A single-center open-label randomized parallel-group superiority trial to compare the efficacy of psychedelic and biomedical framing of intravenous ketamine for treatment-resistant depression - the KetSet trial

Etikprövningsmyndigheten
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Protocol Synopsis in Swedish

Ketaminbehandling mot terapiresistent depression – inramningens betydelse

Depression är en vanlig och funktionsnedsättande sjukdom som orsakar lidande för individen och närstående, livstidsprevalensen i Sverige är 23% för män och 36% för kvinnor. En tredjedel av dessa depressiva episoder svarar inte på två eller fler adekvata antidepressiva behandlingar och benämns då Terapiresistent Depression (TRD).

Ketamin är i Sverige ett godkänt läkemedel mot depression som nässpray. Nässprayen är dyr, medelkostnad 120.000 kr, därför och på grund av bättre effekt används ofta ketamin som intravenös behandling istället för nässpray mot depression. Ketamin som injektionsvätska är ett sedan flera decennier godkänt anestesiläkemedel och har en låg kostnad. Det är välkänt att ketamin kan ge egenartade upplevelser, och även förekommer i olaglig rekreationell användning i russyfte. Det finns gott om vetenskapligt underlag för att intravenöst ketamin har en snabbt insättande och antidepressiv effekt även mot TRD. Därför har behandlingen börjat användas mer och mer, både i Sverige och internationellt.
Hur intravenöst ketamin används varierar. Oftast ges behandlingen vid upprepade tillfällen under några veckor. Enligt ett biomedicinskt synsätt är effekten av ketamin huvudsakligen kemisk, och infusionsrelaterade upplevelser ses som biverkningar. Enligt ett psykedeliskt synsätt är effekten av ketamin knuten till intensiteten i de infusionsrelaterade upplevelserna som därför ska förstärkas för att maximera behandlingens effekt.
Huruvida inramningen påverkar effekten av behandlingen är inte studerat.

Denna studie lottar därför patienter som är ordinerade ketaminbehandling mot depression mellan de två inramningarna. Läkemedelsordinationen är redan gjord och kommer inte att påverkas av studiedeltagande eller ej. Behandlingen ges enligt klinisk rutin, för närvarande 6 st infusioner fördelat på fyra veckor. Studieprotokollet jämför de två inramningarna av behandlingen (psykedelisk, biomedicinsk). Vi planerar att inkludera 120 patienter, 60 i varje studiearm.

I den biomedicinska inramningen får patienterna information kring ketaminbehandlingen ur ett biomedicinskt perspektiv, dvs information om läkemedlets kända effekter och biverkningar genom en förinspelad video. Informationen återspeglar konsensus bland nordeuropeiska läkare förtrogna med ketaminbehandling, om hur ketamin utövar sin effekt. Den vanligaste biverkningen är dissociation under infusionen. Efter ketamininfusionerna blir patienterna intervjuade med det vanligt förekommande formuläret CADSS (Clinician Administered Dissociative State Scale) för att mäta graden av dissociation under infusionen.
I den psykedeliska inramningen presenteras ketaminbehandlingen i en video ur ett psykedeliskt perspektiv. Informationen återspeglar konsensus enligt experter som förordar detta synsätt. Dissociation beskrivs som en annorlunda upplevelse som kan ha terapeutiska effekter. Inför infusionen ges deltagarna en kort mindfulnessövning, erbjuds musik och ögonbindel under infusionen för att förstärka upplevelsen. Efter infusionen intervjuas de om samt samtalar om upplevelsen.

Det primära utfallsmåttet är medelskillnaden i depressionssymtom mellan grupperna före och åtta veckor efter avslutad ketaminbehandling mätt av oberoende skattare. Deltagarnas biverkningar och upplevelser av behandlingen kartläggs också i detalj. Utfallet på 1 års sikt följs

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upp i nationella register avseende arbetsförmåga, vård- och läkemedelskonsumtion och tecken på missbruk (lagföringar, diagnoser kopplade till missbruk). Studiens resultat förväntas ge kunskap om hur man bör ge ketamin på ett så kostnadseffektivt sätt som möjligt.

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Summary

Trial Title:
KetSet: A single-center open-label randomized parallel-group superiority trial comparing the efficacy of psychedelic and biomedical framing of intravenous ketamine for treatment-resistant depression.

Scientific Acronym: KetSet

Study Design:
Single-center, open-label, randomized, parallel-group superiority trial with blinded outcome assessment.

Study Setting:
Psychiatric secondary care clinic (Brain Stimulation Unit, Skaraborg Hospital, Skövde, Sweden).

Participants:
Adults (>18 years) diagnosed with treatment-resistant depression (TRD) who have been prescribed intravenous ketamine according to clinical routine.

Sample Size:
N = 120 (60 per group). Power 0.8, α = 0.05, effect size d = 0.4.

Interventions:

- **Psychedelic framing:** Participants receive pre-recorded information presenting the ketamine treatment as an opportunity for learning through the acute subjective effects of ketamine. Encouraged use of blindfold, music, mindfulness; post-infusion integration interview.
- **Biomedical framing:** Participants receive pre-recorded information presenting ketamine as a pharmacological antidepressant; dissociation described as side effect; post-infusion CADSS/BPRS assessment.
- Infusion protocol identical across groups (~0.5 mg/kg IV over 40 minutes, 6 sessions over 4 weeks according to clinical routine).

Primary Outcome:
Change in depressive symptoms from baseline to three months after first infusion, measured by blinded raters using MADRS.

Key Secondary Outcomes:

- Depression trajectory (MADRS, MADRS-S)
- Response/remission rates
- Tolerability, discontinuation, adverse events
- Quality of life, social and behavioral measures
- Acute experience measures (MEQ-4, CEQ-7, CADSS, 11D-ASC, PIS, etc.)
- Therapeutic alliance (WAI-SR/WAI-SRT)
- Expectancy

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- Cost-effectiveness and long-term outcomes (registry-based: work ability, healthcare use, substance-related diagnoses, convictions)

Randomization and Blinding:
Randomized 1:1 in eCRF according to a randomly generated sequence.
Participants and treating staff unblinded; outcome assessors blinded.

Data Analysis:
Independent t-test for primary endpoint. Mixed-effects linear models for longitudinal data. Sensitivity analyses include dose/kg covariate.

Duration:
Inclusion expected to take 3 years. Follow-up: 1 year via national registers.

Ethics and Monitoring:
Approved by Swedish Ethical Review Authority (pending). Monitoring by Gothia Forum. Data stored pseudonymized in REDCap under Västra Götalandsregionen's data protection standards.

Trial Registration:
(To be registered prior to start of enrollment)

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Administrative Information

Protocol Version

Version 1

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Introduction

1 Background and Study Rationale

1.1 Treatment-Resistant Depression (TRD)

Major depressive disorder is a leading cause of disability globally (Malhi & Mann 2018). Despite the availability of multiple treatment modalities, including antidepressant pharmacotherapy, psychotherapy and electroconvulsive therapy (ECT), a substantial proportion of patients do not achieve remission, and many who initially respond subsequently relapse. In Sweden, approximately 11.1% of patients with depression fail to respond to at least three adequate treatment trials and are thereby classified as treatment-resistant depression (TRD). Individuals with TRD are disproportionately represented within psychiatric services, present with higher rates of psychiatric comorbidity, utilize twice as many outpatient resources, three times as many inpatient care days and have a 23% increased risk of premature death compared to patients diagnosed with regular depression (Lundberg et al., 2023). These findings underscore the need for novel and effective therapeutic approaches for TRD.

1.2 Ketamine Treatment for Depression

Ketamine, a dissociative anesthetic, has demonstrated rapid-acting antidepressant effects in patients with TRD (Alnefeesi et al., 2022; Nikolin et al., 2023). In Sweden, ketamine treatment is considered an alternative to ECT when the condition is not considered to be sufficiently severe, or clear prognostic indicators for efficacy of ECT are absent (e.g. psychomotor retardation, psychotic features) (Ekstrand et al., 2022; Nordenskjöld & Movahed, 2023).

Current clinical practice typically involves intravenous infusions administered two to three times per week over a period of three to six weeks, although other treatment regimens have been explored. The antidepressant effects of ketamine are often transient, with symptom improvement frequently diminishing within weeks following single or short-course administrations (Li et al., 2022). Ketamine is classified as a controlled substance due to its abuse potential. To date, there is a lack of long-term follow-up studies assessing whether ketamine treatment for depression is associated with an elevated risk of substance misuse or dependence (Le et al., 2022).

1.3 Ketamine in the Context of Psychedelic Research

Ketamine is increasingly conceptualized within the broader category of psychedelic agents, as it can produce profound acute alterations in subjective experience and has been shown in preclinical studies to enhance neuroplasticity through mechanisms partially overlapping with classical psychedelics (Ko et al., 2022; Garel et al., 2023; Agnorelli et al., 2025).

The ketamine-induced experience is strongly context-dependent. The construct of “set and setting” - referring to an individual’s mindset and the surrounding environment – has been recognized as a critical determinant of psychedelic experiences (Greenway, 2023). Patient mindset prior to dosing, together with therapeutic context, can significantly shape the phenomenology of the ketamine experience, which may encompass perceptual, cognitive, and at times existential dimensions distinct from ordinary consciousness.

Accumulating evidence suggests a correlation between intensity of acute altered states of

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consciousness and therapeutic outcomes in psychedelic-assisted treatments, including ketamine for depression. However, it remains unclear whether these subjective experiences are necessary mediators of antidepressant effects (E-Wen mcCulloch et al., 2024). There is a need for larger cohorts in psychedelic studies to evaluate safety, efficacy and cost-effectiveness, and there is a lack of knowledge about the relationship between subjective effects and treatment outcomes (Ko et al., 2022, E-Wen McCulloch et al., 2024).

1.4 Purpose

The purpose of this study is to:

- Evaluate the impact of the therapeutic framing (i.e., treatment setting) on clinical outcomes of ketamine therapy in TRD.
- Systematically characterize the acute subjective experiences induced by ketamine and assess their relationship with treatment outcomes.
- Investigate long-term outcomes following ketamine treatment in TRD.

1.5 Objectives and endpoints

Primary objective and endpoint

The primary objective is to evaluate the efficacy of a **psychedelic framing** of ketamine treatment for treatment-resistant depression (TRD) as compared with a **biomedical framing**. The central null hypothesis is that there is no difference between psychedelic framing and biomedical framing in the reduction of depressive symptoms with ketamine infusion treatment for TRD.

The **primary endpoint** will be assessed as the mean difference between randomized groups in changes in depressive symptoms 12 weeks from baseline measured with the Montgomery-Asberg Depression Rating Scale (MADRS).

Secondary objectives

To evaluate:

I. Changes in depression measures across the entire treatment period
II. Tolerability, discontinuation, and adverse events
III. Quality of life, daily life routine, subjective sleep quality, social contact, screen time, loneliness and satisfaction with life
IV. Rate and intensity of acute subjective experiences induced by the ketamine infusion, and their relation to treatment outcome.
V. The association of therapeutic alliance with the treatment outcome
VI. Mystical experiences and other subjective factors associated with psychedelic-assisted treatments in ketamine treatment for depression
VII. Impact of expectancy on treatment outcome
VIII. Cost-effectiveness of both interventions
IX. 1-year outcome regarding drug-related convictions or diagnoses, work ability, need for social transfers, utilization of inpatient care, and psychotropic medication prescriptions
X. The ketamine-induced experience in a population with TRD in a psychedelic framing of ketamine treatment

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Secondary endpoints

I. The difference between the groups in the secondary endpoints will be evaluated to support the secondary objectives:
   a. Change in self-reported depression measures across the entire treatment period (baseline, week 2, 3, 4, 5, 8 and 12) as MADRS-S scores.
   b. Response rate (50% decrease) at all time points post-infusion 1 (MADRS and MADRS-S)
   c. Remission rate (defined as MADRS or MADRS-S <11) at all subsequent time points post-infusion 1
   d. Time to hospitalization due to depression or treatment for depression after infusion 6 within follow-up (12 months)
   e. Suicidal ideation item on the MADRS-S measured after the first week of treatment
   f. Suicidal ideation item on the MADRS-S across the entire treatment period

II. Tolerability, discontinuation, and adverse events
   a. Tolerability will be examined by comparing rates of any adverse events, mild, moderate and severe adverse events respectively
   b. Mean sum scores on the modified Ketamine Side Effect Tool (KSET)
   c. Time to treatment discontinuation across weeks 1-12 between groups

III. Quality of life and health, satisfaction with life, subjective sleep quality, perceived social support, screen time, loneliness and satisfaction with life in both groups.
   a. Quality of life will be examined with a Visual Analogue Scale (VAS 0-100) for quality of life and health at baseline, week –2, 1, 2, 3, 4, 5, 8, 12 and 30
   b. Subjective sleep quality, perceived social support, screen time, loneliness and satisfaction with life at baseline and week 12, measured with:
   -the Brief Pittsburgh Sleep Quality Index (B-PSQI)
   -the brief Social Provisions Scale (SPS-5)
   -Screen Time Questionnaire (ScrT)
   -the UCLA 3-Item Loneliness Scale
   -the Satisfaction With Life Scale (SWLS)

IV. Rate and intensity of patients' acute subjective experiences induced by the ketamine infusion will be measured differently between the treatment groups during and after the infusion since it is considered inherent to the intervention:
   a. In the psychedelic framing:
      i. Self-reports on the acute ketamine-induced experience will be asked for with a semistructured interview after every infusion. Reports will be transcribed and manually content analysed to obtain quantitative results on how subjective experiences are altered in the ketamine-induced experience in patients with TRD in a psychedelic setting.
      ii. Self-report questionnaires after every infusion (MEQ-4 and CEQ-7)
   b. In the biomedical framing:
      i. Clinician Administered Dissociative States Scale (CADSS) and Brief Psychiatric Rating Scale (BPRS)
      ii. Self-report questionnaires after every infusion (MEQ-4 and CEQ-7)

V. Therapeutic Alliance
   a. All patients experience of therapeutic alliance measured at inclusion, televisits, and at follow-up with the Working Alliance Inventory - Short Revised (WAI-SR)

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   b. Therapeutic alliance reported by clinician at inclusion, televisits, andat follow-up with Working Alliance Inventory - Short Revised Therapist (WAI-SRT)

VI. Mystical experiences and other subjective factors associated with psychedelic-assisted treatments measured after the treatment in both groups one week posttreatment
   a. Mystical Experience Questionnaire (MEQ-30)
   b. Psychological Insight Survey (PIS)
   c. The Challenging Experience Questionnaire (CEQ-7)
   d. Emotional Breakthrough Inventory (EBI-6)
   e. 11 dimensions of Altered State of Consciousness Scale (11D-ASC)

VII. Impact of expectancy on treatment outcome
   a. Treatment Expectation Questionnaire (T-Ex)

VIII. Economic effects of the extra resources needed for the experience-centered framing compared to the biomedical framing to assess the cost-effectiveness of a Montreal Model-inspired ketamine treatment for depression

IX. 1-year outcome regarding drug-related convictions or diagnoses, work ability, need for social transfers, utilization of inpatient care, and psychotropic medication prescriptions
   a. Occurrence of a drug-related conviction or substance use disorder during the follow-up period (binary variable)
   b. Sum of declared income subtracted by social transfers during the follow-up period (continuous variable)
   c. Number of days spent as an inpatient (continuous variable)
   d. Average daily defined dose of prescribed psychotropic medication for the follow-up period.

X. Quantitative data from content-analysis of reports from semistructured interviews with the patients in the psychedelic arm after the infusions

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Methods

2 Study Design

The KetSet trial is a single-center open-label parallel-group superiority trial comparing the efficacy of a psychedelic framing with a biomedical framing on the efficacy of ketamine infusions for TRD. The primary endpoint will be depressive symptoms measured with the Montgomery Åsberg depression rating scale (MADRS) at baseline and 12 weeks. The study is conducted in a secondary psychiatric hospital in Western Sweden (catchment area of 250 000). The psychiatry department hosts inpatient and outpatient services for approximately 10 000 patients.The majority of patients with depression are treated in primary care. Referral to psychiatry is warranted in cases of severe depression with suicidality, complex psychiatric comorbidity, or TRD. The prevalence of TRD in patients treated in the psychiatric services is therefore much higher than in primary care.

2.1 Patient involvement

A pilot study on ketamine-assisted treatment for depression was conducted within our team (Enholm et al., unpublished data), exploring experiential outcomes (including the Mystical Experience Questionnaire – MEQ-30, Psychological Insight Scale – PIS, and Clinician-Administered Dissociative States Scale – CADSS) as well as participants' subjective experiences of different components of the treatment model (n = 10). The evaluated components included music, mindfulness, eye mask, psychological support, and behavioral activation.

From this pilot, we learned that the therapeutic experience varies substantially across individuals, and no clear predictive factors for these differences could yet be identified. Participants reported that music was particularly meaningful; while standardized playlists provided a supportive structure, allowing patients to choose their own music can enhance their sense of agency and engagement in the therapeutic process.

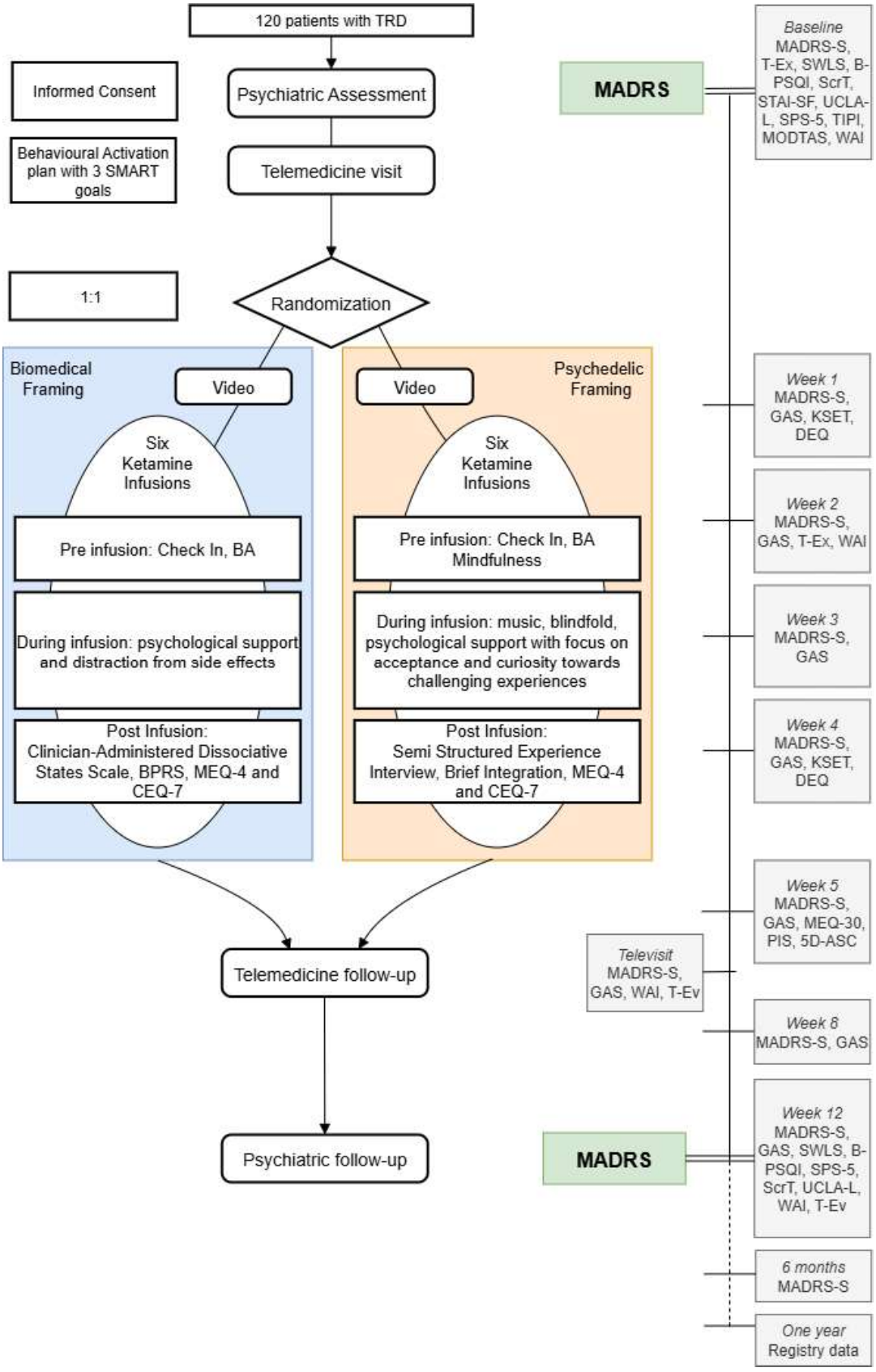
The pilot study also indicated that our model was associated with high tolerability and few adverse effects compared with outcomes reported in previous studies, although the small sample size precluded statistical inference.

Insights from this pilot study have directly informed the design of the current KetSet-trial. Specifically, we have refined the timing of questionnaires and interviews to minimize disruption of the therapeutic process, and we emphasize clear patient education about the rationale and intended effects of each treatment component. The integration of these lessons aims to enhance participant comfort, engagement, and the ecological validity of the experiential setting.

Many patients have said in the follow-up assessment that the experience is ineffable and that it is hard to prepare someone for what it will be like. They have encouraged us to do this study and to add the qualitative interview study of the actual ketamine induced experience.

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2.1 Flowchart



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3 Study Population

Patients with a diagnosis of TRD prescribed intravenous ketamine for depression who meet the inclusion criteria are eligible. A decision of referral for ketamine treatment generally requires a diagnosis of moderate to severe depression and non-response to at least two previous antidepressant treatments of adequate length and dosage. Full inclusion and exclusion criteria are provided below.

At the initial clinical visit following the prescription of ketamine treatment, patients will be informed about the study. They will receive both oral and written information about the study and will be given adequate time to review the material, reflect, and ask questions. Thereafter, informed consent will be obtained by a clinician affiliated with the research team or by a research assistant trained in the consent procedure.

3.1 Inclusion Criteria

1. Age >18 years
2. Being prescribed ketamine treatment for depression at the unit for brain stimulation at Skaraborg Hospital, Skövde.
3. Being able to read and understand the patient information handout.
4. Provision of written informed consent after reading the patient information handout.

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3.2 Exclusion Criteria

Patients are evaluated exclusion criteria according to clinical routine and cannot be screened for trial participation unless they are prescribed ketamine according to clinic guidelines. All patients prescribed ketamine treatment for depression are eligible for enrollment if they fulfill the inclusion criteria.

Clinical exclusion criteria are:

1. Primary psychotic disorder
2. Current substance use disorder (SUD)
3. Uncontrolled hypertension and/or other contraindications deemed to risk the safety and efficacy of the ketamine treatment.

3.3 Randomization Process and blinding

Eligible patients who enroll will be randomized to one of the two groups; the psychedelic framing group or the biomedical framing group. Participants will be randomized in the eCRF system, with a sequence provided at the discretion of the study statistician.

Study personnel will be aware of treatment allocation. Participants will not be blinded to their assigned intervention but will not receive detailed descriptions of the alternative intervention.

Baseline assessment of the primary outcome will be made prior to randomization in order to minimize bias. Outcome assessors conducting post-treatment evaluations of the primary

outcome will remain blinded to treatment allocation. Participants will be instructed not to disclose details regarding their treatment experience at the post-treatment evaluation.

3.4 Participant withdrawal or discontinuation from the study

Patients who decline participation or decide to discontinue the study after randomization will be registered as such. Age, sex, and reasons(s) for failing screening or discontinuing will be recorded in a rejection log.

3.5 Evaluable Patients

A patient is considered evaluable and the data eligible for analysis if the patient has been randomized to one of the treatment arms and had at least the first infusion. Patients terminating the study before this point but after randomization will not be included in the analysis population.

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4 Interventions

The studied interventions in this trial are the framing of the ketamine treatment for depression. Ketamine treatment will be given according to the clinical routine in identical fashion in both groups. The medical procedures regarding ketamine are described briefly under 4.1 and in detail, but in Swedish, in the clinical guideline in the appendix.

4.1 General interventions associated with the ketamine treatment

The general interventions are not part of the clinical trial and represent the clinical routine according to which ketamine is prescribed. General interventions are identical for all study participants and include:

1. Dosing, duration, and schedule for ketamine infusions according to clinical routine.
    1. 0,5 mg/kg racemic ketamine, flexible dosing to optimal weight BMI 18-30 and to response and tolerability
    2. Infused intravenously for 40 minutes
    3. Six infusions for 4 weeks. Optimally two per week the first two weeks and one per week the last two weeks. Due to holidays and unforeseen events scheduling of infusions may vary.
    4. Identical procedure for the setup of goals for behavioral activation (BA) according to SMART principles in liaison with the assigned healthcare professional.
    5. The presence of staff in the room for the entirety of the ketamine infusion and a nurse in close proximity to the treatment room.
    6. Safety monitoring during infusion, including vital signs before the infusion and every 15 minutes during the infusion and 60 minutes post-infusion. Medications (Ondansetron) will be available to manage side effects as needed according to clinical routine. The nurse will continuously monitor physiological and psychological safety and intervene if risks emerge. A physician will be on site and available throughout the duration of the treatment session in case any significant medical side effects or safety concerns arise. If patients experience severe distress or disorientation, infusion can be paused or terminated according to pre-specified clinical guidelines.

These general interventions are part of the ketamine treatment for depression as it is given according to clinical routine. Administered dose for every infusion, any medication given as needed and vital signs out of normal range will be documented in the study database.

4.2 Study interventions

The study interventions are psychological and environmental in nature. They do not influence the decision, procedure or follow-up of the ketamine treatment per se, which is made according to clinical routine.

Participants will be randomly assigned to one of two different therapeutic framings that constitute the two study interventions: biomedical framing or psychedelic framing.

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Biomedical framing

Pre-treatment: The framing is presented through a pre-recorded video. In the biomedical framing, ketamine is presented as an antidepressant psychoactive medication. Perceptual alterations are described as transient side-effects associated with the infusion.

During ketamine infusions: The assigned health care professional monitors and is always present with the participant to provide psychological support, responds as appropriate to any questions asked by the participant and interacts with the participant as needed.

After infusion completion: Clinician Administered Dissociative Statas Scale (CADSS), Brief Psychiatric Rating Scale (BPRS) and a modified Ketamine Side Effect Tool (K-SET) questionnaire is administered to the patient, covering side-effects associated with treatment. Open-ended questions regarding side-effects are asked. The patient fills in self-report questionnaires about their experience during the infusion.

Psychedelic framing

Pre-treatment: The framing is presented through a pre-recorded video. In the psychedelic framing, the acute ketamine-induced experience is presented as potentially transformative.

During ketamine infusions: The assigned health care professional monitors and is always present with the participant to provide psychological support. The professional adapts the level of support according to the patient's individual needs but always encourages the participant to an openness for immersing in mind-altering experiences during treatment.

After infusion completion: A semi structured interview about the treatment experience is conducted as soon as the treatment is completed. Open-ended questions regarding side-effects are asked. The patient fills in self-report questionnaires about their experience during the infusion.

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Table 1. Key components of and differences between the study interventions

Therapeutic framing	Biomedical framing	Psychedelic framing
Rationale	• Neurobiological effects that address neurochemical and structural deficits	• Transformative mind-altering experience that may catalyze insight, growth, and recovery
Framing	• "Dissociation" as an adverse effect of treatment • "Set and setting" of little importance • Neurobiological model	• Framed as "psychedelic"; critical for benefits • "Set and setting" of essential importance • Mind-altering model
Protocol components	• Assigned monitoring health care professional with ques and answers diverting from the treatment experience	• Assigned monitoring health care professional with ques and answers directing attention toward immersion in the experience. • Use of mindfulness, blindfolds and music is encouraged.
Treatment characteristics	• Acute psychoactive effects minimized/mitigated • Benefits primarily maintained through the resolution of neurochemical deficits	• Acute psychoactive effects enhanced with non-pharmacological adjuncts (e.g., blindfolds, music) • Benefits maintained through experiences facilitating personal growth

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5 Adherence

Adherence to the assigned interventions will be monitored by independent observers according to a pre-specified checklist for the central characteristics associated with the two interventions (see appendix). The rate and interval for monitoring will be decided in collaboration with an external party.

6 Procedures

A schedule of assessments is provided below.

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6.1 Schedule of assessments

Timepoint	assessment Visit	televisit prep	randomization	video	pre-infusion 1	**infusion 1**	post-infusion 1	pre-infusion 2	**infusion 2**	post-infusion 2	pre-infusion 3	**infusion 3**	post-infusion 3	pre-infusion 4	**infusion 4**	post-infusion 4	pre-infusion 5	**infusion 5**	post-infusion 5	pre-infusion 6	**infusion 6**	post-infusion 6	questionnaires	televisit follow-up	questionnaires	assessment follow-up	six month follow-up	One year registryfollo
Week	-2 (-6 - 0)	-1 (-6 - 0)	0 (0 - 1)	0 (0 - 1)	1			1			2			2			3			4			5	6	8	12 (10 - 14)	30(28-32)	56
Physical visit	X					X			X			X			X			X			X				X		
Televisit		X																						X				
Watch video				X																								
Questionnaires	X				X		X			X	X		X					X			X		X	X	X	X	X	
Eligibility Screen	X																											
Informed Consent	X																											
Physician	X					X																			X			
Nurse/health professional		X				X			X			X			X			X			X			X				
INTERVENTIONS																												
BA-planning/follow up		X			X			X			X			X			X			X				X		X		
Ketamine infusion						X			X			X			X			X			X								
Psychedelic																												
Mindfulness						X			X			X			X			X			X								
Music						X			X			X			X			X			X								
Blindfolds						X			X			X			X			X			X								
Rolling Integration							X			X			X			X			X			X							
Interview/report							X						X									X							
Biomedical																												
Interview: CADSS, BPRS							X			X			X			X			X			X							
GENERAL QUESTIONAIRES																												
MADRS-S	X				X						X						X					X	X	X	X	X	X	
EQ-VAS	X				X						X						X					X	X	X	X	X	X	
T-Ex Pat	X				X						X																	
SWLS	X																									X		
B-PSQI	X																									X		
ScrT	X																									X		
STAI-SF	X																									X		
MODTAS	X																									X		
TIPI	X																											
UCLA Loneliness	X																									X		
SPS-5	X																									X		
WAI-SF	X												X											X		X		
GAS					X						X						X			X			X	X	X	X		
MEQ-4							X			X			X			X			X			X						
CEQ-7							X			X			X			X			X			X						
KSET										X												X						
DEQ										X												X						
PIS																							X					
MEQ-30																							X					
5D-ASC																							X					
T-Ev Pat																								X				
CLINICIAN-ADMINISTERED																												
MADRS	X																									X		
T-Ex Clin	X						X						X															
WAI-SF Clin	X												X											X		X		
Patient-reported side effects								X			X			X			X			X				X		X		
T-Ev Clin																								X		X		

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To provide a comprehensive understanding of the treatment pathway and clarify how the study interventions are integrated, the full course of ketamine treatment is described in detail below, rather than restricting the description to study-specific procedures.

6.2 Recruitment

Patients prescribed ketamine treatment at the Brain Stimulation Clinic, Skaraborg Hospital (Skövde), will be screened for eligibility. Patients with treatment-resistant depression (TRD) are referred to the Clinic by psychiatrists at the Department of Psychiatry, Skaraborg Hospital, from both inpatient and outpatient services. Referrals are reviewed by a psychiatrist, resident physician, and nurse. Eligible patients are scheduled for an evaluation interview and a psychiatric assessment with a physician.

All patients who have completed the initial assessment at the Brain Stimulation Clinic and who are approved to initiate ketamine treatment for depression are eligible for study enrolment. Inclusion criteria for ketamine treatment set by the clinic is a diagnosis of moderate to severe depression and non-response to at least two previous antidepressant treatments of adequate length and dosage. Exclusion criteria are primary psychotic disorder, current substance use disorder (SUD), uncontrolled hypertension and/or other contraindications deemed to risk the safety and efficacy of the ketamine treatment. The criteria are permissive by design in order to be clinically representative of the TRD population.

6.3 Psychiatric Assessment

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At the Brain Stimulation Clinic, each patient undergoes a comprehensive psychiatric consultation with a physician. During this visit, a detailed medical history is obtained, with particular attention to depression, psychosis, and substance use disorders, in order to evaluate the appropriateness of ketamine treatment. The assessment also includes a brief exploration of the patient's daily life, routines, social context, and lifestyle, which provides a foundation for later behavioral activation planning. If ketamine treatment is prescribed, the patient is invited to participate in the study.

The physician or research nurse provides oral and written information about the trial, and the patient is given the opportunity to ask questions before deciding on participation. Informed consent is obtained prior to any study-specific procedures. Following consent, the Montgomery–Åsberg Depression Rating Scale (MADRS) is administered by the physician. Patients are then asked to complete baseline self-report questionnaires designed to assess clinical symptoms and individual traits that may be influenced by treatment.

Baseline demographic and clinical data are collected from the psychiatric assessment and the electronic medical record (Melior) and entered into the eCRF/REDCap. Variables recorded include year of birth, gender, employment status, relationship status, religion and highest level of education. Psychiatric history is documented, including current and past diagnoses, duration of the current depressive episode, number of previous depressive episodes, year of first onset, and history of suicide attempts. Ongoing and previous treatments are registered, including inpatient care, pharmacological and psychotherapeutic interventions, electroconvulsive therapy (ECT), and repetitive transcranial magnetic stimulation (rTMS). In addition, relevant medical diagnoses and information regarding past and present substance use are collected

6.4 Televisit to plan Behavioral Activation, 3 SMART goals

A healthcare professional contacts the patient to schedule infusion sessions and collaboratively define three behavioral activation goals using the SMART framework (Specific, Measurable, Achievable, Relevant, Time-bound) (Garel et al., 2023).

6.5 Six visits for ketamine infusion

Each patient will undergo six ketamine infusion sessions. In accordance with clinical routine, patients arrive having fasted for at least two hours prior to treatment to minimize the risk of nausea, but they are instructed to continue taking their regular medications as prescribed. Upon arrival, a nurse or other assigned healthcare professional (e.g., psychologist, assistant nurse, research assistant) welcomes the patient and performs a brief check-in. The patient is then seated in a hospital bed in a reclined or prone position with a pillow and blanket for comfort. Vital signs are monitored throughout the infusion: blood pressure, heart rate and oxygen saturation are recorded every 15 minutes. Before initiating the infusion, attending clinician or trained assistant nurse conduct a short discussion with the patient regarding their progress with behavioral activation goals and any challenges encountered since the last session.

In the psychedelic intervention arm, patients are invited to use a blindfold and are guided through a five-minute mindfulness exercise, delivered either by the trained clinician or assistant nurse, or via an audio recording. Patients are encouraged to listen to music through provided headphones, either from their selection or from a curated playlist specifically designed for psychedelic therapy (see Appendix X). They are further guided to remain open and curious toward their subjective experiences during the infusion.

In the biomedical arm, the use of music and blindfolds is not suggested. If patients bring their own and choose to use them, this is permitted and documented in the case report form (CRF). Attending clinician/assistant nurse in this arm provide cues to distract patients from the subjective effects rather than to engage with them.

Ketamine is administered intravenously at a dose of 0.5 mg/kg over a period of 40 minutes, using an infusion pump. Dose can be adjusted by the physician due to BMI or tolerability. Throughout the session, a clinician or trained assistant nurse remains present and provides support as needed. Following the infusion, assessments differ by treatment arm.

In the biomedical framing, the Clinician-Administered Dissociative States Scale (CADSS) and Brief Psychiatric Rating Scale (BPRS) is administered.

In the psychedelic framing, patients are interviewed about their experience using a semi-structured guide (Appendix X) and subsequently take part in a debriefing session. Clinician time is matched in both arms.

During the infusion and immediate post-infusion interview, one staff member remains with the patient. Patients stay for observation for one hour post infusion under the supervision of a nurse. During this period, patients are offered light refreshments such as fruit, sandwich, and tea or coffee. When patients have regained sufficient visual acuity, they are asked to complete a short questionnaire about the infusion experience (Appendix). If blood pressure and orientation are

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within normal limits, patients may be discharged one hour post infusion; if not, they remain under observation until parameters normalize, or a physician determines otherwise.

One week after the final infusion session, patients complete a set of follow-up questionnaires.

6.6 Televisit - follow-up

A nurse or healthcare professional contacts each patient by telephone two weeks after treatment completion to assess well-being and progress.

6.7 Psychiatric follow-up, treatment evaluation

Three months after the ketamine treatment starts, the patient is reassessed by a physician as part of the clinical routine and a summary report is provided to the referring psychiatrist. For the study the patient will fill in questionnaires digitally (see flow table) about symptoms, lifestyle, sleep quality, trait absorption, treatment evaluation and working alliance. The clinician will also rate treatment evaluation and working alliance. In close proximity to this follow-up, up an external rater not involved in the ketamine treatment will administer MADRS.

6.8 6-month follow-up, digital surveys (part of quality control registry)

In the clinical routine patients are followed up with MADRS-S and EQ-VAS for quality control of the treatment. In this study we will use this already standardized routine and add the GAS-questionnaire. These questionnaires are filled in electronically.

6.9 1-year follow-up, registry

Individual-level data covering at least one year of follow-up post treatment are obtained from the National Board of Health and Welfare (the Patient Register, the Prescribed Drug Register), the Swedish National Council for Crime Prevention (the Criminal Justice Register), and Statistics Sweden (the LISA Register) and compiled into a database.

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7 Measures and Outcomes

All questionnaires are provided in the appendix.

Montgomery-Asberg Depression Rating Scale (MADRS)

The MADRS is a 10-item depression rating scale developed in 1979 to be more sensitive to symptom changes induced by antidepressants than currently available instruments (Montgomery and Åsberg, 1979). The MADRS has been used for assessing primary outcomes in registration trials for new pharmacological agents for treating MDD including ketamine (Daly et al., 2018).
The MADRS includes questions on the following symptoms: 1) Reported sadness, 2) Apparent sadness, 3) Inner tension, 4) Reduced sleep, 5) Reduced appetite, 6) Concentration difficulties, 7) Lassitude, 8) Inability to feel, 9) Pessimistic thoughts, and 10) Suicidal thoughts. Items are scored via a clinical interview that progresses from more broadly phrased questions about symptoms to more detailed queries that allow a precise rating of severity. Items are rated to capture the patient's clinical state over the prior week. Each item yields a score of 0 to 6, and higher scores indicate more severe depression. The overall score ranges from 0 to 60. Various studies have suggested cut scores from < 9 to <12 as a definition of remission. For the current study, remission will be defined as a score ≤ 10. Response will be defined as ≥ 50% decrease compared to the last measurement before dosing.

MADRS-S is the self-rating version of MADRS. Apart from item 1 in MADRS, which is deleted from MADRS-S, the two scales are identical. To reduce the risk of functional unblinding during collection of the primary outcome , the last MADRS assessment will be conducted by a rater blinded to participant allocation.

MADRS ratings will be performed at the psychiatric assessment on the day of inclusion, normally two weeks before the start of the infusions and three months after the start of infusions. At the day of psychiatric assessment, results of MADRS (item 2-10) and MADRS-S before dosing will be used for validation purposes. The result on each MADRS item will be documented by the interviewer in the eCRF at time of interview.

MADRS rating post -treatment: The study person will be given a written instruction not to comment on if randomization has taken place, or to which condition he/she believes he/she was randomized, or on any potential experiences during the dosing session. He/she shall only respond to the MADRS questions from the interviewer. After the end of the interview, the interviewer will complete the Blinding questionnaire (see below).

MADRS self-rating (MADRS-S)
In order to get preliminary information on time to response and remission, duration of clinical effect, the self-rating version of MADRS (Svanborg et al., 2001) will be administered at inclusion (same time as MADRS), week 1 (before the first infusion), week 2, 3, 4, 5, 6, 8, 12 and at the six month follow up electronically to Redcap and the embedded eCRF. MADRS-S data will be monitored by study personnel daily on weekdays, and in case of missing data or signs of increased suicidality the participant will be contacted the same day for follow up and potentially referred to a suitable health care unit.

EQ-VAS

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The visual analogue scale (VAS) for quantification of overall health status from the self -reported EuroQoL 5-Dimension (EQ-5D) (Sobocki et al., 2007) is administered with MADRS-S. It is part of clinical routine and hence will be electronically registered via Redcap to the eCRF.

Brief Psychiatric Rating Scale (BPRS)

The BPRS is a clinician-administered scale developed by Overall and Gorham (1962) to assess a broad range of psychiatric symptoms, including psychotic symptoms (e.g., hallucinations, unusual thought content, emotional withdrawal) and affective symptoms such as anxiety and depression. It consists of 18 items rated on a 7-point Likert scale, with higher scores indicating greater symptom severity. The BPRS is widely used in psychiatric research and clinical practice to track changes in general psychopathology across treatment modalities. In the current study, the BPRS will be administered after every infusion in the biomedical arm to capture changes in global psychiatric symptomatology and partly for the same reason as CADSS (below) is administered to match clinician time and to resemble biomedical settings.

Clinician Administered Dissociative States Scale (CADSS)

The CADSS (Bremner et al., 1998) is a clinician-rated instrument designed to quantify acute dissociative states. It consists of 23 items rated across three domains: depersonalization (sum of items 3–7, 20, and 23), derealization (sum of items 1, 2, 8–13, 16–19, and 21), and amnesia (sum of items 14, 15, and 22). CADSS is the most widely used scale to assess treatment-emergent dissociative symptoms caused by ketamine and was assessed for validity in the context of ketamine treatment with a Cronbach alpha of 0.937 (Mello et al., 2021; Castle et al., 2017; van Schalkwyk et al., 2018).

In this study, the CADSS will be used only in the biomedical framing, partly due to matching clinician time since rolling integration and interviews are done in the psychedelic arm but also because it is commonly administered in a biomedical setting of ketamine treatment thus resembling common ketamine trials in a biomedical framing (Dahan et al., 2024). The CADSS will be administered approximately 5–10 minutes following each infusion to characterize the acute psychoactive effects of ketamine in a biomedical framing.

Challenging Experience Questionnaire (CEQ-7) and Mystical Experience Questionnaire (MEQ-4)

The CEQ-7 and MEQ-4 are short self-report measures validated for use in psychedelic studies (Strickland et al., 2024). The CEQ-7 assesses the intensity of challenging or difficult experiences, including anxiety, grief, fear of insanity, isolation, physical distress, and paranoia. The MEQ-4 is a brief version of the Mystical Experience Questionnaire and captures core features of mystical-type experiences such as unity, transcendence, sacredness, and ineffability. Both scales provide efficient characterization of the phenomenological spectrum of psychedelic-occasioned states. In the current study, CEQ-7 and MEQ-4 will be administered to all patients after every infusion when the clinician administered surveys are finished, hence about 20-30 min after the infusion ended. If the patient has blurred vision or problems filling these in digitally on site during the observation time after the infusion, staff will help them.

Cognitive Fusion Questionnaire (CFQ-7)

The CFQ-7 is a brief self-report instrument designed to assess the extent to which individuals become entangled with, and dominated by, the content of their thoughts (i.e., cognitive fusion).

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In this study, the CFQ-7 will be administered at baseline to capture each participant's current level of cognitive fusion, and again post-treatment to assess change from baseline. We will then examine the association between percentage change in cognitive fusion and percentage change in symptom severity on the Montgomery-Åsberg Depression Rating Scale (MADRS), in order to explore whether changes in cognitive fusion may function as a potential mediator of treatment response.

5-Dimensional Altered States of Consciousness Questionnaire (5D-ASC)

5D-ASC (Dittrich, 1998) measures altered states of consciousness and contains 94 items with visual analogue scales. The questionnaire consists of five subscales/dimensions (i.e. Oceanic Boundlessness, Anxious Ego Dissolution, Visionary Reconstructuralization, Auditory Alterations and Reduction of Vigilance) and 11 lower-order scales. It is well-validated and widely used to characterize the subjective effects of various psychedelic drugs. 5D-ASC will be administered digitally one week post the six infusions ended.

Drug Effect Questionnaire (DEQ)

The DEQ (Morean et al., 2013) is a self-report measure commonly used in psychopharmacology to assess the immediate subjective effects of psychoactive substances. It evaluates dimensions such as overall drug effect, liking, wanting more, and feeling high. The DEQ has been validated across a variety of substances and provides a concise measure of acute subjective drug responses, including reward-related and aversive aspects. In this trial, the DEQ will be administered immediately following infusion two and six. If the patient answers that they want more of the drug, a question is added about when, due to possibly differ from wanting more of future antidepressant effects and wanting more due to drug craving usually more associated with addictive properties. No studies on ketamine treatment has used this scale to our knowledge and it will be interesting to see if it correlates to long-term outcomes on registry data (1-3 years) that could point toward addiction.

Goal Attainment Scale (GAS)

The Goal Attainment Scale (GAS), developed by Kiresuk and Sherman (1968), is a self-rated scale that uses a semiquantitative method integrating the patient's individual treatment expectations by evaluating outcomes against specific, measurable, attainable, relevant, and time-bound (SMART) goals. Each goal is rated according to achievement on a five-point scale (−2, −1, 0, +1, +2) based on a predefined plan specifying what each step on the scale represents. In general terms, a score of 0 corresponds to achieving the goal, +1 corresponds to approximately 50% more progress than expected, and +2 corresponds to 100% more than expected, whereas −2 represents 100% worse than expected (see Appendix "Form" for an example). GAS scores across multiple goals can be converted into a standardized T-score, facilitating comparisons between individual patients with different goals as well as between different treatment modalities. This approach may therefore be particularly relevant for patients with major depressive disorder (MDD). (McCue et al., 2021; Turner-Stokes, 2009)

GAS will be administered weekly for the first 6 weeks and then at every follow up until 6 months post infusion (i.e. week 1, 2, 3, 4, 5, 6, 8, 12, 30)

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Mystical Experience Questionnaire (MEQ-30)

The MEQ is a self-report measure developed to assess the immediate effects of classic psychedelics. It is based on Stace's conceptual framework of mystical experiences (Stace, W. T. Mysticism and Philosophy. (MacMillan Press, 1960), and covers the major dimensions of classic mystical experience: unity, transcendence, noetic quality, sacredness, positive mood, and ineffability/paradoxicality. The MEQ has been administered in various forms in a number of studies over the past 50 or more years (Griffiths et al., 2011; Griffiths et al., 2006; Bogenschutz 2015; Garcia-Romeu et al., 2015; Griffiths et al., 2008; Maclean et al., 2012). Items on the questionnaire are rated on a 6-point scale, from 0 (none; not at all) to 5 (extreme; more than ever before in my life). A factor analysis conducted by MacLean et al. found that the revised version (MEQ30), is a psychometrically sound instrument for assessing psychedelic-occasioned mystical experience (Madlean et al., 2012) . MEQ-30 will be administered digitally one week after the six infusions.

Pittsburgh Sleep Quality Index, Brief (B-PSQI)

Sleep quality will be assessed using the Brief Pittsburgh Sleep Quality Index (B-PSQI), a shortened version of the original PSQI developed to reduce participant burden while maintaining coverage of core sleep domains (Buysse et al., 1989). The brief version includes items assessing habitual bedtime, sleep latency, total sleep duration, use of sleep medication, and overall perceived sleep quality during the past month.

Although the B-PSQI has shown promising psychometric properties and preliminary validation in non-clinical samples, it remains under further study, and therefore results will be interpreted with caution. The original PSQI is a widely validated and extensively used measure of subjective sleep quality, demonstrating good internal consistency (Cronbach's α typically 0.70–0.83) and strong associations with objective sleep and health outcomes (Carpenter & Andrykowski, 1998; Mollayeva et al., 2016).

In the present trial, the B-PSQI will be administered electronically at baseline and at three-month follow-up assessment to capture changes in subjective sleep quality over time

Psychological insight Survey

The Psychological Insight Scale (PIS) (Peill et al., 2022) is a validated self-report measure designed to assess the degree of psychological insight following a psychedelic experience. The scale evaluates domains such as self-understanding, emotional processing, and perceived relevance to mental health and personal well-being. Higher scores on the PIS have been associated with greater therapeutic benefit and improved psychological outcomes following psychedelic-assisted therapy.
In the present trial, the PIS will be administered one week after the final ketamine infusion to assess the extent of psychological insight elicited by the treatment. In our pilot study (not finilized at the moment) we saw a trend that PIS correlated with treatment outcome.

Satisfaction with Life Scale (SWLS)

SWLS (Diener et al., 1985) was developed as a measure of subjective well-being. The high convergence of self- and peer-reported measures of subjective well-being and life satisfaction provide strong evidence that subjective well-being is a relatively global and stable phenomenon.

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SWLS is shown to be a valid and reliable measure of life satisfaction, suited for use with a wide range of age groups and applications. SWLS is a brief 5-item self-report measure with value statements on a scale ranging from 1-7. SWLS will be administered digitally at baseline and at the three-month follow-up assessment.

Screen Time Questionnaire

The Screen Time Questionnaire was developed by Kyle Greenway and colleagues (Garel et al., 2023) as part of research expanding the extra-pharmacological model of psychedelic drug action to include the delayed influence of "set and setting" factors in daily life. The questionnaire is designed to assess patterns of digital media use and their potential relationship to mood, attention, and integration processes following psychedelic experiences.

The Screen Time Questionnaire includes self-reported estimates of average daily time spent on (1) social media, (2) video or computer games, and (3) television or streaming services during the past two weeks. It also includes a single item on how frequently participants have background media (e.g., TV or streaming) on while engaging in other activities, reflecting multitasking and environmental media exposure.

Response options are categorical (e.g., "None," "Less than 1 hour," "1–3 hours," "4–6 hours," "More than 6 hours"), with frequency ratings ranging from "Never" to "Almost always" for background use. The Swedish translation used in this study is included in Appendix: Questionnaires.

This measure will be administered digitally at baseline and three-month follow-up.

Social Provisions Scale 5 (SPS-5)

The SPS-5 (Orpana et al., 2019) is a validated shortened version of the Social Provisions Scale, designed to assess perceived social support across five functional domains: attachment, social integration, reassurance of worth, reliable alliance, and guidance. Each item is rated on a Likert scale, and higher scores indicate stronger perceived social support. In the current study, the SPS-5 will be administered at baseline and three-month follow-up.

State-Trait Anxiety Measure (STAI-SF)

The STAI-SF (Marteau & Bekker, 1992) is a shortened version of the original State-Trait Anxiety Inventory, designed to efficiently assess state anxiety. The instrument focuses on transient symptoms of anxiety such as tension, worry, and nervousness. It has been validated as a reliable measure for repeated use in clinical trials. In this study, the STAI-SF will be administered at baseline and at three-month follow-up assessment.

Ten-Item Personality Inventory-(TIPI)

The TIPI (Gosling et al., 2003) is a brief measure of the Big Five personality traits: openness, conscientiousness, extraversion, agreeableness, and emotional stability. Despite its brevity, it has been shown to provide valid estimates of broad personality domains, making it useful in large-scale or resource-limited research contexts. In the present trial, the TIPI will be administered once at baseline to characterize individual differences in personality.

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Treatment Expectation and Treatment Evaluation

The Treatment Expectation and Evaluation questionnaires were developed by Beckman for the ongoing psilocybin trial CAPSI (protocol registered in CTIS 2023-505532-35-00). Beckman has approved our use of these questionnaires in this trial.

The Expectation questionnaire is a compilation of questions regarding the participants' expectation of the forthcoming treatment in five areas: Their treatment expectation; whether they will feel safe and seen during sessions; if they think the treatment will help them; and if the treatment will make them satisfied. The questions are answered on a scale ranging from 0 (not at all) to 4 (to a very high degree). At the end of the form, participants will also answer a question regarding how much they think the treatment will reduce their depression on a scale ranging from 0-100. The questionnaire will be administered digitally at baseline and before the third infusion to explore if there is a difference in expectations when the different framings have started.

Treatment Evaluation is a compilation of questions regarding the participants' treatment experience in five areas: Their experience during sessions; if they felt safe and seen; if they think the treatment was helpful; and if the treatment made them satisfied. The questions are answered by the participants on a scale ranging from 0-4. At the end participants will also answer a specific question regarding how much they think the treatment will reduce their depression on a scale ranging from 0 to 100, and a question regarding any recent lifestyle changes. The questionnaire will be administered digitally one week after the last treatment session.

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UCLA Loneliness Scale

The UCLA Loneliness Scale – Short Form is a brief, validated self-report instrument developed to measure subjective feelings of social isolation and perceived loneliness (Hughes et al., 2004; Russell, 1996). The short version consists of three core items assessing how often the respondent feels a lack of companionship, feels left out, or feels isolated from others. Responses are rated on a 3-point Likert scale ranging from 1 (“Hardly ever”) to 3 (“Often”).

Higher scores indicate greater perceived loneliness. The short form has shown good internal consistency and strong correlations with the full 20-item UCLA Loneliness Scale, while minimizing participant burden (Hughes et al., 2004).

The Swedish translation used in this study is provided in Appendix: Questionnaires, it is not previously validated. The measure will be administered at baseline and at the three-month follow-up to explore potential changes in perceived loneliness.

Working Alliance Inventory – Short (WAI-S)

This swedish translation of the short form also contains two additional questions regarding empathy and collaboration, as defined in the Motivational Interviewing Treatment Integrity (MITI). This questionnaire was translated by Beckman for the CAPSI trial (protocol registered in CTIS 2023-505532-35-00).

The Working Alliance Inventory (Horvath & Greenberg, 1989) and the Working Alliance Inventory - Short (Tracey & Kokotovic, 1989) are widely used measures of alliance in both psychotherapy and research settings. The WAI was originally derived from a well-researched framework on the

working alliance developed by Bordin (1979). WAI-S contains 12 items rated on a seven points scale. It provides a summary of the total working alliance and three subscales to assess primary components of the working alliance: Goal (i.e., agreement with regard to the treatment goals), Task (i.e., agreement with regard to the tasks) and Bond (i.e., the empathic bond between the client and the therapist). In this study, the clinician and the participant each complete WAI-S digitally at baseline, third infusion, one week and two months post the sixth infusion.

Manual for conducting semi-structured Interviews on the Experience

For participants in the experience-centered arm, a semi-structured post-infusion interview will be conducted to explore the subjective experience of ketamine within a therapeutic setting. The interviews serve a dual purpose: as part of the intervention itself by emphasizing and integrating the patient's lived experience, and as a research method for systematic analysis of the phenomenological features of the ketamine experience in this context.

The interview manual is developed by Katja Valli, who has conducted similar interviews exploring subjective experiences induced by ketamine and other anesthetic agents (Radek et al., 2021). The guide is designed to capture perceptual, cognitive, emotional, and existential aspects of the experience, while maintaining a calm, empathic, and non-judgmental interview atmosphere appropriate for participants in a potentially sensitive post-infusion state. However, the participant will be guided back to the actual experiential contents of the experience and not their interpretations regarding these. The interpretation, significance, potential insights, and their application to the patient's life constitute the ongoing integration process conducted post-interview, as part of the "rolling integration," which is influenced by the Montreal Model and regarded as a component of the psychedelic framing intervention.

Interviews are initiated approximately 5 minutes after infusion completion, once the participant is able and accepts to communicate. The interviewer records the time elapsed since the end of infusion and ensures that the participant feels ready to engage.

The interview guide is included in the Appendix Questionnaires. It contains open-ended questions addressing sensory, emotional, cognitive, and existential dimensions of the experience, as well as potential shifts in self-perception.

All interviews will be audio-recorded, transcribed verbatim, and de-identified. The transcribed material will be analyzed using a quantitative content analysis, in which identified experiential domains are assigned categorical or ordinal values (e.g., presence, intensity). These quantified data will then be used for descriptive and correlational analyses in relation to clinical outcomes such as depression scores, psychological insight, mystical experiences and altered states of consciousness.

The interview will be conducted after infusion 1, 3 and 6 in the psychedelic framing.

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Modified Tellegen Absorption Questionnaire (MODTAS)

The MODTAS (Tellegen & Atkinsson, 1974) is a 34-item self-report scale measuring trait absorption, defined as the tendency to become deeply immersed in sensory, imaginative, or experiential states. Absorption has been associated with altered states of consciousness and predicts responsiveness to psychedelic experiences (Haijen et al., 2018). In this study, the MODTAS will be administered at baseline to assess individual differences in absorption as a potential moderator of treatment response, but also at the three-month follow-up as an exploratory outcome if there is any difference in absorption after the two different framings. It is not validated as a questionnaire for this.

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8 Statistical Analysis

8.1 Power calculation

Based on a balance of logistical conditions and clinical significance of the findings, a difference in MADRS-scores of 4.5 points in the primary endpoint is deemed relevant to identify. It is the mid-estimate of the minimal important difference for MADRS.scores (Hengartner & Plöderl, 2022). This corresponds to an effect size of .52 Cohen *d*
Based on a two-sided alpha value = 0.05 and 80% power, a sample of N=120 participants is required. The established clinical activities at SkaS for ketamine treatment can treat approximately 120 patients per year. Based on available statistics at the clinic, it is estimated that significantly more patients are eligible for the treatment than the range of treatments allows. We estimate that at least 70-80% of the participants will enroll in the trial, following the clinical routine for treatment decisions. Patient inclusion is therefore expected to be completed within 3 years of starting. The target sample size is set to 120 for outcome measures at 3 months. Based on clinical experience, the drop-out rate at 3 months is minimal.

8.2 Primary analysis and key secondary outcomes

The statistical analysis plan for the primary and secondary outcomes of the RCT are prepared by a statistician as follows:
Primary endpoint: MADRS scores will be analyzed using a mixed-models for repeated measurements (MMRM) specification including all post-baseline MADRS ratings up to and including the primary endpoint (month 3). Baseline MADRS ratings will be included as a covariate, treatment framing (biomedical or psychedelic) and (weeks) will be included as fixed factors, and the interaction between treatment framing and time will similarly be included. Within-subject correlations over time will be modelled as a random effect using an unstructured covariance matrix. Should that model fail to converge, an autoregressive structure with heterogeneous variance will be used instead, and should that also fail to converge an autoregressive structure with homogeneous variance will be used. Should all such MMRM models fail to converge, the results from the sensitivity analyses using analysis of covariance (ANCOVA) will be considered primary. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom. The primary statistical test will be the estimated marginal mean contrast for the treatment framing factor at endpoint. All other MADRS outcomes will be considered exploratory.
As a sensitivity analysis, the primary endpoint will be assessed using ANCOVA on the intention-to-treat (ITT) population. The ITT population is defined as all patients with at least one MADRS rating (including baseline) that were randomized to each group. Missing data will be imputed using the last-observation-carried-forward (LOCF) principle, i.e., with missing observations being replaced by the last non-missing observation. The model will include treatment framing as a fixed factor and baseline MADRS score as a covariate, with the parameter estimates for the treatment framing factor being the outcome of interest.
Secondary endpoints: Secondary endpoints will be analyzed analogously to the primary endpoint, including appropriate modifications relative to the nature of the data (e.g., a generalized linear mixed model and/or logistic regression for dichotomous outcome measures). Sensitivity analyses assessing potential covariates – such as ketamine dose per kilogram – will be conducted as appropriate.
If the results for the primary outcome are inconclusive, e.g., if the primary analysis yields a weakly significant contrast while the sensitivity analysis using ITT is weakly non-signifcant,

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additional sensitivity analyses using bayesian linear regression may be performed. Such analyses will use weakly informative priors (β ~ N[0,5]) - corresponding to a prior belief centred at no effect with most mass between ±10 MADRS points - and compute posterior probabilities for the effect being inside and outside, respectively, a region of ±3.4 MADRS points (corresponding to an ES of 0.4). Sensitivity analyses varying the SD of the prior between 2 to 10 will be included.

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9 Safety Management

Risks associated with participation in this study and mitigation strategies associated with these:

9.1 Risks associated with worsening depression

Participants with worsening depressive symptoms during treatment will be monitored and managed according to clinical routine. This may include liaison with psychiatric services for suicide risk assessment, adjunct medication prescriptions or day- or inpatient care as clinically indicated.

9.2 Risks associated with collection of potentially sensitive information

All collected data will be stored on a secure electronic database. All research staff will complete GCP training to promote the proper conduct of scientific research in humans.

9.3 Risks associated with recordings of sessions

The report on the ketamine-induced experience in the psychedelic framing will be audio recorded for content analysis as part of this study. There is a risk that these recordings of sessions will make participants feel monitored, controlled and/or in any other way uncomfortable. However, recording of treatment sessions is a standard procedure in graduate and advanced therapist training, and as long as clients understand the purpose of the confidential recordings, they are often happy to consent (Brown et al., 2013; Ellis, 2010)

9.4 Risks Associated with Psychiatric Questionnaires and Interviews

The study questionnaires and interviews may uncover strong and potentially disturbing feelings about the participant's emotional state and private life. Care will be taken to collect the "minimum necessary" information required for study purposes and so that it can be used as part of the therapeutic process In the event that a patient becomes unduly distressed appropriate steps will be taken to meet the distress either by the staff or the physician responsible for the ketamine treatment.

9.5 Abuse Liability and Monitoring

Because the psychedelic arm of the intervention is designed to reduce anxiety and "disliking" associated with the acute effects of ketamine, there is a theoretical risk that increased "liking" of the drug and overall positive subjective effects may elevate abuse liability. To monitor this potential risk, we will administer the Drug Effects Questionnaire (DEQ) twice during the study in both arms.

Additionally, the Challenging Experience Questionnaire (CEQ-7) will be used to assess any difficult or adverse acute experiences related to ketamine administration, as psychedelic experiences may be both more intensely liked and more challenging in this context.

To further distinguish between immediate desire for more ketamine versus more remote or hypothetical desire, an extra item will be added to the DEQ: if a participant indicates that they would like more of the drug, they will also be asked when they would prefer that additional dose (e.g., "right now / later today", "tomorrow", "next week", "next month", etc.). This temporal anchoring is intended to help differentiate between craving or impulsive desire (which may

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signal higher risk of misuse) versus more reflective, delayed desire (which may carry lower risk) and could also be related to perceived antidepressant effect and the wanting of that.

Participants who express an immediate desire ("right now" or equivalent) will receive additional monitoring and if needed clinical safety assessments.

Abuse risk is further limited in clinical routine since ketamine is not supplied to the participant to take home (which is the case in some clinics after the Covid pandemic increased telehealth and home administration of ketamine) but rather is administered under careful clinical supervision in a restrictive setting.

9.6 Adverse Events, Reporting and Safety Management

Ketamine-related AEs are quite common (Ekstrand et al., 2022), therefore the clinical routine includes monitoring blood pressure, heart rate and saturation; and always having one clinician or assistant nurse in the room for observation and if needed psychological support. This study is not a study of ketamine per se but the non-pharmacological adjuncts surrounding the treatment, i.e., the framing. It has been shown that adding music to ketamine treatment can lessen the increase in blood pressure (Greenway et al., 2024) and we believe that the different framings in this study may impact the rate of ketamine-related AEs. Hence, we write how the AE's will be handled here.

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An adverse event (AE) is defined as any untoward medical or psychological occurrence in a study participant, whether or not it is considered related to the intervention. This includes changes in clinical status, vital signs, or other clinically significant findings during routine assessments. Treatment-emergent adverse events (TEAEs) are events that occur after randomization or that worsen in intensity or frequency following treatment. A serious adverse event (SAE) is any event resulting in death, a life-threatening condition, hospitalization or prolongation of existing hospitalization, persistent or significant incapacity, or any important medical event that may jeopardize the participant's health or require intervention to prevent serious outcomes.

Vital signs will be closely monitored during infusions according to clinical routine. Events will be classified as AEs if:

- systolic blood pressure exceeds 160 mmHg or diastolic blood pressure exceeds 100 mmHg on three separate readings
- there is a clinically significant decrease in blood pressure
- heart rate exceeds 100 beats per minute for a sustained period of 3 minutes or longer. Transient spikes of shorter duration will be monitored but not classified as AEs unless associated with other clinical concerns
- a clinically significant decrease in heart rate occurs

Other common ketamine-related AEs include transient dissociation, perceptual alterations, euphoria, temporary increases in blood pressure or heart rate, nausea, headache, dizziness, and mild anxiety or restlessness during or immediately after infusion.

AE intensity will be rated as mild, moderate, or severe. Mild events are noticeable but well tolerated and require minimal or no intervention. Moderate events interfere with functioning or

require intervention. Severe events require significant intervention or pose substantial risk to the participant. Causality will be assessed by the principal investigator (PI) and clinical staff, who will determine whether there is a reasonable possibility that the intervention or study procedures caused the event.

The study design acknowledges that framing may influence the subjective experience of side effects. In the psychedelic framing, dissociative or perceptual effects are presented as potentially therapeutic. It is hypothesized that participants in this arm may tolerate these psychological AEs better, potentially leading to fewer dropouts or distress-related complaints. In the biomedical framing, the same side effects are presented as transient adverse effects, which may increase the likelihood of experiencing them as unpleasant or distressing.

Participants will be observed continuously during infusions, and all AEs and SAEs will be recorded from the time of informed consent until three months, after that the participants are normally referred back to their psychiatrists as part of the clinical routine. The PI is responsible for ensuring participant safety and for initiating appropriate medical management, including withdrawal from the study if required. For each AE or SAE, the following information will be recorded: participant study ID, study intervention, start date and time of the intervention and AE, a brief description of the event, seriousness criteria, and causality assessment.

9.7 Data Monitoring and Stopping Rules

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Given that intravenous ketamine is already an established clinical treatment for TRD and prescribed independently prior to enrollment in the trial, no independent Data Monitoring Committee (DMC) for safety surveillance will be established.

The trial may be temporarily paused or stopped prematurely if serious adverse reactions are deemed probably or definitely related to either of the interventions (i.e., the biomedical or psychedelic framing). Such a decision will be made jointly by the PI, sponsor, and clinical leadership, with immediate notification to the Ethics Review Authority (Etikprövningsmyndigheten, EPM).

10 Study monitoring, auditing, and documentation

10.1 Monitoring Oversight and Responsibilities

Monitoring will be supported by Gothia Forum, using qualified monitors who are independent of the study team and not directly involved in trial conduct.

A Monitoring Plan will be developed prior to study initiation, defining the scope, frequency, and methodology of monitoring activities. Monitoring will commence once all necessary trial prerequisites are in place, including:

- Approvals from the Swedish Ethical Review Authority (Etikprövningsmyndigheten, EPM)
- Site initiation and staff training in GCP and study-specific procedures.

10.2 Monitoring Procedures

Monitoring will be conducted both remotely and, when appropriate, on-site. The primary focus will be to verify that:

- The rights, well-being, and safety of participants are protected.
- Informed consent is properly obtained and documented.
- Study procedures are conducted in accordance with the approved protocol and GCP.
- Data entered into the electronic Case Report Form (eCRF) are accurate, complete, and verifiable from source records.
- Adverse events (AEs) and serious adverse events (SAEs) are adequately recorded

10.3 Deviation Reporting and Corrective Actions

Any protocol deviations identified during monitoring will be documented and assessed for impact on participant safety or data integrity. Where necessary, Corrective and Preventive Actions (CAPA) will be implemented, which may include additional training, data review, or process improvements.

During or after the study, the regulatory authorities and/or the EPM may request access to all source documents, CRFs, and other protocol documentation for on-site audit or inspection.

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11 Confidentiality and data security

Subjects who participate in the trial are coded with a trial-specific identification number. All subjects are registered in a subject identification list (subject enrollment and identification list) that connects the subject's name and personal number with a subject number/trial identification number.

The electronic case report form (eCRF) system used in this trial is REDCap (Research Electronic Data Capture), a secure, web-based platform designed for compliant and efficient data collection in clinical research. REDCap supports role-based access control, audit trails, and multi-factor authentication to ensure data integrity and traceability. All data are encrypted both in transit and at rest. The system enforces real-time validation checks, including field constraints, required fields, and conditional logic to minimize entry errors. Automated calculations and standardized input formats further enhance data accuracy. User permissions are strictly managed to prevent unauthorized access or modifications. REDCap also maintains comprehensive audit logs for all data changes, supporting regulatory compliance and monitoring. These measures collectively ensure that data collected during the trial are secure, accurate, and reliable.

The pseudonymized database will be stored in encrypted servers monitored by Västra Götalandsregionen, accessible by authorised study personnel only.

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