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Title

Trial protocol of an open-label safety and feasibility pilot study of ketamine-assisted psychotherapy for methamphetamine use disorder (the KAPPA trial)

Authors

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Abstract

Introduction: Methamphetamine use disorder is a significant public health concern. No pharmacological treatment options currently exist for methamphetamine use disorder, and psychotherapy is only moderately effectiveness. Preliminary evidence suggests that ketamine-assisted psychotherapy produces sustained improvements in substance use and mental health symptomatology. In addition to direct antidepressant properties, ketamine is hypothesised to increase synaptogenesis and facilitate neuroplasticity, in turn prolonging and enhancing the effects of psychotherapy. Given the withdrawal-associated dysphoria and neurocognitive impairments characterising methamphetamine use disorder, ketamine-assisted psychotherapy may improve the efficacy of psychotherapy alone by addressing these features and facilitating therapeutic engagement. This study aims to investigate the safety and feasibility of subanaesthetic ketamine in combination with psychotherapy (cognitive behavioural therapy) for adults with MAUD. Changes in methamphetamine use, cravings and withdrawal, quality of life, and treatment satisfaction will also be explored.

Methods and analysis: This is an open label, single arm clinical trial. Twenty adults meeting DSM-5-TR criteria for methamphetamine use disorder who are seeking to reduce or cease methamphetamine use will be enrolled in the study through a single-site specialist outpatient stimulant treatment service in inner Sydney (St Vincent's Hospital, Sydney). A four-week course with three subcutaneous ketamine doses (0.75mg/kg to 0.9mg/kg, titrated according to tolerability) at weekly intervals and four sessions of cognitive behavioural therapy (one at treatment initiation and 3 within 24-48 hours following each ketamine administration session) will be delivered. Safety and feasibility will be assessed over an 8-week period. Secondary outcomes (changes in methamphetamine use, cravings, withdrawal, quality of life, and treatment satisfaction) will be assessed over a 24-week period.

Ethics and dissemination: This study has been approved by the St Vincent's Hospital Human Research Ethics Committee, reference 2023/ETH00530. Study findings will be disseminated

through articles in scientific, peer-reviewed journals, and at national and international conferences.

Trial Registration: ANZCTR: ACTRN12624000895583

Protocol version: The trial protocol (Version 4.0) was approved on 24 June 2024.

Keywords: methamphetamine; substance use disorder; ketamine; cognitive behavioural therapy

Strengths and limitations of this study

- The KAPPA study is the first to examine the safety and feasibility of ketamine-assisted psychotherapy for methamphetamine use disorder
- Structured clinical intervention of standardised manual-based cognitive behavioural therapy alongside a rigorous low-cost subcutaneous racemic ketamine dosing protocol allows for ready reproducibility
- Moving beyond abstinence, the study tests the feasibility of measuring validated secondary outcomes that align with harm-reduction and person-centred approaches, including reduction in methamphetamine use and improved quality of life
- A strength of the study is the use of structured clinical interviews to screen and characterise the sample
- There is a risk of high attrition rates over the course of the study

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Competing interests: None declared.

Authors' contributions: KF and BC prepared the first draft of the protocol. All authors contributed to conception, design, and revision of the protocol.

Trial Sponsor: St Vincent's Hospital, Sydney (svhs.research@svha.org.au)

Roles and responsibilities (sponsor and funder): The sponsor and funder have no role (nor ultimate authority) with regards to study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication.

Introduction

Background and Rationale

Methamphetamine is the most widely consumed synthetic stimulant drug worldwide,[1] representing a significant public health concern. Frequent methamphetamine use is associated with a variety of health problems including mental health conditions, insomnia, cardiovascular conditions, cognitive deficits and a risk of drug induced psychosis.[2,3] Methamphetamine Use Disorder (MAUD) often involves increasing tolerance to methamphetamine and continued use to avoid the withdrawal symptoms that follow abrupt cessation.[4] In 2020-2021 in Australia, methamphetamine accounted for 8.2% of all drug-related hospitalisations and is associated with an increasing rate of drug-related deaths (almost four times higher in 2022 compared to 2000),[5] highlighting a need for a greater range of effective treatments for this group.

No regulatory-approved pharmacological treatment options currently exist for MAUD. Evidence to date for candidate therapeutic agents from a variety of drug classes is promising, but limited.[6-11] The current standard of care therefore relies on psychosocial interventions, primarily Cognitive Behavioural Therapy-based approaches,[12] which show modest effectiveness.[13] Relapse to methamphetamine use rates are high, with only one-quarter of individuals remaining abstinent after one year following residential rehabilitation.[14] Further, treatment outcomes differ depending on levels of use, with poorer outcomes observed in people who use methamphetamine frequently compared to those who use less frequently. Limited efficacy may be due in part to psychosocial interventions not sufficiently addressing cravings and the presence of negative affect during withdrawal, leading to relapse,[15] or common neurocognitive difficulties observed in MAUD including executive dysfunction, poor working memory, impulsivity, and decision-making difficulties.[16] Supporting psychological interventions with adjuvant pharmacotherapy may overcome some of these challenges, an approach which is beginning to show promise with other substance use disorders (SUD).[17]

Combined treatment approaches using ketamine and different forms of psychotherapy (referred to as Ketamine-Assisted Psychotherapy; KAP) have recently been shown to sustained improve treatment outcomes for a variety of mental health and SUDs.[18,19] Ketamine is a well-characterised dissociative anaesthetic, acting primarily through antagonism of the glutamatergic n-methyl-d-aspartate (NMDA) receptor. Racemic ketamine is used therapeutically as an anaesthetic agent and analgesic (administered parenterally) and in its s-enantiomer form as esketamine, administered intranasally for treatment resistant depression (TRD). Glutamatergic dysregulation has been implicated in depression.[20-23] Subanaesthetic doses of ketamine induce rapid reversal of depression symptoms that can be sustained for up to 7 days after one infusion.[22,24] The anti-depressant properties of ketamine are of particular interest for amphetamine use disorders given findings that chronic amphetamine administration results in depletion of dopamine receptors and dopamine release, leading to a negative affective state during withdrawal,[15] and increasing the risk of relapse.[25] While there is significant heterogeneity in how ketamine has been administered in clinical studies to date (e.g. intravenous infusion vs. subcutaneous injection, dosage, course of treatment), preliminary data suggest that subanaesthetic doses of ketamine may have efficacy for treatment of SUDs. Ketamine monotherapy for cocaine, heroin and alcohol use disorder (AUD) has produced short-lived improvements in self-administration and abstinence compared to placebo.[19,26,27] While ketamine provides a unique, rapid onset of antidepressant action for chronic mental health conditions including SUDs, its therapeutic effect is temporally limited. Symptom reductions are frequently transient (typically lasting 4-7 days), with repeated administrations required to maintain positive effects.[28-30]

In KAP approaches, it is hypothesised that ketamine may prolong and enhance the effect of psychotherapy by increasing synaptogenesis and promoting neural pathways which facilitate neuroplasticity.[18,19] Ketamine-enhanced neuroplasticity is thought to facilitate emotional learning, evoke emotionally arousing phenomenological experiences, reduce

defensiveness and enhance treatment adherence and engagement.[18] While no studies to date have examined KAP for MAUD specifically, promising findings for other SUDs have been reported. A small randomised controlled trial (RCT; n = 55) of ketamine-assisted (0.5mg/kg single IV infusion) mindfulness-based relapse prevention therapy (MBRP) for cocaine dependence showed 48.2% abstinence compared to 10.7% in the active control group (midazolam + MBRP), with the odds of end-of-study abstinence in the ketamine group being 6 times that in the midazolam group (odds ratio=5.7, x^2=5.34, df =1, p=0.02). Further, those in the ketamine group were 53% less likely to relapse or discontinue treatment compared to controls over the 5-week study period.[31] An RCT (n = 40) examining ketamine-assisted (0.71mg/kg single IV infusion) motivational enhancement therapy for AUD reported a lower proportion of participants in the ketamine group using alcohol (8/17, 47.1%) compared to controls (13/22; 59.1%) across the 21-days following drug administration.[32] Sustained effects have been reported in AUD, whereby those receiving ketamine-assisted (three 0.8mg/kg IV infusions once weekly) MBRP had more days abstinent over 6 months compared to three other groups (ketamine + psychoeducation; placebo + MBRP; placebo + psychoeducation) (mean difference = 10.1, 95% CI = 1.1, 19.0).[33] Longer-term effects in other SUDs have also been reported. An RCT (n = 70) in people with heroin dependence using both a high (2.0mg/kg) and low (0.2mg/kg) IM ketamine dose and existential-oriented psychotherapy reported higher rates of abstinence for the high dose group vs. low dose group, with effects sustained over 24 months.[34]

Supporting the putative impact of ketamine in enhancing effects of psychotherapy more broadly, positive effects of ketamine-assisted cognitive behavioural therapy (CBT) in TRD have also been reported, with CBT sustaining the antidepressant effects of IV ketamine (6 doses, 0.5mg/kg, over 3 weeks) over a 17-week period (Quick Inventory of Depressive Symptomatology-Self report scores F = 4.58, p = 0.033; d = 0.71, 95% CI – 0.30 to 1.70).[35] Furthermore, improvements in cognitive control (e.g. executive control, including updating and maintenance) were associated with clinical improvement following ketamine treatment in

a subset of patients. This provides some support for the hypothesis that, along with its rapid antidepressant properties, ketamine may also improve cognitive control, while CBT strengthens and maintain these improvements.[35] A combined approach of ketamine and CBT may therefore have strong potential for MAUD given the neurocognitive impairments and withdrawal-associated dysphoria that appear to hamper psychotherapy effectiveness in this population.

Objectives

This study aims to determine the safety and feasibility of subcutaneously administered racemic ketamine (three doses, once per week) alongside four sessions of weekly CBT for adults with MAUD, in an outpatient setting. We hypothesise that ketamine-assisted psychotherapy will be safe and feasible in this context.

Secondary objectives are to explore changes from baseline to Week 5, 8 12 and 24 in methamphetamine use, cravings and withdrawal and quality of life, as well as treatment satisfaction.

Methods and analysis

Study setting and design

This study is an open-label, single-arm pilot clinical trial. This paper reports on the study protocol in line with Standard Protocol Items Recommendations for Interventional Trials (SPIRIT) guidance.[36]

The study will be conducted in an outpatient stimulant treatment clinic (the 'Stimulant Treatment Program'; STP), at St Vincent's Hospital, Sydney (SVHS), Australia. SVHS, a public teaching hospital, is the study sponsor. Participants will be referred directly from the

clinic. Advertising to local health service providers and social media will also be used to enhance recruitment.

Patient and public involvement

This study is designed and conducted without any involvement from participants or the public. Study results will be disseminated to participants and the public via the National Centre for Clinical Research in Emerging Drugs website.

Participants and recruitment

Eligibility criteria

Eligible participants will be adults, who meet DSM-5-TR criteria for MAUD and are seeking treatment to cease or reduce methamphetamine use. Inclusion and exclusion criteria are outlined in **Table 1**.

Participant timeline

Figure 1 gives an overview of the flow of participants through the study. The total study duration for each participant is a maximum of 168 days. This comprises a screening period (window of up to 2 weeks), a 4-week treatment period, end of treatment (Week 5), primary endpoint at Week 8 and two additional follow-up visits (Week 12, Week 24).

Potential participants who express interest in the study will be pre-screened and those who meet basic criteria will proceed to informed consent. Informed consent will be obtained from each participant by the Principal Investigator or delegated medical officer. Participants will then be formally screened for eligibility. Screening for eligibility will include medical review and a structured clinical interview (the MINI International Neuropsychiatric Interview 7.0.2; MINI)[37] for SUDs, major depressive disorder, bipolar disorder and psychosis. The Columbia Suicide Severity Rating Scale Screener (CSSRS-6)[38] will be used to assess

for history of suicidal ideation or suicide attempts. Eligible participants will be enrolled in the study. Baseline assessments to characterise the sample include demographic information, the Wender Utah Rating Scale (WURS)[39] to retrospectively evaluate the presence of childhood ADHD symptoms; and the Substance Use Goals and Expectations to measure treatment goals and expectations (SURGE, unpublished). Qualitative interviews (one per participant) will be conducted during Weeks 5 to 8. The full schedule of assessments is outlined in **Table 2**.

Intervention

The intervention consists of three subcutaneous racemic ketamine doses at weekly intervals and four sessions of CBT (one at commencement of the intervention and three within 24-28 hours following each ketamine administration session) (see **Figure 2**).

Medication

The medication under investigation is the Therapeutic Goods Association (TGA) approved ketamine 100mg/ml, available in Australia formulated in liquid solution for intravenous and intramuscular injection as an anaesthetic agent.[40,41] A total of three subcutaneous subanaesthetic doses, at least 7 days apart, will be administered by a study nurse to the abdomen once weekly during clinic visits at Weeks 2, 3 and 4. The starting dose will be 0.75mg/kg, increased to a maximum dose of 0.9mg/kg at subsequent visits as tolerated. The dose can be reduced to 0.6 or 0.5mg/kg if not tolerated (see **Table 3**). Tolerability will be assessed by the study doctor guided by the Ketamine Side Effect Tool (KSET),[42] with the clinician assigning tolerability prior to discharge based on subjective participant reports and objective observations.[42,43] Acceptable safety and tolerability profiles have been demonstrated in subcutaneous doses of up to 0.9mg/kg.[43] The study nurse will continuously monitor the participant at 120 minutes post ketamine administration and alert the Principal Investigator or appropriately qualified delegate in the case of any adverse event

of concern, which will be managed according to clinical need (e.g. conservatively, continued support for up to a further 120 minutes).

Psychotherapy

The 4-session manualised Cognitive Behavioural Therapy (CBT) program developed by Baker et al[44] will be provided by trained therapists to all participants in the trial, with adaptations suitable for the KAP approach. For the purposes of this study, therapists are defined as staff with qualifications in a relevant health discipline (such as counselling, nursing, social work, psychology, psychiatry), including trainees with adequate skills, that have undergone training on the use of the manual and in ketamine-assisted psychotherapy. Each session will last approximately 1.5 hours. The initial assessment will take place as part of psychotherapy session 1, reviewing: (1) alcohol and other drug use history, (2) mental health assessment, (3) participant's readiness to change methamphetamine use, and (4) information about what will happen during the first ketamine dose session. One week later, a preparation session will be undertaken immediately prior to ketamine dose 1. Psychological preparation and pre-injection relaxation exercises have been previously shown to reduce the anxiety and distress that might emerge with ketamine administration.[45] As in previous studies,[31,46,47] participants will be guided through grounding exercises (e.g. relaxation and breathing) immediately prior to ketamine administration and encouraged to use these should any discomfort or anxiety emerge. As part of preparation, study participants will be briefed on what to expect after drug administration and given the opportunity to ask any questions they may have, and a discharge information sheet will be provided. Within 24-48 hours following ketamine dose 1, psychotherapy session 2 will be undertaken, beginning with an integration focus where experiences of the ketamine administration will be briefly explored and used to guide the subsequent CBT material. This approach will also be used for the remaining sessions. Therapists will co-ordinate the four sessions to occur at least one week apart. Session 1 will occur during Week 1; Sessions 2, 3 and 4 will occur during Weeks 2,3 and 4 respectively within 24-48 hours of participants receiving study medication. Session

checklists will be completed post-session by the therapist to assess treatment fidelity and discussed during group supervision with a senior psychologist. As per Baker et al,[44] study participants will be encouraged to complete homework tasks in-between sessions.

Outcomes

The primary outcomes are safety and feasibility. Safety will be assessed by treatment emergent adverse events (AEs) across the duration of the study, categorised by system organ class (SOC). These will be described by seriousness, severity, causality and expectedness.[48,49] AEs will be documented at each clinic visit. Subjective descriptions of AEs provided by participants will be transcribed verbatim and reported in accordance with the Medical Dictionary for Regulatory Activities (MedDRA) terminology, developed under the auspices of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). Severity will be graded from Grade 1 (mild) to Grade 5 (death) by the site Principal Investigator.[50] Causality will be determined by the site Principal Investigator, and expectedness in accordance with international guidelines and Australian product labels for ketamine hydrochloride 100 mg/ml for injection.[40,41] Any known reaction listed on the product label will be considered potentially causally related. Adverse events will be elicited through structured assessment with the KSET.[42] Additional safety measures (see **Table 2** for administration timepoints) include: (i) blood pressure and heart rate during ketamine administration sessions, (ii) dissociative effects as measured by the Clinician-Administered Dissociative States Scale (CADSS-6),[51] (iii) elevated mood as measured by the Young Mania Rating Scale (YMRS [item 1]),[52] (iv) suicidality as assessed with the C-SSRS, (v) non-medical use liability as measured by the Drug Effects Questionnaire (DEQ-5),[53,54] and (vi) changes in other drug use (including ketamine) as measured by Timeline Follow Back (TLFB).[55]

Feasibility will be assessed by: (i) time taken to recruit the sample; (ii) proportion of ineligible participants at pre-screening and screening; (iii) number of participants who receive

3 doses of ketamine, (iv) number of participants who complete 3+ sessions of psychotherapy, (v) retention rate over the full duration of the study, and vii) acceptability of the intervention, assessed via qualitative interviews.

Secondary outcomes include measures of preliminary efficacy and potential mediators. Efficacy measures include: (i) self-reported change in past 28-days of MA use from baseline to Week 5 (post treatment), Week 8 (primary endpoint), Week 12 and Week 24, (ii) presence of methamphetamine in urine assessed through POC UDS at Week 5, Week 8, Week 12 and Week 24, (iii) changes in methamphetamine craving as measured by the Visual Analogue Scale - Craving (VAS-C)[56] and withdrawal symptoms assessed on the Amphetamine Withdrawal Questionnaire (AWQ)[57] from baseline to Week 5, Week 8, Week 12 and Week 24, (iv) changes in quality of life as measured by the World Health Organisation Quality of Life – Brief Version (WHOQOL-BREF)[58] from baseline to Week 5, Week 8, Week 12 and Week 24, and (v) treatment satisfaction (TSQM-II) at Week 5, Week 8.

Potential mediator measures are changes in: (i) depression scores on the Patient Health Questionnaire-9 (PHQ-9)[59] from baseline to Week 5, Week 8, Week 12 and Week 24, (ii) anxiety scores on the Generalised Anxiety Disorder Scale-7 (GAD-7)[60] from baseline to Week 5, Week 8, Week 12 and Week 24, iii) emotion regulation scores on the Difficulties in Emotion Regulation Questionnaire (DERS)[61] from baseline to Week 5, Week 8, Week 12 and Week 24, (iv) sleep quality scores on the Insomnia Severity Index (ISI)[62] from baseline to Week 5, Week 8, Week 12 and Week 24, (v) HIV and other sexually transmitted infection risk behaviours as measured by the Substance Use Sex Index (SUSI)[63] from baseline to Week 5, Week 8, Week 12 and Week 24, (vi) subjective medication effects on the Hood Mysticism Scale (HMS)[64] 120 minutes post ketamine administration, (vii) cognitive control and flexibility as measured by the Emotional N-back task[65] at baseline and 24 hours post third ketamine administration, (viii) cognitive control as measured by the Emotional Stroop task[35] at baseline and 24 hours post third ketamine administration.

Sample size

The study is not powered to determine efficacy. The study will recruit 20 participants, as is convention in pilot studies.[66]

Participant retention and withdrawal

The study site will make all reasonable efforts to follow participants for the course of the study. Efforts to minimise loss to follow-up will include respecting participant time commitments, formal tracking procedures including multiple ways to be contacted and strong interpersonal skills of study personnel.

Stopping criteria

If a participant experiences a Grade 3 or Grade 4 Adverse Event (AE) considered to be causally related to the study medication, no further study medication will be dispensed until the participant has been reviewed by the site Principal Investigator.[50] If the AE is resolved to the satisfaction of the Principal Investigator, the dose can be recommenced, and the participant will be reviewed the subsequent day. If the AE is not resolved or recurs after recommencing the study medication, the site Principal Investigator will consider ceasing the medication and withdrawing the participant from the treatment component of the study. Unless they revoke their consent, all participants withdrawn from treatment will continue to be followed as intention to treat.

Reimbursement

Participants will be reimbursed for participating, in accordance with Australian guidelines for appropriate and equitable payment of participants in research.[67] Participants who consent to partake in the study and complete all the screening assessments will receive a $40 gift card. Reimbursements of $40 gift cards will also be made for each study visit. If the participant chooses to have their qualitative interview scheduled for the same day as

another visit during weeks 5 to 8, they will still receive a separate $40 reimbursement for the interview. The maximum potential amount of reimbursement over the entire duration of the study is $520 of gift cards per person.

Data management

Study data will be collected and managed using REDCap (Research Electronic Data Capture) tools hosted at St Vincent's Hospital, Sydney.[68] REDcap is a secure, web-based software platform designed to support data capture for research studies, providing i) an intuitive interface for validated data capture, ii) audit trails for tracking data manipulation; iii) automated export procedures for seamless data downloads to common statistical packages; and iv) procedures for data integration and interoperability with external sources. In accordance with the National Standard Operating Procedures for Clinical Trials,[69] identifiable information will be stored separately from the main study data. The Participant Identification Log will be stored in a password protected folder on a secure SVHS hosted server. Access to study records within the REDCap database will be limited by using Data Access Groups (DAGs). Only users within a given DAG can access records created by users within that group. Access to components of study records is role-based and can only be granted by the Project Manager. Data will only be made available to investigators who are directly involved in the collection, analysis, or monitoring of study data. Following conclusion of the study, physical and digital records will be stored for a period no less than 15 years as per ICH-GCP guidelines.[48]

Statistical methods

Descriptive statistics will be used to characterise the study sample. Continuous measures such as mean changes in continuous measure scores from baseline across each assessment time point will be analysed using appropriate parametric approaches, such as paired-sample t-tests. For categorical measures such as the presence of AEs, rates will be

analysed using appropriate non-parametric approaches, such as chi-square and relative risk. Quantitative data will be analysed using SPSS Version 29.0.[70] Qualitative interviews will be collected until all trial participants have been approached. Interviews will be thematically analysed to extract key themes across participant responses, using the approach outlined by Braun & Clarke[71]: familiarising with the data, generating initial codes, searching for themes, reviewing themes, defining and naming themes, and producing the report. Qualitative data will be analysed using NVivo Version 14.[72]

Monitoring

Data Safety Monitoring Board (DSMB)

An independent DSMB will be established prior to study recruitment. DSMB membership will include: an addiction medicine specialist; a psychologist; and a pharmacologist (all not otherwise involved with the study). All Serious Adverse Events (SAEs) and Suspected Unexpected Serious Adverse Reactions (SUSARs) will be reviewed by the DSMB quarterly. Following each meeting, the DSMB will advise one of four options: continue study as per protocol, continue study with protocol amendments, suspend study, or discontinue study. The study data will be monitored by a sponsor staff member not otherwise involved in the study, for accuracy, primary endpoint data, and compliance with ICH-GCP[48] and the Australian National Statement on Ethical Conduct in Human Research.[73]

Ethics and dissemination

This study has been approved by the St Vincent's Hospital Human Research Ethics Committee, reference 2023/ETH00530. All participants will provide digital informed consent prior to commencing in the study.

Study findings will be disseminated through articles in scientific, peer-reviewed journals, and at national and international conferences.

Ethics statements

Patient consent for publication

Not applicable.

Discussion

This study will examine the safety and feasibility of ketamine-assisted psychotherapy for the treatment of MAUD in adults in an outpatient setting. Secondary outcomes were selected with a harm-reduction and person-centred lens, including reduction in methamphetamine use, cravings, withdrawal symptoms, and improved quality of life. As overviewed by Pasareanu et al.,[74] SUD treatment has traditionally focused on abstinence but is increasingly incorporating broader positive treatment outcomes. Recovery-oriented outcomes such as quality of life encompass clinical, functional, and personal variables, which hold particular relevance for SUD given the chronic nature of the condition. Other study strengths include the use of structured clinical interviews to screen and characterise the sample, and the use of a standardised manual-based CBT alongside a low-cost subcutaneous ketamine dosing protocol – all of which allow for ready reproducibility. While intranasal and IV ketamine represent the most common routes of administration in studies to date,[75] SC administration was chosen for the current study for several reasons (shorter time of administration, fewer injection-related adverse events, minimal discomfort, cost-effectiveness, and not requiring an anaesthetist for monitoring), and has been used successfully in a large RCT over a 4-week period in adults with TRD,[43] demonstrating safety and efficacy in doses of up to 0.9mg/kg. As this is the first published study to our knowledge utilising SC ketamine in an SUD population, further characterisation of the relative efficacy, tolerability, and safety of different routes of administration in this group is needed.

Comorbid mental health issues in those who use methamphetamine regularly are common.[10] The presence of mild to moderate coexisting depression, anxiety or transient psychotic symptoms do not constitute exclusion criteria in the current study to promote real-

world application of the findings. Further, successful treatment of MAUD requires consideration of comorbid mental health conditions. Given the co-occurring depressive symptomatology and the withdrawal symptoms of dysphoria and anxiety commonly experienced when ceasing methamphetamine use, ketamine-assisted CBT may have particular efficacy for treating MAUD by addressing these symptoms while enhancing psychotherapeutic effects to prevent relapse.

Extra-medical use of ketamine precipitated by prescribed ketamine may be a cause of concern, especially given increasing prevalence of ketamine use disorder has been observed in some countries/regions.[76] As overviewed by Le et al.,[77] in professionally supervised settings, single or repeated IV, IM or oral ketamine administration has not been shown to result in misuse, dependence, diversion and/or gateway activity in patients with TRD. However, extra-medical use liability was not systematically evaluated using validated measures, reports were retrospective in nature, and studies excluded individuals with substance use disorder, thus results are not directly relevant to this study population. A systematic review of ketamine for the treatment of mental health disorders and SUD found no evidence of transition to extra-medical ketamine use or unexpected psychological complications following treatment with ketamine.[78,79] The authors concluded that the relatively modest risk of precipitating ketamine use disorder should not present a barrier to treatment. Nonetheless, the safety and efficacy profile of ketamine in those with SUD requires further investigation. Positively, preliminary evidence supports the potentially beneficial role of ketamine in SUD, with IV ketamine in combination with psychosocial treatment reducing alcohol and cocaine craving and consumption.[31-33] The current study represents an important first step in determining whether these findings extend to the MAUD space.

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Tables and Figures

Figure 1 – Trial timelines

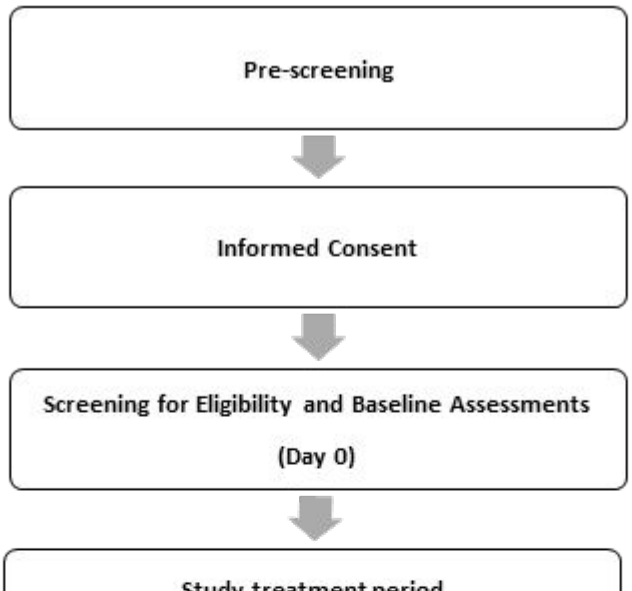

Figure 2

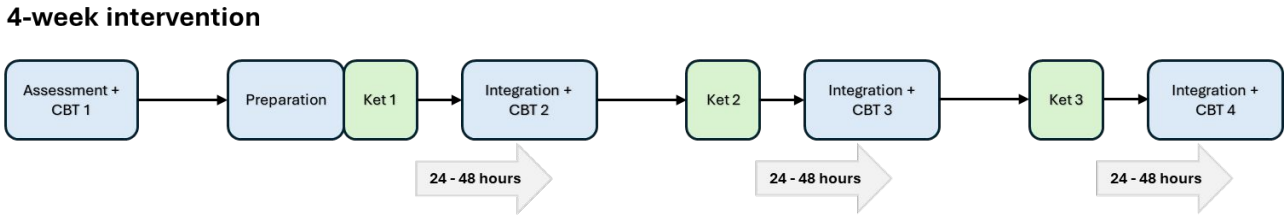

Table 1 – Eligibility Criteria

Inclusion criteria	Exclusion criteria
All participants must / must be:	*All participants must not:*
▪ ≥18 years of age ▪ Able to provide informed consent ▪ Willing and able to comply with all study requirements, as determine by the Principal Investigator ▪ Meets DSM-5-TR diagnostic criteria for Current Stimulant Use Disorder - Amphetamine-Type Substance - as determined by the Principal Investigator and confirmed with the MINI ▪ Urine drug screen (UDS) point of care (POC) test positive for methamphetamine ▪ Willing to register as a client of the St Vincent's Hospital Sydney (SVHS) Stimulant Treatment Program (STP)	▪ DSM-5-TR diagnosis of current or past use disorder for ketamine or ketamine analogues as assessed by MINI ▪ Prescribed or non-prescribed use of ketamine in the previous four weeks ▪ Currently enrolled in another treatment trial of MAUD or clinical trial which is likely to affect safety, data quality or may interfere with participation in this study, as determined by the Principal Investigator ▪ Currently pregnant or breast feeding, or planning on becoming pregnant during the course of the study ▪ DSM-5-TR diagnosis of current psychotic disorder as assessed by the Principal Investigator including review of MINI ▪ Current acute suicidality defined as 'high risk' using the C-SSRS-6 screener or as determined by the Principal Investigator ▪ DSM-5-TR diagnosis of bipolar disorder as assessed by the Principal Investigator including review of MINI ▪ Current DSM-5-TR diagnosis with other substance use disorders, moderate or severe, except tobacco, caffeine, or cannabis as assessed by the Principal Investigator including review of MINI. Opioid use disorder permitted if stable on opioid agonist treatment; OAT) (i.e. no dose changes for six weeks if on oral OAT and maximum of one missed dose/week. At least three months with no missed doses if on long-acting injectable OAT) ▪ History of sensitivity to ketamine or any other components of this product

	▪ If prescribed antidepressants, the participant must have been on a stable dose for four or more weeks ▪ Contraindications to ketamine according to Australian Product Information: ○ Severe cardiovascular disease ○ Heart failure ○ Severe or poorly controlled hypertension ○ Recent myocardial infarction ○ History of stroke ○ Cerebral Trauma ○ Intracerebral mass or haemorrhage
▪ Seeking treatment to cease or reduce methamphetamine use ▪ If person of childbearing potential, willing to avoid pregnancy for study duration	▪ Any other medical or psychiatric condition which in the opinion of the Principal Investigator would make participation hazardous. In particular, caution if severe liver, kidney or bladder disease, and also caution if elevated cerebrospinal fluid pressure, increased intraocular pressure, acute intermittent porphyria, seizures, hyperthyroidism, pulmonary or upper respiratory infection, intracranial mass lesions, a presence of head injury, globe injuries, or hydrocephalus. ▪ Likely or planned surgery, travel, incarceration or other engagement during the study that may interfere with study participation

Table 2: Schedule of assessments

Week	0	1	2		3		4		5	8*	12	24
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12
Day	0	1	5/6	7	12/13	14	19/20	21	28	56	84	168
Intervention		CBT 1	KET 1	CBT 2	KET 2	CBT 3	KET 3	CBT 4				
Informed Consent	x											
MINI[a]	x											
C-SSRS-6	x											
Medical assessment	x											
Concomitant Medications	x		x		x		x		x	x	x	x
Other Psychological care	x		x		x		x		x	x	x	x
Height, weight,	x											
Vital signs[b]	x		$x^{0, 15, 60, 120}$		$x^{0, 15, 60, 120}$		$x^{0, 15, 60, 120}$		x	x	x	x
POC – Urine Drug Screen[c]	x		x^{PRE}		x^{PRE}		x^{PRE}		x	x	x	x
Urinary Hcg (if applicable)	x		x^{PRE}		x^{PRE}		x^{PRE}					
Eligibility	x											
Demographics	x											
SURGE	x											
WURS	x											
TLFB - MA	x		x		x		x		x	x	x	x
VAS-C for MA	x		x		x		x		x	x	x	x
AWQ	x								x	x	x	x
WHOQOL-BREF	x								x	x	x	x
TSQM-II									x	x		
Medical Review			x		x		x			x		
Adverse Events			x		x		x		x	x	x	x
C-SSRS-SLV			x		x		x		x	x	x	x
TLFB – ketamine	x		x		x		x		x	x	x	x
TLFB – other substances	x								x	x	x	x
VAS-C for Ketamine	x		x		x		x		x	x	x	x
KSET – acute treatment			$x^{60, 120}$		$x^{60, 120}$		$x^{60, 120}$					
YMRS			$X^{PRE,POST}$		x^{POST}		x^{POST}					
CADSS-6			X^{POST}		x^{POST}		x^{POST}					
DEQ-5			x^{POST}		x^{POST}		x^{POST}					
HMS			x^{POST}		x^{POST}		x^{POST}					
PHQ-9	x								x	x	x	x
GAD-7	x								x	x	x	x
DERS	x								x	x	x	x
ISI	x								x	x	x	x
SUSI	x								x	x	x	x
Emotional N-back task	x							x^{PRE}				
Emotional Stroop	x							x^{PRE}				
Qualitative Interview[d]										x		

*Primary Endpoint **AWQ** Amphetamine Withdrawal Questionnaire **CADSS-6** Clinician Administered Dissociation States Scales **C-SSRS** Columbia-Suicide Severity Rating Scale **C-SSRS** Columbia-Suicide Severity Rating Scale – Since Last Visit **DERS** Difficulties in Emotion Regulation Scale **DEQ-5** Drug Effects Questionnaire **GAD-7** Generalised Anxiety Disorder Scale-7 **HMS** Hood Mysticism Scale **ISI** Insomnia Severity Index **KSET** Ketamine Side Effect Tool **MA** Methamphetamine **MINI** Mini-International Neuropsychiatric Interview **PHQ-9** Patient Health Questionnaire **POC** Point of Care **SURGE** Substance Use Goals and Expectations **SUSI** Substance Use & Sex Index **TLFB** Timeline Follow-Back **TSQM** Treatment Satisfaction Questionnaire for Medication **VAS-C** Visual Analogue Scale – Craving **WURS** Wender-Utah Rating Scale **WHOQOL-BREF** World Health Organisation Quality of Life Brief Version **YMRS** Young Mania Rating Scale

(a) MINI modules A (major depressive disorder), C (bipolar disorder), I and J (alcohol and substance use disorders), K (current psychotic disorder), 0 (rule out medical, organic or drug causes), (b) Blood pressure, heart rate, oxygen saturations, respiratory rate (c) POC also considered a measure of efficacy (d) Qualitative interviews (optional) will be conducted during Week 5 to Week 8.

Table 3 – Study drug schedule

Ketamine 1	Tolerability	Ketamine 2	Tolerability	Ketamine 3
0.75mg/kg	Well tolerated	0.9mg/kg	Well tolerated	0.9mg/kg
			Moderately tolerated	0.9mg/kg
			Poorly tolerated	0.75mg/kg
	Moderately tolerated	0.75mg/kg	Well tolerated	0.75mg/kg
			Moderately tolerated	0.75mg/kg
			Poorly tolerated	0.6mg/kg
	Poorly tolerated	0.6mg/kg	Well tolerated	0.6mg/kg
			Moderately tolerated	0.6mg/kg
			Poorly tolerated	0.5mg/kg

BMJ Open

Protocol of an open-label safety and feasibility pilot study of ketamine-assisted psychotherapy for methamphetamine use disorder (the KAPPA trial)

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Primary Subject Heading:	Addiction
Secondary Subject Heading:	Addiction
Keywords:	Substance misuse < PSYCHIATRY, Psychosocial Intervention, Drug Therapy, Feasibility Studies, Safety

Title

Protocol of an open-label safety and feasibility pilot study of ketamine-assisted psychotherapy for methamphetamine use disorder (the KAPPA trial)

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Abstract

Introduction: Methamphetamine use disorder is a significant public health concern. No pharmacological treatment options currently exist for methamphetamine use disorder, and psychotherapy is only moderately effectiveness. Preliminary evidence suggests that ketamine-assisted psychotherapy produces sustained improvements in substance use and mental health symptomatology. In addition to direct antidepressant properties, ketamine is hypothesised to increase synaptogenesis and facilitate neuroplasticity, in turn prolonging and enhancing the effects of psychotherapy. Given the withdrawal-associated dysphoria and neurocognitive impairments characterising methamphetamine use disorder, ketamine-assisted psychotherapy may improve the efficacy of psychotherapy alone by addressing these features and facilitating therapeutic engagement. This pilot study aims to investigate the safety and feasibility (time taken to recruit sample, proportion of ineligible participants at pre-screening and screening, number of participants who complete 4 sessions of psychotherapy, retention rate over full duration of study, acceptability of the intervention) of subanaesthetic ketamine in combination with psychotherapy (cognitive behavioural therapy) for adults with MAUD. Changes in methamphetamine use, cravings and withdrawal, quality of life, and treatment satisfaction will also be explored.

Methods and analysis: This is an open label, single arm clinical trial. Twenty adults meeting DSM-5-TR criteria for methamphetamine use disorder who are seeking to reduce or cease methamphetamine use will be enrolled in the study through a single-site specialist outpatient stimulant treatment service in inner Sydney (St Vincent's Hospital, Sydney). A four-week course with three subcutaneous ketamine doses (0.75mg/kg to 0.9mg/kg, titrated according to tolerability) at weekly intervals and four sessions of cognitive behavioural therapy (one at treatment initiation and 3 within 24-48 hours following each ketamine administration session) will be delivered. Safety and feasibility will be assessed over an 8-week period. Secondary outcomes (changes in methamphetamine use, cravings, withdrawal, quality of life, and treatment satisfaction) will be assessed over a 24-week period.

Ethics and dissemination: This study has been approved by the St Vincent's Hospital Human Research Ethics Committee, reference 2023/ETH00530. Study findings will be disseminated through articles in scientific, peer-reviewed journals, and at national and international conferences.

Trial Registration: ANZCTR: ACTRN12624000895583

Protocol version: The trial protocol (Version 4.0) was approved on 24 June 2024.

Keywords: methamphetamine; substance use disorder; ketamine; cognitive behavioural therapy

Strengths and limitations of this study

- The KAPPA pilot study is the first to examine the safety and feasibility of ketamine-assisted psychotherapy for methamphetamine use disorder
- Structured clinical intervention of standardised manual-based cognitive behavioural therapy alongside a rigorous low-cost subcutaneous racemic ketamine dosing protocol allows for ready reproducibility
- Moving beyond abstinence, the study tests the feasibility of measuring validated secondary outcomes that align with harm-reduction and person-centred approaches, including reduction in methamphetamine use and improved quality of life
- A strength of the study is the use of structured clinical interviews to screen and characterise the sample
- There is a risk of high attrition rates over the course of the study

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Authors' contributions: KF and BC prepared the first draft of the protocol. All authors contributed to conception, design, and revision of the protocol. KF is the guarantor.

Trial Sponsor: St Vincent's Hospital, Sydney (svhs.research@svha.org.au)

Roles and responsibilities (sponsor and funder): The sponsor and funder have no role (nor ultimate authority) with regards to study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication.

Introduction

Background and Rationale

Methamphetamine is the most widely consumed synthetic stimulant drug worldwide,[1] representing a significant public health concern. Frequent methamphetamine use is associated with a variety of health problems including mental health conditions, insomnia, cardiovascular conditions, cognitive deficits and a risk of drug induced psychosis.[2,3] Methamphetamine Use Disorder (MAUD) often involves increasing tolerance to methamphetamine and continued use to avoid the withdrawal symptoms that follow abrupt cessation.[4] In 2020-2021 in Australia, methamphetamine accounted for 8.2% of all drug-related hospitalisations and is associated with an increasing rate of drug-related deaths (almost four times higher in 2022 compared to 2000),[5] highlighting a need for a greater range of effective treatments for this group.

No regulatory-approved pharmacological treatment options currently exist for MAUD. Evidence to date for candidate therapeutic agents from a variety of drug classes is promising, but limited.[6-11] The current standard of care therefore relies on psychosocial interventions, primarily Cognitive Behavioural Therapy-based approaches,[12] which show modest effectiveness.[13] Relapse to methamphetamine use rates are high, with only one-quarter of individuals remaining abstinent after one year following residential rehabilitation.[14] Further, treatment outcomes differ depending on levels of use, with poorer outcomes observed in people who use methamphetamine frequently compared to those who use less frequently.[15] Limited efficacy may be due in part to psychosocial interventions not sufficiently addressing cravings and the presence of negative affect during withdrawal, leading to relapse,[16] or common neurocognitive difficulties observed in MAUD including executive dysfunction, poor working memory, impulsivity, and decision-making difficulties.[17] Supporting psychological interventions with adjuvant pharmacotherapy may overcome some of these challenges, an approach which is beginning to show promise with other substance use disorders.[18]

Combined treatment approaches using ketamine and different forms of psychotherapy (referred to as Ketamine-Assisted Psychotherapy; KAP) have shown sustained improvements in treatment outcomes for a variety of mental health and substance use disorders.[19,20] Ketamine is a well-characterised dissociative anaesthetic, acting primarily through antagonism of the glutamatergic n-methyl-d-aspartate (NMDA) receptor. Racemic ketamine is used therapeutically as an anaesthetic agent and analgesic (administered parenterally) and in its s-enantiomer form as esketamine, administered intranasally for treatment resistant depression. Glutamatergic dysregulation has been implicated in depression.[21-24] Subanaesthetic doses of ketamine induce rapid reversal of depression symptoms that can be sustained for up to 7 days after one infusion.[23,25] The anti-depressant properties of ketamine are of particular interest for amphetamine use disorders given findings that chronic amphetamine administration results in depletion of dopamine receptors and dopamine release, leading to a negative affective state during withdrawal,[16] and increasing the risk of relapse.[26] While there is significant heterogeneity in how ketamine has been administered in clinical studies to date (e.g. intravenous infusion vs. subcutaneous injection, dosage, course of treatment), preliminary data suggest that subanaesthetic doses of ketamine may have efficacy for treatment of substance use disorders. Ketamine monotherapy for cocaine, heroin and alcohol use disorder has produced short-lived improvements in self-administration and abstinence compared to active placebo.[20,27,28] While ketamine provides a unique, rapid onset of antidepressant action for chronic mental health conditions including substance use disorders, its therapeutic effect is temporally limited. Symptom reductions are frequently transient (typically lasting 4-7 days), with repeated administrations required to maintain positive effects.[29-31]

In KAP approaches, it is hypothesised that ketamine may prolong and enhance the effect of psychotherapy by increasing synaptogenesis and promoting neural pathways which facilitate neuroplasticity.[19,20] Ketamine-enhanced neuroplasticity is thought to facilitate

emotional learning, evoke emotionally arousing phenomenological experiences, reduce defensiveness and enhance treatment adherence and engagement.[19] While no studies to date have examined KAP for MAUD specifically, promising findings for other substance use disorders have been reported. A small randomised controlled trial (RCT; n = 55) of ketamine-assisted (0.5mg/kg single IV infusion) mindfulness-based relapse prevention therapy for cocaine dependence showed 48.2% abstinence compared to 10.7% in the active control group (midazolam + mindfulness-based relapse prevention therapy), with the odds of end-of-study abstinence in the ketamine group being 6 times that in the midazolam group (odds ratio=5.7, x^2=5.34, df =1, p=0.02). Further, those in the ketamine group were 53% less likely to relapse or discontinue treatment compared to controls over the 5-week study period.[32] An RCT (n = 40) examining ketamine-assisted (0.71mg/kg single IV infusion) motivational enhancement therapy for alcohol use disorder reported a lower proportion of participants in the ketamine group using alcohol (8/17, 47.1%) compared to controls (13/22; 59.1%) across the 21-days following drug administration.[33] Sustained effects have been reported in alcohol use disorder, whereby those receiving ketamine-assisted (three 0.8mg/kg IV infusions once weekly) mindfulness-based relapse prevention therapy had more days abstinent over 6 months compared to three other groups (ketamine + psychoeducation; placebo + mindfulness-based relapse prevention therapy; placebo + psychoeducation) (mean difference = 10.1, 95% CI = 1.1, 19.0).[34] Longer-term effects in other substance use disorders have also been reported. An RCT (n = 70) in people with heroin dependence using both a high (2.0mg/kg) and low (0.2mg/kg) IM ketamine dose and existential-oriented psychotherapy reported higher rates of abstinence for the high dose group vs. low dose group, with effects sustained over 24 months.[35]

Supporting the putative impact of ketamine in enhancing effects of psychotherapy more broadly, positive effects of ketamine-assisted cognitive behavioural therapy (CBT) in treatment resistant depression have also been reported, with CBT sustaining the antidepressant effects of IV ketamine (6 doses, 0.5mg/kg, over 3 weeks) over a 17-week

period (Quick Inventory of Depressive Symptomatology-Self report scores $F = 4.58$, $p = 0.033$; $d = 0.71$, 95% CI – 0.30 to 1.70).[36] Furthermore, improvements in cognitive control (e.g. executive control, including updating and maintenance) were associated with clinical improvement following ketamine treatment in a subset of patients. This provides some support for the hypothesis that, along with its rapid antidepressant properties, ketamine may also improve cognitive control, while CBT strengthens and maintain these improvements.[36] A combined approach of ketamine and CBT may therefore have strong potential for MAUD given the neurocognitive impairments and withdrawal-associated dysphoria that appear to hamper psychotherapy effectiveness in this population.

Objectives

This pilot study aims to determine the safety and feasibility of subcutaneously administered racemic ketamine (three doses, once per week) alongside four sessions of weekly CBT for adults with MAUD, in an outpatient setting. We hypothesise that ketamine-assisted psychotherapy will be safe and feasible in this context.

Secondary objectives are to explore changes from baseline to Week 5, 8 12 and 24 in methamphetamine use, cravings and withdrawal and quality of life, as well as treatment satisfaction.

Study results will inform future randomised controlled trials.

Methods and analysis

Study setting and design

This study is an open-label, single-arm pilot clinical trial. This paper reports on the study protocol in line with Standard Protocol Items Recommendations for Interventional Trials (SPIRIT) guidance (**Supplemental file 1**).[37]

The study will be conducted in an outpatient stimulant treatment clinic (the 'Stimulant Treatment Program'; STP), at St Vincent's Hospital, Sydney (SVHS), Australia. SVHS, a public teaching hospital, is the study sponsor. Participants will be referred directly from the clinic. Advertising to local health service providers and social media will also be used to enhance recruitment.

Patient and public involvement

This study is designed and conducted without any involvement from participants or the public. Study results will be disseminated to participants and the public via the National Centre for Clinical Research in Emerging Drugs website.

Participants and recruitment

Eligibility criteria

Eligible participants will be adults, who meet DSM-5-TR criteria for MAUD and are seeking treatment to cease or reduce methamphetamine use. Inclusion and exclusion criteria are outlined in **Table 1**.

Table 1 – Eligibility Criteria

Inclusion criteria	Exclusion criteria
All participants must / must be:	*All participants must not:*
▪ ≥18 years of age ▪ Able to provide informed consent ▪ Willing and able to comply with all study requirements, as determine by the Principal Investigator ▪ Meets DSM-5-TR diagnostic criteria for Current Stimulant Use Disorder - Amphetamine-Type Substance - as determined by the Principal Investigator and confirmed with the MINI ▪ Urine drug screen (UDS) point of care (POC) test positive for methamphetamine ▪ Willing to register as a client of the St Vincent's Hospital Sydney (SVHS) Stimulant Treatment Program (STP)	▪ DSM-5-TR diagnosis of current or past use disorder for ketamine or ketamine analogues as assessed by MINI ▪ Prescribed or non-prescribed use of ketamine in the previous four weeks ▪ Currently enrolled in another treatment trial of MAUD or clinical trial which is likely to affect safety, data quality or may interfere with participation in this study, as determined by the Principal Investigator ▪ Currently pregnant or breast feeding, or planning on becoming pregnant during the course of the study ▪ DSM-5-TR diagnosis of current psychotic disorder as assessed by the Principal Investigator including review of MINI ▪ Current acute suicidality defined as 'high risk' using the C-SSRS-6 screener or as determined by the Principal Investigator ▪ DSM-5-TR diagnosis of bipolar disorder as assessed by the Principal Investigator including review of MINI ▪ Current DSM-5-TR diagnosis with other substance use disorders, moderate or severe, except tobacco, caffeine, or cannabis as assessed by the Principal Investigator including review of MINI. Opioid use disorder permitted if stable on opioid agonist treatment; OAT) (i.e. no dose changes for six weeks if on oral OAT and maximum of one missed dose/week. At least three months with no missed doses if on long-acting injectable OAT) ▪ History of sensitivity to ketamine or any other components of this product

	▪ If prescribed antidepressants, the participant must have been on a stable dose for four or more weeks ▪ Contraindications to ketamine according to Australian Product Information: ○ Severe cardiovascular disease ○ Heart failure ○ Severe or poorly controlled hypertension ○ Recent myocardial infarction ○ History of stroke ○ Cerebral Trauma ○ Intracerebral mass or haemorrhage
▪ Seeking treatment to cease or reduce methamphetamine use ▪ If person of childbearing potential, willing to avoid pregnancy for study duration	▪ Any other medical or psychiatric condition which in the opinion of the Principal Investigator would make participation hazardous. In particular, caution if severe liver, kidney or bladder disease, and also caution if elevated cerebrospinal fluid pressure, increased intraocular pressure, acute intermittent porphyria, seizures, hyperthyroidism, pulmonary or upper respiratory infection, intracranial mass lesions, a presence of head injury, globe injuries, or hydrocephalus. ▪ Likely or planned surgery, travel, incarceration or other engagement during the study that may interfere with study participation

Participant timeline

Figure 1 gives an overview of the flow of participants through the study. The total study duration for each participant is a maximum of 168 days. This comprises a screening period (window of up to 2 weeks), a 4-week treatment period, end of treatment (Week 5), primary endpoint at Week 8 and two additional follow-up visits (Week 12, Week 24).

Figure 1 – Trial Timelines

Potential participants who express interest in the study will be pre-screened and those who meet basic criteria will proceed to informed consent. Informed consent (**Supplemental file 2**) will be obtained from each participant by the Principal Investigator or delegated medical officer. Participants will then be formally screened for eligibility. Screening for eligibility will include medical review and a structured clinical interview (the MINI International Neuropsychiatric Interview 7.0.2; MINI)[38] for substance use disorders, major depressive disorder, bipolar disorder and psychosis. The Columbia Suicide Severity Rating Scale Screener (CSSRS-6)[39] will be used to assess for history of suicidal ideation or suicide attempts. Eligible participants will be enrolled in the study. Baseline assessments to characterise the sample include demographic information, the Wender Utah Rating Scale (WURS)[40] to retrospectively evaluate the presence of childhood ADHD symptoms; and the Substance Use Goals and Expectations to measure treatment goals and expectations (SURGE, unpublished). Qualitative interviews (one per participant) will be conducted during Weeks 5 to 8. The full schedule of assessments is outlined in **Supplemental file 3**.

Intervention

The intervention consists of three subcutaneous racemic ketamine doses at weekly intervals and four sessions of CBT (one at commencement of the intervention and three within 24-28 hours following each ketamine administration session) (see **Figure 2**).

Figure 2 – Intervention Schedule

Medication

The medication under investigation is the Therapeutic Goods Association (TGA) approved ketamine 100mg/ml, available in Australia formulated in liquid solution for

intravenous and intramuscular injection as an anaesthetic agent.[41,42] A total of three subcutaneous subanaesthetic doses, at least 7 days apart, will be administered by a study nurse to the abdomen once weekly during clinic visits at Weeks 2, 3 and 4. The starting dose will be 0.75mg/kg, increased to a maximum dose of 0.9mg/kg at subsequent visits as tolerated. The dose can be reduced to 0.6 or 0.5mg/kg if not tolerated (see **Table 2**).

Table 2 – Study Drug Schedule

Ketamine 1	Tolerability	Ketamine 2	Tolerability	Ketamine 3
0.75mg/kg	Well tolerated	0.9mg/kg	Well tolerated	0.9mg/kg
			Moderately tolerated	0.9mg/kg
			Poorly tolerated	0.75mg/kg
	Moderately tolerated	0.75mg/kg	Well tolerated	0.75mg/kg
			Moderately tolerated	0.75mg/kg
			Poorly tolerated	0.6mg/kg
	Poorly tolerated	0.6mg/kg	Well tolerated	0.6mg/kg
			Moderately tolerated	0.6mg/kg
			Poorly tolerated	0.5mg/kg

Tolerability will be assessed by the study doctor guided by the Ketamine Side Effect Tool (KSET),[43] with the clinician assigning tolerability prior to discharge based on subjective participant reports and objective observations.[43,44] Acceptable safety and tolerability profiles have been demonstrated in subcutaneous doses of up to 0.9mg/kg.[44] The study nurse will continuously monitor the participant at 120 minutes post ketamine administration and alert the Principal Investigator or appropriately qualified delegate in the case of any adverse event of concern, which will be managed according to clinical need (e.g. conservatively, continued support for up to a further 120 minutes).

Psychotherapy

The 4-session manualised Cognitive Behavioural Therapy (CBT) program developed by Baker et al[45] will be provided by trained therapists to all participants in the trial, with adaptations suitable for the KAP approach. Adaptations are specified in a therapist manual developed specifically for the study (unpublished), detailing “set and setting” considerations

within this context, preparation sessions (i.e. dosing day discussions including intention-setting, grounding exercises facilitated by the therapist and study nurse) and integration discussions (i.e. discussions framing each CBT session in relation to ketamine experiences). For the purposes of this study, therapists are defined as staff with qualifications in a relevant health discipline (such as counselling, nursing, social work, psychology, psychiatry), that have undergone training on the use of the CBT manual and in ketamine-assisted psychotherapy adaptations (2.5 hour training session facilitated by a senior clinical psychologist with experience in CBT and psychedelic-assisted therapy for MAUD). Each psychotherapy session will last approximately 1.5 hours. The initial assessment will take place as part of psychotherapy session 1, reviewing: (1) alcohol and other drug use history, (2) mental health assessment, (3) participant's readiness to change methamphetamine use, and (4) information about what will happen during the first ketamine dose session. One week later, a preparation session will be undertaken immediately prior to ketamine dose 1. Psychological preparation and pre-injection relaxation exercises have been previously shown to reduce the anxiety and distress that might emerge with ketamine administration.[46] As in previous studies,[32,47,48] participants will be guided through grounding exercises (e.g. relaxation and breathing) prior to ketamine administration and encouraged to use these should any discomfort or anxiety emerge. As part of preparation, study participants will be briefed on what to expect after drug administration and given the opportunity to ask any questions they may have, and a discharge information sheet will be provided. Within 24-48 hours following ketamine dose 1, psychotherapy session 2 will be undertaken, beginning with an integration focus where experiences of the ketamine administration will be briefly explored and used to guide the subsequent CBT material. This approach will also be used for the remaining sessions. Therapists will co-ordinate the four sessions to occur at least one week apart. Session 1 will occur during Week 1; Sessions 2, 3 and 4 will occur during Weeks 2,3 and 4 respectively within 24-48 hours of participants receiving study medication. Session checklists will be completed post-session by the therapist to assess treatment fidelity and discussed during group supervision with a senior psychologist. As per Baker et

al,[45] study participants will be encouraged to complete homework tasks in-between sessions.

Outcomes

The primary outcomes of this pilot study are safety and feasibility. Safety will be assessed by treatment emergent adverse events (AEs) across the duration of the study, categorised by system organ class (SOC). These will be described by seriousness, severity, causality and expectedness.[49,50] AEs will be documented at each clinic visit. Subjective descriptions of AEs provided by participants will be transcribed verbatim and reported in accordance with the Medical Dictionary for Regulatory Activities (MedDRA) terminology, developed under the auspices of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). Severity will be graded from Grade 1 (mild) to Grade 5 (death) by the site Principal Investigator.[51] Causality will be determined by the site Principal Investigator, and expectedness in accordance with international guidelines and Australian product labels for ketamine hydrochloride 100 mg/ml for injection.[41,42] Any known reaction listed on the product label will be considered potentially causally related. Adverse events will be elicited through structured assessment with the KSET.[43] Additional safety measures (see **Supplemental file 3** for administration timepoints) include: (i) blood pressure and heart rate during ketamine administration sessions, (ii) dissociative effects as measured by the Clinician-Administered Dissociative States Scale (CADSS-6),[52] (iii) elevated mood as measured by the Young Mania Rating Scale (YMRS [item 1]),[53] (iv) suicidality as assessed with the C-SSRS, (v) non-medical use liability as measured by the Drug Effects Questionnaire (DEQ-5),[54,55] and (vi) changes in other drug use (including ketamine) as measured by Timeline Follow Back (TLFB).[56]

Feasibility will be assessed by: (i) time taken to recruit the sample (with a 12-month study timeframe imposed, based on unpublished studies from our group in similar contexts successfully recruiting 20 participants within this timeframe); (ii) proportion of ineligible

participants at pre-screening and screening; (iii) number of participants who receive 3 doses of ketamine, (iv) number of participants who complete 4 sessions of psychotherapy, (v) retention rate over the full duration of the study, and vii) acceptability of the intervention, assessed via qualitative interviews. As this is the first study of its kind in this population and pilot studies are not generalisable to other contexts[57,58], these will be assessed and reported descriptively. While we conservatively anticipate 50% completion of 4 sessions of CBT and 75% completion of 6-month follow-up assessments based on studies of CBT in this population[13,59], these are not directly comparable given the pharmacotherapy component of the present study design. Therefore, results will be synthesised in consideration of the feasibility to progress to larger studies, taking into account the measures described above and equally so the qualitative acceptability.[60]

Secondary outcomes include measures of preliminary efficacy and potential mediators. These measures include: (i) self-reported change in past 28-days of MA use from baseline to Week 5 (post treatment), Week 8 (primary endpoint), Week 12 and Week 24 as measured by the TLFB,[56] (ii) presence of methamphetamine in urine assessed through POC UDS at Week 5, Week 8, Week 12 and Week 24, (iii) changes in methamphetamine craving as measured by the Visual Analogue Scale - Craving (VAS-C)[61] and withdrawal symptoms assessed on the Amphetamine Withdrawal Questionnaire (AWQ)[62] from baseline to Week 5, Week 8, Week 12 and Week 24, (iv) changes in quality of life as measured by the World Health Organisation Quality of Life – Brief Version (WHOQOL-BREF)[63] from baseline to Week 5, Week 8, Week 12 and Week 24, and (v) treatment satisfaction as measured by the Treatment Satisfaction Questionnaire for Medication (TSQM-II)[64] and the Client Satisfaction Questionnaire (CSQ-8)[65] at Week 5, Week 8.

Potential mediator measures are changes in: (i) depression scores on the Patient Health Questionnaire-9 (PHQ-9)[66] from baseline to Week 5, Week 8, Week 12 and Week 24, (ii) anxiety scores on the Generalised Anxiety Disorder Scale-7 (GAD-7)[67] from baseline to Week 5, Week 8, Week 12 and Week 24, iii) emotion regulation scores on the Difficulties in Emotion Regulation Questionnaire (DERS)[68] from baseline to Week 5, Week 8, Week 12

and Week 24, (iv) sleep quality scores on the Insomnia Severity Index (ISI)[69] from baseline to Week 5, Week 8, Week 12 and Week 24, (v) HIV and other sexually transmitted infection risk behaviours as measured by the Substance Use Sex Index (SUSI)[70] from baseline to Week 5, Week 8, Week 12 and Week 24, (vi) subjective medication effects on the Hood Mysticism Scale (HMS)[71] 120 minutes post ketamine administration, (vii) cognitive control and flexibility as measured by the Emotional N-back task[72] at baseline and 24 hours post third ketamine administration, (viii) cognitive control as measured by the Emotional Stroop task[726] at baseline and 24 hours post third ketamine administration.

Sample size

The study is not powered to determine efficacy. The study will recruit 20 participants, as is convention in pilot studies.[73]

Participant retention and withdrawal

The study site will make all reasonable efforts to follow participants for the course of the study. Efforts to minimise loss to follow-up will include respecting participant time commitments, formal tracking procedures including multiple ways to be contacted and strong interpersonal skills of study personnel.

Stopping criteria

If a participant experiences a Grade 3 or Grade 4 Adverse Event (AE) considered to be causally related to the study medication, no further study medication will be dispensed until the participant has been reviewed by the site Principal Investigator.[51] If the AE is resolved to the satisfaction of the Principal Investigator, the dose can be recommenced, and the participant will be reviewed the subsequent day. If the AE is not resolved or recurs after recommencing the study medication, the site Principal Investigator will consider ceasing the medication and withdrawing the participant from the treatment component of the study.

Unless they revoke their consent, all participants withdrawn from treatment will continue to be followed as intention to treat.

Reimbursement

Participants will be reimbursed for participating, in accordance with Australian guidelines for appropriate and equitable payment of participants in research.[74] Participants who consent to partake in the study and complete all the screening assessments will receive a $40 gift card. Reimbursements of $40 gift cards will also be made for each study visit. If the participant chooses to have their qualitative interview scheduled for the same day as another visit during weeks 5 to 8, they will still receive a separate $40 reimbursement for the interview. The maximum potential amount of reimbursement over the entire duration of the study is $520 of gift cards per person.

Data management

Study data will be collected and managed using REDCap (Research Electronic Data Capture) tools hosted at St Vincent's Hospital, Sydney.[75] REDCap is a secure, web-based software platform designed to support data capture for research studies, providing i) an intuitive interface for validated data capture, ii) audit trails for tracking data manipulation; iii) automated export procedures for seamless data downloads to common statistical packages; and iv) procedures for data integration and interoperability with external sources. In accordance with the National Standard Operating Procedures for Clinical Trials,[76] identifiable information will be stored separately from the main study data. The Participant Identification Log will be stored in a password protected folder on a secure SVHS hosted server. Access to study records within the REDCap database will be limited by using Data Access Groups (DAGs). Only users within a given DAG can access records created by users within that group. Access to components of study records is role-based and can only be granted by the Project Manager. Data will only be made available to investigators who are directly involved

in the collection, analysis, or monitoring of study data. Following conclusion of the study, physical and digital records will be stored for a period no less than 15 years as per ICH-GCP guidelines.[49]

Statistical methods

Descriptive statistics will be used to characterise the study sample. Quantitative analyses will be descriptive and exploratory and include basic measures of central tendency, confidence intervals (CIs) around means or proportions, Cohen's d, and paired sample t-tests to assess pre-post intervention changes. P-vales are considered preliminary and wil be reported with caution, supplemented with appropriate metrics (e.g. CIs). For categorical measures such as the presence of AEs, rates will be analysed using appropriate non-parametric approaches, such as chi-square and relative risk. Quantitative data will be analysed using SPSS Version 29.0.[77] Qualitative interviews will be collected until all trial participants have been approached. Interviews will be thematically analysed to extract key themes across participant responses, using the approach outlined by Braun & Clarke[78]: familiarising with the data, generating initial codes, searching for themes, reviewing themes, defining and naming themes, and producing the report. Qualitative data will be analysed using NVivo Version 14.[79]

Monitoring

Data Safety Monitoring Board (DSMB)

An independent DSMB will be established prior to study recruitment. DSMB membership will include: an addiction medicine specialist; a psychologist; and a pharmacologist (all not otherwise involved with the study). All Serious Adverse Events (SAEs) and Suspected Unexpected Serious Adverse Reactions (SUSARs) will be reviewed by the DSMB quarterly. Following each meeting, the DSMB will advise one of four options: continue study as per protocol, continue study with protocol amendments, suspend study, or

discontinue study. The study data will be monitored by a sponsor staff member not otherwise involved in the study, for accuracy, primary endpoint data, and compliance with ICH-GCP[49] and the Australian National Statement on Ethical Conduct in Human Research.[80]

Ethics and dissemination

This study has been approved by the St Vincent's Hospital Human Research Ethics Committee, reference 2023/ETH00530. All participants will provide digital informed consent prior to commencing in the study.

Study findings will be disseminated through articles in scientific, peer-reviewed journals, and at national and international conferences.

Ethics statements

Patient consent for publication

Not applicable.

Discussion

This pilot study is the first to examine the safety and feasibility of ketamine-assisted psychotherapy for the treatment of MAUD in adults in an outpatient setting. Secondary outcomes were selected with a harm-reduction and person-centred lens, including reduction in methamphetamine use, cravings, withdrawal symptoms, and improved quality of life. As overviewed by Pasareanu et al.,[81] substance use disorder treatment has traditionally focused on abstinence but is increasingly incorporating broader positive treatment outcomes. Recovery-oriented outcomes such as quality of life encompass clinical, functional, and personal variables, which hold particular relevance for substance use disorder given the chronic nature of the condition. Other study strengths include the use of structured clinical interviews to screen and characterise the sample.

While intranasal and IV ketamine represent the most common routes of administration in studies to date,[82] SC administration was chosen for the current study for several reasons shorter time of administration, fewer injection-related adverse events, minimal discomfort, cost-effectiveness, and not requiring an anaesthetist for monitoring), and has been used successfully in a large RCT over a 4-week period in adults with treatment resistant depression,[44] demonstrating safety and efficacy in doses of up to 0.9mg/kg. As this is the first published study to our knowledge utilising SC ketamine in individuals with a substance use disorder, further characterisation of the relative efficacy, tolerability, and safety of different routes of administration in this group is needed.

This intervention also offers some promise in terms of scalability, of particular importance given the concerns of the infrastructure required to implement medication-assisted psychotherapy interventions.[83,84] The two-hour monitoring period requires both appropriate space and staffing but is shorter than the monitoring required for other medication-assisted psychotherapies, while the subcutaneous route requires less intensive monitoring than intravenous administration. Ketamine for injection is also widely available at relatively low cost. The use of a standardised manual-based CBT also allows for scalability terms of workforce readiness and reproducibility. Qualitative data from this study will examine the feasibility and acceptability of these components, and future studies will incorporate cost-effectiveness analyses to inform the future delivery of such interventions in real world settings. Comorbid mental health issues in those who use methamphetamine regularly are common.[10] The presence of mild to moderate coexisting depression, anxiety or transient psychotic symptoms do not constitute exclusion criteria in the current study to promote real-world application of the findings. Further, successful treatment of MAUD requires consideration of comorbid mental health conditions. Given the co-occurring depressive symptomatology and the withdrawal symptoms of dysphoria and anxiety commonly experienced when ceasing methamphetamine use, ketamine-assisted CBT may have particular efficacy for treating MAUD by addressing these symptoms while enhancing psychotherapeutic effects to prevent relapse.

Extra-medical use of ketamine precipitated by prescribed ketamine may be a cause of concern, especially given increasing prevalence of ketamine use disorder has been observed in some countries/regions.[85] As overviewed by Le et al.,[86] in professionally supervised settings, single or repeated IV, IM or oral ketamine administration has not been shown to result in misuse, dependence, diversion and/or gateway activity in patients with treatment resistant depression. However, extra-medical use liability was not systematically evaluated using validated measures, reports were retrospective in nature, and studies excluded individuals with substance use disorder, thus results are not directly relevant to this study population. A systematic review of ketamine for the treatment of mental health and substance use disorders found no evidence of transition to extra-medical ketamine use or unexpected psychological complications following treatment with ketamine.[87,88] The authors concluded that the relatively modest risk of precipitating ketamine use disorder should not present a barrier to treatment. Nonetheless, the safety and efficacy profile of ketamine in those with a substance use disorder requires further investigation. Positively, preliminary evidence supports the potentially beneficial role of ketamine in substance use disorders, with IV ketamine in combination with psychosocial treatment reducing alcohol and cocaine craving and consumption.[32-34] The current study represents an important first step in determining whether these findings extend to the MAUD space

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Tables and Figure Legends (see separate files attached as requested)

Figure 1 – Trial timelines

Figure 2 – Intervention Schedule

Table 1 – Eligibility Criteria

Table 2 – Study Drug Schedule

Table 1 – Eligibility Criteria

Inclusion criteria	Exclusion criteria
All participants must / must be:	*All participants must not:*
▪ ≥18 years of age ▪ Able to provide informed consent ▪ Willing and able to comply with all study requirements, as determine by the Principal Investigator ▪ Meets DSM-5-TR diagnostic criteria for Current Stimulant Use Disorder - Amphetamine-Type Substance - as determined by the Principal Investigator and confirmed with the MINI ▪ Urine drug screen (UDS) point of care (POC) test positive for methamphetamine ▪ Willing to register as a client of the St Vincent's Hospital Sydney (SVHS) Stimulant Treatment Program (STP)	▪ DSM-5-TR diagnosis of current or past use disorder for ketamine or ketamine analogues as assessed by MINI ▪ Prescribed or non-prescribed use of ketamine in the previous four weeks ▪ Currently enrolled in another treatment trial of MAUD or clinical trial which is likely to affect safety, data quality or may interfere with participation in this study, as determined by the Principal Investigator ▪ Currently pregnant or breast feeding, or planning on becoming pregnant during the course of the study ▪ DSM-5-TR diagnosis of current psychotic disorder as assessed by the Principal Investigator including review of MINI ▪ Current acute suicidality defined as 'high risk' using the C-SSRS-6 screener or as determined by the Principal Investigator ▪ DSM-5-TR diagnosis of bipolar disorder as assessed by the Principal Investigator including review of MINI ▪ Current DSM-5-TR diagnosis with other substance use disorders, moderate or severe, except tobacco, caffeine, or cannabis as assessed by the Principal Investigator including review of MINI. Opioid use disorder permitted if stable on opioid agonist treatment; OAT) (i.e. no dose changes for six weeks if on oral OAT and maximum of one missed dose/week. At least three months with no missed doses if on long-acting injectable OAT) ▪ History of sensitivity to ketamine or any other components of this product

	▪ If prescribed antidepressants, the participant must have been on a stable dose for four or more weeks ▪ Contraindications to ketamine according to Australian Product Information: ○ Severe cardiovascular disease ○ Heart failure ○ Severe or poorly controlled hypertension ○ Recent myocardial infarction ○ History of stroke ○ Cerebral Trauma ○ Intracerebral mass or haemorrhage
▪ Seeking treatment to cease or reduce methamphetamine use ▪ If person of childbearing potential, willing to avoid pregnancy for study duration	▪ Any other medical or psychiatric condition which in the opinion of the Principal Investigator would make participation hazardous. In particular, caution if severe liver, kidney or bladder disease, and also caution if elevated cerebrospinal fluid pressure, increased intraocular pressure, acute intermittent porphyria, seizures, hyperthyroidism, pulmonary or upper respiratory infection, intracranial mass lesions, a presence of head injury, globe injuries, or hydrocephalus. ▪ Likely or planned surgery, travel, incarceration or other engagement during the study that may interfere with study participation

Table 2 – Study Drug Schedule

Ketamine 1	Tolerability	Ketamine 2	Tolerability	Ketamine 3
0.75mg/kg	Well tolerated	0.9mg/kg	Well tolerated	0.9mg/kg
			Moderately tolerated	0.9mg/kg
			Poorly tolerated	0.75mg/kg
	Moderately tolerated	0.75mg/kg	Well tolerated	0.75mg/kg
			Moderately tolerated	0.75mg/kg
			Poorly tolerated	0.6mg/kg
	Poorly tolerated	0.6mg/kg	Well tolerated	0.6mg/kg
			Moderately tolerated	0.6mg/kg
			Poorly tolerated	0.5mg/kg

Table 1 – Eligibility Criteria

Inclusion criteria	Exclusion criteria
All participants must / must be:	*All participants must not:*
▪ ≥18 years of age ▪ Able to provide informed consent ▪ Willing and able to comply with all study requirements, as determine by the Principal Investigator ▪ Meets DSM-5-TR diagnostic criteria for Current Stimulant Use Disorder - Amphetamine-Type Substance - as determined by the Principal Investigator and confirmed with the MINI ▪ Urine drug screen (UDS) point of care (POC) test positive for methamphetamine ▪ Willing to register as a client of the St Vincent's Hospital Sydney (SVHS) Stimulant Treatment Program (STP)	▪ DSM-5-TR diagnosis of current or past use disorder for ketamine or ketamine analogues as assessed by MINI ▪ Prescribed or non-prescribed use of ketamine in the previous four weeks ▪ Currently enrolled in another treatment trial of MAUD or clinical trial which is likely to affect safety, data quality or may interfere with participation in this study, as determined by the Principal Investigator ▪ Currently pregnant or breast feeding, or planning on becoming pregnant during the course of the study ▪ DSM-5-TR diagnosis of current psychotic disorder as assessed by the Principal Investigator including review of MINI ▪ Current acute suicidality defined as 'high risk' using the C-SSRS-6 screener or as determined by the Principal Investigator ▪ DSM-5-TR diagnosis of bipolar disorder as assessed by the Principal Investigator including review of MINI ▪ Current DSM-5-TR diagnosis with other substance use disorders, moderate or severe, except tobacco, caffeine, or cannabis as assessed by the Principal Investigator including review of MINI. Opioid use disorder permitted if stable on opioid agonist treatment; OAT) (i.e. no dose changes for six weeks if on oral OAT and maximum of one missed dose/week. At least three months with no missed doses if on long-acting injectable OAT)

	▪ History of sensitivity to ketamine or any other components of this product ▪ If prescribed antidepressants, the participant must have been on a stable dose for four or more weeks ▪ Contraindications to ketamine according to Australian Product Information: o Severe cardiovascular disease o Heart failure o Severe or poorly controlled hypertension o Recent myocardial infarction o History of stroke o Cerebral Trauma o Intracerebral mass or haemorrhage
▪ Seeking treatment to cease or reduce methamphetamine use ▪ If person of childbearing potential, willing to avoid pregnancy for study duration	▪ Any other medical or psychiatric condition which in the opinion of the Principal Investigator would make participation hazardous. In particular, caution if severe liver, kidney or bladder disease, and also caution if elevated cerebrospinal fluid pressure, increased intraocular pressure, acute intermittent porphyria, seizures, hyperthyroidism, pulmonary or upper respiratory infection, intracranial mass lesions, a presence of head injury, globe injuries, or hydrocephalus. ▪ Likely or planned surgery, travel, incarceration or other engagement during the study that may interfere with study participation

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			Moderately tolerated	0.9mg/kg
			Poorly tolerated	0.75mg/kg
	Moderately tolerated	0.75mg/kg	Well tolerated	0.75mg/kg
			Moderately tolerated	0.75mg/kg
			Poorly tolerated	0.6mg/kg
	Poorly tolerated	0.6mg/kg	Well tolerated	0.6mg/kg
			Moderately tolerated	0.6mg/kg
			Poorly tolerated	0.5mg/kg

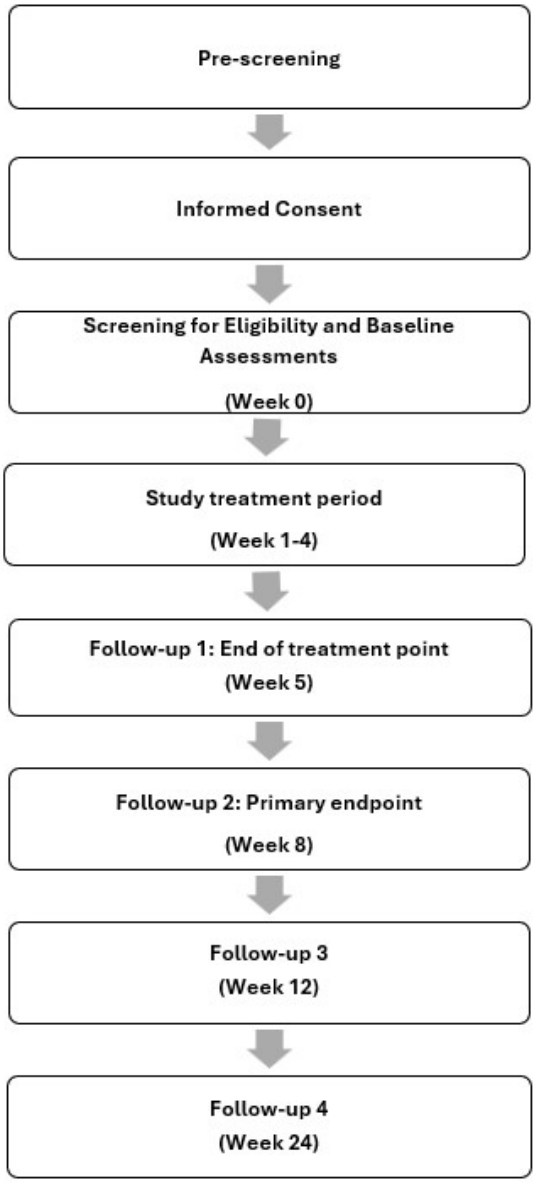

Figure 1 – Trial Timelines

46x93mm (192 x 192 DPI)

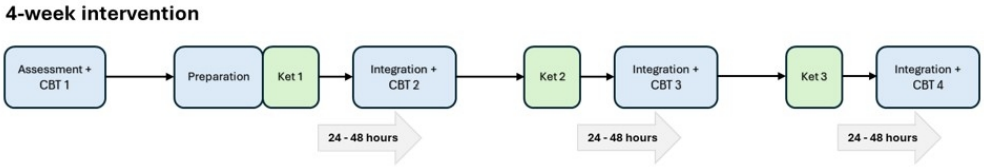

Figure 2 – Intervention Schedule

125x21mm (192 x 192 DPI)

ST VINCENT'S HOSPITAL SYDNEY
A FACILITY OF ST VINCENT'S HEALTH AUSTRALIA

Participant Information Sheet/Consent Form

Interventional Study - *Adult providing own consent*

St Vincent's Hospital, Sydney

Title	An Open-Label Safety and Feasibility Pilot Trial of Ketamine-assisted Psychotherapy for Methamphetamine Use Disorder
Short Title	Ketamine-assisted Psychotherapy for Methamphetamine Use (KAPPA)
Protocol Number	ETH 2024/ETH00530
Project Sponsor	St Vincent's Hospital, Sydney
Principal Investigator	Professor Nadine Ezard
Associate Investigator(s)	Dr Brendan Clifford Dr Krista Siefried A/Professor Gillender Bendi Dr Alexandre Guerin A/Professor Jonathan Brett Dr Michael Millard Dr Robert May Dr Elizabeth Knock Ms Jess Doumany Dr Kathryn Fletcher Mr Liam Acheson
Location	St Vincent's Hospital, Sydney, Alcohol and Drug Service

Part 1 What does my participation involve?

1 Introduction

You are invited to take part in this research project. This is because you have indicated that you currently use methamphetamine and are interested in managing, reducing, or stopping your methamphetamine use. The research project is testing a new treatment for methamphetamine use disorder. The new treatment is called ketamine assisted psychotherapy.

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

Please read this information carefully. Ask questions about anything that you don't understand or want to know more about. Before deciding whether to take part, you might want to talk about it with a relative, friend or your local doctor.

Participation in this research is voluntary. If you don't wish to take part, you don't have to. You will receive the best possible care whether you take part.

If you decide you want to take part in the research project, you will be asked to digitally sign the consent section on a laptop while you are in the clinic. By signing it you are telling us that you:

- Understand what you have read;
- Consent to take part in the research project;
- Consent to have the tests and treatments that are described; and
- Consent to the use of your personal and health information as described.

You will be emailed a copy of this signed Participant Information Sheet/Consent Form to keep.

2 What is the purpose of this research?

There are currently no approved medications in Australia to help treat methamphetamine dependence. This study aims to determine if it is safe and feasible for people who are using methamphetamine to be given a medication, called ketamine hydrochloride, along with psychological therapy, to help manage, reduce, or stop their methamphetamine use.

Medications, drugs and devices have to be approved for use by the Australian Federal Government. Ketamine hydrochloride is approved in Australia as an anaesthetic agent; however, it is currently not approved to treat methamphetamine use disorder. Therefore, this is an experimental treatment for methamphetamine use disorder. This means that this medication must be tested to see if it is a safe and effective treatment for people with methamphetamine dependence. This medication will be provided alongside a psychological therapy called Cognitive Behaviour Therapy (CBT), which is known to be effective for people with methamphetamine dependence.

This research has been initiated by the study doctor, Professor Nadine Ezard. This research is funded by the National Centre for Clinical Research on Emerging Drugs, University of New South Wales.

3 What does participation in this research involve?

If, after reading this information and discussing this research with your doctor, friends or family, you decide to take part, you will be asked to digitally sign the Consent Form confirming that you agree to participate. This study is designed to provide you with ketamine hydrochloride and psychological therapy, as well as your usual standard of care provided by St Vincent's Hospital, Sydney. This means that except for receiving the study medication and psychological therapy, the medical care that you will receive will be the same whether you decide to take part in this research or not.

Screening and baseline assessments

Before you take part in the study, the researchers need to make sure it is safe and appropriate for you to do so. This will involve some screening procedures, including questionnaires, medical assessments, and urine tests. These procedures are as follows:

- Review of your medical history including previous instances of substance use treatment, psychological therapy, and any medications you are taking currently.
- Routine medical screening, including blood pressure, pulse, temperature, and weight. All of these measures are non-invasive.
- Routine urine tests, including:
    - A dip-stick urine drug test for methamphetamine. This will require approximately 2-3 tablespoons (50mL) of urine.
    - A pregnancy test will also be conducted if you are of childbearing potential.
- A clinical interview to assess your mental health history, including:
    - Substance use
    - Psychosis
    - Depression
    - Bipolar disorder
- A series of baseline questionnaires to assess your:
    - Use of substances (including methamphetamine, ketamine, opioids, alcohol, cigarettes, etc.) over the past 4 weeks
    - Craving for methamphetamine
    - Withdrawal from methamphetamine
    - Thoughts of suicide and acts of suicidal behaviour

- Mood symptoms
- Quality of life
- Sleep
- Coping with feelings
- Sex and drug use risk behaviours
- Care received outside St Vincent's Hospital

These screening and baseline procedures (including study questionnaires, which will take approximately 1.5 hours to complete) are expected to take between two and three hours. These procedures can be completed over more than one clinic visit if necessary, but all procedures must be completed within 14 days of consenting to participate in the study.

Intervention

Medication

This study involves a commercially available medication which contains ketamine hydrochloride. The medication is in liquid form and will be administered subcutaneously (injection under the skin, in the anterior abdominal wall). You will be required to receive three doses of this medication in total, once per week, during clinic visits. The dose will be adjusted at each visit depending on your level of tolerability. You will be asked to complete some study questionnaires, which will take approximately 30 mins to complete. These visits are expected to take between two and three hours in total.

Psychological Therapy

You will be required to attend four sessions of psychological therapy in total, once per week, during clinic visits. The psychological therapy provided in this study is Cognitive Behavioural Therapy (CBT), by a trained health professional. Sessions will focus on:

- Motivation and preparing to change methamphetamine use
- Coping with cravings and lapses
- Controlling thoughts about methamphetamine use
- Preparing for future high-risk situations

Each session is expected to take 1.5 hours.

Weekly clinic visits

After enrolling in the study and completing all the screening and baseline measures, you will be required to attend St Vincent's Hospital, Sydney, Alcohol and Drug Service i) twice weekly for a period of 4 weeks, ii) four visits at week 5, 8, 12, and 24. The purpose of these visits is to provide you with the study medication and psychotherapy (first 4 weeks), monitor you for any medication related side effects, and to test your urine for methamphetamine.

Each week, you will be asked about care received outside St Vincent's Hospital, other medications you are taking, and physical health symptoms. Your blood pressure, pulse, temperature, and weight will be recorded at each weekly visit. You will provide a urine sample for a point of care methamphetamine screen, and for pregnancy if you are of childbearing potential. In addition, every four weeks you will be asked about your drug consumption (methamphetamine, opioids, alcohol, and cigarettes/nicotine, etc). At the study visits on week 5, 8, 12, and 24 you will also be asked to complete many of the same questionnaires that you completed at the start of the study, which will take approximately 1.5 hours to complete.

Interview

We would also like to interview you about your experiences related to taking part in the study. Interviews will be semi-structured, meaning that the interviewer will have questions to ask you, but some questions may be changed or skipped depending on what you wish to talk about. Interviews will be conducted one-on-one with a trained research staff member. The interview will take approximately one hour. The interview will focus on your goals around managing your methamphetamine use, your expectations around taking the study medication and psychotherapy, your experiences of taking the study medication and receiving psychotherapy, any concerns relating to the study medication or psychotherapy, and your experience of taking part in the study in general.

Interviews will be conducted in a private treatment or interview room at St Vincent's Hospital, Sydney. For those unable to attend in person, phone or video options will be provided. Interviews will be conducted between Weeks 5 and 8 of the study. Interviews will be audio recorded and then transcribed (written down) in full. Participation in the interview requires that you consent for your interview to be audio-recorded. If you do not wish to participate in the interview, you are still able to participate in the study trial.

Reimbursement

Participation in this study requires thirteen visits to St Vincent's Hospital, Sydney, Alcohol and Drug Service clinic and one interview with a researcher. Given the time burden imposed by participation in this study, you will be reimbursed for your time and associated expenses at each visit. Reimbursements are a fixed amount and will be made after each weekly visit that you attend. The maximum potential amount of reimbursement over the entire duration of the study is $520 of gift cards per person.

Week	Screening	1	2 (Two visits)	3 (Two visits)	4 (Two visits)	5	8	12	24	Interview
Amount	$40	$40	$40 x 2	$40 x 2	$40 x 2	$40	$40	$40	$40	$40*

4 What do I have to do?

There are no lifestyle restrictions or dietary restrictions associated with this project. You may continue to do everything that you normally would. During the screening process, the study doctor will ask you about the medications that you are currently taking. It is important that you tell the study doctor what medications you are taking to ensure that it is safe for you to participate in the study. We also ask that you inform the study doctor if there are any changes to your medications or substance use at any point during the study.

If you take part in this study, you are asked to commit to attending clinic visits to receive ketamine administration and attend psychotherapy sessions. You should not use methamphetamine or any other substances for at least 12 hours prior to having any of the ketamine administration.

It is desirable that your local doctor (i.e. your GP) be advised of your decision to participate in this research project. If you have a local doctor, we strongly recommend that you inform them of your participation in this research project.

5 Other relevant information about the research project

You will be participating in a single group pilot study. In this study, all participants receive the same treatment. There will be up to 20 participants taking part in this study.

This study has been designed to make sure the researchers interpret the results in a fair and appropriate way and avoids study doctors or participants jumping to conclusions.

There are no additional costs associated with participating in this research project. All medication, tests and medical care required as part of the research project will be provided to you free of charge.

This research involves collaboration with researchers from St Vincent's Hospital Sydney and the University of New South Wales.

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

Participation in any research project is voluntary. If you do not wish to take part, you do not have to. If you decide to take part and later change your mind, you are free to withdraw from the project at any stage.

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

Your decision whether to take part or not to take part, or to take part and then withdraw, will not affect your routine treatment, your relationship with those treating you or your relationship with St Vincent's Hospital, Sydney.

7 What are the alternatives to participation?

You do not have to take part in this research project to receive treatment at St Vincent's Hospital. Other options are available; these include counselling and psychosocial support. Your study doctor will discuss these options with you before you decide whether to take part in this research project. You can also discuss these options with your local doctor. If you would like more support with your substance use, please contact:

- The National Alcohol and Other Drug Hotline: 1800 250 015
- St Vincent's Alcohol and Drug Service Centralised Intake line: (02) 8382 1080 (if residing in Sydney)
- St Vincent's Stimulant Treatment Line: (02) 8382 1111
- Lifeline: 13 11 14
- Alcohol and Drug Counselling Online: https://www.counsellingonline.org.au/
- In the case of emergency: 000

This research study differs from standard care for methamphetamine use, as there are currently no medications approved for the treatment of methamphetamine use in Australia.

8 What are the possible benefits of taking part?

We cannot guarantee or promise that you will receive any benefits from this research; however, possible benefits may include reducing or stopping your methamphetamine use. Participation in this research may help to develop effective, evidence-based treatment options for people who use methamphetamine.

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

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

Although the side effects associated with ketamine hydrocholoride are well understood, there may be side effects that the researchers do not expect or do not know about, which may be serious. Tell your study doctor immediately about any new or unusual symptoms that you get at any point during the study.

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

The most common side effects associated with ketamine hydrochloride are nausea, vomiting, and increased salivation. Possible side effects of subcutaneous injection include pain at the injection site (which may persist for 38 hours), bruising, or accidental injection into a blood vessel. The injection site will be observed at 120 minutes, prior to discharge and at scheduled reviews, and any complications will be managed accordingly. Other adverse effects of ketamine hydrochloride include:

- Anorexia
- Anaphylaxis
- Rash
- Confusion, excitation, irrational behaviour

- Hallucinations, vivid imagery, dream-like states, nightmares
- Agitation, anxiety or insomnia
- Movements resembling seizures
- Hypertonia
- Breathing difficulties
- Respiratory depression following rapid IV dose
- Laryngospasm and airway obstruction
- Elevated blood pressure, fast or slow heartbeat, heart palpitations, feeling faint
- Hypotension, arrhythmia
- Double vision or abnormal eye movements
- Elevated intraocular pressure measurement
- Changes in urine colour, pain or burning sensations when urinating, frequently passing small amounts of urine or a persistent urge to urinate
- Acute kidney injury, hydronephrosis, ureteral disorder, haemorrhagic cystitis, cystitis reported during long-term use (>1 month)
- Jaundice
- Drug induced liver injury in extended period use (>3d)
- Abnormal liver function test

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

All participants must avoid pregnancy during the course of the research and for a period of one month after completion of the research project. You should discuss effective methods of avoiding pregnancy with your study doctor.

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

You should advise your study doctor if you have made someone pregnant while participating in the research project. Your study doctor will advise on medical attention for your partner should this be necessary.

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

This research project involves the collection of information about your use of drugs. Participation in the research project includes urine analysis to determine the presence of methamphetamine. That information will be stored in a re-identifiable (or coded) format. In the rare event that SVHS is required to disclose that information, it may be used against you in legal proceedings or

otherwise. These legal obligations apply whether you are involved in a research study or not - any time a person engages in healthcare for substance use disorder, there is an inherent risk in exposure of activity as per legal frameworks. That is, participation in this study will not change the legal obligations that SVHS has in relation to information collected from you.

10 What will happen to my test samples?

This study includes the collection of urine. These collections are a mandatory component of the research. The samples that are collected from you are not retained after testing at the point of care and disposed of in the clinic on the same day.

11 What if new information arises during this research project?

Sometimes during the course of a research project, new information becomes available about the treatment that is being studied. If this happens, your study doctor will tell you about it and discuss with you whether you want to continue in the research project. If you decide to withdraw, your study doctor will make arrangements for your regular health care to continue. If you decide to continue in the research project you will be asked to sign an updated consent form.

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

12 Can I have other treatments during this research project?

Whilst you are participating in this research project, you may not be able to take some or all of the medications or treatments you have been taking for your condition or for other reasons. It is important to tell your study doctor and the study staff about any treatments or medications you may be taking, including over-the-counter medications, vitamins or herbal remedies, acupuncture, or other alternative treatments. You should also tell your study doctor about any changes to these during your participation in the research project. Your study doctor should also explain to you which treatments or medications need to be stopped for the time you are involved in the research project.

13 What if I withdraw from this research project?

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

If you do withdraw your consent during the research project, the study doctor and relevant study staff will not collect additional personal information from you, although personal information

already collected will be retained to ensure that the results of the research project can be measured properly and to comply with law. You should be aware that data collected by St Vincent's Hospital up to the time you withdraw will form part of the research project results. If you do not want them to do this, you must tell them before you join the research project.

14 Could this research project be stopped unexpectedly?

This research project may be stopped unexpectedly for a variety of reasons. These may include reasons such as:

- Unacceptable side effects
- The medications being shown not to be effective
- The medications being shown to work and not need further testing
- Decisions made by local regulatory/health authorities

15 What happens when the research project ends?

Should you require treatment for methamphetamine dependence in the future, you will be offered the clinic's usual care of counselling and psychosocial support and follow-up. The study drug ketamine hydrochloride is currently not licensed for use outside of clinical trials for the treatment of methamphetamine use in Australia. When the study is finished, you should speak to your Doctor about the treatment options available to you.

If you would like to find out about the results of the research, please advise your study coordinator who will be able to email you a one-page summary of the findings after the analysis is completed.

Part 2 How is the research project being conducted?

16 What will happen to information about me?

By signing the consent form you consent to the study doctor and relevant research staff collecting and using personal information about you for the research project. Any information obtained in connection with this research project that can identify you will remain confidential. While confidentiality cannot be fully assured despite stringent security measures, the researchers will ensure that all processes are in place to avoid a privacy and confidentiality breach. All information that is collected about you for the purposes of this study will be recorded with a code number instead of your name. Your information will only be used for the purpose of this research project and it will only be disclosed with your permission, except as required by law.

Information obtained during the research project are subject to inspection (for the purpose of verifying the procedures and the data) by the relevant authorities and authorised

representatives of the Sponsor, St Vincent's Hospital, Sydney, the institution relevant to this Participant Information Sheet, or as required by law. By signing the Consent Form, you authorise release of, or access to, this confidential information to the relevant study personnel and regulatory authorities as noted above.

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

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

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

After the study has been completed, all study-related documents will be stored securely for 15 years in line with national research guidelines, and then securely destroyed.

17 Complaints and compensation

If you suffer any injuries or complications as a result of this study, you should contact the study team as soon as possible and you will be assisted in arranging appropriate medical treatment. In the event of loss or injury, the parties involved in this research project have agreed that you may be entitled to seek compensation for any injuries or complications resulting from the study if your injury or complication is sufficiently serious and is caused by unsafe Investigational Product or by the negligence of one of the parties involved in the study (for example, the researcher, the hospital, or the treating doctor). You may wish to seek legal advice to explore your options. You do not give up any legal rights to compensation by participating in this study.

If you receive compensation that includes an amount for medical expenses, you will be required to pay for any medical treatment required for your injury or complication from those compensation monies. If you are not eligible for compensation for your injury or complication under the law, but are eligible for Medicare, then you can seek medical treatment required for your injury or complication free of charge as a public patient in any Australian public hospital. If you are not eligible for Medicare you may be able to claim compensation back via your private health insurance.

18 Who is organising and funding the research?

This research project is being conducted by St. Vincent's Hospital, Sydney and is being funded by the National Centre for Clinical Research on Emerging Drugs (NCCRED), the University of

New South Wales. NCCRED is funded by the Australian Government Department of Health and Aged Care.

St. Vincent's Hospital, Sydney, may benefit financially from this research project if, for example, the project assists St. Vincent's Hospital, Sydney to obtain approval for a new drug.

You will not benefit financially from your involvement in this research project even if, for example, your samples (or knowledge acquired from analysis of your samples) prove to be of commercial value to St. Vincent's Hospital, Sydney.

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

St. Vincent's Hospital, Sydney will receive a payment from the University of New South Wales, National Centre for Clinical Research on Emerging Drugs for undertaking this research project.

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

19 Who has reviewed the research project?

All research in Australia involving humans is reviewed by an independent group of people called a Human Research Ethics Committee (HREC). The ethical aspects of this research project have been approved by the HREC of St Vincent's Hospital, Sydney.

This project will be carried out according to the *National Statement on Ethical Conduct in Human Research (2023)*. This statement has been developed to protect the interests of people who agree to participate in human research studies.

20 Further information and who to contact

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

If you have any medical problems which may be related to your involvement in the project (for example, any side effects), you can contact the principal study doctor (clinical contact person) as follows:

Clinical contact person

Name	Nadine Ezard
Position	Principal Investigator
Telephone	02 8382 1111
Email	Nadine.Ezard@svha.org.au

If you have any general enquiries about the study or want any further information concerning this study, you can contact the general enquiries contact person as follows:

General enquiries contact person

Name	Lucy Flood
Position	Clinical Trial Coordinator
Telephone	<<telephone number>>
Email	Lucy.flood@svha.org.au

For matters relating to research at the site at which you are participating, the details of the local site complaints person are:

Complaints contact person

Name	Research Office Manager
Position	Research Office Manager
Telephone	02 8382 4960
Email	svhs.research@svha.org.au

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

Reviewing HREC approving this research and HREC Research Officer details

Reviewing HREC name	St Vincent's Hospital, Sydney HREC
Position	Research Officer
Telephone	02 8382 4960
Email	svhs.research@svha.org.au

Local HREC Office contact (Single Site -Research Governance Officer)

Name	Research Governance Officer
Position	Research Governance Officer
Telephone	02 8382 4960
Email	svhs.research@svha.org.au

ST VINCENT'S HOSPITAL SYDNEY
A FACILITY OF ST VINCENT'S HEALTH AUSTRALIA

Consent Form - *Adult providing own consent*

Title	An Open-Label Safety and Feasibility Pilot Trial of Ketamine-assisted Psychotherapy for Methamphetamine Use Disorder
Short Title	Ketamine-assisted Psychotherapy for Methamphetamine Use (KAPPA)
Protocol Number	ETH 2024/ETH00530
Project Sponsor	St Vincent's Hospital, Sydney
Coordinating Principal Investigator/ Principal Investigator	Professor Nadine Ezard
Associate Investigator(s)	Dr Brendan Clifford Dr Krista Siefried A/Professor Gillender Bendi Dr Alexandre Guerin A/Professor Jonathan Brett Dr Mike Millard Dr Robert May Dr Elizabeth Knock Ms Jess Doumany Dr Kathryn Fletcher Mr Liam Acheson
Location	St Vincent's Hospital, Sydney, Alcohol and Drug Service

Declaration by Participant

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

I understand the purposes, procedures and risks of the research described in the project.

I give permission for my doctors, other health professionals, hospitals or laboratories outside this hospital to release information to St Vincent's Hospital, Sydney concerning my disease and treatment for the purposes of this project. I understand that such information will remain confidential.

I consent to participate in the optional qualitative interview and for the interview to be audio-recorded:

☐ Yes ☐ No

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

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

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

Name of Participant (please print) _____

Signature _____ Date _____

Declaration by Study Doctor/Senior Researcher†

I have given a verbal explanation of the research project, its procedures and risks and I believe that the participant has understood that explanation.

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

Signature _____ Date _____

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

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

ST VINCENT'S HOSPITAL SYDNEY
A FACILITY OF ST VINCENT'S HEALTH AUSTRALIA

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

Title	An Open-Label Safety and Feasibility Pilot Trial of Ketamine-assisted Psychotherapy for Methamphetamine Use Disorder
Short Title	Ketamine-assisted Psychotherapy for Methamphetamine Use (KAPPA)
Protocol Number	ETH 2024/ETH00530
Project Sponsor	St Vincent's Hospital, Sydney
Principal Investigator	Professor Nadine Ezard
Associate Investigator(s)	Dr Brendan Clifford Dr Krista Siefried A/Professor Gillender Bendi Dr Alexandre Guerin A/Professor Jonathan Brett Dr Mike Millard Dr Robert May Dr Elizabeth Knock Ms Jess Doumany Dr Kathryn Fletcher Mr Liam Acheson
Location	St Vincent's Hospital, Sydney, Alcohol and Drug Service

Declaration by Participant

I wish to withdraw from participation in the above research project and understand that such withdrawal will not affect my routine treatment, my relationship with those treating me or my relationship with St Vincent's Hospital, Sydney.

Name of Participant (please print) _____

Signature _____ Date _____

Declaration by Study Doctor/Senior Researcher†

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

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

Signature _____ Date _____

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

Supplemental File 3 - Schedule of Assessments

Week	0	1	2		3		4		5	8*	12	24
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12
Day	0	1	5/6	7	12/13	14	19/20	21	28	56	84	168
Intervention		CBT 1	KET 1	CBT 2	KET 2	CBT 3	KET 3	CBT 4				
Informed Consent	x											
MINI[a]	x											
C-SSRS-6	x											
Medical assessment	x											
Concomitant Medications	x		x		x		x		x	x	x	x
Other Psychological care	x		x		x		x		x	x	x	x
Height, weight	x		x		x		x					
Vital signs[b]	x		$x^{0, 15, 60, 120}$		$x^{0, 15, 60, 120}$		$x^{0, 15, 60, 120}$		x	x	x	x
POC – Urine Drug Screen[c]	x		x^{PRE}		x^{PRE}		x^{PRE}		x	x	x	x
Urinary Hcg (if applicable)	x		x^{PRE}		x^{PRE}		x^{PRE}		x	x	x	x
Eligibility	x											
Demographics	x											
SURGE	x											
WURS	x											
TLFB - MA	x		x		x		x		x	x	x	x
VAS-C for MA	x		x		x		x		x	x	x	x
AWQ	x								x	x	x	x
WHOQOL-BREF	x								x	x	x	x
TSQM-II									x	x		
CSQ-8									x	x		
Medical Review			x		x		x			x		
Adverse Events		x	x	x	x	x	x	x	x	x	x	x
C-SSRS-SLV			x		x		x		x	x	x	x
TLFB – ketamine	x		x		x		x		x	x	x	x
TLFB – other substances	x								x	x	x	x
VAS-C for Ketamine	x		x		x		x		x	x	x	x
KSET – acute treatment			$x^{60, 120}$		$x^{60, 120}$		$x^{60, 120}$					
YMRS			$X^{PRE,POST}$		x^{POST}		x^{POST}					
CADSS-6			X^{POST}		x^{POST}		x^{POST}					
DEQ-5			x^{POST}		x^{POST}		x^{POST}					
HMS			x^{POST}		x^{POST}		x^{POST}					
PHQ-9	x								x	x	x	x
GAD-7	x								x	x	x	x
DERS	x								x	x	x	x
ISI	x								x	x	x	x
SUSI	x								x	x	x	x
Emotional N-back task	x							x^{PRE}				
Emotional Stroop	x							x^{PRE}				
Qualitative Interview[d]										x		

*****Primary Endpoint **AWQ** Amphetamine Withdrawal Questionnaire **CADSS-6** Clinician Administered Dissociation States Scales **C-SSRS** Columbia-Suicide Severity Rating Scale **C-SSRS** Columbia-Suicide Severity Rating Scale **–** Since Last Visit **CSQ-8** Client Satisfaction Questionnaire **DERS** Difficulties in Emotion Regulation Scale **DEQ-5** Drug Effects Questionnaire **GAD-7** Generalised Anxiety Disorder Scale-7 **HMS** Hood Mysticism Scale **ISI** Insomnia Severity Index **KSET** Ketamine Side Effect Tool **MA** Methamphetamine **MINI** Mini-International Neuropsychiatric Interview **PHQ-9** Patient Health Questionnaire **POC** Point of Care **SURGE** Substance Use Goals and Expectations **SUSI** Substance Use & Sex Index **TLFB** Timeline Follow-Back **TSQM-II** Treatment Satisfaction Questionnaire for Medication

VAS-C Visual Analogue Scale – Craving **WURS** Wender-Utah Rating Scale **WHOQOL-BREF** World Health Organisation Quality of Life Brief Version **YMRS** Young Mania Rating Scale

(a) MINI modules A (major depressive disorder), C (bipolar disorder), I and J (alcohol and substance use disorders), K (current psychotic disorder), 0 (rule out medical, organic or drug causes), (b) Blood pressure, heart rate, oxygen saturations, respiratory rate (c) POC also considered a measure of efficacy (d) Qualitative interviews (optional) will be conducted during Week 5 to Week 8.