As they are experimental treatments, they must be tested to see if they are effective treatments for Parkinson's Disease. These treatments have been selected as prior research has shown that these medications have possible protective effects on the nervous system.

The purpose of this study is to determine the effectiveness of the three medications (all of which have known safety and tolerability records) in slowing the progression of Parkinson's Disease and maintaining a positive effect for a period after the medication has been stopped. Effectiveness of the medications will be compared when participants are taking their regular Parkinson's disease medications, and when they are not, to determine whether positive effects are maintained. Using rating scales and questionnaires, the study will also assess participants' cognition e.g. memory, and general health, and whether the medications impact involuntary movements, quality of life, changes in mood and anxiety, non-motor symptoms and physical activity. The study will explore effective doses and the use of new blood markers and genes in determining the benefits of the study medications.

This study is being conducted in Australia. There will be a total of 240 participants enrolled in the study at approximately 8 hospitals/clinics in Australia.

Current prescription medications for motor symptoms of Parkinson's disease include levodopa, dopamine agonists, monoamine oxidase type B (MAO -B) inhibitors, and amantadine. The aim of these medications is to improve motor function and quality of life. If you participate in this research, you will be allowed to continue taking your regular doses of these medications. If there are any changes to your Parkinson's Disease symptoms while participating in the study your medication may be modified if considered necessary by your study doctor.

Surgical deep brain stimulation is also an established treatment for motor symptoms in patients with moderate to severe Parkinson's disease. Surgical treatment is an option when motor symptoms continue to respond to levodopa but fluctuations and involuntary movements become disabling. If you have had prior surgical treatment such as deep brain stimulation Transcranial Direct-Current Stimulation, red light therapy or continuous infusion therapy for Parkinson's disease, you will not be able to participate in this research. If you do participate in this research but changes to your motor symptoms indicate that surgical deep brain stimulation is recommended, if you choose to have this surgery you will not be able to continue to participate in this study.

3 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 (randomisation). You will have a 1 in 4 chance of receiving one of the study medications, Alogliptin, Nilvadipine or Albuterol or placebo. A placebo is a medication with no active ingredients. It looks like the real thing but is not.

This is a double-blind study. This means that neither you nor your study doctor will know which treatment you are receiving. However, in certain circumstances your study doctor can find out which treatment you are receiving. This research project has been designed to make sure the researchers interpret the results in a fair and appropriate way and avoids study doctors or participants jumping to conclusions.

The study consists of a total of 6 scheduled visits. The screening visit will be two weeks before Visit 2. Your study medication will be assigned at Visit 2 and you will take this medication twice each day for 48 weeks. During this treatment period, you will have study visits every 12 weeks. At Visit 5 (week 48) your study medication will be stopped. You will then have one more clinic visit 12 weeks later (Visit 6). You will also be contacted via phone for a safety check 4 weeks after starting the study medication.

The total length of your involvement in the study from the screening visit to your last study visit will be 62 weeks.

The study medications will be in the form of capsules to be taken by mouth twice per day, once in the morning and once in the evening. If you are assigned active medication i.e. Alogliptin, Nilvadipine or Albuterol, the dose of medication you receive will be the standard dose that is approved for use in other conditions. The active medications will be enclosed in a capsule so you will not know which medication you are taking. The study medication should be stored at room temperature.

You will be provided with a study diary to record the time and number of capsules you take every day. The study staff will explain to you how to complete your diary.

You will be asked to bring study medication including all unused capsules, any empty packaging and your study diary with you to every study visit.

Study Procedures

Before you can receive study treatment, you will need to come in for screening tests and assessments to see if the study is suitable for you. The screening visit will be completed about 2 weeks before the start of study treatment.

Visit 1/Screening Visit

You will be asked to sign this informed consent form before any screening tests are done as part of this study. The following screening assessments will then be performed:

- You will be asked about your Parkinson's Disease, your non-Parkinson's Disease medical history and other illnesses, your current symptoms and medications.
- You will be assessed for depression using the Patient Health Questionnaire (PHQ-9)
- Physical examination, measurement of vital signs (heart and breathing rate, temperature, and sitting and standing blood pressure), and your weight and height.
- Standard blood tests (e.g. cell counts, chemistry, sugars, and a pregnancy test, only in woman who are able to get pregnant) requiring approximately 20mL (about 4 teaspoons) of blood;
- Collection of 22ml (or 4 teaspoons) of blood, less than half a teaspoon of saliva and a urine sample to study biomarkers and genes that are associated with Parkinson's Disease. 5mL (1

teaspoon) of the blood will be stored for future research
- Urine tests to check your general health
- Electrocardiogram (ECG) to check the electrical activity of your heart;

The visit should take approximately 2 hours. The results of these tests will determine if the study is suitable for you. If the results of the screening tests indicate that the study is not suitable for you, you will not be able to continue to participate. If this is the case the study doctor will discuss this with you and make arrangements for your regular health care to continue.

Visits during the Treatment Period

Visit 2
You will be asked to attend this visit after at least an eight hour overnight fast (no food or drink, except water). You will be asked to attend this visit in the morning before taking the first dose of your usual Parkinson's Disease medication. You will need to bring your usual medication with you and take it at the clinic after certain tests have been completed by your study doctor. You will be provided with light refreshments after certain tests have been done. The following assessments will be performed during this visit:

- Review of current medications
- Measurement of vital signs and weight
- Standard blood tests (e.g. cell counts, chemistry, sugars, and a pregnancy test, only in woman who are able to get pregnant) requiring approximately 20mL (about 4 teaspoons) of blood
- Collection of 45mL (8 teaspoons) of blood, and saliva and urine samples for biomarker research and storage of blood (5mL or 1 teaspoon) for future research
- Before taking your normal Parkinson's Disease medication your motor symptoms will be assessed, via the Movement Disorder Society - Unified Parkinson Disease Rating Scale ("MDS-UPDRS") Part III physical assessment
- After taking your usual medication for Parkinson's Disease, the following will be done:
    - MDS-UPDRS Part I, II, III and IV physical examination to assess disease severity
    - And you will be asked to complete the following questionnaires;
        - Montreal Cognitive Assessments (MoCA) to assess cognition e.g. memory
        - Parkinson's Disease Questionnaire (PDQ-39) to assess your quality of life
        - Unified Dyskinesia Rating Scale (UDysRS) to assess involuntary movements
        - Hospital Anxiety and Depression Scale (HADS) to assess mood and anxiety
        - Physical Activity Scale for the Elderly (PASE) to assess your physical activity
        - Non-Motor Symptoms Scale (NMSS) to assess your symptoms which are not related to movement
        - Patient's Global Impression of Change (PGIC) to assess your overall impression of your current health

      Completion of these questionnaires will take about 30minutes. If you become tired or distressed while completing them, let a member of the research team know. You might need a rest or refreshment.

If the screening tests show that the study is not suitable for you, you will not be able to continue in the study. Other treatment options will be discussed with you. If the study is still suitable for you, your study medication will be assigned, you will be instructed on how to take it, and you will take your first dose in the clinic during this visit. You will be provided with enough study medication to last until the next study visit, and a study diary to take home.

This visit should take approximately 2 to 3 hours.

4 Week Safety Check – Via Telephone

You will receive a telephone call from a study staff member to ask about your health since the last visit, if there have been any changes to your medication, and also how many capsules of the study medication you have taken since you began study treatment.

Visit 3 / Week 12
You will be asked to attend this visit after at least an eight hour overnight fast (no food or drink, except water). You will be provided with light refreshments after certain tests have been done. You will need to take your usual Parkinson's Disease medication at home before attending this visit. You will need to bring your study medication and study diary with you. The following tests will be completed during this visit:

- Review of your health and medications
- Measurement of vital signs and weight
- Electrocardiogram (ECG)
- Collection of 20ml (or 4 teaspoons) of blood for standard blood tests
- Collection of 20ml (or 4 teaspoons) of blood, and a saliva and urine sample for biomarker research and storage of blood (5mL or 1 teaspoon) for future research
- The following assessments and questionnaires will be completed:
    - MDS-UPDRS Part I, II, III and IV physical assessment
    - PGIC questionnaire
    - UDysRS
    - PDQ-39
    - HADS
    - NMSS
    - PASE
- Review of returned study medication and study diary.

This visit should take approximately 2 to 3 hours.

Visit 4 / Week 24
You will be asked to attend this visit in the morning before taking your usual Parkinson's Disease medication. You will need to bring your usual medication with you and take it at the clinic as directed by your study doctor. You will also need to bring your study medication and study diary with you. The following assessments will be completed during this visit:

- Review of your health and medications
- Measurement of vital signs and weight
- Collection of 45mL (8 teaspoons) of blood, for biomarker research including storage of blood (5mL or 1 teaspoon) for future research
- MDS-UPDRS Part I, II, III (to be completed both before and after usual Parkinson's Disease medication) and IV physical assessment
- PGIC questionnaire
- Review of returned study medication and study diary.

This visit should take approximately 2 to 3 hours.

Visit 5 / Week 48
You will be asked to attend this visit in the morning before taking your usual Parkinson's Disease medication. You will need to bring your usual medication with you and take it at the clinic as directed by your study doctor. You will also need to bring your study medication and study diary with you. The following assessments will be completed during this visit:

- Review of your health and medications
- Physical examination, measurement of vital signs and weight

- Electrocardiogram (ECG)
- Collection of 45mL (8 teaspoons) of blood, and saliva and urine samples for biomarker research including storage of blood (5mL or 1 teaspoon) for future research
- The following assessments and questionnaires will be completed:
    - MDS-UPDRS MDS-UPDRS Part I, II, III (to be completed both prior and after usual PD medication) and IV physical assessment
    - MoCA
    - PGIC questionnaire
    - UDysRS
    - PDQ-39
    - HADS
    - NMSS
    - PASE
- Final dose of study medication
- Review of returned study medication and completed diary

This visit should take approximately 2 to 3 hours.

Visit 6 / Week 60 – Final Study Visit
You will be asked to attend this visit in the morning prior to taking your usual Parkinson's Disease medication. You will need to bring your usual medication with you and take it at the research site as directed by your study doctor. The following assessments will be completed during this visit:

- Review of your health and medications
- Measurement of vital signs and weight
- Collection of 45mL (8 teaspoons or 10% of a typical blood donation) of blood, and saliva and urine samples for biomarker research including storage of blood (5mL or 1 teaspoon) for future research
- The following assessments and questionnaires will be completed:
    - MDS-UPDRS Part I, II, III (to be completed both before and after usual Parkinson's Disease medication) and IV physical assessment
    - MoCA
    - PGIC
    - UDysRS
    - PDQ-39
    - HADS
    - NMSS
    - PASE

This visit should take approximately 2 to 3 hours.

If you decide to stop participating at any stage throughout the study before Week 48, you will be asked to return to the clinic for one final visit. The Visit 5 procedures will be completed at this visit.

4 What do I have to do?

If you decide to participate:

- You need to attend the clinic visits and cooperate in the study procedures as described in Section 3 above
- You must not take part in any other studies while you are taking part in this study
- You need to inform your study doctor 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 your study doctor if you start any new medication or stop any medication that you are already taking. This includes prescribed or over the counter products, even if used short term (such as a pain killer for headache)
- You need to keep your diary up to date and bring it to every study visit
- Return all study medication and packaging of used medication to every visit
- You need to inform the study doctor if you decide not to continue in the study. You don't have to give a reason for your decision

5 Other relevant information about the research project

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

You will be reimbursed up to $50 per visit for any reasonable travel, parking, meals, and other expenses associated with the research project visit, provided you can produce receipts.

Your local doctor will be advised of your decision to participate in this research project.

6 Do I have to take part in this research project?

Participation in any research project 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 project at any stage.

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

Your decision whether to take part or not 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 [Site name].

7 What are the alternatives to participation?

You do not have to take part in this research project to receive treatment at [INSERT SITE NAME]. You may continue getting care for your disease without being in this research project or you may be able to take part in another research project. Your study doctor will discuss these options, including their possible benefits and risks, with you before you decide whether or not to take part in this research project. You can also discuss the options with your local doctor.

8 What are the possible benefits of taking part?

We cannot guarantee or promise that you will receive any benefits from this research.
The study medications are experimental in Parkinson's Disease, so study treatment may or may not have any direct medical benefit to you. Others may benefit from the information learned in this study. This research may help to develop a new therapy for others with similar conditions.

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

Medical treatments often cause side effects. You may have none, some, or all of the effects listed below, and they may be mild, moderate, or severe. If you have any of these side effects, or are worried about them, talk with your study doctor. Your study doctor will also be looking out for side effects.

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

Many side effects go away shortly after treatment ends. However, sometimes side effects can be serious, long lasting or permanent. If a severe side effect or reaction occurs, your study doctor may need to stop your treatment. Your study doctor will discuss the best way of managing any side effects with you.

Alogliptin:

Information on the frequency of side effects is based on the following categories: ; common (1 in 100 to less than 1 in 10 people); uncommon (1 in 1000 to less than 1 in 100); rare (1 in 10,000 to less than 1 in 1000);

Common (1 in 100 to less than 1 in 10):

- Headache
- Infection of the upper respiratory tract
- Nasopharyngitis, which is an infection on the inside of the nose and back of the throat

Uncommon (1 in 1000 to less than 1 in 100):

- Swelling in arm or leg caused by blocked lymph flow
- Kidney impairment
- Low blood sugar level
- Vomiting
- Anxiety
- Inflammation of the Pancreas

Rare (1 in 10,000 to less than 1 in 1000):

- Heart failure
- Sudden serious allergic reaction which may cause death
- Angioedema (swelling of the area beneath the skin affecting the deeper layers)

Other reported side effects:

- Serious allergic reaction that causes fever, aches and pains in the joints, skin rash and swollen lymph glands were observed in patients treated with Alogliptin in clinical trials.
- Stevens-Johnson syndrome which is a rare, serious disorder of skin and mucous membranes has been reported with Alogliptin after the drug was marketed.

Nilvadipine:

Common side effects associated with Nilvadipine result from its vasodilator effects (preventing the muscles in the walls of the arteries and veins from tightening and the walls from narrowing which results in blood flowing more easily through the blood vessels) and include the following side effects based on the following categories: common (1 in 100 to less than 1 in 10 people); uncommon (1 in 1000 to less than 1 in 100); rare (1 in 10,000 to less than 1 in 1000);

Common (1 in 100 to less than 1 in 10):

- Facial Flushing, which means sudden reddening of the face
- Hot Flashes, which is a sudden feeling of warmth, usually most intense over the face, neck and chest, and profuse sweating
- Headaches, Irregular heartbeat

Uncommon (1 in 1000 to less than 1 in 100):

- Metabolism and nutrition disorders: Elevated levels of chemicals in the liver and kidneys.
- Nervous System Disorders: Headache, dizziness, instability, lightheadedness
- Digestive organs disorders: Anorexia, abdominal pain, abdominal discomfort, nausea
- Others: Irregular heartbeat, Headache, Rash, itching, sudden reddening of face, hotness, blood rushing to the head, sudden reddening of the face and/or neck, swelling, and a general feeling of discomfort, illness, or unease

Rare (1 in 10,000 to less than 1 in 1000):

- Metabolism and nutrition disorders: Elevated levels of chemicals in the kidneys.
- Difficulty in breathing
- Nervous System Disorders: Drowsiness, insomnia, numbness, tremors (uncontrolled shaking)
- Digestive organs disorders: Vomiting, constipation, diarrhea, inflammation of the mouth and lips, dry mouth, heartburn
- Others: Allergic to light, Gingival hypertrophy (overgrowth of gum tissue around the teeth), chest pain, chest discomfort, frequent urination, tinnitus (perception of noise or ringing in the ears), elevated fat levels in blood, cough, inflammation of the eyes leading to redness and watery eyes.

Albuterol:

Information on the frequency of side effects is based on the following categories: common (1 in 100 to less than 1 in 10 people); uncommon (1 in 1000 to less than 1 in 100); rare (1 in 10,000 to less than 1 in 1000); very rare (less than 1 in 10,000); not known (frequency cannot be estimated from the available data).

Common (1 in 100 to less than 1 in 10):

- Metabolism and nutrition disorders: changes such as decreased blood potassium level or high blood sugar level, increased blood levels of insulin, fatty acids, and other chemicals
- Nervous system disorders: headaches, restlessness, heart palpitations, fine tremor (uncommon with longer use), dizziness (uncommon with longer use)
- Cardiac disorders: fast heartbeat and palpitations (particularly at high dosage)
- Gastrointestinal disorders: nausea (uncommon with longer use)
- Skin and tissue disorders: sweating (uncommon with longer use)
- Muscle and connective tissue disorders: muscle cramps (uncommon with longer use)

Uncommon (1 in 1000 to less than 1 in 100):

- Muscle and connective tissue disorders: muscle pain

Rare (1 in 10,000 to less than 1 in 1000):

- Cardiac disorders: increase or decrease in blood pressure, chest pain or fast heartbeat

- Gastrointestinal disorders: mouth and throat irritation, heartburn
- Kidney and urinary disorders: abnormalities with doing a wee

Very rare (less than 1 in 10,000):

- Immune systems disorders: allergic reactions including itchy skin, hives, swelling of the lower layer of skin/tissue just under the skin, bruising, rash, irritation of the small airways or wheezing, drop in blood pressure, and collapse
- Nervous system disorders: hyperreactivity, abnormal hyperactive behavior, sleep disorders, hallucinations
- Cardiac disorders: irregular heartbeat, decreased blood supply to the heart/ heart attack
- Respiratory and chest disorders: worsening of breathing and wheezing (treatment should be stopped immediately in that case)
- Kidney and urinary disorders: hypersensitivity reactions (e.g. kidney inflammation)

Not known (frequency cannot be estimated from the available data):

- Metabolism and nutrition disorders: cases of lactic acidosis have been reported during Albuterol therapy. Symptoms include abdominal or stomach discomfort, decreased appetite, diarrhea, fast, shallow breathing, a general feeling of discomfort, muscle pain or cramping, and unusual sleepiness, tiredness, or weakness.

Your study doctor will monitor you throughout the study for side effects. If you experience any of the described side effects or have any other problems, you must immediately tell the study staff or your study doctor. For emergency afterhours care, go to your nearest hospital emergency department, or if this is not possible, dial the emergency phone number (000) and alert the study doctor and study staff as soon as possible.

While participating in the study you will continue taking your regular doses of medications e.g. levodopa, dopamine agonists, MAO -B inhibitors, amantadine, for the treatment of Parkinson's disease symptoms. If there are any changes to your Parkinson's Disease symptoms during the study, your regular medication may be adjusted (increased or decreased) if considered necessary by your study doctor.

[Non-Catholic Wording – retain/delete as required for site specific PICSF]

Pregnancy Risks

The effects of Alogliptin, Albuterol and Nilvadipine on the unborn child and on the newborn baby are not completely known. Because of this, it is important that research project participants are not pregnant or breast-feeding and do not become pregnant during the course of the research project. You must not participate in the research if you are pregnant or trying to become pregnant, or breast-feeding. If you are female and child-bearing is a possibility, you will be required to undergo a pregnancy test prior to commencing the research project. If you are male, you should not father a child or donate sperm for at least 3 months after the last dose of study medication.

Both male and female participants are required to use effective contraception during the course of the research and for a period of 3 months after completion of the research project. You should discuss methods of effective double barrier contraception with your study doctor.

[For female participants] If you do become pregnant whilst participating in the research project, you should advise your study doctor immediately. Your study doctor will withdraw you from the research project and advise on further medical attention should this be necessary. You must not continue in the research if you become pregnant. Your study doctor will invite you to sign a separate consent form to allow monitoring of your pregnancy and the birth and the health of your child up to twelve months of age.

[For male participants] You should advise your study doctor if you father a child while participating in the research project. Your study doctor will advise on medical attention for your partner should this be necessary. The study doctor will then provide you with a separate consent form inviting your partner to approve access to medical information to allow monitoring of the pregnancy, and the birth and the health of the child up to twelve months of age.

If you become upset or distressed as a result of your participation in the research, the study doctor will be able to arrange for counselling or other appropriate support. Any counselling or support will be provided by qualified staff who are not members of the research project team. This counselling will be provided free of charge.

[Catholic Wording – retain/delete as required for site specific PICSF]

The effects of Alogliptin, Albuterol and Nilvadipine on the unborn child and on the newborn baby are not known. Because of this, it is important that research project participants are not pregnant or breast-feeding and do not become pregnant during the course of the research project. You must not participate in the research if you are pregnant or trying to become pregnant, or breast-feeding. If you are female and child-bearing is a possibility, you will be required to undergo a pregnancy test prior to commencing the research project. If you are male, you should not father a child or donate sperm for at least 3 months after the last dose of study medication.

Both male and female participants must avoid pregnancy during the course of the research and for a period of 3 months after completion of the research project. You should discuss effective methods of avoiding pregnancy with your study doctor.

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

[For male participants] You should advise your study doctor if you father a child while participating in the research project. Your study doctor will advise on medical attention for your partner should this be necessary.

Procedural Risks

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

ECG (electrocardiogram)
For the ECGs you will have pads placed on different parts of your body. There is no pain or discomfort during an ECG; however, removing the pads may cause some irritation to your skin.

You will be asked to attend some study visits before taking your usual morning dose of dopaminergic medication (Sinemet or / Kinson/Madopar/Stalevo/Sifrol) to allow the assessment of your Parkinson's disease before medication. For some people this may result in some discomfort due to stiffness, slowness and reduced walking speed. You will be able to take your medication after the study doctor has completed certain examinations and these symptoms will then resolve. There are no further consequences of delaying your usual medication in this way. If you are concerned about the effects of this please discuss this with your study doctor.

10 What will happen to my test samples?

The study is designed to test first whether the medications used impact the clinical symptoms of Parkinson's disease or your health, and second if there was a biological impact. The medical implications of such results, if any, will require further validation and potentially other studies like this one.

Local Laboratory Samples
Blood and urine samples collected for standard safety evaluations will be tested at the local laboratory. These samples will be labelled with your name and date of birth, as they would be if you were not in the research study. However, when the results from the testing of your samples are transferred to the study sponsor, they will not contain your name, only your study participant number. These samples will be securely destroyed after testing, according to the local laboratory's standard procedures

Central Laboratory Samples
Blood, urine and saliva research samples will be sent to a central laboratory for processing. The central laboratory is located at the University of Sydney. These samples will be labelled with your study participant number. The samples will not include your name or other information that could identify you. Your blood samples will be separated into DNA (deoxyribonucleic acid which holds the genetic material to build all cells), RNA (ribonucleic acid which reads and transcribes DNA into proteins), blood cells, plasma and serum.

Some of these blood products will be distributed to other Australian APM collaborative laboratories for testing, and the remaining samples stored for additional testing depending on the trial outcomes, or for further scientific biomarker discovery for Parkinson's and related diseases. The storage of these samples for future research is called "biobanking or biorepository". A biorepository is a type of facility that receives, stores, processes and distributes biological samples as well as the study data related to those samples. Biobanks provide scientists with access to the samples and study data to conduct research. It is not possible to predict all of the ways in which biorepositories might be used in the future, so it is not possible to tell you exactly how your sample will be used. However, this future research may also include genetic research. The sponsor will send your **coded** study data collected in the study to the biorepositories along with your sample. The APM biorepository is located at the University of Sydney and Garvan Medical Research Institute. These sites have been chosen to house the biorepository due to the international recognition of their expertise in Parkinson's disease research, and on their available infrastructure and expertise in handling and storing the different types of biospecimens collected.

Management of the biorepository will be through the biobank working committee and an independent scientific advisory and review committee that report to the Steering Committee of the Australian Parkinson's Mission on all processes associated with the biorepository and standardized testing of the samples.

Only those associated with the biorepository will have access to the coded data from the trial, data from the standardized and research tests, and information on the number, type and location of samples held by the biorepository through a secure, password-protected database kept on a secure, password-protected server in a secure, restricted-access building. Large, raw data files will also be kept on secure, password-protected servers in secure, restricted-access buildings by the data custodians, and their locations stored in the secure, password-protected database of the biorepository.

Analyses of your sample may include but is not limited to the following:

1. Measuring levels of different proteins, hormones, fats and RNAs in blood, urine and saliva to look for biomarkers

Biomarkers are molecules found in the blood that are a sign of a normal or abnormal process or disease – in this case related to Parkinson's disease. A biomarker may be used to see how well the body responds to a treatment for a disease or condition. Researchers hope to identify biomarkers that will help us understand:

- how your disease may behave with or without treatment,
- what kind of side effects a person might have when they receive different kinds of treatment,
- how your condition might respond to the study treatment,
- which patients might benefit the most from this type of treatment.

2. Genetic research

Genes are made of DNA – the chemical structure carrying your genetic information that determines many human characteristics such as the colour of your eyes or hair. Researchers study genes in order to understand why some people have certain conditions and why some people do not. Our genes are like a set of instructions that help bodies to work properly. We all have approximately 20,000 genes. This is called our genome. Some of our genome is unique to each of us, but we do share most of it with our relatives.

Recent developments in science and technology mean that it has become possible to look at the whole of a person's genome at once, to try to understand more about the genetic causes for disease. In this study we are planning to see whether there are any gene variations in all 20,000 of your genes, using a technique called Whole Genome Sequencing (WGS). By using WGS we can see if there are any relationships between your genetic material and the response to the study drug therapy, as well as any relationships to Parkinson's disease.

In a small number of study participants WGS will unexpectedly reveal variations in genes that may be important to you and your family i.e. genetic information unrelated to Parkinson's disease although considered of significance to the health of you and/or your family. These genetic variation can increase the risk of other health conditions e.g. cancer.

Genetic information is available to research participants for conditions where there is the potential for prevention, early detection and reducing the risk of the condition. Some people wish to know this information and some do not. In the consent form we will ask you to indicate if you wish to be informed or not be informed about these unexpected genetic findings. If you choose to be informed, and we identify a genetic finding of relevance to you and/or your family's health, we will send you a letter explaining that unexpected genetic information has been identified. The letter will contain the contact details (phone number and email) of a Genetic Counsellor who can provide you with further information about the genetic variation and what it may mean for you and your family. The genetic counsellor can also arrange an appointment for you at a specialist genetics clinic. If there is an unexpected genetic finding and you choose to be informed we will provide the report regarding the finding to the genetic counsellor and inform them that you have been sent a letter about the finding. The genetic counsellor will keep your information confidential. You will be asked to nominate a next of kin who can receive unexpected genetic findings in the future, in the event you are deceased. This is because the genetic information may have relevance to family members.

In the event that there is an unexpected genetic finding and you choose to be informed of this information, it may have implications for life insurance policies. Life insurance premiums are assessed on the applicant's health risks taking into consideration past and present health, family history, other risk factors such as smoking as well as any genetic information. The Moratorium on Genetic Tests in Life Insurance came into effect from 1 July 2019 and will end on 30 June 2024. This means that from 1 July 2019, for 5 years, insurers will not be able to use genetic test results when considering an insurance application up to the value of $500,000 (for death and total permanent disability), $200,000 for trauma and $4,000 a month for income protection. For further information please see: https://www.genomicsinfo.org.au/resources/

If you have any questions about life insurance we recommend you speak with your insurer before making a decision whether or not to be informed of unexpected findings. The moratorium applies to insurance companies who are members of the Financial Services Council of Australia.

3. Use of stored blood cells

In addition to using stored blood cells for biomarker measurements, these cells may also be used for cell models of disease (where cells are grown in a culture and manipulated to induce a disease state that treatments can be tested on). Cell models could include the generation of induced Pluripotent Stem (iPS) cells from the stored blood cells. Blood cells can be reprogrammed to become pluripotent that is, they have the ability to form all cell types of the body, including cells of the brain. iPS cells have almost all the same properties as embryonic stem cells, but are not made from an embryo. The use of these brain cell models will allow different cells of the brain to be used in discovery research to further the understanding of the mechanisms of disease and importantly to identify and/or test suitable therapies. Testing of potential therapies in cell models is a valuable approach to assess potential effectiveness before they are considered for a subsequent clinical trial involving patients. Each person's cells have unique genetic information (see above) and therefore the disease is likely to differ slightly in everyone, thus the need for this type of research. The iPS cells are not for use in patient cell replacement based studies/therapies.

Samples utilised for the biomarkers indicated and WGS testing will be fully used except those samples added to the biorepository. The samples will be managed, stored, tested and disposed of in accordance with good laboratory practice and applicable local regulations. The research using your samples will not affect your ongoing medical care.

11 What if new information arises during this research project?

Sometimes during the course of a research project, 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 doctor will tell you about it in a timely manner and discuss with you whether you want to continue in the research project. If you decide to withdraw, your study doctor will make arrangements for your regular health care to continue. If you decide to continue in the research project, you will be asked to sign an updated consent form.

Also, on receiving new information, your study doctor might consider it to be in your best interests to withdraw you from the research project. If this happens, he/ she will explain the reasons and arrange for your regular health care to continue.

12 Can I have other treatments during this research project?

Whilst you are participating in this research project, you may not be able to take some or all of the medications or treatments you have been taking for your condition or for other reasons. It is important to tell your study doctor and the study staff 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 study doctor about any changes to these during your participation in the research project. Your study doctor should also

explain to you which treatments or medications need to be stopped for the time you are involved in the research project.

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

13 What if I withdraw from this research project?

If you decide to withdraw from the project, please notify a member of the research team before you withdraw. This notice will allow that person or the research supervisor to discuss any health risks or special requirements linked to withdrawing.

If you do withdraw your consent during the research project, the study doctor and relevant 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 project 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 research project results.

14 Could this research project 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
- The study is canceled by University of Sydney.

This research project 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.

15 What happens when the research project ends?

The study medications are not yet proven for use in Parkinson's Disease. Therefore, you will not be able to continue to receive the study medication indefinitely. When the study ends, the study doctor will discuss treatment choices with you.

If you wish, the study doctor will provide you with a summary of the results of the study when they become available, usually about 6 months after the study ends.

16 What will happen to information about me?

By signing the consent form you consent to the study doctor and relevant research staff collecting and using personal information about you for the research project. Any information obtained in connection with this research project that can identify you will remain confidential. Your medical records are confidential. Any information about you that is sent out of the study site will have a code and will not show your name or address, or any information that directly identifies you. Your collected information will be labelled with a unique study code only. Your information will only be used for the purpose of this research project and it will only be disclosed with your permission, except as required by law.

Information about you may be obtained from your health records held at this and other health services for the purpose of this research. By signing the consent form you agree to the study team accessing health records if they are relevant to your participation in this research project.

Your health records and any information obtained during the research project are subject to inspection (for the purpose of verifying the procedures and the data) by the relevant government health authorities, such as the Therapeutic Goods Administration (TGA), and authorised representatives of the Sponsor, University of Sydney, the Human Research Ethics Committee that reviewed this project, the institution relevant to this Participant Information Sheet, [Site name], or as required by law. By signing the Consent Form, you authorise release of, or access to, this confidential information to the relevant study personnel and regulatory authorities as noted above.

All study information will be stored securely in the *[insert name]* Department at *[insert name of institution]* for the duration of the study and then transferred to a secure storage facility.

The information will be kept until at least 15 years following the closure of the study. After this time, it will be securely destroyed.

It is anticipated that the results of this research project will be published and/or presented in a variety of forums. In any publication and/or presentation, information will be provided in such a way that you cannot be identified, except with your permission.

Information about your participation in this research project may be recorded in your health records.

In accordance with relevant Australian *and/or [Name of state/territory]* privacy and other relevant laws, you have the right to request access to your information collected and stored by the research team. You also have the right to request that any information with which you disagree be corrected. Please contact the study team member named at the end of this document if you would like to access your information.

Any information obtained for the purpose of this research that can identify you will be treated as confidential and securely stored. It will be disclosed only with your permission, or as required by law.

Your samples and your study data may be given to qualified researchers in the research community (which may include national and international researchers from academia, charitable organisations and 'for-profit' private companies, such as pharmaceutical companies).

Researchers who would like to do future research using your biorepository samples will sign agreements that control use of the study data and the samples. They will not be permitted to disclose or to transfer study data or samples to anyone else. They will also not be permitted to use samples or study data for purposes other than those included in the agreements. Researchers will also agree that they will not attempt to re-identify you from your study data and samples.

The information from the biobank will be available only to researchers who have received prior scientific and Human Research Ethics Committee approval for their research.

A description of this clinical trial will be available on ANZCTR. 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.

17 Complaints and compensation

If you suffer any injuries or complications as a result of this research project, you should contact the study team as soon as possible and you will be assisted with arranging appropriate medical treatment. If you are eligible for Medicare, you can receive any medical treatment required to treat the injury or complication, free of charge, as a public patient in any Australian public hospital.

You may have a 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 caused by the drugs or procedures, or by the negligence of any of the parties involved in the study. If you receive compensation that includes an amount for medical expenses, you will be required to pay for your medical treatment from those compensation monies.

If you suffer an injury as a result of your participation in this research project, you may be able to seek compensation through the courts. Participants in this study are covered by a no-fault insurance provided by the University of Sydney. It is the recommendation of the independent ethics committee responsible for the review of this trial that you seek independent legal advice before taking any steps towards compensation for injury.

18 Who is organising and funding the research?

This research project is being conducted and funded by The Australian Parkinson's Mission. The study is sponsored in Australia by The University of Sydney. The University of Sydney have contracted Novotech (Australia) Pty Limited to monitor the study and collect and analyze study results.

By taking part in this research project you agree that samples of your blood, saliva, and urine (or data generated from analysis of these materials) may be provided to The Australian Parkinson's Mission.

The Australian Parkinson's Mission may directly or indirectly benefit financially from your samples or from knowledge acquired through analysis of your samples. In the event, the Australian Parkinson's Mission does benefit financially, any funds would be used for future Parkinson's Disease research.

You will not benefit financially from your involvement in this research project even if, for example, your samples (or knowledge acquired from analysis of your samples) prove to be of commercial value to The Australian Parkinson's Mission

In addition, if knowledge acquired through this research leads to discoveries that are of commercial value to The Australian Parkinson's Mission the study doctors or their institutions, there will be no financial benefit to you or your family from these discoveries.

[Site name] will receive a payment from The Australian Parkinson's Mission for undertaking this research project to be able to facilitate the work conducted.

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

19 COVID-19

In light of the COVID pandemic, the Australian Parkinson's Mission would like to alert participants that all sites will be working to the national guidelines which may involve confirming the participants health status prior to their scheduled visit and rescheduling visits in the event that you are sick with the flu or COVID-19. At your visit, the site will request your COVID-19 status.

20 Advice and Information

If you have any further questions regarding this study, please do not hesitate to contact Dr(s) _____ on _____ . The Bellberry Human Research Ethics Committee has reviewed and approved this study in accordance with the National Statement on Ethical Conduct in Human Research (2007) – incorporating all updates. This Statement has been developed to protect the interests of people who agree to participate in human research studies. Should you wish to discuss the study or view a copy of the Complaint procedure with someone not directly involved, particularly in relation to matters concerning policies, information or complaints about the conduct of the study or your rights as a participant, you may contact the Operations Manager, Bellberry Limited on 08 8361 3222. All study participants must be provided with a signed and dated copy of the Participant Information Sheet and Consent Form for their personal records.

Consent Form - *Adult providing own consent*

Title	A Randomized, Double-Blind, Parallel-Group, Placebo-Controlled, 60 Week, Phase II Clinical Trial of Three Re-Purposed Medications in Moderate Severity Parkinson's Disease
Protocol Number	APM001
Project Sponsor	The University of Sydney. The Australian Parkinson's Mission
Principal Investigator	

Associate Investigator(s) *(if required by institution)*	[Associate Investigator(s)]
Location *(where CPI/PI will recruit)*	[Site name]

Declaration by Participant

I have read the Participant Information Sheet or someone has read it to me in a language that I understand.

I understand what research is being done, what participating involves for me and the risks if I participate in this research.

I understand the research involves biological sample collections that will be used for future research related to Parkinson's Disease. These samples will be stored in the APM biorepository.

I understand that if I chose to receive unexpected genetic findings from whole genome sequencing that it may affect life insurance products.

I *do not want* ☐ or

I *do want* ☐ to be made aware of unexpected genetic findings.
(tick and initial one)

and I nominate _____ of _____, as next of kin, to be given my unexpected genetic findings in the future in the event I am deceased.

I consent to my treating Doctor/s being notified of my participation in this study and of any clinically relevant information.

I give permission for my doctors, other health professionals, hospitals or laboratories outside this hospital to release information to [Site name] concerning my disease and treatment for the purposes of this project. I understand that such information will remain confidential.

I have had an opportunity to ask questions and I am satisfied with the answers I have received.

I understand if I fail the study screening and cannot continue to participate in the study:

I *want* ☐ or

I *do not want* ☐ my samples collected during the screening visit used for future research.

I have been given the opportunity to have a member of my family or another person present while the study is explained to me.

I am 18 years or over.
I freely agree to participate in this research project as described and understand that I am free to withdraw at any time during the study without affecting my future health care.

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

Name of Participant (please print) _____

Signature _____ Date _____

Under certain circumstances (see Note for Guidance on Good Clinical Practice CPMP/ICH/135/95 at 4.8.9*) a witness* to informed consent is required.*

Name of Witness* to
Participant's Signature (please print) _____

Signature _____ Date _____

* Witness is not to be the investigator, a member of the study team or their delegate. In the event that an interpreter is used, the interpreter may not act as a witness to the consent process. Witness must be 18 years or older.

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) _____

Signature _____ Date _____

† A senior member of the 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.

Form for Withdrawal of Participation - *Adult providing own consent*

Title	A Randomized, Double-Blind, Parallel-Group, Placebo-Controlled, 60 Week, Phase II Clinical Trial of Three Re-Purposed Medications in Moderate Severity Parkinson's Disease
Protocol Number	APM001
Project Sponsor	The University of Sydney. The Australian Parkinson's Mission
Coordinating Principal Investigator/ Principal Investigator	[Coordinating Principal Investigator/Principal Investigator]
Associate Investigator(s) *(if required by institution)*	[Associate Investigator(s)]
Location *(where CPI/PI will recruit)*	[Site name]

Declaration by Participant

I wish to withdraw from participation in the above research project and understand that such withdrawal will not affect my routine treatment, my relationship with those treating me or my relationship with [Site name] .

Name of Participant (please print) _____

Signature _____ Date _____

In the event that the participant's decision to withdraw is communicated verbally, the Study Doctor/Senior Researcher will need to provide a description of the circumstances below.

Declaration by Study Doctor/Senior Researcher†

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

Name of Study Doctor/
Senior Researcher† (please print) _____

Signature _____ Date _____

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

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