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| **Participant Information Sheet**Nicholas HoehConsultant PsychiatristDepartment of Psychological MedicineSchool of MedicineThe University of AucklandBuilding 507, Level 3, 22-30 Park Road, GraftonAuckland 1023, New ZealandTelephone: 64 9 923 7703Email: n.hoeh@auckland.ac.nzwww.fmhs.auckland.ac.nz |
| Study title: | **Ketamine-assisted therapy in Depression** |
| Locality:Ethics committee ref: | **Auckland University****20/NTA/163 /AM01** |  |  |
| Lead investigator:Contact number: | **Dr. Nicholas Hoeh****+64 9 923 7703** |  |  |

You are invited to take part in a study on the antidepressant effects of ketamine given in a therapeutic context. Whether or not you take part is your choice. If you don’t want to take part, you don’t have to give a reason, and it won’t affect the care you receive. If you do want to take part now, but change your mind later, you can pull out of the study at any time.

This Participant Information Sheet will help you decide if you’d like to take part. It sets out why we are doing the study, what your participation would involve, what the benefits and risks to you might be, and what would happen after the study ends. We will go through this information with you and answer any questions you may have. You do not have to decide today whether or not you will participate in this study. Before you decide you may want to talk about the study with other people, such as family, whānau, friends, or healthcare providers. Feel free to do this.

If you agree to take part in this study, you will be asked to sign the Consent Form on the last page of this document. You will be given a copy of both the Participant Information Sheet and the Consent Form to keep.

This document is 10pages long, including the Consent Form. Please make sure you have read and understood all the pages.

Voluntary Participation and Withdrawal From This Study

Your participation in this study is entirely voluntary. It is up to you if you take part or not. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you don’t want to take part you don’t have to give a reason. If you decide to take part you are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive from us.

What is the purpose of the study?

In this study we are investigating the potential antidepressant properties of the drug ketamine, given via intramuscular injection when combined with a therapeutic setting and follow-up psychological support and integration. Ketamine is normally used as an anaesthetic but research shows that much lower doses of ketamine than used in anaesthetics may reduce depression and improve psychological wellbeing. There is additional research that repeated treatments with ketamine can result in a longer period of treatment response and symptom improvement. The form of ketamine being used in this study is not currently approved for use as an antidepressant, although it is currently used as an “off-label” treatment overseas for individuals who have not responded to other therapies. A variant form of ketamine, called esketamine has recently been approved by regulatory agencies for treating depression. Although this is a promising development for severe and/or “treatment resistant” depression, the current cost and manner of delivery of esketamine may limit its availability to a small number of patients. It is therefore important to research other safe and effective ways of using ketamine for people with treatment-resistant depression. In this study, we are going to study the antidepressant effects when participants receive intramuscular injections of ketamine and participate in integration sessions with a therapist. While the dose of ketamine provided will be substantially lower than an anaesthetic dose, it will likely temporarily alter your perception (for more detail, see the following section). Research with ketamine and similar agents suggests that having a perception-altering experience increases the likelihood of positive outcomes.

* The primary goal of our research is to find out if ketamine given in a therapeutic context combined with psychological support and integration can be tolerated and reduce symptoms of depression. As a secondary aim, we are examining how to improve and extend the duration of treatment response to ketamine in a therapeutic setting.
* If you take part in this study, the ketamine you receive will affect your central nervous system, and perception for up to three hours, although its effects will lessen over this time and you will return to feeling normal. After each ketamine experience, you may experience antidepressant effects for up to two weeks, although some people may not respond at all and others may experience mood improvements for longer.
* Ketamine ExperienceParticipating in this study will not entitle you to ongoing treatment with ketamine or similar drugs after the conclusion of the study. In the future, ketamine, esketamine or similar drugs may be available in the New Zealand Healthcare system for the treatment of severe and/or treatment-resistant depression.
* We are a group of scientists and clinicians who are studying the therapeutic potential of ketamine in treatment-resistant depression and are based at the University of Auckland and Auckland District Health Board. This study has been approved by a health and disability ethics committee. Contact details are given at the end of this sheet.

How is the study designed?

The study is an open label trial and aims to recruit up to thirty patients with treatment-resistant depression or treatment-resistant bipolar disorder in a depressive episode. A rater will conduct the outcome assessments following the ketamine sessions.

The study will take 7 months. Participation in this study will require 7 visits: One Screening/consent visit, three Ketamine Experience visits, and three Integration sessions, which will occur one to three days after each Ketamine Experience. The integration sessions may occur in person or via video platform. Our study team will also contact you by video or telephone on four occasions. For a study timeline, please see page 6.

On each Study Day, a moderate-high dose of ketamine will be administered to you twice via intramuscular injection. On the first Ketamine Experience, the first ketamine dose will be 0.5mg/kg (or 0.3mg/kg if you weigh more than 100kg) followed by an optional dose of 20mg to 40mg after twelve-fifteen minutes assuming the first dose is well tolerated. The doses of ketamine administered on the second and third Ketamine Experiences can be adjusted by the study clinician in consultation with you based on your first Ketamine Experience.

Blood and urine samples will be collected from all participants as part of screening. The tests will screen for deficiencies commonly found in depression as well as abnormal thyroid and liver function. A positive test for recreational drugs using a multi-panel screen will result in halting the trial. Heart rate, blood pressure, and oxygen saturation will be monitored prior to treatment and twelve minutes after injection and one hour after injection by the supervising clinician.

Follow-up assessments will occur after each Ketamine Experience visit, and then one week, one month, three months and six months after your last Ketamine Experiences visit.Each follow-up assessment will take approximately fifteen minutes. If you give consent to being emailed study questionnaires, you will complete these online. If you do not provide such consent or lack internet access, the research team will complete the questionnaires with you during the interview.

Who can take part in the study?

You are reading this sheet because your healthcare provider thought that you might be eligible and/or you have contacted us after seeing an advertisement. This study will take approximately thirty hours of your time and involve up to seven visits to our research centre. For a study timeline, please see page 6.

You may be eligible to participate in the study if you:

* Are 18 years or above and less than 70;
* Have a diagnosis of Major depressive disorder or Bipolar disorder and are on mood stabilizing medication with current depressive episode for at least three months, as assessed by a clinical interview;
* Have responded inadequately to at least two antidepressant courses, one of which may be your current depressive episode;
* Meet the cut-off score on an established self-report measure of depression;
* Have been stable on any psychotropic medications for at least 4 weeks prior to the Ketamine Experience;
* Are able and willing to comply with all study requirements, in the research team’s opinion and
* Are willing and able to give informed consent for participation in the trial.

You will not be eligible to participate in the study if you:

* Are pregnant, breastfeeding or are planning to get pregnant during the study;
* Have significant renal or hepatic impairment;
* Weigh less than 50kg or more than 120kg;
* Are unable to speak or write English;
* Have a cardiovascular condition including (but not limited to) severe cardiovascular disease, heart failure, severe or poorly controlled hypertension, recent myocardial infarction and history of stroke;
* Have an abnormal heart rate or blood pressure checked at screening;
* Have participated in another research trial involving an investigational product in the past 12 weeks;
* Have a history of significant psychotic episode(s);
* Have any unstable medical or neurologic condition;
* Are planning any major changes to psychotropic medication you’re currently taking;
* Are at imminent risk of suicide as determined by the research team;
* Are likely to undergo ECT treatment;
* Have had a substance use disorder in the last 6 months;
* Have a history of abuse of ketamine or phencyclidine;
* Have known hypersensitivity to Ketamine or its components;
* You have another medical condition for which use of ketamine is planned, for example, pain control;
* Are currently using any of the medications memantine, amantadine, rimantadine, dextromethorphan, or procyclidine.
* Have been regularly using any other medication the research team considers is contraindicated;
* Are unable to fast for four hours prior to administration of ketamine; or
* Have any other condition judged by the research team as likely to impact on your ability to complete the trial.

If you are accepted to participate in the study, you may still be excluded if you decide to change antidepressant medications or engage in other therapies for your depression or another psychological condition during the study. This is because it will limit our ability to attribute any changes in outcomes you experience to participating in the study. We therefore please ask that you do not change your treatment for the 30 days you are receiving treatment in the study. Our research team will be in communication with your mental health provider on an ongoing basis in the event of adverse events from the study intervention, or an absence of therapeutic benefit. This communication would include a discussion about a withdrawal, change, or additional medication. We will encourage participants to have a consultation with their mental health provider within a month of finishing the treatment phase of the study, so that mental health providers can contact the research team with further queries.

What will my participation in the study involve?

* On the first day you will undergo Screening/Consent via video or phone. We will explore your eligibility to take part in the study, after which you may give consent to participate. This session will take **approximately** **60** minutes. As well as accessing your medical records, we will ask you questions about your physical and mental health, as well as drug use history to confirm whether you are eligible to take part. This will be conducted by the study nurse.
* At this Screening/Consent session, you will also complete several questionnaires, some of which are long and contain potentially distressing questions. You will complete some of these questionnaires at each of the follow-up assessments.
* If you are eligible, we will send you a LabTests form for you to take to a LabTests Centre and give blood samples to check your health. We will pay for this. Following testing, your blood will be disposed of using established guidelines for discarding biohazard waste.
* If you are eligible and agree to take part in the study, you will then be scheduled for an in-person visit to the centre to complete measurements including weight, blood pressure, pulse, oxygen saturation and urine tests. There will also be further assessments to determine your suitability for the study. This will be conducted by a clinician, and with the involvement of a study therapist.
* Once completing these assessments, the remainder of the visit will involve preparing you for the ketamine experience. You will be invited to talk openly about your personal history including thoughts on the origins of your depression. We will discuss ketamine’s psychological effects, and briefly simulate aspects of the experience, such as listening to a sample of the session music while wearing eyeshades. This will be undertaken by a therapist.
* You will then take part in three, ideally consecutive weeks, in which you will receive weekly **treatment sessions with** Ketamine **,** followed by an Assessment of outcome measures, and an Integration Session with the study therapist.
* Every Ketamine session and Integration session will be conducted in-person at the research centre. The Assessment will be done the day after the Ketamine session, and can either be done via video or phone, or in-person at the same time as the Integration session. The Integration sessions will take place one to three days following the Ketamine sessions. This timeframe is subject to change dependent on participant and research team availability.
* When you come in the morning for each **Ketamine Experience**, Ketamine Experiencewe will ask that you come having not eaten for four hours prior to receiving ketamine.
* We will ask you the same types of questions as we did in the first session and recheck some measurements. On each Ketamine Experience you will receive the ketamine through one injection into your shoulder, thigh or buttocks followed by an optional second injection twelve minutes later. You may decline this second dose and if you choose to do so, you will still be included in the study and your data will still be collected. **After receiving any dose of ketamine,** you will be required to stay until such time as the research team consider, and advise you that it is safe for you to leave. A clinician will remain close by to monitor you and provide guidance and support for the duration of your ketamine experience.
* We will audio and videotape these sessions for two reasons: 1) to better understand, and learn about your qualitative experience of the ketamine session and 2) to ensure consistency of treatment approach between therapists. Any information you give us during and after the ketamine experience and at any other time of the study will remain private and confidential. You may request a copy of your audio and video recordings. Further details about how your privacy and confidentiality will be protected is outlined in the data management plan which is available to review as part of the consent process.
* During the ketamine experience, you may have access to information typically outside your conscious awareness (in your subconscious) and/or you may have an experience of yourself beyond your personal identity, for example, feeling connected to the wider universe. You may experience an increase in positive feelings, such as peacefulness or joy, or an increase in negative feelings such as fear or sadness, and/or neutral emotional states, all of which are temporary. Clinicians and researchers do not consider any particular type of experience as more important than another, or that positive feeling states are more beneficial than negative ones. Although ketamine is a safe and approved medicine, you may experience brief unpleasant side effects. **These can include feeling “spaced out” or drunk, nausea, vomiting, increased or decreased blood pressure, double vision, irregular heartbeat and muscle rigidity. These side effects should wear off within an hour of receiving the medication**. Given the ketamine doses we will be using, it is very unlikely that you will experience more severe side effects.
* You should not drive to our research centre on the Ketamine Experience. Ideally a family member or friend will pick you up and support your return to your residence.
* Each follow-up assessment will be conducted the day following the Ketamine Experience. If possible, this will be conducted at the same time as the Integration Session, however this will be dependent on therapist availability. This follow-up may be done at the research centre or via video.
* Each Integration session will take approximately three hours and will include an opportunity to share your experiences with a member of the research team as well as an interview about your mental health. We will also audio and videotape each Integration session for the reasons as outlined above.
* We will call you one week, one month, three months and six months after your final treatment with ketamine to check on your health status and do an interview with you on the phone or by video.
* You will be required to make a total of seven in-person visits to the research centre, including the Preparation session, three Ketamine Experiences, and three Integration sessions. All other sessions can and will be conducted via phone or video unless it is more practical for the participant and research team to be done in-person.
* If you are of Māori descent, you are encouraged to consult with your whanau, hapu or iwi regarding participation in this project*.*

Preparation

+

Screen

 (In-person)

Week 2

Week 3

Week 1

Integration Session 2

Consent

+

Screen

 (Video or Phone)

Ketamine Experience 1

Assessment (Video or Phone or In-person)

Integration Session 1

Ketamine Experience 2

Assessment (Video or Phone or In-person)

Ketamine Experience 3

Assessment (Video or Phone or In-person)

Integration Session 3

Assessment (Video or Phone)

**1 WEEK**

Assessment (Video or Phone)

**1 MONTH**

Assessment (Video or Phone)

**3 MONTHS**

Final Assessment(Video or Phone)

**6 MONTHS**

*Timeline of the study:* You will visit our centre up to 7 times (Consent/Preparation Visit, Ketamine Experience 1, Ketamine Experience 2, Study 3 and Integration Sessions 1, 2, and 3. Our study team will also contact you by video or telephone on three occasions, and you will be sent links via email to complete questionnaires one week, four weeks, three months, and six months after the Ketamine Experience 3. The study will take approximately 7 months.

**Dosing ranges**

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|  | **If you weigh between:****50-100kg** | **If you weigh between:****100-120kg** |
|  | **1st dose** | **2nd dose (optional)** | **1st dose** | **2nd dose (optional)** |
| **Ketamine Experience 1** | 0.5mg/kg | 20 – 40mg | 0.3mg/kg | 20 – 40mg |
| **Ketamine Experience 2** | 0.5 – 0.75mg/kg | 20 – 40mg | 0.3 – 0.5mg/kg | 20 – 40mg |
| **Ketamine Experience 3** | 0.5 – 0.75mg/kg | 20 – 40mg | 0.3 – 0.5mg/kg | 20 – 40mg |

What will happen to my blood and urine samples?

* Urine samples will be collected from you on screening day. The results of the urine drug analysis and pregnancy test will be recorded, and the urine sample will be disposed of as per policy guidelines.
* You will be referred to LabTests for blood testing. The results from these tests will be recorded and the blood collected will be disposed of as per LabTest policy guidelines.
* Blood samples will be collected to screen for deficiencies commonly found in depression. You will be required to complete the following tests: complete blood count, liver function tests, and thyroid stimulating hormone. Abnormal results will not automatically result in exclusion from the study.
* Screening and safety tissue samples (and their results) will be labelled with identifiers. The LabTests laboratory will not be authorised to share your blood and urine sample with third parties.
* The blood test results are required to be identifiable to ensure that in the event of major abnormalities, your healthcare providers will have access to relevant information.
* The laboratory is Good Laboratory Practice (GLP) compliant, meaning that the facilities are secure with tissue access restricted to those staff directly involved in their analysis.
* The blood and urine samples will be retained for seven days and then securely destroyed as per LabTests policy (<https://www.labtests.co.nz/privacy-and-policy/>).
* You may withdraw consent for the collection of blood and urine samples at any time, without providing a reason. The samples collected prior to your withdrawal will continue to be used and analysed for the purpose of the study.

Our study requires participants to provide urine and blood samples. We acknowledge that personal and health information is a tāonga (treasure) and will be treated accordingly. We will not retain any samples and will ensure culturally appropriate processes regarding data management including maintaining privacy, communication with Whānau when appropriate.

What are the possible risks of this study?

It is possible that the ketamine experience may trigger a memory of something distressing from your past. In the event this happens, you will be given instructions on how to cope with the difficult feelings that may arise for you during the experience. You will be given an opportunity to debrief with a clinician afterwards, and will be provided with further monitoring and support if necessary.

* If you are a woman it is preferable that you are using contraception but we will take a urine sample from you to confirm that you are not pregnant on the screening day.
* If you are experiencing difficulties from the study experience you should contact us immediately. We can then arrange appropriate care for you.
* People with liver or kidney problems, with cardiovascular problems, with a history of psychosis or who take certain other medications, should not take ketamine. During the screening visit our medical staff will check to make sure it is safe for you to participate in the study.
* In the event that a condition which is assessed to be a clinical abnormality is detected through lab tests or clinical examination you will be informed of this and will be advised to consult your general practitioner or other health professional of your choice. You should be aware that once you have been informed that a clinical abnormality has been detected this could affect your ability to obtain insurance whether or not you take the matter further*.*

What are the possible benefits of this study?

Initial research suggests that after participating in ketamine experiences like the ones in this study, you may experience a reduction in depressive symptoms for up to two weeks, although some people may not respond at all and others may experience improvements in their mood for longer. If you experience this benefit, this is likely due to the neurobiological effects of ketamine. You may also experience psychological benefits in the form of greater insight and clarity in relation to your depression; its causes, factors keeping low mood going, and things you would like to address to move forward.

Will any costs be reimbursed?

We will pay for any costs that you incur taking part in the study. If you require a taxi to get to and from the study then we can arrange and pay for this. We will also provide meal vouchers on the Ketamine Experience. We will reimburse you for any other costs relating to the study. We recognise that taking part in the study will take around thirty hours of your time and will provide you with $50 of vouchers at the end of the study in recognition of this inconvenience.

What if something goes wrong?

If you were injured in this study, which is unlikely, you may be eligible to apply for compensation from ACC just as you would be if you were injured in an accident at work or at home. This does not mean that your claim will automatically be accepted. You will have to lodge a claim with ACC, which may take some time to assess. If your claim is accepted, you will receive funding to assist in your recovery.

If you have private health or life insurance, you may wish to check with your insurer that taking part in this study won’t affect your cover.

What will happen to my information?

During this study the researchers, nurses and other designated study staff will record information about you and your study participation. This includes results of any study assessments as well as video and audio recordings during the Ketamine Experiences and Integration Sessions. These recordings will be accessed and transcribed by a member of the study team or a contracted transcriber who has signed a confidentiality agreement. The video and audio recordings are unable to be corrected. You are entitled to request copies of your personal recordings. In the event of your withdrawal of consent from the study, the video and audio recordings will be destroyed.

Specific supervisors/therapists will be shown your video footage to assess the quality of the therapy provided by the therapists. The video and audio recordings and any material will be stored securely and de-identified where possible. The footage will only be shown to qualified supervisors and therapists relevant to the study. We will always ask your permission before showing any footage for training or educational purposes outside of the study.

If needed, information from your hospital records and your GP may also be collected. You cannot take part in this study if you do not consent to the collection of this information. Further details about how your privacy and confidentiality will be protected is outlined in the data management plan which is available to review as part of the consent process.

What happens after the study or if I change my mind?

* **The medication that you receive during the study will not be available to you after your participation in the study, as ketamine is not approved for the treatment of depression in New Zealand.**
* At the conclusion of the study your personal data will be kept in locked cabinets in secure rooms at the University of Auckland and kept for ten years. They will be shredded after this time. All electronic data files will be kept in a de-identified format such that there is no risk that you could be identified from these data. Your data will be identified by a unique trial specific number in any database. Your name and any other identifying detail will not be included in any trial data electronic file.
* Following open-data guidelines, your de-identified data may be uploaded onto publicly accessible databases. Only members of the study team and appropriate regulatory bodies will be able to access your data and health information.

Can I find out the results of the study?

It can take quite a long time for us to analyse data from these kinds of studies. We hope to be able to tell you the final results one to two years after completion of the study. We plan to publish the results in scientific journals. Please let a member of the study team know if you would like a summary of the results in an easy to read format.

Who is funding the study?

This study is funded by a grant from the Oakley Mental Health Foundation. The members of the research team are affiliated with either the University of Auckland or the University of Oregon.

Who has Approved the study?

This study has been approved by an independent group of people called a Health and Disability Ethics Committee (HDEC), who check that studies meet established ethical standards.

Who do I contact for more information or if I have concerns?

If you have any questions, concerns or complaints about the study at any stage, you can contact:

 *Dr Nicholas Hoeh*

*Consultant Psychiatrist*

 *Phone:* +64 9 923 7703

 *Email: n.hoeh@auckland.ac.nz*

If you want to talk to someone who isn’t involved with the study, you can contact an independent health and disability advocate on:

Phone: 0800 555 050
Fax: 0800 2 SUPPORT (0800 2787 7678)
Email: advocacy@advocacy.org.nz

Website : https://www.advocacy.org.nz/

If you require cultural support please contact the administrator for He Kamaka Waiora Māori Health Team on 09 486 8324 ext 42324.

You can also contact the health and disability ethics committee (HDEC) that approved this study on:

 Phone: 0800 4 ETHICS

 Email: hdecs@health.govt.nz

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| **Consent Form** |  |

**Please tick to indicate you consent to the following**

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| I have read, or have had read to me in my first language, and I understand the Participant Information Sheet.  | Yes 🞏 |  |
| I have been given sufficient time to consider whether or not to participate in this study. | Yes 🞏 |  |
| I have had the opportunity to use a legal representative, whanau/ family support or a friend to help me ask questions and understand the study. | Yes 🞏 |  |
| I am satisfied with the answers I have been given regarding the study and I have a copy of this consent form and information sheet. | Yes 🞏 |  |
| I understand that taking part in this study is voluntary (my choice) and that I may withdraw from the study at any time without this affecting my medical care. | Yes 🞏 |  |

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| I consent to the research staff collecting and processing my information, including information about my health. | Yes 🞏 |  |
| I consent to the research staff sending me questionnaires to my email address to enable me to complete these online at the assessment points. I understand that my answers to these questionnaires will be stored on a secure University of Auckland server, and will only be accessible to the research staff.  | Yes 🞏 |  |
| I consent to the research staff texting me on my personal mobile to notify me of study visits and assessment points. I understand that my mobile number will not be available to anyone other than the research staff.  | Yes 🞏 |  |
| If I decide to withdraw from the study, I agree that the information collected about me up to the point when I withdraw may continue to be processed. | Yes 🞏 |  |
| I consent to my GP or current provider being informed about my participation in the study and of any significant abnormal results obtained during the study. | Yes 🞏 |  |
| I understand that there may be risks associated with the treatment in the event of myself or my partner becoming pregnant. I undertake to inform my partner of the risks and to take responsibility for the prevention of pregnancy. | Yes 🞏 |  |
| I consent to the video and audio recording of my ketamine sessions **experience**(delete) and Integration sessions .  | Yes 🞏 |  |
| I agree to an approved auditor appointed by the New Zealand Health and Disability Ethic Committees, or any relevant regulatory authority or their approved representative reviewing my relevant medical records for the sole purpose of checking the accuracy of the information recorded for the study. | Yes 🞏 |  |
| I understand that my participation in this study is confidential and that no material, which could identify me personally, will be used in any reports on this study. | Yes 🞏 |  |
| I understand the compensation provisions in case of injury during the study. | Yes 🞏 |  |
| I know who to contact if I have any questions about the study in general. | Yes 🞏 |  |
| I understand my responsibilities as a study participant. | Yes 🞏 |  |
| I wish to receive a summary of the results from the study. | Yes 🞏 | No 🞏 |

If yes provide contact details (email)

**Declaration by participant:**

I hereby consent to take part in this study.

|  |
| --- |
| Participant’s name: |
| Signature: | Date: |

**Declaration by member of research team:**

I have given a verbal explanation of the research project to the participant, and have answered the participant’s questions about it.

I believe that the participant understands the study and has given informed consent to participate.

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| Researcher’s name: |
| Signature: | Date: |