Participant Information Sheet

Title:

Ketamine and Brain Imaging in Patients with Treatment Resistant Anxiety

Locality:	**Dunedin**	Ethics committee ref.: 17/STH/143
Lead investigator:	**Prof Bruce Russell**	Contact phone number: 03 4797272

You are invited to take part in a study evaluating changes in mood, imaging and other assessments in response to ketamine, in patients with treatment resistant Generalised Anxiety Disorder (GAD) and/or Social Anxiety Disorder (SAD). 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 would 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 10 pages long, including the Consent Form. Please make sure you have read and understood all the pages.

WHAT IS THE PURPOSE OF THE STUDY?

Anxiety is a major clinical health problem and anxiety disorders are the most common mental health disorders in NZ, however we don't yet understand why many patients with anxiety are resistant to treatment.
Ketamine is a medication used for over 40 years for a number of purposes. At very high doses, it is used as an anaesthetic; at lower doses it can relieve pain. There is evidence

that low dose ketamine can lead to improvement in anxiety in some patients with treatment resistant anxiety.
An important aim of this study is to identify differences in brain activity in patients with treatment resistant anxiety compared with healthy volunteers, by comparing a range of brain imaging, brain wave and blood data. This information may help us develop better treatments for you.

At Visit 3 you will receive a single intramuscular injection of either ketamine or fentanyl, prior to brain imaging (MRI) and brain wave (EEG) testing. Neither you nor study staff will know which treatment you will receive. Blinding of study medication is an important aspect of the study's design, and can help reduce potential biases. Fentanyl is a short acting treatment for pain, and ketamine is also used for treating pain. Side effects of both medications are described below (page 6).

At the end of the first phase of the study we will offer an optional extension phase for up to 6 weeks of ketamine treatment (once or twice weekly dosing) to any patient who has completed the study.

Please note that ketamine is not approved by Medsafe for treating anxiety and is being used "off-label" for this study. This means that its use is not backed by a body of clinical trial data reviewed and approved by Medsafe.

WHAT WILL MY PARTICIPATION IN THE STUDY INVOLVE?

To participate in this study you need to meet the following inclusion criteria:

- You have either GAD (generalized anxiety) or SAD (social anxiety) that has not responded to standard treatment (psychotherapy and/or medication).
- You are between 18 and 45 years of age
- You meet study safety requirements

We will assess these criteria during the screening process.
We will check to see you are in good general health (we will record your blood pressure, heart rate, temperature, respiratory rate, height and weight) and will get blood and urine tests, including a pregnancy test in women and a urine screen for drugs of abuse. We will ask you about your current and past treatments for anxiety and any relevant physical health concerns. If you are referred by your GP or psychiatrist they will provide relevant health and medication information.

You may remain on your current psychiatric medications and psychotherapy, but may not change these in the 4 weeks prior to brain imaging.

All study drug dosing, blood sampling and electroencephalograms (EEG's recording brain waves) will happen in the Fraser Building in Cumberland St, Dunedin. The Stop Signal Task (computer task) will take place in the William James Building, Leith Walk, University of Otago. The MRI scans will happen at Pacific Radiology in Great King Street. The actual time you will be involved in the study is approximately a week – with 4 visits to the clinic.

- **Visit 1** you will come to the William James Building at the University for a Stop Signal Task (computer task). Following this if you have not had ketamine previously you will come into the Fraser Building to have a test dose – this is to make sure that you show a positive response to ketamine.
- We will do an assessment of your mood/anxiety using questionnaires and you will complete a CADSS (Clinician Administered Dissociation Symptom Scale) scale to measure levels of dissociation. By dissociation we mean that you may experience confusion, a dream-like state or changes in perception, and these symptoms are recorded on the questionnaire We will ask you to complete an orientation questionnaire and a Trail-making test which is a cognitive test. We will also ask you to complete a BPIC (Bladder Pain Interstitial Cystitis) questionnaire about bladder function/pain.
- We will record your vital signs.
- You will then be dosed with ketamine (1mg/kg) by intra muscular injection into your upper arm.
- We will continue to take your vital signs and assess your mood, cognition and dissociation with questionnaires.
- We will complete an orientation checklist and discharge checklist to ensure you are ok to go home

Your visit on this day will last between 1 ½ -3 ½ hours, depending on whether you need to have a test dose of ketamine.

The next 3 visits are usually the following week.

Monday - Visit 2 you will come to the Fraser Building at an arranged time – we will arrange a taxi for you if needed. Your visit to the clinic on this day will last approx. 2 hours – and will consist of the following:

- We will do an assessment of your mood/anxiety using questionnaires. We will record your vital signs.
- You will go to Pacific Radiology for an MRI scan.

Tuesday - Visit 3 you will come to the Fraser Building at an arranged time – we will arrange a taxi for you if needed. Your visit to the clinic on this day will last approx. 4 ½ hours – and will consist of the following:

- We will escort you to SCL lab for a blood test.
- Taking blood samples may have important cultural significance for Maori participants and we encourage discussion or consultation with whanau before deciding whether to take part.
- We will do an assessment of your mood/anxiety using questionnaires and you will complete a CADSS scale, orientation questionnaire, Trail-making test and BPIC questionnaire.
- We will record your vital signs.
- You will have a resting EEG

- You will then be dosed with either ketamine (1mg/kg) or fentanyl (50mcg) by intra muscular injection into your upper arm. You will not know which one of the study drugs you are receiving.
- We will continue to take your vital signs and assess your mood and dissociation with questionnaires.
- One and half hours after dosing you will have a further resting EEG
- Two hours after dosing you will go to Pacific Radiology for an MRI scan.
- After the MRI scan you will come back to the Fraser Building We will continue to take your vital signs and ask about any side-effects you notice. We will do further assessment of your mood/anxiety, cognition and level of dissociation.
- We will complete an orientation and discharge checklist to ensure you are ok to go home.
- On completion of the study requirements for the day we will arrange for a taxi to take you home if necessary.

Friday - Visit 4, which is 3 days after dosing, you will come to the Fraser Building at an arranged time. Your visit to the clinic on this day will last approx. 3 hours.

- We will escort you to SCL lab for a blood test.
- We will do an assessment of your mood/anxiety and bladder using questionnaires
- We will record your vital signs and ask about any side-effects you noticed following treatment on Visit 3
- You will have a resting EEG
- Following the EEG to you will go to Pacific Radiology for an MRI scan

Post-Study Optional Extension Phase of Treatment

After completing the study you would be able to take part in an optional extension phase of ketamine treatment (0.5-1mg/kg) doses once or twice weekly for 4-6 weeks. This treatment will happen at the Fraser Building. The purpose of these repeated doses would be to see if we can produce a long-term improvement in your anxiety symptoms (that is, when we stop dosing, that your anxiety does not return). You will need to arrange your own transport to come to the Fraser Building for treatment and to return home. You should be escorted home by a responsible person. Because ketamine may affect your ability to drive, you should not drive a car until the day after treatment. We recommend you have someone at home with you the night after dosing.

Electrical recording procedure (EEG)

Preparation- Hair products and natural oils on our scalp make it difficult to record your brain rhythms. It is important to us that you come with a clean scalp, so please wash your hair either the day before or the day of the study. Your hair must be dry. Please avoid using any hair products on the day of the study.

For the resting EEG You will put on a cap which is connected up to electrodes that measure your brain waves. We will fill the electrodes (small metal discs) attached to the cap with a gel that conducts brain signals from your scalp to our recording system. You will be asked

to relax for 10 minutes, opening and closing your eyes when the experimenter asks you to.

For the computer Stop Signal Task you will sit down with a computer screen in front of you and be asked to press buttons on the computer mouse in response to stimuli presented on the computer screen or via audio – this usually takes 30-40 minutes.

Magnetic Resonance Imaging Procedure (MRI)
MRI is a non-invasive medical scanning technique that provides images of the inside of the human body with a high degree of detail and accuracy – for this study the head is being imaged. The MRI machine uses a magnetic field and radio waves, together with an advanced computer system. It builds up a series of images, each one showing a thin slice of the area being examined.

You will lie on a table that slides into the magnet at the start of the scan. During the scan, loud knocking noises are heard due to rapid switching of magnetic fields – earplugs are provided to reduce the noise level. Scan time will last approximately 30 minutes for each MRI.

WHAT ARE THE POSSIBLE BENEFITS AND RISKS OF THIS STUDY?

What are the possible benefits? You may find that your anxiety symptoms improve or disappear, or you may not experience any improvement. There is evidence that ketamine may be an effective treatment for anxiety. However, it is not considered a proven treatment at present. We do not know if any improvement in your anxiety symptoms will be maintained by a course of this medication.

What are the side-effects? The most common side effects of ketamine include feeling woozy in the head, drowsy, and dizzy; numbness in the face and tongue; having your arms and legs feeling heavy or not connected to you; feeling unsteady on your feet. Some people have reported emotional changes, such as feeling high, anxious or sad. Nausea is occasionally reported. You may have a small increase in blood pressure. These side effects are most noticeable around 10-20 minutes after injection, and are generally gone after 40-60 minutes.

The most common side effects of fentanyl are drowsiness, slowed breathing, slowed heart rate and/or nausea/vomiting. These effects will be noted within 10 minutes of injection, and may last for 1-2 hours.

What are the risks for me? Risks include: discomfort from an intra muscular injection; the side effects from the ketamine or fentanyl injection (as described above). The ketamine injection may not improve your anxiety at all after just one dose. For the EEG electrodes, there is a small risk of allergic skin reaction to the electrode gel and of minor scalp discomfort during gel application. Patients who are claustrophobic may feel uncomfortable being in the MRI.
If there were any incidental findings after MRI we would notify you and with your consent, your GP.

Long term effects of ketamine: There are reports that abuse of ketamine (daily dosing, at doses 5-30 times higher than used in this study) can lead to bladder problems (increased frequency of urination, pain during urination and incontinence) and problems with cognition. Given the low doses and infrequent dosing schedules in this study, these problems are unlikely to occur. Cognition and bladder function will be monitored during the study using questionnaires and you should inform study staff if you experience any changes.

Reproductive Risks: There is no information on either ketamine or fentanyl's safety in pregnancy or breastfeeding. Because of this, it is important that participants are not pregnant or breast-feeding and do not become pregnant during the course of the study. If you are female and child-bearing is a possibility, you will be required to undergo a pregnancy test prior to commencing the study.
We advise both males and females use effective contraceptive methods while participating in this study.

If you are female and you do become pregnant whilst participating in the study, you should advise study staff immediately. The study doctor will withdraw you from the study and advise on further medical attention should this be necessary. You must not continue in the study if you become pregnant.

WHO PAYS FOR THE STUDY?

There will be no cost to you to participate in this study; all screening and treatment is without charge.

The study is being paid for with funds from the University of Otago

Reimbursement for Participating:
You will be reimbursed with vouchers to the value of $200.00 for recognition of the costs incurred associated with participating in this study. Reimbursement requires completion of all visits according to study requirements; if you only complete some of the visits your reimbursement would be reduced proportionally.

WHAT IF SOMETHING GOES WRONG?

If you are injured in this study, which is unlikely, you would be eligible for compensation from ACC just as you would be if you were injured in an accident at work or at home. 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 ARE MY RIGHTS?

Your participation in this study is entirely voluntary. You do not have to participate, and you may withdraw from this study at any time and without any disadvantage of any kind.

We will inform you of any new information collected in this study, such as if we are able to identify specific regions of the brain affected in patients with treatment resistant anxiety.

WHAT HAPPENS AFTER THE STUDY OR IF I CHANGE MY MIND?

If you change your mind, you can withdraw from this study at any time. Your treatment will continue with your usual medical team (GP or community psychiatrist).

If you complete the first phase of the study, you would be able to take part in an optional extension phase of ketamine treatment (0.5-1mg/kg) doses once or twice weekly for 4-6 weeks. The purpose of these repeated doses would be to see if we can produce a long-term improvement in your anxiety symptoms (that is, that is, when we stop dosing, that your anxiety does not return). At this stage, this treatment is experimental and will not be available as a continuation treatment. If there has been a recurrence of your anxiety symptoms you should attend your regular treating doctor. Treatment options after the study include standard treatment options for anxiety – these include medication and psychological therapy.

All data collected will be securely stored in such a way that only those involved in the research program will be able to gain access to it. At the end of the project any personal information will be destroyed immediately except that, as required by the University's research policy, any raw data on which the results of the project depend will be retained in secure storage for ten years, after which it will be destroyed.

All blood samples collected during the research will be destroyed at the end of the study. The results will be published in an international scientific journal. The data included in this publication will not be able to identify you. If you want access to your personal data later you will need to record the identification number used for your particular tests. You are most welcome to request a copy of the results of the project should you wish.

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:
Professor Bruce Russell, School of Pharmacy; tel 03 479 7272; email bruce.russell @otago.ac.nz

Professor Paul Glue, Dept. of Psychological Medicine; tel 021 243 3372; email: paul.glue@otago.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

For Maori health support:
To ensure ongoing cultural safety, the University of Otago encourage those who identify as Māori, and who are participating in health research or clinical trials, to seek cultural support and advice from their own Kaumātua or Whaea in the first instance.

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

Consent Form

Please tick to indicate you consent to the following

I have read, or have had read to me in my first language, and I understand the Participant Information Sheet.		
I have been given sufficient time to consider whether or not to participate in this study.		
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. This may be important in deciding about collection of blood samples,.		
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.		
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.		
I consent to the research staff collecting and processing my information, including information about my health.	Yes ☐	No ☐
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 ☐	No ☐
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.		
I understand the compensation provisions in case of injury during the study.		
I know who to contact if I have any questions about the study in general.		
I understand my responsibilities as a study participant.		
I wish to receive a summary of the results from the study.	Yes ☐	No ☐

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.

Researcher's name:

Signature: Date: