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Ketamine-Assisted Recovery (KARE): protocol for an open-label pilot trial of ketamine-assisted psychotherapy for publicly insured patients with methamphetamine use disorder and HIV risks

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ABSTRACT

Introduction Methamphetamine use disorder (MeUD) is a debilitating condition with no FDA-approved pharmacotherapies that has been associated with poor neurological, psychiatric and cardiovascular outcomes, particularly among low-income populations. The use of methamphetamine also increases risks for sexually transmitted infections (STIs) by reducing behavioural inhibitions while enhancing sexual libido, disproportionately affecting sexual and gender minorities. The overlap of MeUD with HIV risks and psychological trauma underscores the need for innovative, accessible and culturally responsive therapies. Ketamine-assisted psychotherapy (KAP), which has shown promise for treatment-resistant depression and other substance use disorders, has yet to be explored for MeUD. The Ketamine-Assisted Recovery (KARE) trial seeks to address this gap.

Methods and analysis KARE is an open-label pilot study enrolling N=12–24 Medicaid-insured or Medicare-insured adults with moderate-to-severe MeUD and HIV risk factors. Participants will undergo three office-based intramuscular ketamine (0.50–0.75 mg/kg) sessions in combination with seven sessions of motivational enhancement therapy over 5 weeks. Recruitment efforts target community-based organisations, outpatient clinics offering HIV and STI testing/treatment, and substance use disorder treatment programmes. Feasibility, acceptability and tolerability will be assessed via recruitment and a priori retention benchmarks, surveys and semistructured interviews exploring participants' perceptions of KAP and ketamine's misuse potential. Safety will be evaluated through systematic monitoring for adverse events and serial measurement of vital signs during dosing. Secondary outcomes will measure changes in methamphetamine use, craving, withdrawal, HIV risk behaviours and psychological distress, as well as psychological and cognitive flexibility as potential mechanisms of ketamine's effects, laying the groundwork for future randomised controlled trials.

Ethics and dissemination Ethics approval has been obtained from the University of California, San Francisco Institutional Review Board (24-41588) and the Research Advisory Panel of California (202422S). Results will be disseminated through national conferences, peer-reviewed publications and presentations to community-based stakeholders.

Trial registration number NCT06538285.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The trial will recruit publicly insured patients, focusing on low-income and minoritised populations that have been historically underrepresented in psychedelic research.
⇒ The study intervention uses an inexpensive and easily administered form of ketamine and employs community-based therapists experienced in working with the target population, establishing a culturally responsive and accessible framework for investigating psychedelic therapies in diverse populations.
⇒ The use of mixed quantitative and qualitative analyses will provide nuanced insights into the feasibility, acceptability and safety of therapeutic ketamine for patients with methamphetamine use disorder.
⇒ The study is conducted at a research facility located within a local public health department, representing a novel approach to psychedelic science, aligning clinical research with public health priorities.
⇒ While an open-label design and small sample size preclude statistical efficacy analysis or precise effect estimation, findings will yield critical feasibility data and implementation insights to inform the design of future randomised controlled trials.

INTRODUCTION

Methamphetamine use disorder (MeUD) is an increasingly prevalent and disabling condition for which new and accessible treatments are desperately needed.[1–7] Involved in over 30%

of US overdose deaths in 2021,[1] methamphetamine has been strongly linked to poor mental and physical health outcomes, including cardiovascular disease, mood disorders and psychosis.[8 9] Its use also significantly increases HIV transmission risk, particularly among low-income populations and sexual and gender minorities, in whom the prevalence of methamphetamine use is greater than the general population.[10–18] As a psychostimulant, methamphetamine increases sexual libido while reducing behavioural inhibitions,[13 14] leading to increased risk behaviours for acquiring and transmitting sexually transmitted infections[15–17] and decreased adherence to HIV treatment and pre-exposure prophylaxis (PrEP) medications.[18–22]

Currently available MeUD treatments are limited in efficacy and accessibility.[4–7] Contingency management—a behavioural approach involving immediate, tangible rewards to reinforce positive behaviours—is the most effective therapy[6] but faces real-world implementation challenges and generally lacks sustained efficacy following the termination of incentives.[23] Evidence-based pharmacotherapies, including mirtazapine and the combination of bupropion with extended-release naltrexone, are off-label and have demonstrated only modest benefits,[24–26] leaving psychosocial interventions as the most utilised treatment options, despite limited evidence and high rates of drop-out.[7]

Ketamine, a dissociative anaesthetic approved by the U.S. Food and Drug Administration (FDA) in 1970, has emerged as a promising therapeutic agent when used in low-dose regimens for treatment-resistant depression, suicidal ideation and some substance use disorders.[27–32] These effects have been attributed to psychedelic-like properties that ketamine exhibits when administered at subanaesthetic dosages, which can result in varied non-ordinary states of consciousness.[33 34] Although the drug's direct effects are generally short-lived, when paired with psychotherapy, the shifts in consciousness induced by ketamine may provide an opportunity for powerful meaning-making, insight and transformation, facilitating lasting behavioural change.[35–37]

Early-phase trials have demonstrated the safety and preliminary efficacy of ketamine-assisted psychotherapy (KAP) in treating cocaine, alcohol and opioid use disorders[38–46]—conditions that, like MeUD, are often intertwined with psychological trauma.[47 48] In particular, given clinical and mechanistic overlap among stimulant use disorders, findings from a randomised controlled trial of KAP for cocaine use disorder suggest promise for the drug's utility in MeUD.[40] In that study, 55 patients with cocaine use disorder were randomised to receive a single dose of intravenous ketamine versus midazolam in combination with 5 weeks of mindfulness-based relapse prevention therapy; receipt of ketamine was associated with significantly increased end-of-treatment abstinence from cocaine (48% vs 11%)—an effect durable at 6 months follow-up (44% vs 0%).[40]

These apparently antiaddictive effects of ketamine are thought to be mediated by prefrontal cortex glutamate modulation, which may stimulate neuroplasticity, supporting one's ability to learn and sustain new, healthier behaviours.[31–34 49–51] The stimulation of neuroplasticity following ketamine has been evidenced by increased levels of brain-derived neurotrophic factor,[50 51] a key protein important for learning and memory,[52] the levels of which are significantly diminished during protracted methamphetamine withdrawal.[53–55] Ketamine administration has also been associated with a brief, subacute reopening of the 'social reward learning critical period'—a period of selective gene transcription during which the nervous system exhibits heightened sensitivity to ethologically relevant stimuli and increased malleability for synaptic, circuit and behavioural modifications.[56] Ketamine-induced neuroplasticity may thus augment the effectiveness of psychotherapy provided in the days following drug administration[34–36]—ultimately allowing for changes in self-representation and promoting long-term behaviour changes that may lead to decreased methamphetamine use.

This protocol explores the feasibility, acceptability and safety of KAP as a novel intervention for low-income patients with MeUD, addressing the urgent need for effective therapies for this vulnerable and understudied population.[57]

METHODS AND ANALYSIS

Overall study design

Ketamine-Assisted Recovery (KARE) is an open-label pilot feasibility trial (N=12–24) evaluating the office-based administration of intramuscular (IM) ketamine (0.50–0.75 mg/kg) in combination with manualised psychotherapy for publicly insured individuals with moderate-to-severe MeUD and risks for acquiring or transmitting HIV (figure 1). While the intravenous route has been studied more extensively,[58] the use of IM ketamine has been demonstrated to be safe and well-tolerated,[59 60] while also offering greater accessibility due to its lack of need for extensive nursing support.[61 62]

A 10-visit KAP intervention takes place over 5 weeks (35±7 days), with two follow-up assessment visits 4 and 12 weeks post-KAP. The primary efficacy endpoint is the change in methamphetamine use over the 30 days pre-KAP and post-KAP, measured by a modified Timeline Follow-Back (TLFB) procedure,[63] corroborated by urine drug screens and a novel hair biomarker for methamphetamine concentrations. Recruitment was initiated in February 2025, and study activities are projected to proceed until June 2026.

Patient and public involvement

A Community Consulting Group—comprising people with lived experience with MeUD, representatives from partnering local non-profit organisations and community-based organisations that serve individuals with MeUD and HIV in the San Francisco Bay Area, and participants of prior clinical trials focused on MeUD treatment—was

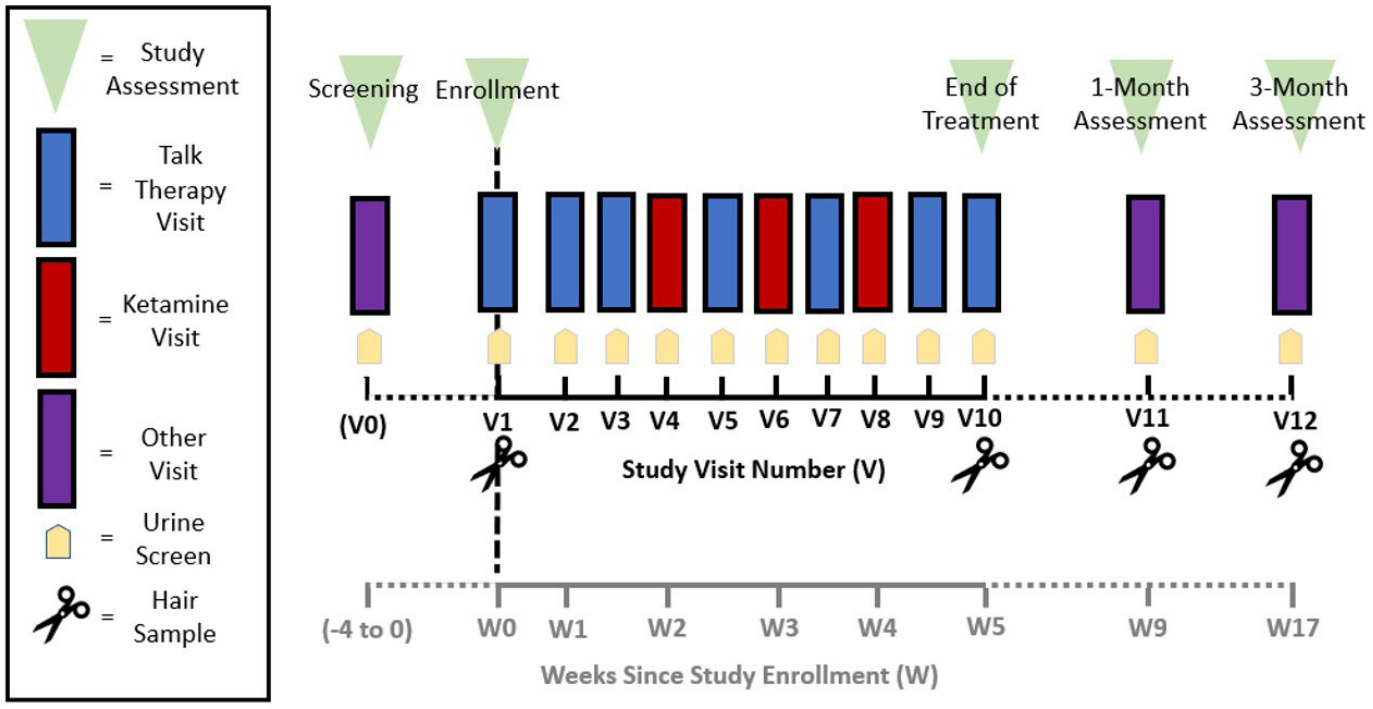

Figure 1 Study schema for KARE pilot trial. KARE, Ketamine-Assisted Recovery.

convened to inform the study's development in May 2024, prior to finalising the study protocol and obtaining necessary regulatory approvals. The research questions, trial design, outcome measures and recruitment plans were refined through discussions with this group, ensuring that they were aligned with community priorities and the real-world challenges faced by those at risk. This collaborative approach has helped ensure that the study is patient-centred, ethically sound and directly responsive to the public's needs.

Recruitment

Recruitment targets publicly insured patients with MeUD and HIV risk factors in the San Francisco Bay Area, including primary care clinics, non-profit organisations, syringe access sites, sexual health clinics and residential substance use treatment programmes. Both active and passive recruitment strategies are used, with materials directing interested individuals to the KARE trial website or to contact study staff for further information.

Screening

Referred patients first complete a phone screen (15–30 min), during which study staff obtain verbal consent to assess eligibility based on a subset of inclusion criteria (#3–8, table 1). Eligible individuals are subsequently scheduled for an in-person screening visit within 28 days during which written informed consent and Health Insurance Portability and Accountability Act (HIPAA) authorisations are obtained prior to collecting detailed demographic, contact, medical and psychiatric information. Assessments during in-person screening include the Structured Clinical Interview for DSM-5[64], Columbia Suicidality Severity Rating Scale (C-SSRS[65]), Adverse Childhood Experiences questionnaire (ACEs[66]) and a comprehensive substance use history. Methamphetamine and other substance use over the prior 30 days are documented using an adapted TLFB,[63] along with information on any prior use of pharmacologic or behavioural MeUD treatments and, when applicable, adherence to HIV treatment or PrEP medications.

Participant-reported assessments are followed by a physical and mental status examination and the collection of clinical data, including blood samples (for chemistry, haematology and inflammatory biomarkers), a urine sample (for drug screening and pregnancy testing for individuals of biologically female sex at birth), and a 12-lead ECG. If participants meet all eligibility criteria (table 1), they are scheduled for all 10 KAP intervention visits, with the first therapy session (V_1) occurring within 28 days of screening (V_0).

Intervention

The KARE trial intervention consists of three once-weekly, office-based administrations of IM ketamine (on V_4, V_6 and V_8) and seven sessions of manualised motivational enhancement therapy (MET) held within a framework of attachment-informed psychotherapy.[67 68] These include three predrug 'preparatory' talk therapy sessions (V_1–V_3) and four postdrug 'integration' sessions (V_5, V_7, V_9 and V_{10}) (figure 1). The intervention aims to address the critical roles of 'set' (psychological mindset) and 'setting' (environment),[69] fostering a robust therapeutic alliance between participants and community-based therapists, who not only meet licensure requirements outlined in the FDA's Draft Guidance for investigations involving psychedelic drugs[70] but also have prior training in and

Table 1 KARE trial inclusion and exclusion criteria

Inclusion criteria	
1	Age 18–69 years of age at time of in-person screening
2	Meets Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria for moderate or severe methamphetamine use disorder
3	Interested in reducing or stopping methamphetamine use
4	Insured by MediCal, MediCare or Healthy San Francisco
5	Self-reports use of methamphetamine on ≥7 out of 30 days prior to informed consent *OR* ≥7 out of 30 days prior to enrolment in residential drug treatment
6	Has a diagnosis of HIV OR used PrEP within the past 90 days OR reports ≥1 risk behaviour for HIV (including anal or vaginal sex under the influence of methamphetamine; condomless sex with a partner of serodiscordant or unknown HIV status; or use of shared injection supplies) within the past 90 days
7	Speaks and understands English
8	Permanently housed ≥30 days OR enrolled in residential drug treatment ≥5 days at time of informed consent
9	Able and willing to provide informed consent and adhere to the visit schedule
10	If necessary, willing to be contacted by a study therapist daily for 7 days after each ketamine session
11	Feels comfortable, capable and willing to adhere to the following Lifestyle Considerations throughout the study: (a) abstain from methamphetamine and cocaine ≥48 hours before scheduled ketamine dosing; (b) abstain from non-prescribed opioids, cannabis, benzodiazepines, alcohol or other drugs ≥24 hours before scheduled ketamine dosing; (c) consume no more than 1 cup of caffeine (eg, coffee or tea) the morning of planned ketamine visits; (d) if routinely prescribed/dispensed opioids (eg, buprenorphine or methadone), will continue current regimen for duration of the trial; (e) continue receiving any current, routine behavioural or pharmacologic mental health interventions outside of the trial and avoid engaging in any new interventions
12	Agrees to use highly effective contraception for at least 1 month prior to and for 2 months following ketamine visits *OR* reports that they (and/or their partner(s)) are not of childbearing potential
Exclusion criteria	
1	Significant prior use of ketamine for non-anaesthetic purposes, as determined by the investigators
2	Significant cognitive impairment (ie, score <24 on Folstein Mini–Mental Status Exam)
3	Any lifetime history of intracranial haemorrhage
4	Currently known to have an intracranial mass
5	History of ischaemic or embolic stroke in the last 12 months.
6	History of seizure in the last 6 months
7	Current psychosis or any lifetime history of schizophrenia or schizoaffective disorder or any personality disorder that, in the opinion of the PI, would interfere with study participation
8	Currently engaged in OR planning to engage in contingency management during the planned study period
9	Current medications include benzodiazepines, intramuscular naltrexone, clozapine, lamotrigine, azelastine, orphenadrine, thalidomide, psychostimulant medications, CYP2B6 inhibitors or CYP2B6 inducers
10	Has active suicidal ideation with intent (ie, C-SSRS Suicidal Ideation score≥4 and Reason for Ideation >1)
11	Has baseline hypertension (≥150 systolic or ≥90 diastolic blood pressure) after repeated measurements
12	Any lifetime history of aneurysmal vascular disease, dissection or arteriovenous malformation
13	Any history of cardiac arrest or myocardial infarction within the last 12 months
14	Has a corrected QT interval>480 msec on 12-lead electrocardiogram (using Bazzett's formula)
15	Any known history of clinically significant arrhythmia, including ventricular fibrillation; ventricular tachycardia; bradycardia<40 BPM; or atrial fibrillation without rate or rhythm control in the past 12 months
16	Has Alanine or Aspartate Aminotransferase (ALT or AST) ≥3× Upper Limit of Normal (ULN); total bilirubin ≥1.5×ULN; estimated glomerular filtration rate (GFR) <30 mL/min or currently on dialysis
17	Currently pregnant, breastfeeding or unwilling to use birth control throughout the study
18	Currently pending legal proceedings with potential for incarceration during planned study period
19	Treated with another investigational drug or intervention in the last 30 days
20	Has any physical or mental health condition which, per the clinical judgement of the investigators, interferes with safe study participation or adherence to study procedures

C-SSRS, Columbia Suicidality Severity Rating Scale; KARE, Ketamine-Assisted Recovery; PrEP, pre-exposure prophylaxis.

experience providing KAP and working with the target population. Participants' preferences for the gender, sexual orientation, race and/or ethnicity of their study therapists are accounted for whenever possible.[57 71–73] All ketamine and psychotherapy sessions take place in a private, comfortable physical environment designed to resemble a living room to promote relaxation and familiarity. The 5-week structure and number of sessions were

selected to balance treatment intensity with feasibility in the context of serving structurally vulnerable populations. This schedule also reflects a pragmatic adaptation of protocols implemented at Alchemy Community Therapy Center—a nonprofit sliding-scale psychedelic therapy clinic in the San Francisco Bay Area and community partner in this trial—where several study therapists received training. Notably, the protocol includes more preparatory therapy sessions than most prior KAP trials, given the high levels of trauma, psychiatric comorbidity and instability in this patient population. This design was intended to ensure sufficient time to build therapeutic rapport and support psychological safety prior to dosing.

The 5-week intervention follows a structured KARE Therapy Manual, adapted from publicly available sources for use with publicly insured MeUD patients, combining MET and attachment-informed psychotherapy techniques.[74–76] The adapted manual is available from the authors by request, with a brief description of each visit's activities described below. Each session is audio-recorded for fidelity assessments.

Preparatory sessions: The three preparatory sessions, each lasting 60–90 min, focus on building rapport, discussing overall treatment goals (eg, reduced methamphetamine use, abstinence, etc), and providing psychoeducation to prepare participants for ketamine dosing.

- Session V_1: The study therapist introduces the intervention, reviews the participant's history of methamphetamine use and any ACEs, discusses expectations and applies MET Phase I techniques such as eliciting self-motivational statements, reflectively listening and reframing perceptions of methamphetamine use.[74]
- Session V_2: The therapist transitions towards supporting the participant in developing commitment towards change as well as providing psychoeducation regarding ketamine, safety protocols and stress-management tools.[75] A preketamine-dosing guideline handout is reviewed, which includes reminding the participant of abstinence agreements prior to dosing sessions (ie, 48 hours for stimulant drugs and 24 hours for other non-prescribed substances).
- Session V3: The third session focuses on strengthening the participant's commitment to changing their methamphetamine use through the application of MET Phase II techniques[74] (eg, communicating free choice and evaluating the pros and cons of change). The session ends with a discussion of the participant's intention for their first ketamine session—a process that has been demonstrated to increase the likelihood of mystical-type experiences and decrease challenging experiences in studies of classic psychedelics.[77]

Ketamine sessions: Ketamine dosing sessions (V_4, V_6, and V_8) are 2–3 hours in duration.

- Safety protocols include predosing vital sign evaluation, optional anti-nausea medication and serial measurement of blood pressure and oxygen saturation at 15–30 min intervals postdosing. Rescue medications are available for severe anxiety or agitation.
- To simulate real-world clinical practice settings in which ketamine therapy is offered, the supervising study clinician (medical doctor, doctor of osteopathic medicine, or nurse practitioner) exits the treatment room following IM dose administration but conducts real-time, on-site video-monitoring of the full dosing sessions, facilitated primarily by the participant's study therapist.
- The ketamine dose range (0.50–0.75 mg/kg IM) is based on prior research suggesting that this dosage produces a moderate psychoactive effect associated with therapeutic benefit for both depression and cocaine use disorder, while remaining well-tolerated.[29 38–40] Because participants' sensitivity to ketamine is not known beforehand, the first dosing session (V_4) commences with a lower dose of ketamine 0.5 mg/kg IM, after which participants may increase to ketamine 0.75 mg/kg IM if prior dose(s) were well-tolerated on the basis of both subjective assessment of tolerability by the participant and study clinician as well as objective thresholds for changes in vital sign measurements over 120 min postdosing.
- During dosing sessions, participants have the option to lie down or sit on a couch and listen to a curated music playlist via headphones or speakers. They may choose to reflect internally, communicate verbally with their study therapist, or alternate between the two. Study therapists are trained to cultivate a non-judgemental stance and intentional therapeutic presence using an attachment-informed psychotherapy approach. Unlike the more active MET interventions used in preparation and integration sessions, therapists take on a more receptive role in which they veer away from guiding or directing the participant's ketamine experience. Instead, they embody the qualities necessary for building a secure attachment relationship.
- Ketamine's dissociative and psychedelic properties facilitate emotional exploration, introspection and reduced psychological defenses, which may offer participants an opportunity to increase their window of tolerance while exploring memories or revisiting past traumatic experiences.[78] In the event of psychologically challenging experiences, such as anxiety or confusion, the study therapist provides verbal reassurance and, when consented to prior to the session, supportive touch.[79]
- As the drug effects wear off about 45–60 min postdosing, therapists guide participants through a brief therapeutic interview to reflect on their experience. Reflection questions are provided to support further introspection on any thoughts, feelings or bodily sensations that arise under the acute effects of ketamine.
- Participants must remain onsite for at least 120 min after dosing and undergo a brief safety check by the study clinician before departing via study-provided transportation or in the company of a designated support person (ie, a caregiver or friend who has been instructed on how best to support the participant that

evening). Participants must agree not to drive themselves home nor to drive later that same day.

Integration sessions: Integration therapy occurs 1–3 days after each ketamine session and 1 week after the final dosing visit. These sessions support participants in processing their ketamine experiences by (1) asking open-ended questions intended to elicit introspective, interpersonal, spiritual or noetic insights and (2) linking such insights to motivation and commitment to changing methamphetamine use.

Session V_5

The study therapist facilitates a narrative exploration of the first ketamine experience and prepares the participant for their next ketamine session.

Session V_7

In addition to exploring potential insights from the participant's second ketamine session, the therapist introduces a 'Change Plan Worksheet' (CPW) to document treatment goals and evolving care plans, with the continued use of MET Phase II techniques.[74] In advanced preparation for their eventual termination from study-embedded therapy sessions, the study therapist also provides participants with a list of referrals to suitable community-based aftercare programmes offering free, low-cost or sliding-scale individual therapy, group-based therapy or ketamine-assisted therapy.

Session V_9

The therapist supports the participant by eliciting a narrative of their third ketamine session using reflection material, continues to apply phase II principles of MET, and revisits the CPW initiated during V_7.

Session V_{10}

During this final session, the study therapist reviews the participant's overall experience with the KAP intervention, reinforces key motivators for change and supports their transition out of the study, including reviewing and discussing the prepared list of referrals to aftercare programmes provided to them during visit 7.

Follow-up

Assessment visits are conducted by research staff at 4 and 12 weeks post-KAP to collect patient-reported outcomes and hair samples evaluating changes in methamphetamine use as well as any changes in substance use treatment engagement, HIV risk factors and mental health outcomes (online supplemental file 1). During these visits, participants will be explicitly asked about any subsequent use of ketamine, whether in clinical or non-clinical settings.

Sample size

The KARE trial aims to enrol 12 participants, a common benchmark for feasibility studies.[80–82] Prior single-arm pilot trials of psilocybin therapies for substance use disorders have included 10–15 participants[83 84]–which has been sufficient to assess the feasibility, acceptability, and preliminary safety of these similarly complex drug-assisted therapy interventions to support considerations for expansion through later phase trials. If additional funding is secured, the KARE pilot trial is approved to enrol up to 24 participants, which may provide a more robust impression of potential challenges associated with recruiting and retaining low-income, minoritised individuals.

Outcomes

Mixed methods will be used to assess the feasibility, acceptability, safety, tolerability and therapeutic potential of KAP for this population (online supplemental file 1).

Feasibility and acceptability endpoints

Feasibility will be evaluated by measuring rates of recruitment, retention during the KAP intervention and attrition over post-KAP assessment visits. A theory-informed questionnaire focused on KAP acceptability is elicited on the final intervention visit (V_{10})[85] and a 45–60 min semistructured interview is conducted post-KAP (V_{11}) to capture nuanced perspectives of the intervention among study participants.

Safety and tolerability endpoints

Safety is monitored through systematic evaluation for adverse events (AEs) via participant self-report at every study visit and direct observation during ketamine dosing sessions. Serial vital signs are recorded throughout dosing, and participants complete short forms of the Mystical and Challenging Experience Questionnaires[86] to evaluate the subjective intensity of ketamine experiences. The C-SSRS is administered weekly during the intervention and at all follow-up visits to assess suicidality.[65]

Therapeutic potential endpoints

To explore KAP's therapeutic potential, changes in methamphetamine use, HIV treatment or PrEP adherence, and sexual risk behaviours are measured using an adapted TLFB interview at each visit.[63] In addition to days of use, the TLFB procedure documents the approximate quantity of methamphetamine used by participants each day in grams and money spent. Urine and hair samples are also collected to track changes in methamphetamine content. Other participant-reported outcomes include measures of methamphetamine craving (Visual Analogue Craving Scale), withdrawal symptoms (Amphetamine Cessation Symptom Assessment)[87] and psychological distress (Patient Health Questionnaire-9 [PHQ-9],[88] Generalized Anxiety Disorder-7 [GAD-7],[89] Perceived Stress Scale[90]) at multiple timepoints (online supplemental file 1). Exploratory measures of psychological and cognitive flexibility will also be assessed preketamine and postketamine as potential mechanisms underlying drug effects (Personal Psychological Flexibility Index[91] and Wisconsin Card Sorting Test[92]).

Data analysis plan

Quantitative analyses of feasibility and acceptability

A priori criteria for feasibility include recruitment of at least 20% of screened participants, 70% completion rate for KAP intervention visits (V_1-V_{10}) and 50% for follow-up visits (V_{11}-V_{12}). These feasibility benchmarks are informed estimates drawn from prior studies involving structurally vulnerable populations, including individuals with stimulant use disorders.[24] Descriptive statistics will summarise participant responses to a postintervention questionnaire assessing KAP acceptability.

Qualitative analyses of feasibility, acceptability and safety

Semistructured interviews will be transcribed, coded inductively and analysed thematically by the research team using a comparative and iterative process. If more than 30% of participants express any specific concern regarding feasibility (eg, difficulties adhering to the visit schedule), acceptability (eg, serious dislike of KAP procedures or the duration of treatment) or safety (eg, cravings for or increased proclivity toward non-clinical use of ketamine), the protocol will be modified to address any such issues when considering the design of larger trials of KAP's efficacy in MeUD.

Quantitative analyses of safety and tolerability

Predetermined criteria for the safety and tolerability of KAP include zero treatment-related serious adverse events (SAEs). Descriptive statistics will summarise raw scores from questionnaires measuring the intensity of the acute experiences evoked by ketamine.[89] Vital sign thresholds indicating potential concern for participant safety during ketamine administration include an increase in heart rate of more than 25 beats per minute, systolic blood pressure of more than 40 mm Hg, and diastolic blood pressure of more than 25 mm Hg. These thresholds are based on established human safety data and a meta-analysis of haemodynamic responses to ketamine in patients with psychiatric conditions.[93]

Quantitative analyses of therapeutic potential

Summary statistics will describe changes in measures of ketamine's therapeutic potential over time, including methamphetamine use (via TLFB and hair samples),[63] drug craving and withdrawal symptoms,[87] risk behaviours for HIV transmission or acquisition, psychological distress,[88–90] and psychological and cognitive flexibility.[91 92] Results will be presented graphically via mean trends overlaid on individual trends.

Significance

The lack of effective and accessible treatments for MeUD remains a critical barrier to addressing rising rates of drug-related morbidity and mortality across the USA, as well as HIV incidence and disease progression among vulnerable populations.[10 94 95] By evaluating the feasibility, acceptability and preliminary safety of a novel, low-cost KAP intervention for publicly insured patients with or at risk of HIV, the KARE trial explores a promising and innovative approach to reducing MeUD-related harms. This pilot study represents an essential first step in developing future investigations into the efficacy of KAP for MeUD treatment and HIV prevention outcomes.

Equally important, this trial underscores an urgent need to ensure that novel addiction therapies—including psychedelics—are studied in populations that have been disproportionately impacted by systemic inequities that often underlie substance use disorders.[57] By focusing explicitly on publicly insured patients who lack access to commercially available ketamine therapy, emphasising cultural inclusivity and tailoring its approach to the needs of socioeconomically vulnerable communities, the KARE trial establishes a framework for integrating psychedelic therapies into care models for populations that have been historically neglected by this field.[96–99] This work paves the way for future research on psilocybin-based and MDMA-based interventions as these therapies move towards broader regulatory and legal acceptance, contributing to more equitable and impactful solutions for addiction and HIV prevention.

Ethics and Dissemination

Ethics approval for this study has been granted by the University of California Investigational Review Board (24-41588) and the Research Advisory Panel of California (202422S). The trial is being conducted under an Investigational New Drug application from the US Food and Drug Administration (172270). Findings will be shared through presentations at national conferences, publication in peer-reviewed journals, and engagement with community-based stakeholders in the San Francisco Bay Area. Additionally, targeted efforts will be made to disseminate results through policy briefs and collaborations with advocacy organisations to ensure the data reaches diverse audiences, including researchers, practitioners, policymakers and the affected communities.

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Correction notice This article has been updated since it was first published for a typographical error in the Methods and analysis section of Abstract.

Contributors NJM conceived of this study and wrote the initial draft of this protocol. BA and IA consulted on the design of the trial intervention and contributed to the development of the therapy manual. BA, JM, PH, PC and MOJ provided input and mentorship on the overall study design and edited the final protocol. NJM is the guarantor.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

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