**Protocol Title: An open-label feasibility study of ketamine-assisted therapy**

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[In some studies, greater detail may be required. Researchers should add further information if this is indicated. For guidance, refer to Chapters 12, 13 and 14 of the National Ethical Standards for Health and Disability Research and Quality Improvement (2019). 34](#_Toc93410705)

[For return of results, researchers are directed to Standards 11.45 – 11.49 for general guidance about return of results and incidental findings; Standards 14.23 – 14.26 (in relation to incidental findings arising from tissue) and Standards 14.37 – 14.41 (in relation to incidental genetic results). 34](#_Toc93410706)

[Researchers must also comply with other data and tissue legislation, regulations, and codes. 34](#_Toc93410707)

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# KEY TRIAL CONTACTS

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# SYNOPSIS

|  |  |
| --- | --- |
| Trial Title | An open-label feasibility study of ketamine-assisted therapy |
| Trial Design | Open-label trial  |
| Trial Participants | Patients with Treatment-Resistant depression in Major Depressive Disorder and Bipolar disorder |
| Planned Sample Size | n = up to 30 |
| Treatment duration | 3 weeks |
| Follow up duration | 6 months |
| Planned Trial Period | 2 years |
| Primary Outcome Measure | Change in depressive symptomology measured with the Montgomery-Asberg Depression Rating Scale |
| Investigational Medicinal Product | Racemic ketamine (Ketalar**®**)  |
| Dose and Route of Administration | First Session: 0.5mg/kg(0.3mg/kg if participant >100kg) with an optional second dose of 20-40mg after 12-15 min IMSecond Session: 0.5mg/kg-0.75mg/kg (0.3mg/kg-0.5mg/kg if participant >100kg) with an optional second dose of 20-40mg after 12-15 min IM Third Session: 0.5mg/kg-0.75mg/kg (0.3mg/kg-0.5mg/kg if participant >100kg) with an optional second dose of 20-40mg after 12-15 min IM  |

# ABBREVIATIONS

|  |  |
| --- | --- |
| AE | Adverse event |
| BDNF | Brain-derived neurotrophic factor |
| BP | Bipolar disorder |
| CAEQ | Credibility and Expectancy Questionnaire |
| CEQ | Challenging Experience Questionnaire |
| CF | Consent Form |
| CRF | Case Report Form |
| CSSRS | Columbia Suicide Severity Rating Scale  |
| FDA | Food and Drug Administration (USA) |
| GCP | Good Clinical Practice |
| GP | General Practitioner |
| HDEC | Health and Disability Ethics Committee |
| IM | Intramuscular |
| KAT | Ketamine assisted therapy |
| MDD | Major Depressive Disorder |
| MADRS | Montgomery-Asberg Depression Rating Scale |
| NMDA | N-Methyl-D-Aspartate |
| PI | Principal Investigator |
| PIS | Patient Information Sheet |
| SAE | Serious Adverse Event |
| SAR | Serious Adverse Reaction |
| SCS | Self-Compassion Scale |
| SRS | Session Rating Scale |
| SUSAR | Suspected Unexpected Serious Adverse Reactions |
| TMF | Trial Master File |

# BACKGROUND AND RATIONALE

Depression is the most prevalent mental health disorder in New Zealand [1] and is the second leading cause of disability in the world [2]. In New Zealand, anxiety and depressive disorders account for 5.3% of all health loss as measured by disability adjusted life years [3]. Despite the large range of behavioural and pharmacological therapies currently available, effective treatments for many depressed patients are often elusive. An estimated 35% of depressed patients fail to respond to 4 or more antidepressant medications [4]. For such “treatment-resistant” patients, talk-therapy modalities such as cognitive behavioural therapy typically deliver modest benefits and/or inadequately guard against risk of depressive relapse [5-7]. Further, at particular risk are individuals with suicidal ideation, for whom the delayed onset of current anti-depressants may be unacceptably slow. It is imperative to examine new treatment modalities with more rapid onset of response, and/or that may treat chronically depressed patients who have failed existing treatments.

One therapeutic modality that shows early promise as a treatment for chronically depressed patients is Ketamine-assisted therapy (KAT). KAT is a unique method used primarily in the United States and Europe to date, to address mental health conditions including depression, anxiety, post-traumatic stress disorder, chronic pain and addiction [8]. Offered by health professionals with both medical and psychological skill sets, KAT involves administering perception-altering doses of ketamine to patients within a therapeutic setting. Within KAT, altered states of consciousness are thought to allow patients a reprieve from rigid thinking and behavioural patterns, and an expanded awareness in which insight and alternative perspectives on personal difficulties can arise[9]. Although current KAT models differ in the degree to which clinicians actively engage in the therapeutic process, a central premise is that patients access their own “inner healing intelligence” or individual capacity to move towards health and wellbeing. Consistent with models of psychedelic psychotherapy in general, it is believed that optimal “set” (patient’s mind-set) and “setting” (environmental factors) in KAT are more likely to result in superior treatment outcomes.

Initial research conducted in three private KAT practices has demonstrated the effectiveness of KAT for depression and anxiety, particularly for those with severe, and/or treatment-resistant depression[10]. A growing demand for KAT is suggested by the rapid increase in KAT clinics and training programs in the USA. Despite this interest, and the early indication of KAT’s potential for treatment-resistant depression, there are few empirical studies of KAT and none have been conducted in a New Zealand context. Moreover, to the best of our knowledge, no research has yet examined factors that may enhance the “setting” aspect of KAT and thereby improve treatment outcomes. In this study, we will conduct an open-label feasibility trial to explore the testing study procedures, validity of tools, and recruitment rate in order to design a larger study involving use of ketamine in combination with psychotherapy with a treatment-resistant population. Assuming feasibility of KAT is demonstrated in the current study, a subsequent study could be designed to compare IM ketamine with IV ketamine, without a psychotherapy component. This would be a study with greater statistical power and would help inform clinicians and funders about service development.

**KAT as distinct from other therapeutic ketamine paradigms**

In elaborating the need for further empirical study of KAT, it is important to briefly review the historical use of ketamine in psychiatry [11] and to differentiate KAT from other therapeutic ketamine paradigms. Ketamine was first developed in the late 1960’s as an analogue of phencyclidine. Ketamine has a high affinity to N-methyl-D-aspartate receptor as an antagonist in addition to diffuse activity at opioid, adrenergic receptors, and several serotonin and norepinephrine transporters [12-14]. Ketamine has widespread use as an anaesthetic and analgesic agent. Ketamine has a demonstrated safety record in emergency room settings with medically compromised populations including in paediatrics and the elderly. The potential of ketamine to address psychiatric and psychological difficulties was first identified in the early 1970’s[15]. Ketamine’s role in treating addiction was also documented by Krupitsky [16]. The National Institute of Mental Health in USA began exploring the potential of ketamine to treat Major Depressive Disorder in the late 1990’s [17]. Low dose ketamine (relative to anaesthetic doses) delivered to patients by an IV infusion demonstrated a robust but short-lived response even after one treatment. This treatment approach was further developed with follow up IV sessions to maintain a response and an emphasis was placed on avoiding or minimising accompanying dissociative experiences [18-20]. While IV ketamine is still widely-used in the USA for intractable mental health conditions including depression, critiques of this model include its expense, limited duration of effects, and singular focus on the symptoms, rather than the root causes of depression [21].

In parallel to the development of the IV ketamine model, some clinicians began providing patients with ketamine in other forms including oral, sublingual, and intranasal formulations to treat depressive episodes and other psychiatric conditions [22]. Most recently, the enantiomer esketamine (the S enantiomer of racemic ketamine) delivered through an intranasal system has been granted FDA approval as add on therapy with an antidepressant for people with treatment-resistant depression and acute suicidal ideation[23]. Although esketamine represents a significant advance in treatment options for acutely unwell patients, its high cost and delivery model currently limit its availability to relatively few patients. Given the challenges of other therapeutic ketamine paradigms, alternative frameworks, which may address some of these limitations, require empirical investigation.

KAT first began in the 2000’s when a number of clinicians started using medium to higher dose intramuscular [IM] administered ketamine “off-label” in office-based settings in combination with psychotherapy. [24]. For the sake of clarity, the terms “medium-” and “high dose” are used here to refer to doses of ketamine that are in the psychedelic range, but are significantly lower than those used for anaesthetic purposes. A “medium”-dose is considered ~0.5 mg/kg and a “high”-dose is ~ 1.5 mg/kg. Compared to the IV Ketamine model, KAT offered a significant paradigm shift as insights from patients’ psychedelic experiences were intentionally leveraged for positive change in their lives, a process elaborated on in the section below. Recent controlled studies have shown that IM injections and IV infusions of Ketamine lead to comparable plasma concentrations [25] and equivalent acute antidepressant effects [26]. However, compared to IV infusions, IM Ketamine is considered less cumbersome, expensive and requires less close monitoring [26, 27]. The safety record of KAT in office-based settings for psychiatric care has been well established [27] and initial concerns about tolerance and addiction as well as urologic complications have not been demonstrated [28]. Finally, despite early studies indicating the potential of KAT for alcohol dependence, heroin addiction and end-of life anxiety [29, 30]there are few recent studies of KAT. Given the relative lack of empirical study of KAT, and the limitations of other therapeutic ketamine paradigms, further evaluation of KAT is due.

**Dose considerations**

In line with KAT’s status as an emerging treatment paradigm, no standardised protocol yet exists in relation to the number of treatment sessions, and the doses required to yield improved outcomes. However, treatment sessions in KAT are broadly distinguishable in terms of whether low, or moderate-high doses of ketamine are delivered. Some more recent models of KAT for patients with a background of trauma, but not necessarily depression, use low doses of ketamine as an adjunct to psychotherapy [10]. Low doses are also useful initially to establish personal sensitivity to ketamine [31]. In moderate-high doses, ketamine has dissociative and psychedelic effects, which have been shown to facilitate profound transpersonal experiences [32]. These experiences are thought to help people in a variety of ways, offering important clarity and insight into one's struggles, adding a spiritual dimension to on going therapeutic work, and facilitating a sense of meaning and interconnectedness. Preparation reduces anxiety before high-dose sessions, and integration sessions are intended to help patients integrate any insights/altered perspectives into their lives post-treatment [33]. Preliminary research suggests that the effects of IV Ketamine are dose-dependent, that is, the more fully dissociative the experience, the greater the treatment response [34]. There is also evidence that patients can experience significant and enduring reductions in depression from one high-dose experience of the psychedelic drug psilocybin, and anecdotal reports of the same following a single high-dose ketamine in KAT [35-38] For these reasons, participants in the proposed study will be administered a moderate-high dose of IM ketamine in each ketamine session, which is intended to maximise treatment response.

**Time variable fractal image viewing as a facilitator of response**

The influence of set and setting as a component of KAT has not been explored in the literature, but is widely accepted by KAT practitioners. The clinical environment is designed with the intention to foster a relaxed, safe, and inwardly focused environment. Additionally, some practitioners have offered time variable fractal images as part of the preparatory stage of treatment with anecdotal claims of benefit. The term fractal is a description of the mathematical phenomenon of recurring self-similar structures or patterns that repeat at increasing magnifications. Empirical research in the field of environmental psychology has demonstrated that viewing natural scenes provides benefits including improved mood, reduced anxiety, and increased focus of attention [39, 40]. There is an identified convergence of physiological response between viewing static fractal images and natural scenes. Interestingly, fractal structures are evident in the natural world (clouds, trees, mountains) as well as in the anatomical structure of animals (neurons, veins)[41].Similar to the viewing of natural scenes, there is a demonstrated physiological impact of fractal viewing, including fractal preference and human response. The fractal preference of most individuals overlaps strikingly with the dimensional range of fractals in natural environments. In order to quantify the visual complexity of the fractal images used in our study we employed the traditional mathematical parameter called the fractal dimension *D*. For a smooth line (containing no fractal structure) *D* has a value of 1, while a completely filled area (also containing no fractal structure) *D* has a value of 2. The repeating patterns of the fractal line have a *D* value between 1 and 2. As the increasing amount of fine structure in the fractal mix of repeating patterns the *D* value moves away from 1 and moves closer to 2. Behavioural research confirms that the complexity preference of humans lie in the narrow range of 1.3 to 1.5 which maps closest to *D* values occurring in nature like clouds, trees, and mountains and might also induce a relaxed state [42, 43]. Our decision to use time varying fractals in this proposed study reflects the anecdotal reports from clinicians as well as the fact that time varying stimuli can be expected to maintain observer’s attention for longer periods.

Although anecdotal clinical claims have been made about the enhancement of the clinical efficacy of KAT by the concurrent provision of fractal images this has never been empirically evaluated. As an initial step, we will therefore measure tolerability of time variable fractal images prior to receiving ketamine in this study. If tolerability of fractal imagery is established, we envisage testing whether fractal imagery administration prior to KAT yields superior outcomes in a subsequent study.

**Personality factors predictive of acute and long-term response**

Little research has yet investigated factors that may be predictive of acute and longer-term responses to KAT, although there is preliminary indication of superior treatment outcomes among older patients and those with severe symptom burden [33]. Studies from the wider psychedelic therapy literature have, however, begun to explore the impact of personality variables, in order to improve the ability to predict how an individual might respond to a psychedelic. For example, the personality trait of absorption, defined as the tendency to get caught up in one’s imagination or in sensory experience has been found to strongly predict a “mystical-type” experience to psilocybin [44]. The term “mystical-type experience”, considered synonymous with Maslow’s term “peak experience”, is described as experiencing disorientation in space and time, feeling free of inner conflict, and a sense of oneness with the universe [45]**.** Regarding the long-term relevance of mystical experiences, several controlled studies suggest that they predict superior treatment outcomes [35-38].

The personality trait neuroticism has been shown to predict the occurrence of a challenging experience to high-dose psilocybin [46]. One study has suggested that challenging psychedelic experiences are beneficial in the long term, but not if the duration of struggle in the acute experience dominates the entire experience [47]. Whether trait absorption and neuroticism, and/or the occurrence of mystical versus challenging experiences, predict similar acute and long-term responses to KAT, is as yet unknown. Measurement of these constructs will also be useful in the context of a randomised controlled trial.

# AIMS AND HYPOTHESES

1. Aim: To assess the antidepressant effects of KAT provided in patients with treatment-resistant depression.

Hypothesis: That KAT treatment will provide significant clinical benefit in this treatment resistant population.

Measure: Clinical benefit will be measured as percentage change in the Montgomery-Asberg Depression Rating Scale (MADRS) at 4hr and 1 day after each ketamine session, and subsequently 7 day and 28 days, 3 months, and 6 months post-treatment [48, 49] .

1. Aim: To quantify the tolerability of KAT provided with fractal imagery in patients with treatment-resistant depression

# Measures: Tolerability of treatment will be measured using a Likert scale [50]

and qualitative interview with participants.

1. Aim: To assess the feasibility of conducting future larger studies of KAT in patients with treatment-resistant depression.

Measures: This will include the testing study procedures, validity of tools, and estimation of the recruitment rate, as well as the loss to follow up of enrolled patients.

1. Aim: To explore personality dimensions as contributing to tolerability and response to a psychedelic ketamine treatment.

Hypotheses: That individuals high in trait absorption will be more likely to have a mystical-type experience as measured by the 5D-ASC, and such experience will be associated with a greater reduction in depression.

That individuals high in trait neuroticism will be more likely to experience some challenging aspects to their psychedelic experience as measured by the CEQ, which will be associated with a greater reduction in depression.

# LIST OF OUTCOME MEASURES

The primary outcomes measure for this trial is the change in depressive symptomology measured with the MADRS.

In addition, the following standardised scales will be used as secondary outcome measures:

* HAM- A
* QIDS
* 5-Dimensional Altered States of Consciousness Rating Scale (5D-ASC)
* Big Five Inventory 2 (BFI-2)
* Modified Tellegen Absorption Scale (MODTAS)
* Challenging Experience Questionnaire (CEQ)
* HERO Wellness Scale [51]
* Likert tolerability scale
* Credibility and Expectancy Questionnaire (CAEQ)
* Session Rating Scale
* Self Compassion Scale (SCS)

Additionally, rates and diversity of people being screened, recruited, and participating in the study will be measured.

# TRIAL DESIGN

**Study Design**

The overall trial design is an open-label trial in up to thirty patients with treatment-resistant depression or treatment-resistant bipolar disorder in a depressive episode.

Procedures will take place at the Clinical Research Centre at the Auckland University Faculty of Medical and Health Sciences. Preliminary screening will be done via video platform (Screening/Consent Visit). Participants will be screened for eligibility, and willingness to participate in the study during this visit. Participants must provide informed consent to participate. This will take up to two hours. Participants will also be provided with a LabTest form to get screening blood work completed.

On a separate day, the participants will have further in person screening at the Centre to confirm their suitability. This will include urine pregnancy (if relevant) and drug tests, vital signs, and weight measurements. On this visit, the participant will also meet with the therapist for the Preparation session. This will take up to three hours. This and all subsequent meetings with the study team members including the therapist will be recorded. We will audio and videotape these sessions for two reasons: 1) to better understand, and learn about the participant’s qualitative experience of the ketamine session and 2) to ensure consistency of treatment approach between therapists conducting the integration sessions. Any information given by the participant in the integration sessions, and at any other time of the study will remain private and confidential. Further details about privacy and confidentiality are outlined in the data management plan which is available to review as part of the consent process.

The participant will then attend the Centre for Ketamine Experience 1. During Ketamine Experience 1, the participant will receive up to two intramuscular ketamine injections and undergo assessment. Medications to manage and treat nausea and elevated blood pressure will be available to participants. This Ketamine Experience will take up to six hours. A further assessment will take place the following day via video. One to three days after Ketamine Experience 1, the participant will return to the Centre or attend via video platform for an interaction with the therapist (Integration Session 1) and clinical assessment. The Integration Session will take between two and three hours. This session will include an opportunity to share the participant’s experiences with the therapist, and to explore ways of integrating any important insights that may promote the participant’s recovery from depression in to their lives, as well as an interview about the participant’s mental health. This will also be used to provide psychological support about the ketamine experience.

The participant will have two more ketamine treatment sessions (Ketamine Experience 2, Ketamine Experience 3) on a weekly basis. These will be conducted similar to Ketamine Experience 1, although there might be some changes in ketamine doses as determined by the research team, in consultation with the participant. Each Ketamine Experience session will be followed with an assessment and integration session one to three days after each Ketamine Experience (Integration Session 2, Integration Session 3).

The participant will then have further video or telephone assessments one week, one month, three months and six months after the last ketamine treatment (Ketamine Experience 3).

Preparation

+

Screen

 (In-person)

Week 2

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**

Week 3

*Figure 1: Overall study procedure, visits and follow-ups for patients.*

Additional follow-up interviews via telephone or video will occur four times after the last Integration Session (Integration Session 3) and will take approximately fifteen minutes. Where participants have given consent to being emailed study questionnaires, they will complete these online. If participants do not provide such consent or lack internet access, the research team will complete the questionnaires with them during the interview.

Initial Assessment

Pre-ketamine therapist session

Ketamine
Experience

Final Assessment

+ Outcome Measures

Rest and Recovery

Ketamine IM initial dose

Optional Ketamine IM follow-up dose12-15 mins later

Welcome & Screen

Discharge

**Summary of Ketamine Experience Procedures**

**Psychiatric Assessments:**
MADRS, QIDS, HAM-A, HERO, MODTAS, 5D-ASC, Likert Tolerability Scale

**Medical Assessments:**
BP, Pulse, Pulse Ox, Weight, UA, U-Preg

**Final Assessment:**
Medical

**Initial Assessment:**
Medical & Psychiatric

012345678

Time
(hrs)

*Figure 2. Ketamine Experience procedure for participants.*

**IM Dosing ranges**

|  |  |  |
| --- | --- | --- |
|  | **Participant Weight: 50-100kg** | **Participant Weight: 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 |

# PARTICIPANT IDENTIFICATION

## Trial Participants

Up to 30 depressed patients who meet DSM-5 criteria for Major Depressive Disorder or Bipolar Disorder will complete this study. These patients will be recruited from Community Mental Health Centres, Liaison Psychiatry Services, GP practices, private psychiatry clinics in the greater Auckland region, and via convenience sampling*.* In addition, advertisements will be placed through , group emails directed towards mental health clinicians in the Auckland region, in local newspapers/noticeboards, and on Facebook allowing patients to make initial contact directly with the research team.

## Inclusion Criteria

The participant may enter the trial if ALL of the following apply:

* Participant is willing and able to give informed consent for participation in the trial.
* Male or female, aged 18 years or above and less than 70.
* In the Investigators’ opinion, is able and willing to comply with all trial requirements.
* Major Depressive Disorder or Bipolar Disorder and on mood stabilizing medication with current depressive episode for at least three months, as assessed by a Clinical Interview using DSM-5 criteria.
* MADRS >20.
* An inadequate response to at least two antidepressants courses (Antidepressant Treatment History Form) one of which can include the current episode.
* To have been stable on any psychotropic medication for at least four weeks prior to the Ketamine Experience.

## Exclusion Criteria

The participant may not enter the trial if ANY of the following apply:

* Female participant who is pregnant, lactating or planning pregnancy during the course of the trial.
* Significant renal or hepatic impairment.
* Cardiovascular conditions including severe cardiovascular disease, heart failure, severe or poorly controlled hypertension, recent myocardial infarction, history of stroke, cerebral trauma, or intracerebral mass or haemorrhage.
* Abnormal heart rate or blood pressure checked at screening.
* Participants who have participated in another research trial involving an investigational product in the past 12 weeks.
* History of significant psychotic episode(s).
* Any unstable medical or neurologic condition.
* Planned major changes to psychotropic medication.
* Imminent risk of suicide as determined by the CSSRS and MADRS/clinical interview.
* Planned or probable use of ECT.
* Active substance use disorder in the previous 6 months.
* Regular use of any medication deemed to be contraindicating as judged by the attending study physicians
* Inability to speak or read English.
* Any history of abuse of ketamine or phencyclidine.
* Contraindication to the use of ketamine according to manufacturer guidelines including hypersensitivity to the drug or its components.
* Planned use of ketamine, for example, for pain control.
* Unable to fast for four hours prior to administration of ketamine.
* Any other condition judged by the treating clinician as likely to impact on the ability of the participant to complete the trial.
* Body-weight <50kg or >120kg.
* Current use of the following medications: memantine / amantadine / rimantadine / dextromethorphan/procyclidine.

## Pilot participants

We propose to study up to five healthy pilot participants so that we can pilot our drug delivery and data collection procedures. These participants will be paid $50 in vouchers for time they give to the study. Exclusion criteria will be as in 8.3. Inclusion criteria will be as per 8.2 excluding requirements 4 onwards.

# TRIAL PROCEDURES

## Recruitment

We will inform clinicians working in primary care settings as well as community mental health centres and liaison psychiatry services throughout the Auckland that the study is taking place. We will also recruit via convenience sampling and directly through social media. If referring clinicians have patients that they think are suitable for the study, then they will pass an information sheet about the study to the participant with study contact details. An initial screening will be by a researcher in response to phone contact either directly from the patient or from the patient’s referring clinician.   People who pass this phone screening will be given an appointment for their first Consent Visit through video platform or at the Clinical Research Centre. Where a participant makes direct contact with the research team, the screening process will be the same. The research team will contact the participant’s primary care provider to inform them of the participant’s involvement in the study. Please refer to Appendix 1 for the online advertising template.

## Informed Consent

Written and verbal versions of the Participant Information Sheet and Informed Consent form will be presented to the participants detailing no less than: the exact nature of the trial; what it will involve for the participant; the implications and constraints of the protocol; the known side effects and any risks involved in taking part. It will be clearly stated that the participant is free to withdraw from the trial at any time for any reason without prejudice to future care, and with no obligation to give the reason for withdrawal.

The participant will be allowed as much time as they would like to consider the information, and will have the opportunity to question the Investigator, their GP or other independent parties to decide whether they will participate in the trial. Written Informed Consent will then be obtained by means of participant dated signature and dated signature of the person who presented and obtained the Informed Consent. The person who obtains consent will be an investigator in the trial. A copy of the signed Informed Consent form will be given to the participant. The original signed form will be retained in the TMF.

Verbal consent will be reconfirmed at the start of each Ketamine Experience.

## Ketamine Experience Discontinuation/Withdrawal of Participants from Trial Treatment

Each participant has the right to withdraw from the trial at any time. In addition, the Investigator may discontinue a participant from the trial at any time if the Investigator considers it necessary for any reason including:

* Pregnancy
* Ineligibility (either arising during the trial or retrospectively having been overlooked at screening)
* Significant protocol deviation
* Significant non-compliance with treatment regimen or trial requirements
* An adverse event which requires discontinuation of the trial medication or results in inability to continue to comply with trial procedures
* Disease progression which requires discontinuation of the trial medication or results in inability to continue to comply with trial procedures
* Withdrawal of consent
* Loss to follow up

The reason for withdrawal will be recorded in the CRF.

If the participant is withdrawn due to an adverse event, an Investigator will arrange for follow-up visits or telephone calls until the adverse event has resolved or stabilised.

## Definition of End of Trial

The end of trial is the date of the last follow-up interview of the last participant.

## 9.5 Schedule of Procedures

|  |  |  |  |
| --- | --- | --- | --- |
| **Procedures** |  |  | Total Visits 7. Follow-up interviews by Video/Phone  |
| Screening and consent | **Preparation and screen** | **Ketamine Experience 1** | Follow-up | **Integration 1** | **Ketamine Experience 2** | Follow-up | **Integration 2** | **Ketamine Experience 3** | Follow-up  | **Integration 3** | Follow-up1 Week | Follow-up 1 Month | Follow-up 3 Months | Follow-up 6 Months |
| Informed consentAnd preparation |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Demographics |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Medical history & Diagnosis |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Medical Examination |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Laboratory tests |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Eligibility assessment |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Treatment with ketamine |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Integration |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Psychiatric Questionnaires |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |

**Items in bold are sessions that will be undertaken in-person at the Research Centre.**

## Summary of Procedures

*Demographics, Medical History, Medical Examination and Diagnosis*

Demographics, medical history, medical examination and confirmation of diagnosis will be documented in the CRF.

*Laboratory Tests*

All patients will provide urine samples as part of screening at the in person Screening/Consent Visit. A positive test for recreational drugs using a multi-panel screen will result in halting the trial for that patient. All females will be given a pregnancy test. A positive pregnancy test will halt the trial for that patient.

At the video or in person screening visit, patients will be provided with a LabTests referral form for a full blood screen before they attend the first Ketamine Experience. The test will screen for deficiencies commonly found in depression as well as abnormal thyroid and liver function. Abnormal results will not automatically result in exclusion from the study. However, in the case of major deficiencies or abnormalities, patients will be discharged from the study and referred back to their GP.

*Eligibility Assessment*

Diagnosis will be established by psychiatrist and research nurse based on clinical interview and use of the MINI.

*Dispensing of Ketamine*

At each Ketamine Experience, ketamine will be administered up to two times via intramuscular injection. The first dose will be 0.5mg/kg (or 0.3mg/kg for participants >100kg) followed by an optional 20mg to 40mg dose after twelve to fifteen minutes. Heart rate, blood pressure, and oxygen saturation will be monitored prior to treatment and 12-15 minutes after injection and one hour after injection by the supervising clinician. The second ketamine session will have the following dosing regimen: 0.5mg/kg-0.75mg/kg (0.3mg/kg-0.5mg/kg if participant >100kg) with an optional second dose of 20-40mg after 12-15 min. The third ketamine session will have the following dosing regimen: 0.5mg/kg-0.75mg/kg (0.3mg/kg-0.5mg/kg if participant >100kg) with an optional second dose of 20-40mg after 12-15 min.

A series of time variable fractal images (*D* = 1.3) will be viewed for one minute prior to ketamine administration.

*Psychiatric Questionnaires*

* HAM- A
* QIDS
* 5-Dimensional Altered States of Consciousness Rating Scale (5D-ASC)
* Big Five Inventory 2 (BFI-2)
* Modified Tellegen Absorption Scale (MODTAS)
* Challenging Experience Questionnaire (CEQ)
* HERO Wellness Scale [51]
* Likert tolerability scale
* Credibility and Expectancy Questionnaire (CAEQ)
* Session Rating Scale (SRS)
* Self Compassion Scale (SCS)

These take up to an hour to complete. See Attachments

# INVESTIGATIONAL MEDICINAL PRODUCT (IMP)

## Storage of Ketamine

Ketamine will be stored at room temperature in the locked School of Pharmacy stores in the Faculty of Medical and Health Sciences, Auckland University. The School of Pharmacy holds the appropriate licenses to store ketamine.

## Accountability of the Trial Treatment

The attending clinician, who will be a registered medical practitioner in New Zealand, but not necessarily a member of the investigative team, will administer the treatments to be used. All administrations will be logged and signed for by the attending clinician and at least one other member of the investigative team. These records will be held in the TMF.

# SAFETY

## Definitions

|  |  |
| --- | --- |
| Adverse Event (AE) | Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product. |
| Adverse Reaction (AR) | An untoward and unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant.The phrase "response to an investigational medicinal product" means that a causal relationship between a trial medication and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out.All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the trial medication qualify as adverse reactions. |
| Serious Adverse Event (SAE) | A serious adverse event is any untoward medical occurrence that:* results in death
* is life-threatening
* requires inpatient hospitalisation or prolongation of existing hospitalisation
* results in persistent or significant disability/incapacity
 |
| Serious Adverse Reaction (SAR) | An adverse event that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to one of the trial treatments, based on the information provided. |
| Suspected Unexpected Serious Adverse Reaction (SUSAR) | A serious adverse reaction, the nature and severity of which is not consistent with the information about the medicinal product in question. |

## Causality

The relationship of each adverse event to the trial medication must be determined by a medically qualified individual according to the following definitions:

**Related**: The adverse event follows a reasonable temporal sequence from trial medication administration. It cannot reasonably be attributed to any other cause.

**Not Related**: The adverse event is probably produced by the participant’s clinical state or by other modes of therapy administered to the participant.

## Procedures for Recording Adverse Events

All AEs occurring during the trial will be recorded on the CRF, whether or not attributed to trial medication. The following information will be recorded: description, date of onset and end date, severity, assessment of relatedness to trial medication and action taken. Follow-up information should be provided as necessary. Severity of events will be assessed on the following scale: 1 = mild, 2 = moderate, 3 = serious.

## Reporting Procedures for Serious Adverse Events

A complete report of All SAEs will be reported to the Safety Monitoring Committee of the trial within 24 hours. A report will also be sent to the Centre for Adverse Reactions Monitoring following MedSafe guidelines (<https://nzphvc.otago.ac.nz/carm/>).

## Safety Monitoring Committee

The Safety Monitoring Committee for this trial will comprise of two independent medical practitioners.

|  |  |
| --- | --- |
| Dr. Richard WorrallConsultant PsychiatristAuckland District Health BoardRWorrall@adhb.govt.nz | Dr. Paul JonesConsultant PsychiatristAuckland District Health BoardPaulJones@adhb.govt.nz |

In the unlikely event of an SAE being reported the Safety Monitoring Committee may decide to suspend the trial or request suspension until the research protocol is appropriately revised.

##  Safety Protocols

1. In case of unexpected adverse effects, the trial site is located across the road from the Auckland City hospital and the estimated time of transport is approximately 5-10 minutes. The emergency department at the hospital will be notified about our trial and its nature in advance.
2. All patients will be provided with a 24/7 “hotline” number that they can use to contact the study team should they experience psychiatric distress during the study period when they are not on study site. If there are major issues that arise the patient will be reviewed by one of the research team psychiatrists who will then contact the appropriate services, depending on that assessment. Patients’ usual psychiatric care provider will be notified of their participation in the trial prior to that patient being entered into the trial.
3. Should patients experience adverse events such as psychotomimetic reactions, extreme claustrophobia, panic attacks while they are on site, the supervising clinician will administer an appropriate course of treatment (for example, lorazepam).

# STATISTICS

## Description of Statistical Methods

Given the design of the trial, the primary statistic of interest for this trial will be the magnitude of change in MADRS score from baseline. This will be calculated as both a percentage change and Cohen’s d value (with corresponding 95% confidence intervals and p values) using MADRS scores measured at baseline and each time-point. Responder rate, defined as the percentage of participants who achieve a 50% or greater reduction in MADRS score will also be calculated at each time-point.

In terms of feasibility assessment, quality of outcome data collection (dropouts, missing data) will be presented using summary statistics, with frequencies and percentages for categorical variables and means with appropriate measures of spread for continuous variables. Dropouts will be categorised by the investigators as Missing at Random (MAR) or Missing Not at Random (MNAR).

## Power Calculations

Given the open-label nature of the trial comparisons can only be made against baseline. Nevertheless for completeness the following power calculations were performed in G\*Power 3.1 [52]. With a sample size of 30, a significance level of α = 0.05, (1-β) = 0.8 we are powered to see effect sizes of 0.93. Effect sizes reported for ketamine in the literature are typically ~ 1. Any effect size obtained > 0.5 might be considered promising and worthy of future investigation. In terms of correlations of outcome measures with baseline characteristics we are powered to see correlations where r>0.42 (α = 0.05, (1-β) = 0.8).

# DATA AND TISSUE MANAGEMENT PLAN

Please refer to Appendix 2 for the data and tissue management plan.

# TRIAL STEERING COMMITTEE

The role of the Trial Steering Committee (TSC) is to provide overall supervision of the trial. The TSC will be comprised of all the investigators of this study. In particular, the TSC will collaboratively develop and approve the final protocol; oversee progress of the trial, adherence to the protocol, patient safety and consideration of new information; and be responsible for publication and dissemination. The TSC must be in agreement with the final protocol and, throughout the trial, will take responsibility for:

* major decisions such as a need to change the protocol for any reason.
* monitoring and supervising the progress of the trial.
* reviewing relevant information from other sources.

# ETHICAL AND REGULATORY CONSIDERATIONS

## Declaration of Helsinki

The Investigator will ensure that this trial is conducted in accordance with the principles of the Declaration of Helsinki (2008).

## ICH Guidelines for Good Clinical Practice

The Investigator will ensure that this trial is conducted in conformity with relevant regulations and with the ICH Guidelines for Good Clinical Practice.

## Approvals

The protocol, informed consent form, participant information sheet and any proposed advertising material will be submitted to HDEC Committee and relevant District Health Boards for written approval. No research procedures will be commenced until all written approvals are obtained.

## Reporting

The PI shall submit once a year throughout the clinical trial, or on request, an Annual Progress Report to HDEC. In addition, an End of Trial notification and final report will be submitted to HDEC.

## Participant Confidentiality

The trial staff will ensure that the participants’ anonymity is maintained. The participants will be identified only by initials and a participant’s ID number on the CRF and any electronic database. All identifiable documents will be stored securely and only accessible by trial staff and authorised personnel.

## Expenses and Benefits

Reasonable travel expenses for any visits additional to normal care will be reimbursed on production of receipts, or a mileage allowance provided as appropriate. On completion of the study participants will be compensated $50.00 in vouchers for their time. If participants are unable to complete the entire study they will be compensated on a pro rata basis for the amount of the study completed at the discretion of the Principal Investigator.

## Additional Ethical Considerations

Cultural sensitivity - note the section about Māori participants in the PIS. This trial follows guidelines outlined in the Guidelines for Researchers on Health Research Involving Māori (HRC, 2010) and the guidelines on Māori responsiveness outlined on the Auckland University Faculty of Medical and Health Sciences website.

Driving – Participants will be advised not to drive on the Ketamine Experience as their ability to do so could be impaired. It will be confirmed that no patients have driven to the research facility on the day of the study. We will recommend to patients that a family member or friend picks them up after each study and visitor parking is available at the study site.

Potential Adverse Effects – These are summarised in the attached Medsafe datasheet for ketamine. Since ketamine is an approved medicine there is minimal chance of adverse effects given the screening procedures to be implemented. Members of our research team have extensive clinical experience in the administration of ketamine. Appropriate monitoring equipment will be used. See below.

https://www.medsafe.govt.nz/profs/datasheet/k/ketamineinf.pdf

Confidentiality - Will be maintained through use of non-identifiable study identifiers used on all collected data (see study design section).

Notification of Care Provider - We will notify the usual care provider of each patient before they commence the study such that said provider can adjust their care provision if required.

Use of controlled substances - No controlled substance (ketamine) will leave the Faculty of Medical and Health Sciences.

Addiction potential - Ketamine dependence syndromes are rare and the vast majority of individuals who try ketamine will not go on to develop an addictive disorder [53]. In fact, open-label and randomised controlled trials suggest that when ketamine is combined with appropriate psychotherapy that ketamine may have anti-addictive properties [8].

# FUNDING

The Study is funded by a grant from the Oakley Mental Health Foundation.

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#  APPENDIX

**Appendix 1.** *Online Advertising Template*

**Do you have depression?**

***Are you interested in trialling a new treatment for depression?***

If you are aged 18-69, and are currently depressed, and have failed to find benefit from two different anti-depressants, you may qualify for a treatment study involving:

* One video and one in person screening visit to the University of Auckland including blood tests.
* Three all day visits to the University of Auckland for treatment with an experimental medication injected by needle into your muscle. We recommend that you have a friend or family member to support you with transport and recovery for the remainder of this day.
* Three post treatment visits to the University of Auckland to discuss your experiences.

Participants will be reimbursed for their time.

*For more information, please contact our study team:*

Email: **deptrial@auckland.ac.nz**

Phone: **022 4610242**

Study Investigator: Dr. Nicholas Hoeh

Department of Psychological Medicine

School of Medicine, University of Auckland

The study has received ethical approval from

Northern A Health and Disability Ethics Committee

Ref No. 20/NTA/163/ AM01

**Appendix 2.** *Data and Tissue Management Plan*

**DATA AND TISSUE MANAGEMENT PLAN**

**Version: 4**

 **Date: 8 December 2021**

**Protocol : An open-label feasibility study of ketamine-assisted therapy**

**Universal Trial Number: U1111-1259-0551**

**Sponsor: The University of Auckland**

**Site: The University of Auckland**

**Principal Investigator : Dr. Nicholas Hoeh**

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**Note to researchers**

This data and tissue management guide is a template only. Not all sections may be applicable to all studies. If a section is not applicable to your study, please simply write ‘not applicable’ under the section heading, delete the templated text, and move on to the next section.

In some studies, greater detail may be required. Researchers should add further information if this is indicated. For guidance, refer to Chapters 12, 13 and 14 of the National Ethical Standards for Health and Disability Research and Quality Improvement (2019).

For return of results, researchers are directed to Standards 11.45 – 11.49 for general guidance about return of results and incidental findings; Standards 14.23 – 14.26 (in relation to incidental findings arising from tissue) and Standards 14.37 – 14.41 (in relation to incidental genetic results).

Researchers must also comply with other data and tissue legislation, regulations, and codes.

For data, these include: The Privacy Act 2020 and The Health Information Privacy Code 1994, The Health and Disability Commissioner (Code of Health and Disability Services Consumers' Rights) Regulations 1996, HISO 10029:2015 Health Information Security Framework, HISO 10064:2017 Health Information Governance Guidelines, and Digital and Data Technology Services (2020).

For tissue, these include: The Human Tissue Act 2008, the Guidelines on the Use of Human Tissue for Future Unspecified Research Purposes (Ministry of Health. 2007) and Standards for the collection of human tissue for non-therapeutic purposes (eg, NZS 8135:2009).

1. **Introduction**

This Data and Tissue Management Guide outlines how data and tissue will be handled during the study **(An open-label feasibility study of ketamine-assisted therapy)** and after its completion.

1. **Study Structure**

**TABLE 1. STUDY STRUCTURE**

|  |  |
| --- | --- |
| Sponsor |  The University of Auckland |
|  |  |
| Contract Research Organisation |  NA |
|  |  |
| Lead Site (New Zealand) | University of AucklandClinical Research CentreBuilding 50722-30 Park AvenueFaculty of Medical and Health SciencesGraftonAuckland New Zealand |
|  |  |
| Principal Investigator | Dr. Nicholas Hoeh |
|  | Consultant PsychiatristDept of Psychological MedicineSchool of MedicineBuilding 507Level 3, Room 304022-30 Park AvenueGraftonAuckland New Zealand 1023 |
| New Zealand Laboratory(ies) | NA |
| Overseas Laboratory(ies) |  NA |
|  |  |
| Imaging Vendor | NA |
|  |  |

1. **Organisational Data Governance Oversight**

The following institutional data policies apply for the Study:

https://www.auckland.ac.nz/en/about/the-university/how-university-works/policy-and-administration/computing/data-management/data-governance-policy.html

1. **Consent for Data and Tissue Collection and Use**

All participants will be informed of, and provide consent for, the collection and use of their data and tissue for the purposes of this study, and for any mandatory secondary uses. Participants have the option to decline video and audio recording as part of the consent process.

1. **Data and Tissue Collection**

Data will be collected from the following sources:

* Direct communication with the participant
* Study assessments, including laboratory test results, imaging, biomedical monitoring, questionnaires, interviews, and data downloaded from apps
* Participant medical records (if indicated)
* Communications with participant’s clinical care team (if indicated).
* Video and audio recording, if consented to.

Tissue will be collected as follows:

* Urine samples will be collected from each participant 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.
* Participants will be referred to LabTests (https://www.labtests.co.nz) 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. The participants will 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.
* The blood test results are required to be identifiable to ensure that in the event of major deficiencies or abnormalities, the participant’s healthcare providers will have access to relevant information.
* Data and tissue will be collected primarily by the Investigator or designated study staff. All study personnel involved in data and tissue collection will be trained in GCP, study protocol, and collection requirements.
* Data generating assessments may be performed by external third parties suitably qualified by education, training, and experience.

Collection of data and tissue will be limited to that necessary for the specified purposes of the study.

1. **Privacy and confidentiality**

Participants’ privacy and confidentiality will be respected through the protection of their data and tissue as outlined in this plan. The Investigator will comply with legal and regulatory requirements regarding the privacy and confidentiality of participants’ data and tissue.

Participants have the right to access and correct personal data held by the site. This includes screening and safety results.

* 1. **Breach of Privacy / Confidentiality**

A breach of privacy means unauthorised or accidental access to, or disclosure, alteration, loss, or destruction of a participant’s information.

In the event participant privacy and confidentiality is breached during the study, the following steps will be taken:

* Action will be taken to reduce the risk of harm following the breach. Where possible, the recipient will be contacted and asked to destroy or return any electronic the disclosed material.
* The participant will be informed of the breach as soon as practicable (unless the participant is under the age of 16 and notification would be contrary to his/her interests; or notification would be likely to prejudice the health of the participant (after consultation with the participant’s health practitioner, where practicable), and provided with support as required.
* A site quality review will be conducted to ascertain factors contributing to the breach, and any corrective action required to prevent future breaches.
* The approving HDEC will be informed.
* For notifiable privacy breaches of privacy under the Privacy Act 2020, the New Zealand Privacy Commissioner will be notified in accordance with that Act.
1. **Forms of Data and Tissue**
	1. **Identifiable Data and Tissue**

Some Study data will be collected in identifiable form.

Source documents refer to identifiable data collected for the purposes of this study.For the purposes of this data management plan, identifiable data includes the participant’s existing medical / clinical records.

Source documents will be held at the site in identifiable form.

Screening and safety tissue samples (and their results) will be labelled with identifiers. Results will be held in source, to optimise participant safety.

* 1. **De-identified Data and Tissue**

De-identified data and tissue in this study includes but is not limited to

Requisition forms not included in Section 6.1.

* Case Report Forms.
* Safety and screening results entered into the analysis data set.

De-identified tissue and data will carry the participant’s unique study code. The Investigator will retain a log linking participant code with identifiers. This log will not be made available to any external individuals or organizations.

* 1. **Anonymous / Anonymised Data [and/or Tissue].**

De-identified data [and tissue] may be anonymised prior to being made available for future research. Anonymised data and tissue will be irreversibly stripped of the unique participant code and any other identifiers. For audio and video recordings, any identifiable information will be de-identified where possible. The content of the recording will be accessed and transcribed by a member of the study team or a contracted transcriptionist who has signed a confidentiality agreement.

Participants will be informed that anonymous / anonymised data [and tissue] is unable to be accessed, corrected, or withdrawn; and that return of individual results will not be possible. However, participants are entitled to request copies of their personal audio / video recordings. Audio / video recordings are unable to be corrected. In the event of withdrawal from the study, audio / video recordings of the participant will be destroyed.

1. **Access to and Use of Data and Tissue**

Collected data and tissue will be used to answer the research questions and fulfil the study requirements described in the study protocol.

* 1. **Identifiable Data and Tissue**

Identifiable data and/or tissue may be accessed by the following groups:

* The Investigator and designated study staff, to fulfil protocol requirements. For audio and video recordings, this will be viewed by study supervisors or transcriber to assess the quality of the therapy.
* Local laboratory staff, to process, analyse and report blood samples.
* Study monitor(s), for eligibility confirmation and source data verification purposes.
* The Health and Disability Ethics Committee, for legal and regulatory purposes.
* Health, regulatory, or government agencies, for legal and regulatory purposes.
* The participant’s GP or appropriate specialist, to inform them of study participation, and in the event of an incidental finding of potential clinical significance.
* The Medical Office of Health, in the event of a positive result for a notifiable disease.

Rarely, it may be necessary for the Investigator to share identifiable data with people or groups not listed above – for example, in the event of a serious threat to public health or safety, or to the life or health of the participant or another person; or if the data is required for certain legal situations.

Identifiable tissue will be used for analyses as described in the protocol [and laboratory manual].

* 1. **De-identified Data and Tissue**

De-identified data and tissue will be accessed and used by the following groups:

* The Investigator and suitably trained and experienced study staff, to conduct the study.
* The LabTests laboratory, for sample processing, analysis, and reporting purposes.
* The Health and Disability Ethics Committee, to comply with legal and regulatory duties.
* Health, regulatory, or government authorities, to comply with legal and regulatory duties.

The LabTests laboratory will not be authorised to share data and/or tissue with third parties.

De-identified tissue will be used for analyses as described in the protocol [and laboratory manual].

De-identified data may be included in published study results including, but not limited to, peer-reviewed publications, clinical trial registry websites, scientific meetings, and regulatory / marketing submissions.

De-identified data may be included in clinical trial registries and data banks (refer to Section 8.7).

* 1. **[Anonymous/Anonymised] Data [and/or Tissue]**

[Anonymous/Anonymised] data [and/or tissue] may be accessed and used by the groups described in Section 8.2.

Anonymised data [and/or tissue] may also be made available to other researchers, as described in Section 8.5.

* 1. **Sending of Data and Tissue Overseas**

Not applicable

* 1. **Future Use of Data and/or Tissue**

De-identified [and/or anonymised] data [and tissue] may be made available to other researchers on request for future research as specified above and / or will be added to data from other sources to form larger datasets.

In all cases, the Sponsor must be satisfied that appropriate Data [and Tissue] Management Plans are in place and that ethical approval for use has been obtained in accordance with local laws and regulations.

* 1. **Commercial Use of Data and/or Tissue**

Study data [and tissue] analysis may lead to discoveries and inventions or development of a commercial product or producers. The rights to these will belong to the Sponsor. Participants will not receive any financial benefits or compensation from, nor have any rights to, any developments, inventions, or other discoveries arising from this analysis.

* 1. **Data Linking**

Not applicable

* 1. **Databank / Registry and/or Biobank**

Not applicable

1. **storage and Destruction of Data**
	1. **Identifiable Data and Source Documents**

During the study, study-specific source documents will be maintained in locked file cabinets in locked rooms and password protected databases via password protected computers/servers.

Post-study, study-specific source documents will be archived in password protected databases via password protected computers/servers.

Source documents will be retained **for at least ten years** then destroyed by secure shredding and deleting of documents from protected databases.

* 1. **De-identified Data**

Identifiable data will be converted to a de-identified form at the study site, at which point it is entered into electronic case reports reports using a secure data platform. The data platform complies with international and national regulatory requirements for electronic data capture systems in New Zealand. Data entry will be limited to designated study staff trained and experienced in transcribing data for this purpose.

De-identified data generated by the New Zealand laboratory will be entered into electronic case reports reports using a secure data platform.

De-identified data will carry a unique trial specific number. The Investigator will retain a log linking participant code with identifiers.

The de-identified database will remain on University of Auckland servers for up to approximately ten years.

1. **Storage and Destruction of Tissue**
	1. **New Zealand Laboratory(ies)**

LabTests are responsible for the storage, testing/analysis, and destruction of the tissue samples described in section 7.1 and 7.2.

Tissue samples will be labelled as detailed in Section 6.

Tissue samples will be transported to the laboratory by LabTests staff. Chain of custody is recorded as per LabTests policy.

The laboratory is Good Laboratory Practice (GLP) compliant*.* The facilities are secure with tissue access restricted to those staff directly involved in their analysis.

Tissue samples will be retained and then destroyed as per LabTests policy.  https://www.labtests.co.nz/privacy-and-policy/

**Overseas Laboratory(ies)**

* + 1. **Tissue Samples – Mandatory Research**

Not Applicable

* + 1. **Tissue Samples – Optional Research**

Not applicable

Tissue use is restricted to those uses specified in the applicable optional PIS/CF document(s).

1. **Consultation**

Consultation regarding data and tissue management has been undertaken with the following relevant communities/stakeholders including Health and Disability Ethics Committees, local District Health Board locality approval panels including formal Māori consultation.

* 1. **Māori Data and Tissue Sovereignty**

During the study, data and tissue may be collected from participants identifying as Māori . Taking of tissue is a major cultural issue for Māori as it is linked to whakapapa and continuation of Māori as a nation. For some Māori, tissue is considered tapu & imbued with wairua.

Options for karakia will be discussed with participants during the informed consent process.

Personal and health information is a tāonga (treasure) and will be treated accordingly.

Formal Māori consultation for this study will be completed as part of the Locality Approval Process for New Zealand study site(s). Any recommendations for additional measures to improve Māori rights and interests in relation to data [and tissue] will be acted upon.

The principles of whakapapa, whanaungatanga, rangatiratanga, kotahitanga, manaakitanga, and kaitiakitanga are applied in the following ways:

Our project design has been guided by the He Korowai Oranga framework with the goal to achieve Pae Ora (the best health outcomes for Māori ). We have had initial consultation with the Māori leadership at Manawanui (ADHB Māori Mental health team) and plan to continue with a regular dialogue through the process. The development of this relationship with possible introductions to other members of the Māori community will include an invitation to interested parties to the Grafton campus as well as other areas on the community. We anticipate having ongoing dialogue regarding the ethics approval process and initiation of the project to ensure that the principles of Tino Rangatiratanga and Te Ritenga are observed through the recruitment, informed consent and treatment phase of the study. Additionally, continued partnership with Manawanui and other health centres will be emphasized in support of Oritetanga principles to ensure that the Māori population are not disadvantaged.

Our research team will actively seek Māori representation within the team. Our team will prioritize the inclusion of a Māori medical student when reviewing the applicants for research scholarships. The importance of developing the capacity and capability of future Māori clinicians and researchers will be a critical part of addressing systemic inequity.

Regarding research characteristics, our study does require participants to provide urine and blood samples, however we will not retain any samples and ensure culturally appropriate processes regarding data management including maintaining privacy, communication with Whānau when appropriate. We will also consult with *Māori* leadership in the event of complex situations involving kaitiaki (guardianship) Finally, there will also be a qualitative analysis of experiences reported by the participants. In addition to dissemination of results through publications and media, we anticipate providing direct feedback to various clinics including Manawanui regarding the results.

1. **Return of Results**

Screening and safety results will be provided to participants on request.

Participants have the right to request a lay summary of study results. A lay summary of study results will be available in a letter form at the conclusion of the study following data analysis.

Participants have the right to request all their data in de-identified format.

.

* 1. **Incidental Findings**

In the event that a study assessment returns a result of potential clinical significance, the participant will be informed. The participant’s usual doctor and / or an appropriate specialist will be notified, and follow-up will be arranged.

Analyses may provide an individual result that is clinically significant but not clinically actionable. Participants are informed of this possibility in the PISCF, and will be notified in accordance with the protocol and the participant’s stated wishes in the PISCF.

* 1. **Results Arising from Future Research**

**Data**

No future unspecified research is planned for data collected in this study.

**Tissue**

No future unspecified research is planned for tissue collected in this study.

**Databank / Registry / Biobank submission**

Not applicable

1. **Withdrawal of Data and/or Tissue**

Participants may withdraw consent for the collection of data at any time, without providing a reason.

Should a participant withdraw consent, no further data and/or tissue will be collected by study staff.

Data collected prior to the participant’s withdrawal will continue to be used and analysed.

In the event of the participants withdrawing consent for the the study, audio / video recordings of the participant will be destroyed.

Tissue collected prior to the participant’s withdrawal will continue to be used and analysed for the purposes of the study.