PARTICIPANT INFORMATION SHEET AND CONSENT FORM

Study Title: A randomised, double-blind, placebo-controlled crossover pilot study investigating the effects of cannabinol (CBN) 30 mg and 300 mg on sleep architecture and next-day function in insomnia disorder.
Protocol Number: 2021-08-907

Project sponsor: The Woolcock Institute of Medical Research

Co-Principal Investigators: Professor Brendon Yee and Dr Camilla Hoyos

Location: The Woolcock Institute of Medical Research, 431 Glebe Point Road, Glebe, Sydney.

PART 1: WHAT DOES MY PARTICIPATION INVOLVE?

Introduction

This 'Participant Information and Consent Form (PICF)' document tells you about the above-named research project and explains the tests and procedures involved. It also describes information about you that will be obtained, how that information will be used and with whom it will be shared. Knowing what is involved will help you decide if you want to take part in the research.

Please read this information carefully and 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 and you can withdraw at any point. If you don't wish to take part, you don't have to.

If you decide you want to take part in the research project, you will be asked to sign the Consent Form (the last page of this document). 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

You will be given a signed and dated copy of this PICF for your records.

Who is undertaking the project?

This study is being conducted by researchers at the Woolcock Institute of Medical Research and the Lambert Initiative of Cannabinoid Therapeutics, University of Sydney. The study is being supported by funding from the Lambert Initiative for Cannabinoid Therapeutics.

Why am I being invited to participate?

You are invited to take part in this research study because you are an adult aged 25 to 65 years of age with insomnia disorder, who is able to take oral medication.

What is the purpose of this study?

Insomnia symptoms occur in about a third of adults, affecting emotional, social, and physical wellbeing. The current treatments include improving sleep habits, behaviour therapy, identifying and treating a possible underlying cause, and sleep medications. Unfortunately, many of the sleep medications have potential dependency and abuse issues or other undesirable side effects. It has been

suggested that cannabis can help to promote sleep; however, it is still not completely known how cannabis affects sleep.

The cannabis plant contains many '*cannabinoids'*, of which tetrahydrocannabinol (THC) and cannabidiol (CBD) are the two best-known. THC is primarily responsible for getting people intoxicated ("stoned") whereas CBD does not have any intoxicating effects and is thought to have anti-anxiety properties.

Another cannabinoid, cannabinol (CBN), is found in low quantities in the cannabis plant and is produced by the aging of THC. CBN doesn't seem to have any intoxicating effects and has been proposed to help sleep; however, CBN has not been examined on its own for insomnia.

In this study, we are trying to find out whether a pharmaceutical-grade oral CBN medication (*Bod ECS310*) may help people with insomnia disorder. You will be asked to attend the sleep laboratory to examine the effects of the medication on your sleep as well as your functioning (including memory, alertness, and driving ability) the next day.

Please be aware that **Bod ECS310 CBN oil is considered <u>an experimental drug</u>** since it is not currently registered with the Therapeutic Goods Administration (TGA) or elsewhere outside Australia. Approval has not been given for this drug to treat insomnia disorder or any other condition. The TGA has been notified of the study through a Clinical Trial Notification (CTN) scheme, which seeks to regulate the use of unapproved therapeutic goods supplied in Australian clinical trials.

<u>What does participation in this study involve?</u>

We are recruiting adults aged 25 to 65 years of age who have been diagnosed with insomnia disorder, and who are able to take oral medication. We aim to recruit 20 participants.

You cannot take park in the study if you:

- Have a known hypersensitivity to cannabis/cannabinoids;
- Are required to complete mandatory drug testing (e.g. workplace, court order);
- Are currently using medications that impair cognitive (i.e. mental) function, e.g. opioids, benzodiazepines, stimulants;
- Work regular night shifts; or
- Undertake overseas travel within the past month of your scheduled visits.

If you agree to participate in this study, we first need to confirm the study is suitable for you. Your eligibility for the study will be determined at an initial screening visit (see below).

If you are willing and eligible to participate, you will be asked to complete 3 research sessions at the Woolcock Institute of Medical Research in Glebe. At each Treatment Session, you will receive the study treatment before completing some tests and sleeping in a private sleep suite. Each Treatment Session will begin in the evening (around 5pm) and you will leave the next day (around 11am). Each Treatment Session will be separated by a minimum of two-weeks. The activities involved in each Treatment Session are described below.

This study is a randomised, double-blinded, crossover trial. This means you will receive each of the 3 different study treatments (i.e., one per Treatment Session across three separate sessions), in a random order:

- Lower dose CBN
- Higher dose CBN
- Placebo

The study is "placebo-controlled", meaning that, on one of these Treatment Sessions, you will receive a treatment that does not contain the active ingredient (CBN). This 'placebo' will look, smell, and taste like the real treatment. By using a placebo, we can be confident that the effects we measure are caused by the CBN.

To avoid accidentally influencing the tests, neither you nor the researchers will know on which Treatment Session you have received the 'placebo' or a dose of the active drug. If it is necessary for your care, we can find out which treatment you have been given.

You will be asked to undergo the following testing procedures at intervals shown in the study schedule later in this document:

Visit 1 – 2: Consent and Screening Visit(s)

Screening will occur at the Woolcock Institute for Medical Research over 1-2 visits within approximately 4-weeks.

An initial medical screening will take 1-2 hours to complete. A researcher will first explain the study requirements to you and then you will have the opportunity to discuss the research with the study doctor. You will then be asked to complete the consent form. Consent must be obtained before we can complete any assessments, including those that will tell us whether you are eligible to participate.

You will then be asked to provide information about your medical history, general and mental health, and past or present patterns of drug use. You will also complete a urine drug screen and, if you are female, a pregnancy test.

You may be asked to complete an overnight sleep study to rule out other sleep disorders (such as sleep apnoea) that may be the cause of your sleep problems. This sleep study may not be necessary if you have already completed one in the past 12 months. The doctor will confirm this with you. If you decide to participate in the study, appointments for your next visits will also be scheduled.

You will be provided with the results of your sleep study and have the opportunity to discuss these results with a sleep physician.

Sleep Diary and Activity Monitoring

You will be asked to complete a daily sleep diary for 1 week prior to each Treatment Session. Prior to each Treatment Session, you will also be asked to wear a wrist-worn activity monitor. The device, similar to a normal watch, will assess your daily activity and sleep/wake cycle. You will be asked to wear it at all times (including while you are sleeping) during this period, only removing for water activities (e.g., showering, swimming).

Visit 3, 4 and 5: Overnight Sleep Study Treatment Session 1, 2, & 3*:*

It is important that you do not drive to or from the study location. We will organise and pay for transport for you to and from the Woolcock Institute. It is possible that the drug may still be in your system the day after you have taken it. This may result in a positive test on road-side drug testing which may result in possible legal implications on your employment and ability to drive. ***Please do not drive or operate heavy machinery until the morning after study discharge.***

Each Treatment Session (including both night and day assessments) will take approximately 18 hours to complete (approximately 5pm on Day 1 until 11am on Day 2).

Overnight Sleep Study Treatment Session 1, 2 and 3 (at least 2 weeks apart)

Once you arrive at the clinic, you will be asked to do the following study procedures:

- *Saliva and breath tests*: These tests will be conducted to confirm drug- and alcohol-free status before starting each Treatment Session. This will take 5 minutes. During each Treatment Session saliva will also be collected four times (twice before sleep and twice upon wake) to measure potential CBN levels.

- *Blood Test:* Two blood samples will be collected (one in the evening and one the next morning). These will be taken from a vein in your arm and the collection process each time takes approximately 10 minutes to complete. The total amount of blood taken for the entire study will be less than 30 mL (equivalent to 1 ½ tablespoons). These samples will be analysed for cannabinoids (e.g., CBN) and other related molecules, which indicate how your body has processed the study drug, called *endocannabinoids* and *metabolites*.

- *Urine samples:* Four urine samples will be collected from you (two in the evening and two the next day). These samples will be analysed for cannabinoids (e.g., CBN), endocannabinoids, and metabolites.

- *Posturography:* You will be asked to stand on a balance board ('posturography') to assess your movement and balance. This task will take around 5 minutes to complete and will be repeated three times during each Treatment Session (twice in the evening and once the next morning).

- *Memory consolidation tasks:* You will be asked to complete memory consolidation tasks twice at each Treatment Session (once in the evening and once the next morning). These will take approximately 30 minutes to complete.

- *Polysomnography (PSG):* PSG, also known as a sleep study, is an overnight sleep assessment commonly used to diagnose sleep disorders. For each Treatment Session, you will have a private suite in the sleep laboratory. Researchers will place small sensors called electrodes on your scalp, temples, chest, and legs using adhesive patches. An elastic belt around your chest will record your breathing patterns. The sensors attach to thin, flexible wires that record data about your sleep, including brain waves, skeletal muscle activity, body movement, limb movement, blood oxygen levels, heart rate, breathing rate, and eye movement.

<u>Daytime Testing</u>

- *Driving Simulation Task*: You will be asked to complete a realistic 30-minute driving simulation task that involves driving through rain, interacting with other vehicles, roadworks, and pedestrians. The driving simulator looks and feels like a car with a steering wheel and pedals with working indicators, lights, and horn. You will be asked to wear part of the EEG equipment during the driving simulator task, which will allow us to measure your brain activity.

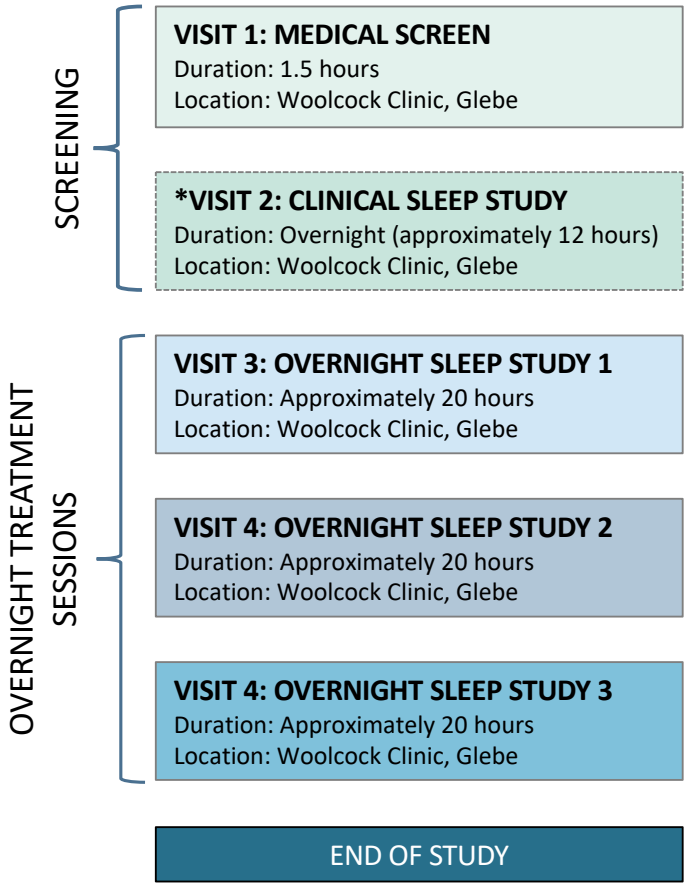
- *Questionnaires:* You will be asked to complete a set of questionnaires on a computer about your sleep quality, insomnia symptoms, psychological wellbeing, and mood. This will take approximately 30 minutes to complete.

- *Psychomotor vigilance test (PVT):* The PVT is a computer-based task that measures alertness. Each PVT will take approximately 10 minutes to complete. You will be asked to complete a PVT twice during each Treatment Session (the next morning after you wake up).

This type of testing is done to further our knowledge about how the study drug works and it will not produce the type of results that will have any useful meaning that would affect your health or treatment. Therefore, you may or may not be informed of the results of the tests.

A description of this clinical trial is available on the U.S National Library of Medicine Clinical Trial Registry under the trial registration ID NCT05344170.

Schedule of Visits



*A clinical sleep study may not be necessary if you have already completed one in the past 12 months. Please refer to page 3 of this document.

What are my responsibilities during the study?

If you agree to participate in this study, you agree to comply with the conditions in this information document. If you cannot, or do not wish to accept this responsibility, then we cannot accept you as a participant in the study.

Please **do not consume alcohol or caffeine** in the 24-hours before each overnight sleep study or Treatment Session. You will be sent home if you test positive to a breath or saliva test.

In the nights prior to your overnight sleep study visits we ask that you keep regular sleep patterns.

You must not take any **sleep medication** or **recreational drugs** throughout the entire study period. **A positive drug test result may lead to exclusion from this study.**

You may also be asked to take a Covid-19 Rapid Antigen Test prior to each overnight sleep study.

Can I have other medicines or treatments during this study?

Yes, you may take other medications or treatments necessary for your health. However, you must tell us about any medications or procedures you may be using. This is in your interest as well as important for the study because they may interact or interfere with the study drug.

You must tell us about any prescription or over-the-counter medications, vitamins, or herbal remedies you are taking. You must tell us if you are having other alternative procedures (for example, osteopathy, chiropractic, dietetics, acupuncture) or therapies (psychological or otherwise). You must also tell us about any changes to these while you are participating in the clinical study.

Do I have to take part?

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 at any stage from the study. If you do decide to take part, you will be given this Participant Information Statement 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 withdraw, will not affect your routine treatment, your relationship with those treating you or any ongoing relationship with the Woolcock Institute of Medical Research or University of Sydney. If you choose not to join the study, the study doctor will discuss other options with you.

What are the possible benefits of taking part?

This research study will further medical knowledge and may improve treatment of insomnia disorder in the future, even if it is not of direct benefit to you.

What are the potential risks of taking part?

A. CBN in oil

Medical procedures, medicine, and tests often have side effects. You may have no side effects, some, or all the side effects listed below. These side effects 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 and the study team will also monitor for side effects.

There may also 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 the intervention 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 procedure. Your study doctor will discuss the best way of managing any side effects with you. Some unwanted effects may actually not be related to the study, nevertheless it is important to document these.

CBN has not been studied enough to know what potential side effects may be. While studies of CBN have not identified any side effects in humans, only a few studies have administered CBN to humans in the higher dose being examined in this study. The study drug also contains more CBN than is typically consumed in recreational cannabis.

While CBN is not available through doctor prescription in Australia, many cannabis retailers are selling CBN products in other countries (e.g., the United States). These products typically contain less CBN than the highest dose of CBN in this study. Potential side effects reported by CBN retailers include:

- Tiredness or drowsiness
- Dizziness
- Loss of appetite
- Dry mouth

- Unusual dreams

You should get medical help and contact the study doctor or staff if you have any of these or any other side effects during the study. For urgent assistance please call 000.

A member of the research team will phone you the evening after each Treatment Session, and one week later, to assess your wellbeing.

B. Pregnancy and risks to unborn child

It is important that women participating in this study **are not pregnant, or breast-feeding, and do not become pregnant** during the course of the study.

If you are a woman of childbearing potential, the researchers will perform a pregnancy (urine) test at screening and before each Treatment Session. You should use reliable contraception (such as oral contraceptive, or long-acting reversible contraception such as a hormonal implant, injection, or IUD) during the study. If at any time you think you may have become pregnant, it is important to let the researchers know immediately. If you are a male with a female partner, you should use reliable contraception (e.g., condoms) during the entire study. If at any time you think your sexual partner may have become pregnant, it is important to let the researchers know immediately.

C. Blood collection

Blood collection may cause some discomfort, bruising, minor infection, or bleeding which may last 1-2 days.

Will I be paid to take part in this research project?

All treatment, medication, and study-related tests will be provided at no cost to you.

You will be reimbursed for any reasonable travel to and from the Woolcock Institute of Medical Research for all Treatment Sessions. All meals and snacks during your stay will be provided to you at no cost. You will also be compensated for your time commitment to the study with a maximum amount of $1,200 provided upon completion of the final overnight sleep study.

What will happen to information about me?

We will keep all personal information confidential and securely stored. 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. Only the approved study doctor and research staff will have access to this information.

Any information obtained in connection with this research project that can identify you will remain confidential. This information will be stored in a re-identifiable (or coded) format – that is, it is possible to use the code to re-identify you. All data will either be stored in password-protected files on a secure server that is regularly backed or as paper-based documents that will be securely locked in a filing cabinet at the Woolcock Institute of Medical Research. All data will be stored securely for at least 15 years after which it will be destroyed.

Any data that is made publicly available via a conference, scientific publication, or media will be presented as group data therefore it will not be possible to identify you. Australian and NSW privacy law gives you the right to request access to your information that the researchers have collected and stored. The law also gives you the right to request corrections to any information about you that you disagree with. Please contact the study team (see Page 10 of this document) if you would like to access your information.

Your information will only be used for the purpose of this research, 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. 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 prior to any future use of the data.

By completing the consent form, you also agree to the study team accessing health records if they are relevant to your participation in this study.

Your study records may be reviewed by:

- Woolcock Institute of Medical Research – the study sponsor
- People who work with the sponsor on the study
- Government agencies, such as the Australian Therapeutic Goods Administration (TGA)
- Bellberry HREC, a group that reviews and approves research studies. For more information, please refer to Part 2 of the PICF (*Who has reviewed the research project*).

What will happen to my test samples?

If you agree to participate in this study, we will collect blood, urine, and saliva samples. Blood and saliva samples will be stored securely for later testing; urine samples will be tested on collection and discarded shortly thereafter. The collection of these blood, urine and saliva samples is a mandatory requirement of the study.

Plasma will be extracted from the blood samples and stored in -80°C freezers at the Woolcock Institute of Medical Research, Glebe until analysis. Only the approved investigator team will have access to these samples. Plasma samples will then be transported to the Lambert Initiative for Cannabinoid Therapeutics, University of Sydney for analysis of endocannabinoids, cannabinoids, and their metabolites before being securely destroyed.

Will there be any genetic tests involved?

There are no genetic tests in this study.

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.

Additionally, you may be withdrawn from the study by the study team for the following reasons:

- Unacceptable side effects;
- If you do not follow the instructions of the clinical site staff; or
- If the study doctor decides it is in the best interest of your health and welfare to stop.

Finally, the study could be unexpectedly stopped by the sponsor or the study team and you would then be withdrawn from the study.

What if new information arises during the study?

Sometimes during the course of a research project, new information becomes available about the treatment that is being studied. If this happens, your study doctor will tell you about it 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 may be asked to sign an updated consent form.

What happens when the research project ends?

The study treatments will not be made available to you after the research project ends. After your participation in the study has ended, we will arrange a clinical follow-up appointment with your physician if deemed necessary by the chief medical investigator.

Any published results will be available to all participants when requested. It is usual for a number of months to elapse before definitive results of this type of study are available. These may be published without any identifiable information in medical journals that are available to the public. You should feel free to ask the study staff about this.

PART 2: HOW IS THE RESEARCH PROJECT BEING CONDUCTED?

Who has reviewed the research project?

All research in Australia involving humans is reviewed by an independent group of people called a Human Research Ethics Committee (HREC). 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.

The conduct of this study at Woolcock Institute of Medical Research has been authorised by the Woolcock Institute of Medical Research, any person with concerns or complaints about the conduct of this study may also contact the Research Governance Officer on (02) 9114 0412, email: Grigori.kaplan@woolcock.org.au and quote the project number [2021-08-907].

Compensation for Injury

If you suffer any injuries or complications because 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.

If you are injured as a result of your participation in this trial, you may be entitled to compensation. Sponsors of clinical trials in Australia have agreed that the guidelines developed by their industry body, Medicines Australia, will govern the way in which compensation claims from injured participants are managed by sponsors.

However, as guidelines, they do NOT in any way dictate the pathway you should follow to seek compensation. The sponsor is obliged to follow these guidelines. These guidelines are available for your inspection on the Medicines Australia Website (www.medicinesaustralia.com.au) under Policy – Clinical Trials – Indemnity & Compensation Guidelines. Alternatively, your study doctor can provide you with a hardcopy of the guidelines.

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.

Who should I contact if I need further information?

The person you may need to contact will depend on the nature of your query.

If you want any further information concerning this project or if you have any medical problems which may be related to your involvement in the project (for example, any side effects), you can contact the study doctor on +61 0404 086 028 or any of the following people:

For general enquiries about this project or if you want to reschedule an appointment, you can contact the following person:

General enquiries and appointments

Name	Isobel lavender
Position	Clinical Trial Coordinator
Telephone	+61 481 475 730
Email	Isobel.lavender@sydney.edu.au

The conduct of this study has been authorised by the Woolcock Institute of Medical Research. Any person with concerns or complaints about the conduct of this study may contact the Research Governance Officer:

Research Governance Officer

Name	Grigori Kaplan
Position	Governance Officer
Telephone	02 9114 0412
Email	Grigori.kaplan@sydney.edu.au
Please quote the study title & project number: Cannabinol for insomnia (2021-08-907)	

If you have any complaints about any aspect of the project, the way it is being conducted or any questions about being a research participant in general, then you may contact:

Reviewing HREC approving this research and HREC Executive Officer details

Reviewing HREC name	Bellberry Limited
HREC Executive Officer	Operations Manager
Telephone	(08) 8361 3222
Email	bellberry@bellberry.com.au
Please quote the study title & project number: Cannabinol for insomnia (2021-08-907)	

This information is for you to keep.

PARTICIPANT CONSENT FORM

Study Title: A randomized, double-blind, placebo-controlled crossover pilot study investigating the effects of cannabinol (CBN) 30 mg and 300 mg on sleep architecture and next-day function in insomnia disorder.

Short Title: CUPID

Protocol Number: 2021-08-907

Project sponsor: The Woolcock Institute of Medical Research

Co-Principal Investigators: Professor Brendon Yee and Dr Camilla Hoyos

Location: The Woolcock Institute of Medical Research, 431 Glebe Point Road, Glebe, Sydney.

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 the purposes, procedures and risks/benefits of the research described in the project.
- I freely agree to participate in this research project according to the conditions in the Participant Information Sheet which I confirm has been provided to me.
- I understand that my involvement in this study may not be of any direct benefit to me.
- 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 have been told that no information regarding my medical history will be divulged to unauthorised third parties and the results of any tests involving me will not be published to reveal my identity.
- I understand that access may be required to my medical records for the purpose of this study as well as for quality assurance, auditing, and in the event of a serious adverse event and I consent to this access.
- I understand that I am free to withdraw from the study at any stage without prejudice to future treatment. If I decide to withdraw from the study, I agree that the information collected about me up to the point when I withdraw will be stored and analysed.
- I am 18 years of age or over.
- I consent to my treating Doctor/s being notified of my participation in this study and of any clinically relevant information noted by the trial doctor in the conduct of the trial.
- I declare that all my questions have been answered to my satisfaction.
- I have read, or have had read to me, and I understand the Participant Information Sheet, Version 3, dated 31/01/2022.

Name of Participant (please print) _____

Signature _____ Date _____

Declaration by Study Doctor:

A verbal explanation of the research project, its procedures and risks has been given to the participant and I believe that the participant has understood that explanation.

Name of Study Doctor (please print) _____

Signature _____ Date _____

The Study Doctor must provide the explanation and provision of information concerning the research project.