Statistical Analysis Plan: Ketamine for reduction of Alcoholic RElapse (KARE)

Trial full title	A phase II, randomised, double-blind, placebo-controlled, multi-site, parallel group clinical trial to examine ketamine as a pharmacological treatment for alcohol dependence in an alcohol dependent population
Trial short title	Ketamine for reduction of Alcoholic RElapse (KARE)
Trial registration number	EudraCT no.: 2015-000222-11
Trial chief investigator	Dr Brigitta Brandner (UCL)
Trial Lead researcher	Professor Celia Morgan (UoE)
Trial project manager	Dr Martin Anyim (UCL)
Trial statistician	Dr Fiona Warren (UoE)
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1. Abbreviations and definitions

Table 1 Abbreviations and definitions

Abbreviation	Full terminology/definition
CONSORT	CONsolidated Standards of Reporting Trials
CTU	Clinical Trials Unit
eCRF	Electronic Case Report Form
EudraCT	European Clinical Trials Database
ITT	Intention to treat
KARE	Ketamine for reduction of Alcoholic RElapse
MRC	Medical Research Council
PI	Principal Investigator
SAP	Statistical Analysis Plan
SOP	Standard Operating Procedure
UCL	University College London
UCLH	University College London Hospitals NHS Foundation Trust
UoE	University of Exeter

2. Statistical guidelines

Analyses are to be conducted in accordance with ICH-9 statistical guidelines for clinical trials and CONSORT reporting checklist for trials [1, 2]. The SAP for this trial has been developed in accordance with the Standard Operating Procedure (SOP): Statistical Principles (SOP number NIHRexe/207/GEN).

3. Trial background

The KARE trial is a phase-II randomised trial comparing an active drug intervention (ketamine) with a placebo (saline), and comparing psychotherapy with no psychotherapy (alcohol education). This trial is funded by the Medical Research Council (MRC), and sponsored by University College London (UCL), Sponsor number 13/0253. The EudraCT reference number is 2015-000222-11. The trial has been approved by the South West – Central Bristol Research Ethics Committee (reference number: 15/SW/0312).

This trial aims to gather data regarding the clinical effectiveness of intravenous ketamine (with and without a concurrent psychotherapy intervention) with regard to prevention of relapse (recommencing alcohol use) in participants who are currently abstinent, but who have a current diagnosis of alcohol dependence. The trial will also gather data regarding safety and tolerability of ketamine, and assess compliance with the drug and psychotherapy interventions. Full details of the trial are set out in the KARE trial protocol, Final Version 12, dated 20.01.2020. This statistical analysis plan (SAP) is written in relation to this protocol.

Participants are randomised individually to their combination of ketamine/placebo and psychotherapy/psychoeducation control using a blocking design. Participants are aware of all available treatment options, and that they could potentially be allocated to any of these. The drug intervention is administered by an anaesthetist who is blinded to the drug intervention allocation and also to the therapy intervention. The psychotherapist cannot be blinded to the therapy intervention, but is blinded to the drug intervention. The patient is also blinded to the drug intervention, but is aware of whether they receive psychotherapy or control.

4. Trial information

4.1 Interventions

KARE has two forms of intervention, a drug intervention and a psychotherapy intervention. The active drug intervention is ketamine, an anaesthetic/analgesic drug, to be administered intravenously. The placebo control

is saline. As well as a drug intervention the participants will receive concurrently either a psychotherapy intervention, or a psychoeducation control intervention. Hence, there are four combinations: (i) ketamine + psychotherapy; (ii) ketamine + psychoeducation; (iiI) placebo + psychotherapy; (iv) placebo + psychoeducation. Participants will receive their allocated drug infusion in 3 doses over 3 weeks. Participants will concurrently receive either psychotherapy or psychoeducation control. The trial will be performed at two sites: Devon (Royal Devon & Exeter Foundation NHS Trust) and London (UCLH).

4.2 Phase of trial

KARE is a Phase II clinical trial (a proof of concept study/feasibility study).

4.3 Randomisation level

Randomisation will be performed by an independent organisation, Sealed Envelope, that specialises in randomisation and online databases for clinical trials (https://www.sealedenvelope.com/). Participants are randomised individually. To aim for balance across the four treatment combinations, a block randomisation will be performed (block sizes are known only to the trial statistician and the designated staff at Sealed Envelope). Randomisation will be performed separately for each site. A list of randomisation allocation codes will be generated in advance by Sealed Envelope, with each code indicating the drug allocation (ketamine or placebo) and the psychotherapy intervention (psychotherapy or psychoeducation). These codes will be sent to the trial statistician, who will generate two envelopes for each participant, one indicating the drug allocation and the other indicating the psychotherapy intervention. These envelopes will be securely delivered to trial staff at each site. The trial unblinded research nurse will receive the drug allocation envelopes for the Devon site, and the hospital pharmacist at UCLH. The trial psychologists at each site will receive the psychotherapy allocation envelopes for the Devon and London sites. When recruited by trial researchers, the participant's data will be entered to the online eCRF database. The participant will be allocated a trial ID number. The randomisation will be performed using the online eCRF database by the trial anaesthetist at each site. This trial ID number will be linked to the next available randomisation allocation code, and this information will be sent via email to the relevant member of the trial team so that they can open the participant's envelope to discover their randomised allocation.

4.4 Study design

KARE has two interventions (drug therapy and psychological therapy), each with two possible forms, resulting in a two by two factorial intervention design, with a total of four possible interventions (Section 4.1).

The drug intervention will be administered by the site anaesthetist, who will be blinded to drug allocation and psychotherapy allocation. Psychotherapy/psychoeducation will be administered by the trial psychologists at each site who will be blinded to the drug allocation. Participants will also be blinded to drug allocation. Participant outcome data will be collected by site investigators who are blinded to drug allocation. The trial statistician will be blinded to both drug allocation and psychotherapy allocation throughout the trial.

Participants will be randomised to the trial after eligibility has been confirmed via prescreening and screening, and after having provided informed consent. The SCRAM-X ankle monitor (measuring alcohol levels in sweat) will be attached at screening. Treatment will commence as soon as possible after randomisation, and continue for a period of 3 weeks (one infusion session and two sessions of psychological therapy/psychoeducation per week). Follow-up data will be collected at 3 and 6 months after baseline. The last follow-up visit is scheduled for 24 weeks post baseline.

4.5 Purpose of the analyses

The purposes of the analyses are as follows:

(i) to provide baseline descriptive data by trial arm;
(ii) to assess the feasibility of data collection;
(iii) to assess loss to follow-up at 3 and 6 months;

(iv) to assess the proportion of missing data at 6 months;
(v) to provide descriptive outcome data by trial arm (ketamine vs placebo, psychotherapy vs psychoeducation, and all four arms individually) at 6 months;
(vi) to provide relative risks (with 95% confidence intervals) for relapse of alcohol consumption comparing (a) ketamine vs placebo; (b) ketamine plus psychotherapy vs ketamine plus psychoeducation; (c) ketamine plus psychotherapy vs placebo plus psychoeducation;
(vii) to provide mean difference (with 95% confidence intervals) for percentage of days abstinent at 6-month follow-up for the same combinations by arm as for (vi); and
(viii) to descriptively report adverse events.

All inferential analyses are to be regarded as exploratory and viewed with caution due to lack of statistical power and multiple testing. For the primary outcomes, the primary analyses will be performed on an intention to treat (ITT) basis using complete case data only (see Section 6.5 for approaches to missing primary outcome data). As a sensitivity analysis, the inferential analyses for the primary outcomes only (vi and vii above) will be performed using only those participants deemed to have a completed their allocated interventions to a specified degree (per protocol analysis). For the participants who receive ketamine, a per protocol treatment will be defined as receiving three or more infusions. No specification of a minimum treatment has been defined for psychotherapy/psychoeducation. Hence, all participants who receive placebo drug therapy will be considered as having been treated per protocol. For the secondary outcomes, only an ITT analysis using complete case data will be performed. All analyses will be performed by a statistician who is blinded to treatment allocation. All analyses will be performed using Stata v14.

4.6 Sample size calculation

As this is a proof of concept study, no inferential analyses are planned, therefore no formal power calculations have been performed. The sample size of 96 (24 participants per treatment combination) was selected for the following reasons. As a proof of concept study, feasibility of recruitment, and desire to minimise the number of subjects, were considerations. If a level of dropout of 50% is observed, this will leave 12 participants per arm, 24 receiving ketamine and 24 receiving placebo. We anticipate a relapse rate of 50% in the placebo arm, and would be able to estimate a reduced relapse rate of 25% in the ketamine arm with a 95% CI width of 37 percentage points (see Protocol Final Version 12, 20.01.2020 Section 13.2.1 for further details).

4.7 Study populations

Inclusion and exclusion criteria for participants are set out in the Protocol, Final Version 12, 20.01.2020 Section 5.

The primary analyses will be performed using the ITT population (participants analysed according to their randomised allocations). Further sensitivity analyses will be performed using the per protocol population (defined in Section 4.5). All analyses will be performed using complete case data only. Participants found to be ineligible after randomisation will be excluded from all analyses.

5. Study objectives and endpoints

5.1 Study objectives

The objectives of the study are as follows (Protocol, Final Version 12, 20.01.2020 Section 3).

Primary objectives

1) To obtain preliminary data on whether ketamine is effective in promoting and prolonging abstinence in alcohol dependent patients following detoxification.
2) To assess safety and tolerability of ketamine in alcohol dependence.

Secondary objectives

1) To make an early assessment on likely compliance to a combined ketamine and relapse prevention based cognitive behavioural therapy (CBT).
2) To obtain preliminary data as to whether ketamine alone is as effective as a combined ketamine and psychotherapy treatment.

5.2 Endpoints

The primary and secondary outcome variables are set out in the Protocol, Final Version 12, 20.01.2020 , Section 13.1 (reproduced in Table 2). There are two primary outcomes:

1) relapse (defined as 5 drinks (8.1 units alcohol) in men and 4 drinks (6.5 units alcohol) in women on a single occasion) at 6-month follow-up; binary outcome; and
2) percentage days abstinent (not using alcohol at all) at 6-month follow-up; percentage, to be analysed as a continuous variable.

The two primary outcomes are to be derived from timeline follow-back.

There are 19 secondary variables, derived from 16 secondary outcomes (Protocol, Final Version 12, 20.01.2020, Section 13.1.2; depression is measured by two variables, Beck Depression Inventory and Hamilton Depression Scale; Short Form Health Survey 12 (SF-12) produces a physical and a mental component scale; psychotic symptoms is measured by two variables, Brief Psychiatric Rating Scale and Psychotomimetic States Inventory).

1) maximum number of days of continuous abstinence within the first 3 months (time-line follow back); continuous;
2) percentage days abstinent at 3 months (time-line follow back); percentage, to be analysed as a continuous outcome;
3) Profile of Mood states; continuous;
4) Beck Depression Inventory; continuous;
5) Hamilton Depression Scale; continuous;
6) Speilberger Trait Anxiety Inventory; continuous;
7) Brief Psychiatric Rating Scale; continuous;
8) Psychotomimetic States Inventory; continuous;
9) Fagerstrom Test of Nicotine Dependence (FTND; smokers only); continuous;
10) Alcohol craving (visual analogue scale); continuous;
11) Alcohol Craving Questionnaire - short-form (ACQ-NOW);
12) Short Form Health Survey 12 (SF-12), physical component scale (PCS); continuous;
13) Short Form Health Survey 12 (SF-12), mental component scale (MCS); continuous;
14) episodic memory (Prose Recall); continuous;
15) delay discounting; continuous;
16) response inhibition (Stop Signal Reaction time); continuous;
17) working memory; continuous;
18) hippocampal functioning (Pattern Recognition Test); continuous; and
19) adverse effects (visual analogue scale); continuous.

5.3 Derived variables

The only derived variables will the binary relapse variable and the number/percentage of days abstinent, to be derived from timeline follow-back data. Further details are to be confirmed.

6 General analysis considerations

6.1 Timing of analyses

An analysis of loss to follow-up only (using count data only) for the ketamine arms will be performed at 3-month follow-up. The trial will be discontinued if more than 42/48 (88%) participants allocated to ketamine are lost to follow-up at 3 months. No further interim analyses are planned (confirmed by funder, December 2019).

The final analyses will take place once all outcome data (after 6-month follow-up is complete) has been entered into the trial database and cleaned. The data manager will liaise with the trial statistician to make the outcome data available for analysis.

Table 2 Outcome variables

Outcome	Variable type	Timepoints measured	Data source/measurement method
Primary outcomes			
Relapse (defined as 5 drinks (8.1 units alcohol) in men and 4 drinks (6.5 units alcohol) in women on a single occasion)	Binary	6 months	Timeline follow-back (participant report)
Percentage days abstinent (not using alcohol at all)	Percentage	6 months	Timeline follow-back (participant report)
Secondary outcomes			
Number of days of continuous abstinence	Continuous	3 months	Timeline follow-back (participant report)
Percentage days abstinent	Continuous	3 months	SCRAM-X Timeline follow-back (participant report)
Profile of Mood states;	Continuous	6 months	Questionnaire: participant report
Beck Depression Inventory	Continuous	6 months	Questionnaire: participant report
Hamilton Depression Scale	Continuous	6 months	Questionnaire: participant report
Speilberger Trait Anxiety Inventory	Continuous	6 months	Questionnaire: participant report
Brief Psychiatric Rating Scale	Continuous	6 months	Questionnaire: participant report
Psychotomimetic States Inventory	Continuous	6 months	Questionnaire: participant report
Fagerstrom Test of Nicotine Dependence (FTND)	Continuous	6 months	Questionnaire: participant report
Alcohol Craving (visual analogue scale)	Continuous	6 months	Questionnaire: participant report
Alcohol Craving Questionnaire (ACQ);	Continuous	6 months	Questionnaire: participant report
Short Form Health Survey 12 (SF-12),	Continuous	6 months	Questionnaire: participant report

physical component scale (PCS)			
Short Form Health Survey 12 (SF-12), mental component scale (MCS)	Continuous	6 months	Questionnaire: participant report
Episodic memory (Prose Recall)	Continuous	6 months	Computer task: participant completed
Delay discounting	Continuous	6 months	Questionnaire: participant report
Response inhibition (Stop Signal Reaction time)	Continuous	6 months	Computer task: participant completed
Working memory	Continuous	6 months	Questionnaire: participant report
Hippocampal functioning (Pattern Recognition Test)	Continuous	6 months	Computer task: participant completed
Adverse effects (visual analogue scale)	Continuous	6 months	Questionnaire: participant report

6.2 Types of analyses

The primary analyses, for both primary and secondary outcomes, will be based on the ITT population, using complete case data only. The primary outcomes will be reported descriptively using ITT data. Inferential analyses for the three two-arm comparisons (ketamine vs placebo; ketamine plus psychotherapy vs ketamine plus psychoeducation; and ketamine plus psychotherapy vs placebo plus psychoeducation) will be performed for the primary outcomes using ITT and per protocol data. The secondary outcomes will be reported descriptively by arm using ITT data, and inferential analyses will be performed using ITT data for the primary two-arm comparison only, ketamine vs placebo.

6.3 Covariates and subgroups

All inferential analyses will be adjusted by site. Due to the small number of participants, and the feasibility nature of the study, no subgroup investigations will be performed.

6.4 Presentation of inferential analyses

For the inferential analyses, the point estimate for the between arm comparison and 95% confidence interval will be reported. Due to the feasibility nature of the study, and the lack of formal power calculation, no *p*-values will be reported.

6.5 Missing data

The primary analyses for primary and secondary outcomes will be based on complete case data only. For the primary outcomes only, we will use multiple imputation to impute any missing data, if data are missing for more than 5% of participants. Individual item missingness for questionnaire outcomes will be dealt with by using the average of reported items to substitute for missing items if no more than a certain number (to be determined for each questionnaire) of items are missing.

6.6 Adverse events

Data on adverse events will be set out descriptively by trial arm.

7 Audit trail

Date of SAP	SAP version number	Date presented to Trial management group/Trial steering committee	Significant amendments since previous version	Date approved
15 June 2016	1.0	15 June 2016	N/A	15 June 2016
2 December 2019	1.1	5 December 2019	1. Inferential analyses to be adjusted by site (Section 7.3)	5 December 2019
27 January	1.1 (supersedes v1.1. 2/12/2019)	27 January 2020	1. Definition of primary outcome refined and data source for primary outcome confirmed (Section 5.2). 2. Protocol version amended in anticipation of submission (Version 12, 20.01.2020)	27 January 2020
11 March 2020	1.2	12 March 2020	1. Confirmation of use of Protocol Final Version 12, 20.01.2020 (throughout).	12 March 2020

8 References

1. *International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. Statistical Principles for Clinical Trials.* Guideline E9. http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E9/Step4/E9_Guideline.pdf(last accessed 25 April 2016)
2. Moher D, Schulz KF, Altman DG. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomised trials. *Lancet.* 2001. 14;357:1191-4.

9 Appendix – example figures and tables

Figure 1 Participant flow diagram

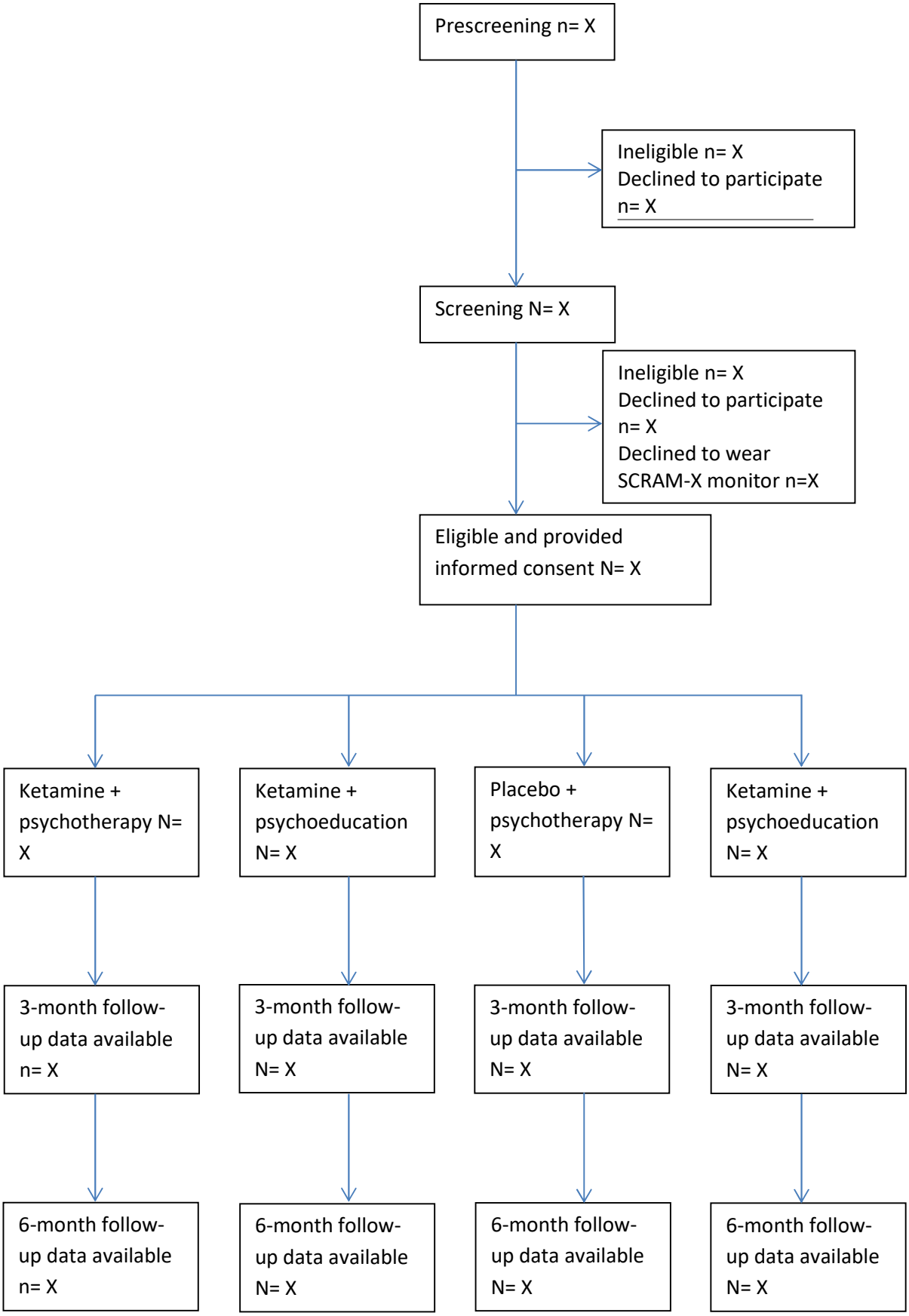

Table 3 Participant characteristics at baseline

Participant characteristic	**Ketamine + psychotherapy (N=)**	**Ketamine + psychoeducation (N=)**	**Placebo + psychotherapy (N=)**	**Placebo + psychoeducation (N=)**
Gender; n (%)				
Male				
Female				
Age; mean (SD); [min, max]				

Table 4 Relapse of alcohol use and percentage of days abstinent at 6-month follow-up: intention to treat population using complete case data.

Outcome	Ketamine (n=)	Placebo (n=)	PT (n=)	PE (n =)	Ketamine + PT (n)	Ketamine + PE (n)	Placebo + PT (n)	Placebo + PE (n)	Ketamine vs placebo RR (95% CI)	Ketamine + PT vs Ketamine + PE RR (95% CI)	Ketamine + PT vs placebo +PE RR (95% CI)
Relapse; n (%) Timeline follow-back											
									Ketamine vs placebo mean difference (95% CI)	Ketamine + PT vs Ketamine + PE mean difference (95% CI)	Ketamine + PT vs placebo +PE mean difference (95% CI)
Percentage days abstinent; mean (SD); median [IQR] Timeline follow-back											

PE: Psychoeducation

PT: Psychotherapy

Table 5 Relapse of alcohol use and percentage of days abstinent at 6-month follow-up: per protocol[a] population using complete case data.

Outcome	Ketamine (n=)	Placebo (n=)	PT (n=)	PE (n =)	Ketamine + PT (n)	Ketamine + PE (n)	Placebo + PT (n)	Placebo + PE (n)	Ketamine vs placebo RR (95% CI)	Ketamine + PT vs Ketamine + PE RR (95% CI)	Ketamine + PT vs placebo +PE RR (95% CI)
Relapse; n (%) Timeline follow back											
									Ketamine vs placebo mean difference (95% CI)	Ketamine + PT vs Ketamine + PE mean difference (95% CI)	Ketamine + PT vs placebo +PE mean difference (95% CI)
Percentage days abstinent; mean (SD); median [IQR] Timeline follow back											

[a]Per protocol population defined as receiving at least three ketamine infusions. No definition of per protocol for placebo, psychotherapy, or psychoeducation interventions.

PE: Psychoeducation

PT: Psychotherapy

Table 6 Relapse of alcohol use and percentage of days abstinent at 6-month follow-up: intention to treat population using complete case and imputed data.

Outcome	Ketamine (n=)	Placebo (n=)	PT (n=)	PE (n =)	Ketamine + PT (n)	Ketamine + PE (n)	Placebo + PT (n)	Placebo + PE (n)	Ketamine vs placebo RR (95% CI)	Ketamine + PT vs Ketamine + PE RR (95% CI)	Ketamine + PT vs placebo +PE RR (95% CI)
Relapse; n (%) Timeline follow back											
									Ketamine vs placebo mean difference (95% CI)	Ketamine + PT vs Ketamine + PE mean difference (95% CI)	Ketamine + PT vs placebo +PE mean difference (95% CI)
Percentage days abstinent; mean (SD); median [IQR] Timeline follow back											

PE: Psychoeducation

PT: Psychotherapy

Table 7 Secondary outcomes at 3-month follow-up

Outcome	Ketamine (n=)	Placebo (n=)	PT (n=)	PE (n =)	Ketamine + PT (n)	Ketamine + PE (n)	Placebo + PT (n)	Placebo + PE (n)	Ketamine vs placebo mean difference (95% CI)
Number of continuous days abstinent[a,b]; mean (SD), median [IQR]									
Percentage days abstinent[a,b]; mean (SD); median [IQR]									

PE: Psychoeducation
PT: Psychotherapy
[a]Abstinent means not using alcohol at all.
[b]Outcomes measured using timeline follow-back.

Table 8 Secondary outcomes at 6-month follow-up

Outcome	Ketamine (n=)	Placebo (n=)	PT (n=)	PE (n =)	Ketamine + PT (n)	Ketamine + PE (n)	Placebo + PT (n)	Placebo + PE (n)	Ketamine vs placebo mean difference (95% CI)
Profile of Mood states; mean (SD), n									
Beck Depression Inventory; mean (SD)									
Hamilton Depression Scale; mean (SD), n									
Speilberger Trait Anxiety Inventory; mean (SD), n									
Brief Psychiatric Rating Scale; mean (SD), n									
Psychotomimetic States Inventory; mean (SD), n									
Fagerstrom Test of Nicotine Dependence (FTND); mean (SD), n									
Alcohol Craving Questionnaire (ACQ); mean (SD), n									

Craving (visual analogue scale; mean (SD), n									
Short Form Health Survey 12 (SF-12), physical component scale (PCS); mean (SD), n									
Short Form Health Survey 12 (SF-12), mental component scale (MCS); mean (SD), n									
Episodic memory (Prose Recall); mean (SD), n									
Delay discounting; mean (SD), n									
Response inhibition (Stop Signal Reaction time); mean (SD), n									
Working memory; mean (SD), n									
Hippocampal functioning (Pattern Recognition Test); mean (SD), n									

Adverse effects (visual analogue scale); mean (SD), n									

PE: Psychoeducation
PT: Psychotherapy