FULL TITLE: A multi-centre investigation of increasing alcohol abstinence with ketamine-assisted psychological therapy in severe alcohol use disorder

SHORT TITLE: MORE-KARE

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Sponsor:	University of Exeter
Sponsor protocol reference:	2022-23-16
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Phase of trial:	Phase III
Version and date of protocol:	V8.0 18/JUN/2024

SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Co-Chief Investigators agree to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928) and any subsequent amendments of the clinical trial regulations, GCP guidelines, the Sponsor's (and any other relevant) SOPs, and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the trial publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the trial will be given; and that any discrepancies and serious breaches of GCP from the trial as planned in this protocol will be explained.

For and on behalf of the Trial Sponsor:

Signature: Date:

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Position: Sponsor representative

Chief Investigator:

Signature: Date:

Name: Dr Stephen Kaar

Scientific lead: Date:

Signature:

Name: Professor Celia Morgan

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ii. LIST OF ABBREVIATIONS

AE	Adverse Event
AlcEd	Alcohol Education
ALT	Alanine transaminase
ALP	Alkaline Phosphate
AR	Adverse Reaction
ASIA	Automated Social Identity Assessment
AST	Aspartate aminotransferase
AUD	Alcohol Use Disorder
AWS	Amazon Web Services
BDI	Beck's Depression Inventory
BP	Blood Pressure
CACE	Complier Average Causal Effect
CAPA	Corrective And Preventative Action
CI	Chief Investigator
CGI	Clinical Global Impression
CRF	Case Report Form
CRN	Clinical Research Network
CTA	Clinical Trial Authorisation
CTIMP	Clinical Trial of Investigational Medicinal Product
CTU	Clinical Trials Unit
DPFB	Development Pathway Funding Scheme
DMC	Data Monitoring Committee
DMP	Data Management Plan
DSUR	Development Safety Update Report
EDC	Electronic Data Capture
EMA	European Medicines Agency
EME	Efficacy and Mechanism Evaluation
ExeCTU	Exeter Clinical Trials Unit
FAQ	Frequently Asked Questions
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	Gamma-GT
GMP	Good Manufacturing Practice
HTTPS	Hyper Text Transfer Protocol Secure

ICF	Informed Consent Form
ICH	International Conference on Harmonisation (of technical requirements for registration of pharmaceuticals for human use).
IMP	Investigational Medicinal Product
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trials Number
ITT	Intention to treat
IV	Intravenous
KARE	Ketamine assisted psychological therapy
LFT	Liver Function Test
MA	Marketing Authorisation
MADRS	Montgomery Ashberg Depression Scale
MBRP	Mindfulness Based Relapse Prevention
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
MICE	Multiple imputation using chained equations
MRC	Medical Research Council
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health and Care Research
NHS	National Health Service
NIAAA	National Institute on Alcohol Abuse and Alcoholism
PI	Principal Investigator
PIC	Participant Identification Centre
PIS	Participant Information Sheet
PPI	Patient and Public Involvement
POCBP	People of Child Bearing Potential
PTSD	Post Traumatic Stress Disorder
RCT	Randomised Control Trial
RDS	Relational Database Service
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SDV	Source Data Verification

SHAPS	Snaith-Hamilton Please Scale
SOP	Standard Operating Procedure
SUD	Substance Use Disorder
SmPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TLFB	Time Line Follow Back
TLS	Transport Layer Security
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
UKCRC	UK Clinical Research Collaboration
USM	Urgent Safety Measure
WHO	World Health Organisation

iii. TRIAL SUMMARY

Trial Title	A multi-centre investigation of increasing alcohol abstinence with ketamine-assisted psychological therapy in severe alcohol use disorder (AUD).	
Internal ref. no. (or short title)	MORE-KARE	
Clinical Phase	3	
Trial Design	Double-blind, randomised, [redacted] multisite, phase III [redacted] trial in participants with severe AUD.	
Trial Participants	Participants with severe alcohol use disorder (AUD)	
Planned Sample Size	280	
Treatment duration	4-12 weeks	
Follow up duration	Six months from randomisation (opportunistic 12 month follow up)	
Planned Trial Period	45 months; 10 months set-up, 24 months recruitment, 6 months follow-up, 5 months analysis and reporting.	
	Objectives	Outcome Measures
Primary objectives and outcome measures	To assess whether KARE therapy [redacted] impacts alcohol use (number of days heavy drinking) over six months (180 days) following the start of treatment in participants with severe AUD, [redacted]	Number of days heavy drinking out of 180 days' follow-up at six months follow-up (Time Line Follow Back: TLFB) – we will aim for 180 continuous days of data to be available. Heavy drinking will be defined using European Medicines Agency (EMA) guidelines (60g/day for males, 40g/day for females).

	[redacted].	TLFB will be cross-referenced with self-report data using the self-breathalyser, BACtrack Skyn (continuous transdermal alcohol monitoring) and alcohol glucuronide urine dipstick and breathalyser at trial visits.
Secondary objectives and outcome measures	Does treatment with ketamine assisted psychological (KARE) therapy [redacted] impact: a. Abstinence over six months (180 days) follow up b. Percentage of heavy drinking days at 180-day follow-up c. World Health Organisation (WHO) risk drinking index	a. Clinical Global Impression (CGI Severity and CGI Improvement) [1] a. Relapse (zero heavy drinking days) at six months (180 days) (TLFB) [2] a. Percentage of days abstinent from alcohol at six months (180 days) (TLFB) [2] a. Liver biomarkers (bilirubin, albumin, GGT, AST, ALT, ALP) b. Percentage of heavy drinking days at 180-day follow-up (TLFB) c. Change in WHO risk level for alcohol of two risk levels: from very high to moderate or high to low, shown to be

		predictive of better quality of life.
	d. Social and role functioning	d. Social functioning (SF-36) [3]
	e. Depression and anhedonia	e. Depressive symptoms (MADRS [4], BDI[5]) e. Anhedonia (SHAPS) [6]
	f. Craving and alcohol dependence	f. Craving (alcohol craving questionnaire) [7] f. Self-efficacy (alcohol abstinence self-efficacy scale) [8] f. Alcohol Dependence Severity Scale (SADQ) [9]
	g. Have a longer-term impact on alcohol use, social functioning and mental health at 12 months (360 days) post randomisation.	g. TLFB [2] g. Change in WHO risk levels g. SF-36 [3] g. BDI [5]
Mechanistic objective	To determine whether changes in depressive and anxiety symptoms, changes in addiction- and depression-	TLFB [2] MADRS [4] BDI [5]

	related aspects of the self-concept, psychological flexibility, readiness to change and family history of AUD following KARE therapy predict reductions in number of days heavy drinking at six months.	BAI APEQ [10] Readiness to change scale [78] Family history (screening) Automated Social Identity Assessment (ASIA) [11]
Qualitative objective	To assess experiences of treatment	Open-ended surveys and semi-structured qualitative interviews
Health economics objective	To establish methods for estimating intervention resource use and costs in a future cost-effectiveness analysis. To assess acceptability of health economic outcome measures.	EQ-5D-5L [12] ICECAP-A [13]
Investigational Medicinal Product (IMP)	Ketamine hydrochloride	
Formulation, Dose, Route of Administration	[redacted] ketamine hydrochloride intravenous (IV) over 40 minutes.	

iv. FUNDING AND SUPPORT IN KIND

The trial is funded by an NIHR EME programme with additional funding from AWAKN Life Sciences Ltd.

v. ROLE OF TRIAL SPONSOR, FUNDER(S), CLINICAL TRIALS UNIT, CHIEF INVESTIGATOR AND SCIENTIFIC LEAD

Sponsor role

The University of Exeter is the Sponsor for this trial. The Sponsor will ensure that the research team has access to resources and support to deliver the research as proposed and that responsibilities for management, monitoring and reporting of the research are in place prior to the study commencing. The sponsor will ensure that there is agreement on recording, reporting and reviewing significant developments as the research proceeds and approve any modifications to design, obtaining requisite regulatory authority approval. Prior to the study commencing the sponsor will be satisfied that:

- The research will respect the dignity, rights, safety and well-being of participants and the relationship with healthcare professionals.
- The Chief Investigator, and other key researchers have the requisite expertise and have access needed to conduct the research successfully.
- The arrangements and resources proposed for the research will allow the collection of high quality, accurate data and the systems and resources will allow appropriate data analysis and data protection.
- Organisations and individuals involved in the research agree the division of responsibilities between them.
- Arrangements are in place for the sponsor and other stakeholder organisations to be alerted to significant developments during the study, whether in relation to the safety of individuals or scientific direction.
- There are arrangements for the conclusion of the study including appropriate plans for the dissemination of findings.

The Sponsor has had input into the design of the trial but overall responsibility for the design lies with the Chief Investigator and scientific lead. The Sponsor is responsible for authorising the initial submission to the Medicines and Healthcare products Regulatory Agency (MHRA), Research Ethics Committee (REC) and Health Research Authority (HRA) and subsequent amendments, ensuring appropriate agreements and indemnity arrangements are in place, overseeing the conduct of the trial and ensuring it adheres to the principles of Good Clinical Practice (GCP) and the UK Policy Framework for Health and Social Care Research, and for archiving at the end of the trial. The Sponsor is not responsible for and has no involvement in the data analysis or interpretation, or for writing manuscripts.

Funder role

The NIHR and Awakn as funders are responsible for providing funds to cover the agreed research costs. The funders are not responsible for and have no involvement in data analysis or interpretation, or for writing manuscripts.

Clinical Trials Unit role

Exeter Clinical Trials Unit (ExeCTU), University of Exeter, is the Clinical Trials Unit responsible for the day-to-day management of the trial. Responsibilities of ExeCTU, the Sponsor, Chief Investigator and scientific lead are defined in detail in a separate task allocation matrix. ExeCTU will be closed on bank holidays and University of Exeter closure days; only emergency trial support will be available at these times.

Chief Investigator

The CI for this trial is Dr Kaar. Dr Kaar has responsibility for overall conduct of the trial, regulatory compliance and medical oversight.

Scientific lead

The scientific lead for the trial is Professor Morgan. Professor Morgan was the grant applicant who conceptualised the trial design and treatment package. Going forwards Professor Morgan will continue to have input into the trial design. Professor Morgan will work with Dr Kaar where appropriate on delegated tasks.

vi. ROLES AND RESPONSIBILITIES OF TRIAL MANAGEMENT COMMITEES/GROUPS & INDIVIDUALS

Trial Steering Committee

The Trial Steering Committee (TSC) will be composed of an independent chairperson with expert knowledge in the subject area, an independent statistician, patient and public involvement (PPI) representative(s) and at least one other independent professional member. The CI, scientific lead, senior trial statistician, trial statistician, trial manager and representatives of the sponsor and funder

will be invited to attend TSC meetings as observers but will not be voting members. The role of the TSC is to monitor and supervise the progress of the trial. The TSC chair and/or TSC committee will review the final protocol prior to submission to MHRA/HRA/REC and approve the Statistical Analysis Plan (SAP) prior to final database lock. The TSC will meet prior to recruitment commencing and at least 6-monthly thereafter. Further details of the roles and responsibilities of the TSC are documented in the TSC charter.

Data Monitoring Committee

The Data Monitoring Committee (DMC) will be composed of a minimum of three independent professional members, including a statistician. The Chief Investigator, scientific lead, senior statistician, trial statistician and trial manager will be invited to attend the open sessions of DMC meetings but will not be voting members. The senior statistician will be unblinded throughout the trial and the trial statistician will remain blinded until the completion of the SAP. Only the unblinded statistician(s) can be invited to the closed section of DMC meetings and will prepare/review unblinded sections of the DMC report. The DMC will monitor accumulating trial data, including safety, and make recommendations to the TSC as to whether there are any ethical or safety issues that may necessitate a modification to the protocol or early closure of the trial. Further details of the roles and responsibilities of the DMC are documented in the DMC charter.

Trial Management Group

The core Trial Management Group (TMG) will be composed of the Chief Investigator, scientific lead, trial statisticians, PPI lead, the trial managers, data manager(s), ExeCTU quality assurance representative, trial consultant pharmacist, supervising therapist and the Sponsor Representative. The wider TMG will include the trial co-applicants, health economist, natural language lead, Clinical Research Network (CRN) representative, and at least one lay representative. The TMG will write the protocol, SAP and participant-facing materials, obtain relevant approvals from the MHRA, REC and HRA, coordinate with NHS Trusts to set up sites and ensure the trial is conducted according to the principles of GCP and the UK Policy Framework for Health and Social Care. The wider TMG will meet at least every three months to discuss wider trial management and issues. The core TMG will meet more frequently depending on the needs of the trial to manage the day-to-day running of the trial, monitor safety, key performance indicators and discuss and resolve emerging issues. Members of the

TMG will analyse the data, interpret the analyses, write reports to the funder and write and submit manuscripts to peer-reviewed journals.

Patient and Public Involvement (PPI) Group

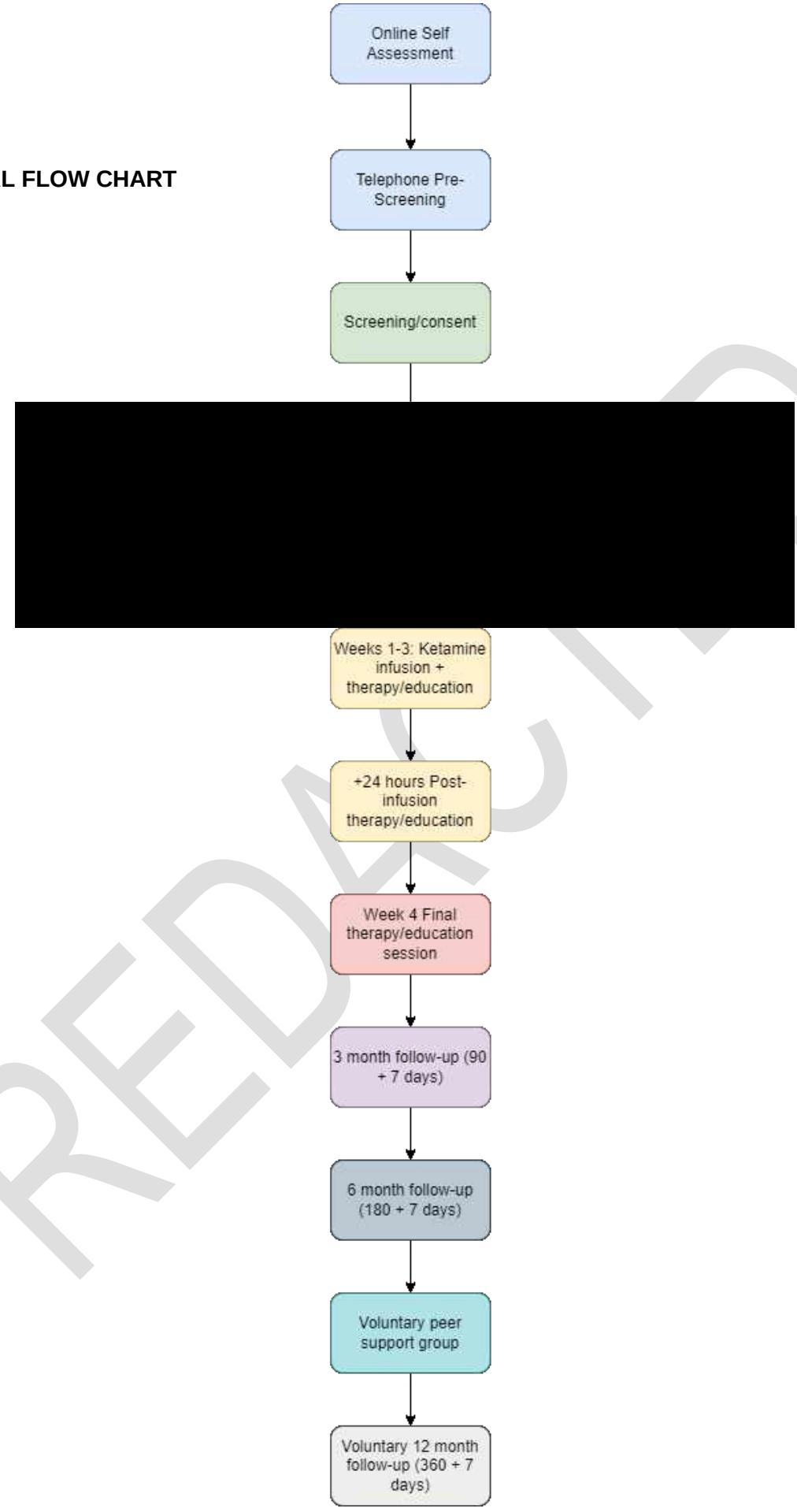
An overarching PPI group will review patient-facing materials prior to ethical review and will have input into any revisions to patient-facing materials throughout the trial. At the start of the project, relevant and supportive stakeholders (user advocacy groups, recovery champions, third sector providers, statutory alcohol services, primary care) will be engaged in a series of regional workshops, led by our area leads and PPI champions. The workshops will take place annually: the first focused on the trial design, recruitment and principles of treatment, the second providing further therapy detail, generating insights and exploring potential treatment delivery in each setting; in the final year of the project all the regional groups will be invited to attend a conference in person (with hybrid options available), where the trial and core PPI team will present the findings and seek early input in a series of focus groups and breakout sessions.

The PPI group will work to raise awareness and educate primary care and addiction staff about the trial.

The PPI group will develop an inclusive and accessible dissemination web-based platform to explain the findings and treatment clearly. Throughout the project, the PPI group, in conjunction with the core trial team, will maintain a journal reflecting their experience of research processes, with a view to disseminating extracts to give insight into the workings of clinical trials for a wider audience.

vii. KEY WORDS:	Ketamine, alcohol use disorder, alcohol abstinence, ketamine-assisted psychological therapy

viii. TRIAL FLOW CHART



1 BACKGROUND

Alcohol use disorders (AUDs) result in 3 million deaths globally per year [14]. Over the last forty years, UK liver disease rates from alcohol have increased by around 250% - during which time they have fallen across much of the developed world [15, 16]. AUDs are among the most prevalent of mental health disorders, with one in five individuals suffering at some point in their lifetime [17]. However, treatment success rates are very low [18], with up to 75% of patients with AUD returning to harmful drinking within 12 months of treatment [19]. Relapse to heavy drinking within 6-12 months of treatment is associated with heavier drinking and greater alcohol-related harms compared to abstainers [20, 21]. There is a clear need for novel treatments to reduce relapse rates and reduce alcohol-related harm, and treat the rising numbers of individuals in the UK who do not respond to existing treatments [22].

Alcohol-related harm is estimated to cost the National Health Service (NHS) £3.5 billion per annum [23] and an estimated £21-52 billion to wider society [24]. In the UK, more than half a million adults have severe AUD and need treatment: but only one in five people with AUD will access it [19]. Treatment adherence in AUD is also the poorest of all mental health services [25]. Furthermore, engagement with services varies geographically with many of the most deprived areas facing the most acute gaps in provision, and worst treatment outcomes [26, 27]. Alcohol-related harms are greatest in marginalised groups, perpetuating health inequalities [19, 28, 29]. Such inequalities have deepened since the start of the COVID-19 pandemic with 58% increases in harmful drinking in the UK and 20% increases in alcohol-specific deaths such as liver disease [30], but 33% of all alcohol-specific deaths occurred in the most deprived 20% of the population [31].

In the UK, more than half a million adults are alcohol dependent, and need assessment and treatment [32]. However, only one in four of those with alcohol dependence seek treatment, and relapse is common [33]. The relevant National Institute for Health and Care Excellence (NICE) guideline [34] recommends a comprehensive assessment, followed by either community-based or residential medically-assisted alcohol withdrawal. But just twelve months after detox, 75% of patients will have returned to heavy drinking [18]. This indicates huge scope for improvement in clinical outcomes. Many patients drop out of treatment, particularly those exhibiting severe alcohol dependence and comorbidities. This is not only wasteful of scarce service resources, but clinically risky as repeated withdrawals from alcohol are associated with an increase in the severity of withdrawal symptoms and can precipitate poor outcomes [35]. Pharmacological interventions including acamprosate, naltrexone, and disulfiram, in conjunction with psychotherapy, have been recommended [34]. However, treatment

effects are modest at best, evidenced by the high rates of returning to heavy daily drinking. We urgently need new approaches to reduce the considerable mortality and morbidity associated with alcohol use disorder.

2 RATIONALE

Research question: Does treatment with Ketamine Assisted psychological therapy for alcohol REduction (KARE) reduce the number of days of heavy drinking at 6 months (180 days) following the start of treatment?

The discovery of ketamine as a rapid acting anti-depressant has had a profound impact on psychiatry, hailed as the greatest advance in the past 50 years [36]. A growing body of research suggests that ketamine is also a promising treatment for AUD. Importantly, in studies in AUD, unlike those in depression, ketamine has been given alongside psychological therapy, which has been suggested to enhance the ketamine treatment effect [37, 38].

Early evidence for the use of ketamine-assisted psychotherapy in the treatment of AUD reported that 70% of participants given ketamine alongside therapy remained abstinent at one year compared to 24% of participants given treatment as usual [38]. Whilst promising, this study was neither controlled nor blinded and was conducted in a unique setting with Russian inpatients.

More than 20 years later, a randomised study of 40 heavy drinkers in the US found that giving a single ketamine infusion (0.71 mg/kg IV) paired with motivational enhancement therapy significantly increased abstinence rates and reduced heavy drinking days over the 21 days post-infusion compared to a midazolam control [38]. Other recent experimental work in heavy social drinkers has found that a single dose of ketamine following a memory reactivation protocol is associated with reduced drinking at 12 months compared to placebo [39].

The most directly relevant ongoing study is a phase II trial currently in recruitment (New York Psychiatric Institute, Columbia University). Key differences between our completed Medical Research Council (MRC)-funded Development Pathway Funding Scheme (DPFS) proof-of–concept study and this ongoing trial are the follow-up periods (six months, as in our studies, is suggested in Food and

Drug Administration (FDA) and EMA regulatory guidance to be a minimum necessary to evaluate efficacy endpoints) and our inclusion of a more severe group of patients with AUD. As our previous study completed in 2020, we are at the forefront of this research globally. The Phase III study proposed in this protocol is the appropriate course to take this work forward.

Current treatment options for AUD are limited. Behavioural and psychological therapies work for some individuals, but effects are rarely long lasting. Licensed adjunctive relapse prevention medicines do not result in sustained robust changes in drinking behaviour for the majority of people treated in England [40]. Relapse prevention pharmacotherapies also have poor adherence and require daily dosing [34], including three times daily for acamprosate [41]. Naltrexone cannot be used if taking an opiate agonist, which is a limitation in the current prescribing climate. Disulfiram is associated with adverse events and toxicity [42].

All existing adjunctive pharmacological therapies are recommended for a minimum of six months to a year if effective [34], whereas our KARE therapy, by comparison, is for a short duration, requiring only four weeks of active treatment. [redacted] Our PPI team noted that the brevity of the treatment would likely improve treatment adherence. The PPI team reported that the short, intensive, individual treatment was an improvement on group therapy programmes that are currently standard care in alcohol treatment services in the community or residential detoxification programmes. Numbers in treatment in the UK are declining and efforts disproportionately focused on prevention, leaving this group of patients underserved by health care systems [35]. The KARE therapy solution, if shown to be efficacious, will lead to an improvement in care by providing a new treatment option for patients who have limited options. This evidence-based treatment may also provide increased service capacity, given the shorter treatment period. Also, the potential for ketamine therapy to simultaneously tackle other mental health issues would lead to an improvement in care of patients, as services may struggle to treat both mental health and alcohol use problems.

The proof of concept for this proposal comes from our MRC-funded Phase II randomised controlled clinical trial, in 96 participants with severe AUD. We observed that [redacted] KARE therapy increased percentage days abstinent from alcohol [redacted]

[redacted]. We included four groups in this proof-of-concept study: 1) ketamine+psychological therapy (*KARE therapy*); 2) ketamine+ alcohol education (AlcEd); 3) placebo+psychological therapy, 4) placebo+AlcEd, to identify whether treatment effects were improved by adding KARE therapy alongside ketamine. Our AlcEd condition was a placebo for the psychological therapy, 7 sessions delivered at the same time points/intervals as psychological therapy was, which matched the time spent with the therapist but included no active psychological intervention.

For the primary outcome of percentage of days abstinent from alcohol at six months' follow-up, the greatest abstinence rate was observed in the KARE therapy arm (*active/active*), then ketamine+AlcEd (active/control), then placebo+psychological therapy (control/active), with lowest abstinence seen in the placebo+AlcEd arm (control/control) (see Figure 1).

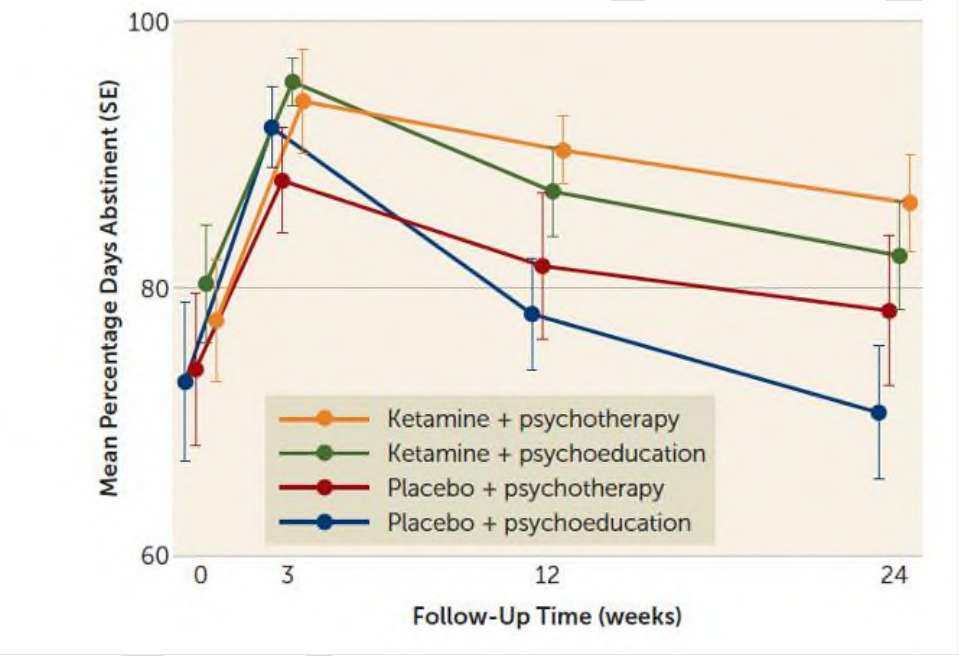


Figure 1: Primary outcome percentage days abstinent from alcohol at six months [43]

We now need to take this work forward to provide definitive evidence of the efficacy of KARE therapy as a treatment for AUD, to inform a step change in treatment of AUD in the UK. [redacted]

[redacted]

In this trial, rather than using saline placebo, we now propose including a very low, sub-therapeutic dose of ketamine to control for the functional unblinding that can occur with ketamine administration [44] by better controlling expectancy, as participants will be told they will receive one of two doses of ketamine. We have found this approach to be effective at better preserving the blind in a previous RCT [45]. Our PPI group also felt that this change may improve retention still further (which was 20% attrition at six months in proof-of-concept study) as participants would be told they would be receiving one of two doses of the study drug.

Ketamine is now established as a rapid acting anti-depressant [44] and esketamine (an enantiomer of the drug) is licensed for use in treatment-resistant depression [46]. Depressive symptoms are rife in alcohol use, particularly following detoxification [47]. Conventional anti-depressants are at best only mildly effective in alcoholism [34], which is problematic as depressive symptoms precipitate relapse [48-50]. Treating depressive symptoms during the vulnerable period post-detoxification may be one mechanism through which ketamine and combined therapy is an effective treatment in AUD.

Ketamine produces a more robust anti-depressant effect in treatment-refractory depressed individuals with a family history of AUD compared to those without [51, 52], likely due to genetic differences, therefore ketamine may also plausibly work more effectively as an antidepressant in AUD compared to in individuals who are depressed without AUD [37]. Our Phase II study observed reductions in depressive symptoms at three months post-ketamine treatment compared to placebo. Advances in machine learning mean we are able to investigate addiction- and depression-related changes to the self-concept by analysing natural language in line with a pattern classifier validated in previous work [53].

Investigating changes in depressive symptoms in AUD following ketamine treatment is important as this has wider implications for service delivery. Alcohol treatment services are often not equipped to treat individuals with other mental health problems; similarly, mental health services do not treat patients with current alcohol problems. This is an insurmountable barrier to treatment for a vast number of people with AUD [23]. Ketamine presents an important potential solution to this problem as

the drug is not only licensed as an antidepressant but is also being trialled in anxiety [54] and Post Traumatic Stress Disorder [44, 55], two other major co-morbidities in AUD. If ketamine can reduce other mental health symptoms concurrently to reducing alcohol use, then this may transform access to treatment for patients with AUD.

3. ASSESSMENT AND MANAGEMENT OF RISK

Excellent safety and tolerability data suggest that the risks of ketamine treatment would be low. Ketamine is currently indicated as an anaesthetic agent for diagnostic and surgical procedures. The use of ketamine for this anaesthetic purpose administers higher doses (1mg/kg to 4.5mg/kg over 60 seconds) than our proposed dose of 0.8mg/kg over 40 minutes, and even at these higher doses ketamine has a very good safety profile [56]. Ketamine is suggested to be used with caution in chronic alcohol dependence and the acutely alcohol-intoxicated patient. However, this is for anaesthetic doses and our phase II study indicated better liver function following treatment. Breathalysers will be used to exclude participants currently intoxicated with alcohol.

The Summary of Product Characteristics (SmPC) states that dose reductions should be considered in alcohol dependent patients: our trial does intend to use less than the minimum clinical dose of 1mg/kg as the SmPC indication is for use in anaesthesia. The SmPC also states that abnormal Liver Function Tests (LFTs) associated with ketamine use have been reported, particularly with extended use (>3 days) or drug abuse. Ketamine will be used at a lower dose than anaesthetic levels and will only be given in 3 isolated low doses, spaced at weekly intervals. Ketamine has a very short half-life and so will be quickly eliminated from the system [57].

3.1 Assessment and management of risk

The trial population and safety monitoring procedures in place in this trial are reflective of the SmPC and clinical experience. The SmPC to be used in this trial relates to anaesthetic doses of ketamine and is not all necessarily relevant given the smaller dose being used in this trial. Mechanisms to detect and address adverse events are in place, according to established CTU procedures (see section 10). A detailed risk assessment has been undertaken by ExeCTU and will be maintained and updated throughout the trial. The risk assessment is stored within the Trial Master File (TMF) and is available upon request from the Trial Manager. This trial has been characterised as type B (risk associated with modified use of an existing product) based on the MHRA risk adaptive approaches to the management of Clinical Trial of Investigational Medicinal Products (CTIMPs) categories as the IMP (ketamine) has

marketing authorisation but the MORE-KARE trial will use the IMP outside of these specifications. Participants with contraindications to ketamine will be declined entry into the trial, as detailed in the exclusion criteria (section 7.2).

A common side effect of ketamine infusion are the psychological effects of the drug. These effects can vary between pleasant dream like states and vivid imagery to out of body experiences and hallucinations. In this trial we are using a dose (0.8mg/kg) much lower than the anaesthetic dose. A review examining these phenomena across 450 volunteers given similar doses to those to be given in this study found only 6 incidences of such mental states that were unpleasant enough to require the infusion to be stopped, all of which remitted completely in the hours following the cessation of the infusion [58]. Patients with schizophrenia given doses of ketamine similar to those administered in this study have been known to have longer lasting psychotomimetic states [59] and for that reason psychosis and schizophrenia in the participants currently or historically are exclusion criteria for the trial (see section 7). Emergence phenomena can be reduced by stopping the infusion. Due to the short half-life of ketamine, once the infusion is stopped these effects should remit very rapidly. Alternatively with co-administration of a benzodiazepine; lorazepam can be administered by the trial medic if the emergence phenomena are intolerable to the participant. Participants will be made aware of the possibility of such AEs in the PIS and during the consenting discussions. Additionally, participants will need to be judged as ‘street ready’ by a medic before leaving the research facility, will be collected by a responsible adult or transport arranged for them, and will be given a 24-hour contact card for emergencies.

Ketamine is sometimes used recreationally and can be a drug of abuse, as such participants with a significant history of substance use disorder other than alcohol and those who have a current substance use disorder (other than alcohol and cannabis) and are seeking treatment (past 12 months) will be excluded from the trial. Anyone with a history of ketamine use disorder will also be excluded. No previous studies giving ketamine to this patient group have found evidence that participants subsequently went on to abuse the drug. We will also be monitoring urine samples from participants throughout the trial for signs of ketamine abuse.

3.2 Potential benefits

We do not know whether KARE therapy is efficacious or not; however, benefits of no longer being dependent on alcohol for participants are considerable and wide-ranging. Physical health would improve, and risks of alcohol-related diseases such as cirrhosis of the liver would decrease. Benefits would also be observed in terms of end users' mental health (depression, anxiety) and improved cognitive function, as well as quality of life. Benefits would be reflected economically, not only in a reduction in burden to the NHS but in more frequent and regular engagement in work activities, benefits to family and a reduction in crime [77]. Alcohol is also associated with considerable acute harms. In 2012, 15,401 deaths in England and 1.24 million hospital admissions are attributable to alcohol consumption [57], therefore benefits would also accrue in a reduction in burden on the NHS and its workforce, in alcohol-related deaths and in other non-fatal acute harms. Importantly for end users, the brief nature of our pharmacological intervention will be less stigmatising than current treatments that require taking pharmacotherapies for prolonged periods.

4 OBJECTIVES AND OUTCOME MEASURES/ENDPOINTS/ESTIMANDS

4.1 Primary objective

To assess whether KARE therapy [redacted] has any effect on alcohol use at six months (180 days) following the start of treatment in participants with severe AUD [redacted].

We hypothesise that KARE therapy [redacted] will promote reduction of harmful alcohol use (number of heavy drinking days on TLFB) at six months following the start of treatment in participants with severe AUD [redacted].

The estimands for the primary objective of the MORE-KARE trial are set out in Table 1 below.

Table 1. Estimands for primary objective of the MORE-KARE trial

Population	People aged 18 and over with severe alcohol use disorder (AUD)
Treatment conditions	[redacted]
Outcome variable	Number of heavy drinking days at 180 days' follow-up
Handling of intercurrent events	1. Treatment policy 2. Principal stratum
Population level summary measure	Between group mean difference

4.2 Secondary objectives

Determine whether or not treatment with ketamine assisted psychological (KARE) therapy [redacted] impacts:

a) Continuous abstinence at six months (180 days) follow-up
b) Percentage days heavy drinking at 180 days' follow-up
c) WHO risk drinking index
d) Social and role functioning
e) Depression and anhedonia
f) Craving and alcohol dependence.

Additional secondary objectives include the following:

g) To establish methods for estimating intervention resource use and costs in a future cost-effectiveness analysis
h) To assess acceptability of health economic outcome measures
i) To assess continuing impact of KARE therapy on alcohol use, social functioning and mental health at 12 months (360 days) post randomisation.

We hypothesise that KARE therapy will promote continuous abstinence at six and twelve months' follow-up, reduce WHO risk drinking index, improve social and role functioning, improve depression

and anhedonia, and reduce craving and alcohol dependence in participants with severe AUD [redacted].

4.2.1 Mechanistic objective

To determine whether changes in depressive and anxiety symptoms following KARE therapy predict reductions in number of days heavy drinking at six months (180 days).

We hypothesise that reductions in depressive and anxiety symptoms at the end of the treatment period (assessed both on validated depression symptom scales, family history and through natural language markers) will predict fewer heavy drinking days at six months.

We hypothesise that increased psychological flexibility (assessed via the recently validated APEQ) and higher readiness to change (assessed via the readiness to change scale) will predict fewer heavy drinking days at six months.

4.3 Outcome measures/endpoints

4.3.1 Primary endpoint/outcome

The number of days heavy drinking at six-month follow-up (Time Line Follow Back : TLFB [60]: the most commonly used method in AUD clinical trials; a minimum of 180 days of data will be required with the measurement period capped at 187 days [43]. Heavy drinking will be defined using EMA guidelines (60g/day for males, 40g/day for females).

TLFB data will be cross-referenced with self-report data using the self- breathalyser, BACtrack Skyn (continuous transdermal alcohol monitoring) and alcohol glucuronide urine dipstick and breathalyser at trial visits.

4.3.2 Secondary endpoints/outcomes

- Clinical Global Impression (CGI Severity: [1])
- Clinical Global Impression (CGI Improvement: [1])

- Reduction in WHO risk for alcohol by at least two risk levels: e.g., from very high to moderate or high to low, shown to be predictive of better quality of life
- Relapse (zero heavy drinking days as defined above 60g/day for males, 40g/day for females 4.3.1) at six months (TLFB [2])
- Percentage of Days Abstinent from alcohol at 6 months (TLFB [2])
- Percentage of heavy drinking days at 180 days' follow-up
- Liver biomarkers (bilirubin, albumin, GGT, AST, ALT, ALP)
- Depressive symptoms (Montgomery Ashberg depression scale; MADRS[4])
- Depressive symptoms (Becks Depression Inventory; BDI [5])
- Social functioning (SF-36 [3])
- Craving (Alcohol Craving Questionnaire [7])
- Anhedonia (SHAPS [6])
- Self-efficacy (alcohol abstinence self-efficacy scale) [8]
- Alcohol dependence (SADQ) [9]

4.4 Exploratory endpoints/outcomes

4.4.1 Mechanistic outcome

We will explore whether (i) changes in depressive and anxiety symptoms, (ii) changes in addiction- and depression-related aspects of the self-concept (iii) psychological flexibility (APEQ) (iv) readiness to change and (v) family history of AUD can predict treatment success (i.e. reductions in numbers of heavy drinking days at six months) by a number of indicators: 1) natural language processing from the 3 things task; 2) family history data collected at screening, 3) changes in traditional depression indexes (MADRS, BDI).

4.4.2 Exploratory sample analysis

We will collect blood samples from participants according to the schedule outlined in Table 2 (page 46). Plasma samples will be analysed for levels of ketamine and the metabolite norketamine, so that exploratory analyses may covary for indivdual differences in drug metabolism.

4.4.3 Open-ended Survey and Semi-Structured Interview

Participants will be invited to take part in an optional qualitative component of the trial. An open-ended survey will be provided to those participants who opt-in to the qualitative aspect of the trial at visit 1 asking about preconceptions around ketamine. A semi-structured interview concerning their experiences with the intervention would then be carried out after their visit 10 (within 3 months) with an academic staff member from the University of Exeter. Data will be analysed using reflexive thematic analysis [62]; around 15-20 participants are likely to be required to reach saturation. [redacted]Three or four participants will be identified from each site, following asking them at randomisation whether they wish to take part.

4.4.4 Feasibility for Health Economic Evaluation

We will explore the feasibility of collecting appropriate data to inform a future cost-effectiveness analysis of KARE therapy. We will establish methods for estimating intervention resource use and costs, and assess the acceptability of outcome measures suitable for use in cost-effectiveness analyses, these being the EQ-5D-5L [12], and the ICECAP-A [13].

4.5 Table of endpoints/outcomes

Objectives	Outcome Measures	Timepoint(s) of evaluation of this outcome measure (if applicable)
To assess whether KARE therapy impacts alcohol use following the start of treatment in participants with severe AUD [redacted].	Number of days heavy drinking (Time Line Follow Back: TLFB) – a minimum of 180 days of data will be required from participants. Heavy drinking will be defined using European Medicines Agency (EMA) guidelines (60g/day for males, 40g/day for females). TLFB will be cross-referenced with self-report data using the	6-month (180 days post randomisation) follow-up

	'self-breathalyser, BACtrack Skyn (continuous transdermal alcohol monitoring) and alcohol glucuronide urine dipstick and breathalyser at trial visits.	
Does treatment with ketamine assisted (KARE) therapy [redacted] impact: a. Abstinence at six months follow up b. Percentage of heavy drinking days at 180 days' follow-up c. World Health Organisation (WHO) risk drinking index d. Social and role functioning	a. Relapse at six months (TLFB) a. Percentage of days abstinent from alcohol at 6 months (TLFB) a. Clinical Global Impression (CGI Severity and CGI Improvement) a. Liver biomarkers (bilirubin, albumin, GGT, AST, ALT, ALP) b. Percentage of heavy drinking days at 180-day follow-up c. Reduction in WHO risk level for alcohol of two risk levels: from very high to moderate or high to low, shown to be predictive of better quality of life d. Social functioning (SF-36)	a. 6-month (180 days post randomisation) follow-up b. 6-month (180 days post randomisation) follow-up c. 6-month (180 days post randomisation) follow-up d. 6-month (180 days post randomisation) follow-up

e. Depression and anhedonia f. Craving and alcohol dependence g. To assess continuing impact of KARE therapy on alcohol use, social functioning and mental health at 12 months post randomisation.	e. Depressive symptoms (MADRS, BDI) e. Anhedonia (SHAPS) f. Craving (alcohol craving questionnaire) f. Alcohol Dependence Severity Scale (SADQ) f. Self-efficacy (alcohol abstinence self-efficacy scale) g. Alcohol use (TLFB) g. Change in WHO risk levels g. Social functioning (SF-36) g. Depressive symptoms (BDI)	e. 6-month (180 days post randomisation) follow-up f. 6-month (180 days post randomisation) follow-up g. 12-month (360 days post randomisation) follow-up
Mechanistic objective: To determine whether changes in depressive and anxiety symptoms, addiction-/depression-related aspects of the self-concept, psychological flexibility, readiness to change, and family history following KARE therapy predict reductions in number of days heavy drinking.	MADRS BDI BAI APEQ Readiness to change scale Family history (screening) Natural language processing of 5 minutes of participant speech data at each time point in the trial using Automated Social	6-month (180 days post randomisation) follow-up

	Identity Assessment (ASIA) – 3 things tasks	
Health economics objectives: To establish methods for estimating intervention resource use and costs in a future cost-effectiveness analysis To assess acceptability of health economic outcome measures	EQ-5D-5L ICECAP-A	6-month (180 days post randomisation) follow-up

5 TRIAL DESIGN

Double blinded, randomised, controlled multi-site phase III [redacted] trial in participants with severe AUD. See Table 2 (page 46) for Schedule of Events.

6 TRIAL SETTING

280 participants will be recruited from primary care and alcohol services using local clinical research networks (CRNs), secondary care and non-statutory alcohol services, forums and social networking, relevant charities such as Alcohol Change, newspaper, radio and TV, in advice centres, via word of mouth and face to face contact. We will recruit in roughly ten hubs covering a wide geographical area across the UK so as to include participants from urban and rural settings, and with a wide range of socio-demographic characteristics. All sites will be required to have obtained management approval and undertake a site initiation visit prior to the start of recruitment into the trial.

Each site will have a research team, with a local Principal Investigator (PI), research nurses, and a Psychological Wellbeing Practitioner (PWP)/assistant psychologist to deliver the therapy component of the trial. A list of participating sites will be maintained by the trial manager and can be found within the TMF.

7 PARTICIPANT ELIGIBILITY CRITERIA

Eligible participants who take part in the trial must meet all of the listed inclusion criteria, and none of the exclusion criteria. Eligibility waivers to inclusion/exclusion are not permitted. Please refer to section 8.1.2 for further information on eligibility assessments.

7.1 Inclusion criteria

1. 18 years old or over
2. Meet DSM-5 criteria for severe AUD
3. Abstinent from alcohol at randomisation (verified with withdrawal symptom checklist and breathalyser BAC level 0.00)
4. Seeking to reduce or quit alcohol long-term.
5. Willing and able to consent and comply with trial procedure.
6. People of childbearing potential and their sexual partners must be willing to use an effective method of contraception* (and must agree to continue for 6 weeks after the last dose of the IMP). Participants must be willing to inform the trial team if pregnancy occurs.
7. People of childbearing potential must have a negative pregnancy test within 28 days prior to being registered for trial treatment and on the day of first treatment.

* Highly effective contraception is defined as one of the following: combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, or transdermal); progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, or implantable); intrauterine device; intrauterine hormone-releasing system; bilateral tubal occlusion; vasectomised partner; practising true abstinence (when this is in line with the preferred and usual lifestyle of the subject). People of child-bearing potential could also be post-menopausal (no menses for 12 months without an alternative medical cause) or be surgically sterile (hysterectomy, bilateral salpingectomy, or bilateral oophorectomy).

7.2 Exclusion criteria

1. Currently taking any other alcohol relapse prevention medication
2. Current uncontrolled hypertension (systolic ≥ 150mm Hg or diastolic ≥ 100mm Hg)
3. Being actively treated for a current co-morbid substance use disorder (SUD) or having been treated in the past 12 months. If the participant is currently in treatment for a comorbid SUD but is abstinent from any substance use and has a negative urine drug screen (except cannabis and benzodiazepine) participant could be included at the discretion of the investigator.
4. History of ketamine use disorder as assessed by the SCID.
5. Pregnant or breast-feeding

6. Not willing to use effective contraception or (people of child-bearing potential) take pregnancy test.
7. Use of another experimental IMP that is likely to interfere with the trial medication within 3 months of trial enrolment.
8. Known allergies to ketamine or excipients of IMP.
9. Meets current criteria for or has a history of any psychotic illness including substance induced psychosis.
10. Current suicide risk as judged clinically and using CSSR or a history of a suicide attempt within the past year.
11. BMI < 16 or > 35
12. Positive urine drug screen for ketamine.
13. Where there are “Special warnings and precautions for use for ketamine infusion” according to the SmPC.
14. Where risk vs benefit ratio is not in favour of giving ketamine, with assessment made by physical examination by medically qualified trial personnel, self-report, or inspection of the medical notes.
15. Received any previous ketamine treatment

8 TRIAL PROCEDURES

Double blinded, randomised, controlled multi-site phase III [redacted] trial in participants with severe AUD. See Table 2 for Schedule of Events.

8.1 Recruitment

8.1.1 Participant identification

The participants will be primarily recruited through Participant Identification Centres (PICs). These centres will be the substance misuse and addiction psychiatry services in all participating NHS Trusts who will review their caseloads and refer potential participants to the research team by directing patients to complete the online self-assessment questionnaire on the trial website. The principal and co-investigators will work to raise awareness and educate all addiction service providers about the trial. Based on previous experience, we expect that recruitment of suitable participants will occur by self-referral through advertising on social media, and also by being identified by their doctor, nurse or other professional in the clinic or service they are attending. Participants will also be identified in primary care (GP practices) with the aid of Clinical Commissioning Groups. PICs will be provided with

a recruitment flyer that can be distributed amongst staff, to promote the trial to potential participants, and to help them remember the key aspects of the trial, e.g., basic inclusion/exclusion criteria, and facilitate discussion. If interested, the potential participant will be directed to a mobile-optimised trial website where a REC approved invitation to participate letter, frequently asked questions (FAQ) and detailed participant information sheet (PIS) will be hosted giving a description of the trial. Potential participants can complete a self-assessment questionnaire on the trial website. For those without internet access, those referring the potential participant on to the trial can print the trial documents for them and provide site contact details to contact the trial team directly. Those who are potentially eligible based on their self-assessment questionnaire answers will have contact details (email address and/or telephone number) for their local site made available to them for potential participants to arrange a follow-up pre-screening phone call with the site. The online self-assessment questionnaire will not collect any data including answers provided. A privacy notice will be included at the beginning of the online self-assessment questionnaire explaining this to potential participants.

Potential participants should make contact with the trial teams either *via* telephone or email to arrange a convenient date for a telephone pre-screen. During this call the research team will discuss the trial in more detail and answer any queries they may have. If they would like to participate, the research team will then go through the detailed pre-screening questionnaire to establish whether the potential participant appears eligible to attend for a full screening appointment. Only non-identifiable general demographic data will be entered in the trial database i.e. age, gender, ethnicity etc at this stage. If the potential participant appears eligible, an appointment will be arranged to see them at the clinical research facility or approved trial site local to them. The potential participant will be sent a detailed PIS *via* post or email based on their preference. A minimum of 24 hours should be allowed between receipt of PIS and informed consent. If a potentially eligible participant is identified prior to detoxification from alcohol, an appointment will be made for after their detoxification (see section 8.1.2.3). At the initial visit with the research team and a medical doctor, the trial will be explained, written informed consent obtained, their eligibility assessed and screening assessments completed. The site will take a full medical history at screening but will write to the GP to inform them of participation in the trial with the participant's consent, and the GP should inform the site within 2 weeks if they have any concerns about the participant taking part in the trial. If no concerns are raised within 2 weeks, a date will be made for them to attend the trial centre for their first treatment visit.

If a potential participant decides prior to the screening visit that they do not want to be involved in the trial, telephone pre-screening source data collected by the research site will be kept until the trial is complete at which time it will be deleted. Non-identifiable data already gathered on the trial screening log will be kept.

We will publicise the trial through forums and social networking, relevant charities such as Alcohol Change, newspaper, radio and TV, in advice centres, *via* word of mouth and face to face contact. All trial publicity advertisement as described here will be submitted and approved by the University of Exeter and REC.

8.1.1.1 Pre-screening

Identification and the pre-screening telephone call should be within 12 weeks of the screening visit, otherwise pre-screening will need to be repeated.

Potential participants can self-refer through an online self-assessment questionnaire hosted on the trial website. For those who are potentially eligible for the trial based on their answers, they will then have a telephone pre-screening assessment carried out by delegated members of the research team. The online self-assessment questionnaire will include:

- Age
- Location i.e. city/town (to help identify which site would be appropriate for participation)
- Current level of drinking
- BMI (height, weight)
- Current or previous diagnosis of schizophrenia
- Current involvement in another clinical trial
- Pregnancy/breastfeeding
- Exclusion medications and allergies

Those who are ineligible based on the answers given on the online self-assessment will be thanked for their interest in the trial and directed to other available resources to help with reducing alcohol use.

The follow-up telephone pre-screening assessment by the research team for those who were potentially eligible after completion of the online self-assessment questionnaire, will be made to conduct the following.

- Discuss the trial.
- Further confirm potential eligibility using the inclusion and exclusion criteria in section 7, and whether the potential participant will be invited for a full screening visit.
- Current alcohol use in units per day for the past 14 days (TLFB).
- Book screening visit for those who continue to be potentially eligible and still express interest in participating.

Those who are ineligible after telephone pre-screen will be thanked for their interest in the trial and directed to other available resources to help with reducing alcohol use.

8.1.2 Screening

For those participants who are deemed potentially eligible based on their pre-screening assessments, a formal screening visit (visit 1) will be carried out to further assess eligibility at a trial site. The screening visit should be carried out between 28 (maximum) to 14 (minimum) day(s) before visit 2 (baseline) visit. The methods of the assessments are explained in section 8.6. Informed consent to participate in the trial prior to the assessments will be carried out at this visit (see section 8.2).

Following screening and eligibility determination by the PI or appropriately delegated member of the research team, those still meeting criteria for inclusion in the trial can be fitted with the BACtrack Skyn device at any time between the screening visit and visit 2. A date for visit 2 will be arranged, within 28 days of the screening date. If 28 days lapses a re-screening visit must be carried out, see section 8.1.2.1 for details. Those who are ineligible after the screening visit will be thanked for their time and directed to other resources aimed at reducing alcohol use.

The screening visit schedule is set out in Table 2. Some repeat screening tests are allowed if participants are deemed ineligible on the basis of blood pressure, breathalyser reading, urine drug screening and BMI, see section 8.1.2.2 for further details.

8.1.2.1 Refresher Screening

If more than 28 days pass between the screening visit and visit 2 (baseline) a refresher screening visit can be run to update the data collected at the initial screening visit to ensure eligibility is still reliable before attending visit 2. Such a refresher session would involve re-running assessments for measures

which could have changed over the course of time between the two visits. The visit schedule is set out below and in Table 2.

Those who are ineligible after the screening visit will be thanked for their time and directed to other resources aimed at reducing alcohol use.

8.1.2.2 Repeat screening tests

If participants are deemed ineligible at any point prior to randomisation, solely based on the following variable physical measures, then participants can be invited back to the trial site to repeat one or more such tests to determine whether these are genuinely outside of protocol eligibility boundaries.

- Breathalyser (If the initial breathalyser reading is >0, participants who wish to continue with detoxification and return once they are abstinent will be re-consented).
- Inflated blood pressure with no evidence of uncontrolled hypertension, e.g., due to situational anxiety or recent alcohol withdrawal.
- BMI outside of trial limits.
- Positive urine drug screen due to recreational drug use, when there is no evidence of a current moderate-severe use disorder.

Table 2. Assessments to be carried out at each visit/time point.

	Pre-Screening (telephone)	Screening	Refresher Screening	Baseline	Treatment Phase						Follow Up		
Visit #	-1	1	1	2	3	4	5	6	7	8	9 F-UP	10 F-UP	Opportunistic 11 F-UP
		14 to 28 days before visit 2	Only to be run if 28 days elapses between screening and visit 2	14 to 28 days after screening	1 to 5 days after visit 2	4 to 21 days after visit 2	1 to 5 days after visit 4	4 to 21 days after visit 4	1 to 5 days after visit 6	4 to 14 days after visit 6	90-97 days after visit 2	180-187 days after visit 2	360-367 days after visit 2
Trial discussion with Participant	x	x	X										
Pre Screening Questionnaire	x												
Informed Consent		X											
Medical History		X	X										
Physical [a]		X	X										
SCID		X	X								X	X	
Withdrawal symptom checklist				X[h]									

	Pre-Screening (telephone)	Screening	Refresher Screening	Baseline	**Treatment Phase**						**Follow Up**		
Visit #	-1	1	1	2	3	4	5	6	7	8	9 F-UP	10 F-UP	Opportunistic 11 F-UP
Vital Signs		X[b]	X[b]	X[b, h, m]	X[b]	X[b, m]	X[b]	X[b,m]	X[b]	X[b]			
Bloods		X[c]	X[c]	X[d, j]		X[d]		X[d]		X[d]	X[d]	X[d]	
Eligibility determination	X	X	X	X[h]									
Urine Drug screen		X[e]	X	X[e, h]	X[f]	X[e]	X[f]	X[e]	X[f]	X[e]	X[e]	X[e]	
Pregnancy Test I POCBP		X	X	X[h]		X		X					
Breathalyser		X	X	X[h]	X	X	X	X	X	X	X	X	
Randomisation				X									
Install / Check BACtrack App		X[g]	X[g]	X[g, h]		X		X		X	X	X	
Self-breathalyser				X[h]	X	X	X	X	X	X	X	X	
IMP administration				X		X		X					
Therapy/education				X	X	X	X	X	X	X			
Adverse Events review				X	X	X	X	X	X	X			
Concomitant Medication review		X	X	X[h]	X	X	X	X	X	X	X	X	
Alcohol and Drug Use History		X	X							X	X	X	

	Pre-Screening (telephone)	Screening	Refresher Screening	Baseline	Treatment Phase						Follow Up		
Visit #	-1	1	1	2	3	4	5	6	7	8	9 F-UP	10 F-UP	Opportunistic 11 F-UP
Family history		X											
Demographic details	X[k]	X[l]											
BDI		X	X	X[i]						X	X	X	X
MADRS		X	X	X[i]						X	X	X	
Columbia Suicide Severity Rating Scale		X	X										
Alcohol Abstinence Self Efficacy Scale		X		X[i]						X	X	X	
SHAPS		X		X[i]		X		X		X	X	X	
ACQ-NOW		X		X[i]	X	X	X	X	X	X	X	X	
KSET		X	X	X[j]		X		X		X	X	X	
CADSS		X	X	X[j]		X		X		X	X	X	
Timeline Follow Back		X	X	X[h]		X		X		X	X	X	X
Drink Diary										X	X	X	X
Fagerstrom Nicotine Dependence				X[i]						X	X	X	
SADQ		X	X								X	X	

	Pre-Screening (telephone)	Screening	Refresher Screening	Baseline	**Treatment Phase**						**Follow Up**		
Visit #	-1	1	1	2	3	4	5	6	7	8	9 F-UP	10 F-UP	Opportunistic 11 F-UP
CTQ				X[i]									
SF-36				X[i]						X	X	X	X
CGI				X[i]						X	X	X	
Hood Mysticism Scale		X		X[i]		X		X		X	X	X	
Change in WHO risk level		X		X[i]						X	X	X	X
EQ5D5L				X[i]								X	
ICECAP-A				X[i]								X	
Expectancy of treatment questionnaire		X											
Treatment guess (BANG blinding index)										X			
3 Things Task				X[i]		X		X		X	X	X	
APEQ					X		X		X	X			
BAI				X[i]						X	X	X	
Readiness to Change scale		X											

	Pre-Screening (telephone)	Screening	Refresher Screening	Baseline	**Treatment Phase**						**Follow Up**		
Visit #	-1	1	1	2	3	4	5	6	7	8	9 F-UP	10 F-UP	Opportunistic 11 F-UP
	Therapist/researcher			Medic/clinician			Research Nurse						

* In the week prior to Visits 2, 4, 6, 8, 9 and 10 participants will be telephoned to remind them of their attendance.

a. Physical – Height, weight, an examination of cardiovascular, respiratory, GI, GU and neurological function to a level of detail that would be expected for a patient due to receive anaesthesia.
b. Vital signs: oral/tympanic temperature, resting pulse, pulse oximetry and blood pressure.
c. Bloods (Screening) – FBC (haemoglobin, white cell count, platelets, mean red cell volume); Liver function (Bilirubin, ALT, ALP, AST, Albumin, gamma-glutamyl transpeptidase (GGT)), Biochemistry (urea, sodium, potassium, glucose, calcium, thyroid stimulating hormone).
d. Bloods (Trial): ketamine; Liver function (Bilirubin, ALT, ALP, AST, Albumin, gamma-glutamyl transpeptidase (GGT)), and platelets.
e. Urine Drug screen (Screening, infusion days and F-UP visits) - (methamphetamine, cocaine, THC, benzodiazepines, amphetamines, morphine, methadone, ketamine).
f. Urine Drug screen (Non-infusion days in the treatment phase) – (methamphetamine, cocaine, THC, benzodiazepines, amphetamines, morphine, methadone,).
g. BACtrack app installed on visit 1/visit 2 – checked and data recorded on subsequent visits
h. Pre-randomisation assessments during the baseline visit (visit 2)
i. Post-randomisation assessments carried out pre-infusion during the baseline visit (visit 2)
j. Post-randomisation assessments carried out pre- and post-infusion during the baseline visit (visit 2)

k. Non-identifiable demographic information will be collected at pre-screening: age, gender and ethnicity

l. Further demographic details will be collected at screening including ethnicity, household income, education level.

m. Vital signs monitoring throughout the infusion will be continuous until the participant has recovered. Monitoring should be recorded on a standard observation chart, stored as source data. The eCRF will record 3 sets of readings, one prior to the infusion, another after the infusion terminates, and then finally after the participants recovery (2 hours post infusion).

8.1.2.3 Post screening therapist phone calls

Those deemed to be eligible after their screening visit who are still drinking will need to safely reduce their alcohol consumption to 0 prior to randomisation (visit 2). We have allowed up to 28 days between screening and baseline visits to allow this to happen. If 28 days passes, the participant will need to be re-screened before randomisation can happen (see section 8.1.2.1). Alcohol reduction must be done in a safe and controlled manner, a medical detoxification may be needed, or in other circumstances support may be needed from local alcohol services or the participant's GP.

All participants invited to a baseline visit will receive four manualised 'support' phone calls from a trial therapist over the course of two to four weeks to monitor self-reported alcohol reduction and support them in preparing to take part in the trial. Potential participants will be supplied with booklets to complete before the phone calls and answers will be discussed over the phone. Booklets will be collected from participants at the baseline visit.

8.1.3 Payment

Participants will be reimbursed for their participation in this trial at an incremental rate to promote participation and reduce drop-out rates. A similar procedure was used in our phase II trial and has been used in previous studies where we have achieved high retention rates in difficult populations. Participants will be paid under the following schedule with high street vouchers: £52 on completion of visit 8, £100 on completion of visit 9 and £100 on completion of visit 10.

Participant travel costs to and from trial sites will be reimbursed where appropriate. Accommodation costs can also be considered for those participants requiring overnight accommodation to facilitate participation.

8.2 Consent

Written informed consent for each participant must be obtained at visit 1 prior to performing any trial related activities.

8.2.1 Online self-assessment

Participants will be able to self-refer to this trial (see section 8.1.1.1). The online self-assessment questionnaire will contain a privacy notice which potential participants will be required to read explaining no data will be stored from this questionnaire.

8.2.2 Telephone pre-screen

Participants deemed potentially eligible based on the answers provided to the online self-assessment questionnaire will be provided with contact details for their local site to arrange a telephone pre-screen. Participants will not have to answer any questions they do not wish to and only non-identifiable generic demographic data will be stored on the trial screening log from the phone calls.

8.2.3 Written screening visit consent

It is the responsibility of the local Principal Investigator (PI), or a person delegated by the PI, to obtain written informed consent from each individual prior to participation in the trial, following provision of the trial PIS and an adequate explanation of the aims, methods, anticipated benefits and potential hazards of the trial. The person receiving consent will be required to have Good Clinical Practice (GCP) certification and be protocol trained, suitably qualified and experienced, and will have been delegated this duty by the CI/PI on the delegation log. A suitably qualified registered Research Nurse or Physician's Assistant can obtain consent, provided that a qualified NHS Medical Clinician is available to discuss any issues identified.

At least 24 hours will be allowed for consideration by the participant before taking part. The PI or delegate will record when the PIS has been given to the participant. The Investigator or their designee will explain that participants are under no obligation to enter the trial and that they can withdraw at any time during the trial, without having to give a reason. No clinical trial procedures will be conducted prior to taking consent from the participant. Consent will not denote enrolment into the trial. Five copies of the completed consent form are required:

(1) The original signed form will be retained at the trial site in the Investigator Site File (ISF).

(2) a copy will be given to the participant.

(3) a copy will be placed in the participant's medical notes or source data files if no medical notes are available.

(4) a copy provided to the participant's GP.

(5) an unredacted copy to be sent to Exeter Clinical Trials Unit *via* RedCap Academic upload.

If new safety information results in significant changes in the risk/benefit assessment, the consent form will be reviewed and updated if necessary and participants will be re-consented as appropriate. Re-consenting can be delegated to appropriately trained trial team members by the PI.

Written informed consent/advice will be via a trial-approved paper Consent Form that is signed, dated in-person (wet ink) by the participant, and countersigned by the delegated staff member receiving informed consent. In addition to completing the consent form (which includes the trial title and date of consent), sites should record key details of the informed consent process in the participants medical record, or source data file if medical notes are not available. A copy of the PIS should also be stored. Participants are not required to provide reasons for taking part in the trial, or not, but if reasons are given, then they should also be documented in their medical record/ source data file and the trial screening log.

8.3 The randomisation scheme

Participants who have been confirmed eligible and have completed screening and pre-randomisation baseline assessments (sections 8.1.2 and 8.6) will be randomised into the trial by a delegated member of the site trial team using a web randomisation system, RedCap Academic. [redacted] Block randomisation will be used, stratified by site. Further details of the randomisation methods will be documented in the Randomisation Requirements template, to be signed off by the senior trial statistician and CI. Details of the randomisation methods will not be shared with members of the trial team who are directly involved in recruiting and randomising participants. Confirmation emails will be generated automatically and sent to the site pharmacy/unblinded research nurses confirming IMP allocation, and a separate email will go to the site therapist confirming therapy/education allocation. A generic email not specifying treatment allocations will be sent to blinded research nurses at the appropriate site, the site PI, the CI, the scientific lead and the trial management team confirming a randomisation has occurred.

Once participants have been randomised, they will not be replaced regardless of compliance or dropout status and will be analysed as part of the estimand using treatment policy as a means of handling non-adherence.

Upon randomisation, participants will be given a trial specific participant card which will have the trial title, IMP details, participant ID and contact details of the out of hours contact in case of emergency.

8.4 Blinding

As this trial is double-blind, neither the participant nor those responsible for their care and evaluation will know which IMP treatment (i.e. which dose of ketamine) participants have been allocated. This will be achieved by unblinded local pharmacy or delegated unblinded personnel at site preparing the syringe/bag for infusion so that the administering team and participant are blind to the IMP dose allocation.

Access to the code break information will be restricted as per the emergency unblinding procedure outlined in section 8.5. Code breaks will be permitted in emergency situations where treatment allocation knowledge is needed for participant care.

Any unblinded interim reports will be provided to the DMC by the unblinded trial statistician and the reports will be securely password-protected.

Therapy/education allocation will not be overtly discussed between the trial therapist and the participant and all sessions will be audio recorded for therapist supervision purposes. Therapists should use blinded language in source data/medical notes so as not to unintentionally unblind other members of the trial team.

At trial entry, all participants will be asked whether they would like to receive a copy of the trial results and if so to provide their consent to be contacted by ExeCTU to send them the results of the trial. Participants will be asked after their 12m follow-up visit or at visit 10 (as appropriate), whether they wish to know their treatment allocation. If so, this information along with the results of the trial will be given to participants after the trial database has been locked and the data analysed.

8.5 Emergency Unblinding

The trial code should only be broken for valid medical or safety reasons e.g. in the case of a severe adverse event where it is necessary for the investigator or treating health care professional to know which

treatment the participant is receiving before the participant can be treated. Subject always to clinical need, where possible, members of the research team should remain blinded.

The code breaks for the trial are held by Exeter CTU through the RedCap Academic system.

Emergency unblinding will be available 24/7 through the RedCap system, accessible to authorised members at site, details to be provided in a separate work instruction. Site teams will hold out of hours unblinding responsibility and can nominate authorised team members to undertake this role.

If the person requiring the unblinding is a member of the investigating team then a formal request to the PI or delegated other medic will be made who will then log into the RedCap Academic web-based system to trigger unblinding.

If the person requiring the unblinding is not the CI/PI then that health care professional will notify the investigating team (*via* the in hours or out of hours telephone number on the participant ID card) that an unblinding is required for a trial participant and an assessment to unblind should be made in consultation with the clinical and research teams wherever possible. Unblinding will take place if in the opinion of a treating physician a participant's health is compromised. The treating physician has the ultimate decision and right to unblind the participant.

Authorised individuals will break the blind by logging into RedCap Academic, a web-based system for the trial, and entering the unique randomisation number (the identifier used for the trial medication). The system will immediately reveal the authorised individual with the unblinded treatment allocation.

On receipt of the treatment allocation details the PI or treating health care professional will deal with the participant's medical emergency as appropriate.

The PI will document the breaking of the code and the reasons for doing so on the unblinding eCRF, in the site file and medical notes. It will also be documented at the end of the trial in any final trial report and/or statistical report.

The PI will notify ExeCTU and the Sponsor's representative in writing as soon as possible following the code break detailing the necessity of the code break.

Trial Committees, where required within their charters, will also be notified in writing in meeting reports.

8.5.1 Unblinding for the submission of SUSAR reports

The following procedure will be used to unblind for the submission of a SUSAR report to the regulatory agency, the MHRA and ethics committee.

An authorised member of the University of Exeter sponsor's office will unblind in the event of a SUSAR report and will therefore, hold administration rights to the unblinding system. The Sponsor will follow the trial work instruction on unblinding. The Sponsor will provide the unblinded information on ICSR. Unblinded information in the SUSAR reports will not be forwarded to the site or ExeCTU and kept in the University of Exeter sponsor file. Site PI should only receive unblinded information if necessary for safety reasons. SUSAR reports will be disseminated to Investigators at site in reports as and when SUSARs occur, but the reports will remain blinded.

8.6 Baseline data

The baseline visit (visit 2) will be carried out on days 14 to 28 after screening. The baseline assessments are outlined in Table 2 (page 46). Some assessments have to be completed prior to randomisation and others can be completed post-randomisation, which is made explicit in Table 2.

Eligibility must be confirmed by the PI or delegated medic prior to randomisation during the baseline visit. Eligibility sign off must be documented in the eCRF as well as in the medical notes.

8.7 Treatment procedures (visits 2 (i.e. baseline; 14 to 28 days after screening), visit 4 (4 to 21 days after visit 2) and 6 (4 to 21 days after visit 4))

Participants will receive a weekly phone call from site staff reminding them of their next appointment date.

Infusion: Randomised participants will receive either 3 infusions of ketamine (0.8mg/kg made up to 50ml with saline over 40 minutes) or 3 infusions of ketamine (0.05mg/kg made up to 50ml with saline over 40 minutes), see section 9. Infusions will be administered over three weeks. The infusion will be prepared by unblinded pharmacy staff) or delegated unblinded site staff at the trial site facility. The infusion dose will be blinded to the research medic/nurse at the trial site who will administer the infusion. The total amount of ketamine hydrochloride to be delivered will be calculated on the participant's weight (0.8 or 0.05 mg/kg). Site pharmacy (or unblinded site staff) will order ketamine and dispense per participant, added to saline (0.9%) to make up to 50ml in syringes/bags for the syringe/infusion pump. Doses will be administered using a computer-controlled syringe pump if a syringe has been prepared, or a computer-controlled infusion pump if an infusion bag has been prepared. Participants will be given the option of whether they would like to listen to non-vocal instrumental music during the infusion to block out environmental noise.

Mindfulness Based Relapse Prevention Therapy (MBRP): A seven session manualised intervention and accompanying workbook developed with alcohol Specialist Clinical Psychologists (the supporting documents will give the details for manual and workbook). MBRP incorporates mindfulness practices alongside traditional cognitive-behavioural relapse prevention interventions [78]. The aim of these 7 sessions is to help to reduce the risk of relapse and support participants to develop an enjoyable and meaningful life without alcohol. It focuses around two broad themes, relapse prevention and promoting wellbeing, with mindfulness practice incorporated throughout the 7 sessions. Homework assignments will be used to promote incorporation of skills and strategies introduced into participants' daily lives.

Relapse prevention: sessions incorporate skills and strategies to reduce the likelihood of relapse and maintain abstinence including; identifying and coping with high-risk situations and triggers, recognising and managing cravings, understanding the role of thinking in drinking and alternative ways of approaching unhelpful thinking processes, identifying and managing early warning signs for drinking (such as outcome expectancies and seemingly-irrelevant decisions), lapse management planning and emergency management planning.

Promoting wellbeing: sessions incorporate methods and tools for promoting a sense of purpose, meaning and life enjoyment as well as managing the day-to-day stresses of life including: looking at values and resources, planning meaningful activities, developing problem solving skills to manage stress, identifying and developing valued roles, and planning for the future.

Mindfulness: In each of the 7 sessions a new mindfulness exercise will be introduced and principles of mindful awareness and responding are emphasised throughout both relapse prevention and promoting wellbeing interventions.

Education control: A 7-session educational programme educating participants about the risks of alcohol use and the effects of alcohol on the brain and body (the supporting documents will also provide more detail). Generic relaxation exercises will be used in each session to match for mindfulness exercises in the therapy condition without active incorporation of mindfulness principles.

All therapy/education sessions will be recorded and the supervising therapists (Bethan Marsh/Luke Mitcheson) will review a subset of recordings during clinical supervision to check adherence to the treatment protocol on a weekly or biweekly basis using the Yale Adherence and Competence Scale. The therapy manual has been incorporated into a step-by-step scripted 'guidebook' for the participant and therapist that was designed to be prescriptive and not based on idiosyncratic formulation to facilitate adherence to the therapy protocol in the proof-of-concept study. If adherence is called into question further training/time with the therapy supervising team would be required.

Participants will be asked to keep a private written or audio journal of their trial experiences in their native language, throughout the six months including their experience of the infusion, which may be discussed with the trial therapist during therapy/education sessions.

After-KARE recovery group: For those participants who complete the trial (up to visit 10/ 6month follow-up) there will be an opportunity to opt-in to an online peer support recovery group which will be composed of participants from the phase II trial and recovery champions from the local alcohol services.

8.8 Visits 3, 5 and 7

Table 2 (page 46) outlines which assessments are to be carried out at each visit.

8.9 Trial assessments

Table 2 (page 46) lists all the trial assessments per visit.

8.9.1 Non laboratory procedures

- Medical History: The medical history will be taken by the delegated trial team member from the participant and by referring to medical notes where possible to assess eligibility.
- Breathalyser tests will be used at each visit for the following reasons:
  - Screening & re-screening – To assess eligibility
  - Visit 2 (baseline visit, 1st infusion) – To assess eligibility/ensure safety of IMP administration/ensure participant is able to complete questionnaires, as well as engage with therapy/education
  - Visits 3, 5, 7 and 8 – To ensure participant is able to complete questionnaires, as well as engage with therapy/education
  - Visits 4 and 6 (2nd and 3rd infusion) – To ensure safety of IMP administration/ensure participant is able to complete questionnaires, as well as engage with therapy/education
  - Visits 9 and 10 - To ensure participant is able to complete questionnaires
  - Once randomised, if a participant attends for any visit highly intoxicated (above 0.035 BAC – legal driving limit) the visit may be terminated (either for the primary purpose of safety on infusion visits or of data integrity on non-infusion visits) and the participant invited to re-attend to complete the visit within the allocated visit window. If the participant fails to attend the re-arranged visit they will be withdrawn from the treatment but will continue follow-up visits.
- Vital Signs: Oral/tympanic temperature, resting pulse, pulse oximetry and blood pressure (BP) measurements will be measured at each visit phase for safety monitoring. During the infusions vital signs will be continuously monitored throughout the infusion and then at 20 minutes intervals until the participant has recovered. This monitoring will be recorded on a standard observation chart, stored as source data. The eCRF will record 3 sets of readings, one prior to the infusion, another after the infusion terminates, and then finally after the participant's recovery.

- Concomitant Medication and allergies: All prescription medication, over-the-counter medication, vitamins, and/or herbal supplements will be recorded on the concomitant medications eCRF and reviewed by a trial medic.
- Physical Examination: Height, weight and oral/tympanic temperature will be recorded.
    - At screening a physician will perform a physical examination of the cardiovascular, respiratory, GI, GU and neurological system to a level of detail that would be expected for a participant due to receive anaesthesia.
- Home assessments:
    - Participants will be required to self-breathalyse each morning using a breathalyser provided by the trial team. Breathalyser information will be recorded in a diary which will be shown to the therapist/research nurse at each visit to record readings.
    - BACtrack Skyn: participants will wear an alcohol monitoring device around their wrist during the trial which measures transdermal alcohol content in sweat. Participants will be required to download the data from their BACtrack Skyn every few days *via* BlueTooth to their iOS device.

The assessment days at which questionnaire and neurocognitive measures will be administered can be found in Table 2. Below is a list of questionnaire and neurocognitive measures and their state of validation:

Validated Interviews and Questionnaires:

- The Structured Clinical Interview for DSM-5 Disorders (SCID) is used to confirm a diagnosis of alcohol use disorder and the absence of current psychiatric diagnoses or SUDs that are listed as exclusion criteria (e.g. psychotic disorders including schizophrenia). This diagnostic schedule is widely used and lasts 20-30 minutes.
- The Clinician Alcohol withdrawal symptom checklist assesses alcohol withdrawal symptoms [63].
- The Beck Depression inventory (BDI) is a 21-item self-rated questionnaire which will be given at varying time points to measure depressive symptoms.
- The Columbia Suicide Severity Rating Scale (C-SSRS) is a 6-item interview used to assess suicidal ideation and behaviour using the “Baseline/Screening” version and will be used to verify the exclusion criteria of subjects with suicidal ideation at the screening visit.

- The Fagerstrom Test of Nicotine Dependence (FTND) is a 5-item scale to index nicotine dependence.
- The SF-36 is a short scale that measures social functioning.
- The alcohol TimeLine Follow Back (TLFB) is a drinking assessment method that obtains estimates of daily drinking and has been evaluated with clinical and nonclinical populations. Using a calendar, people provide retrospective estimates of their daily drinking over a specified time period. Several memory aids can be used to enhance recall (e.g., calendar; key dates serve as anchors for reporting drinking; standard drink conversion). The alcohol TLFB has been shown to have good psychometric characteristics with a variety of drinker groups, and can generate variables that provide a wide range of information about an individual's drinking (e.g., pattern, variability, and magnitude of drinking).
- Participants will be given access to a drink diary to use at home in between Visits 8, 9 and 10. Participants will be asked to record their alcohol consumption every day in between trial visits. Drink diaries are regularly used in alcohol research to record subjective alcohol consumption.
- Alcohol Craving Questionnaire – short-form (ACQ-NOW) is a 12-item scale that assesses current alcohol craving.
- Montgomery-Asberg Depression Rating Scale (MADRS) is a clinical interview used in patients with suspected depression and rates patients on a variety of depression related scales.
- Alcohol Abstinence Self Efficacy Scale is a 20-item self-report questionnaire which evaluates a person's potential to abstain from drinking alcohol.
- Snaith-Hamilton Pleasure Scale (SHAPS) is a questionnaire used to assess the presence of anhedonia.
- Ketamine side-effect scale (KSET) is a questionnaire that assesses acute and longer-term side effects associated with ketamine treatments.
- Clinician-Administered Dissociative States Scale (CADSS) is a structured clinical interview to assess state dissociation rated by clinicians.
- SADQ- Severity of Alcohol Dependence Scale – assesses current severity of alcohol dependence.
- World Health Organisation alcohol use disorders inventory – categorises risk level of current drinking.
- EQ-5D-5L- assesses health-related quality of life.
- ICECAP-A – assesses wellbeing and capability in adults for economic evaluation.
- Stanford Expectancy of treatment questionnaire [64] – assesses patient expectancy of treatment outcome in clinical trials.

- BANG blinding index – assesses the success of blinding in clinical trials [65].
- Clinical Global Impression: provides a brief, stand-alone assessment of the clinician's view of the patient's global functioning prior to and after initiating a trial medication [66]. This will be assessed by a psychiatrist either in person or remotely at trial visits.
- Hood Mysticism Scale is a questionnaire aimed at assessing mystical experiences.
- 3 Things Task is a standardised task to activate context-relevant aspects of the self-concept [67] which allows for the assessment of the self-concept with natural language processing tools such as ASIA [11].
- Acceptance/Avoidance-Promoting Experiences Questionnaire (APEQ) assesses psychological flexibility.
- The Beck Anxiety Inventory (BAI) assesses severity of anxiety using a 21-item questionnaire.
- The Childhood Trauma Questionnaire (CTQ) is a retrospective screening tool for childhood maltreatment in adults.
- The Readiness to Change scale is a 12-item questionnaire looking at motivational stages of change and has been used previously in high-risk alcohol consumers [x].

Questionnaires that are not validated:

- The Pre-Screening questionnaire has been developed to assess suitability for inclusion into the trial.
- A semi-structured interview detailing the participant's alcohol and drug use history will also be used.

8.9.2 Laboratory procedures

In order to assist the identification of pathology and confirm physical health and eligibility for inclusion in the trial, various blood tests and urine tests will be performed. A trial specific laboratory manual will be provided to sites. Tables 3 and 4 below respectively outline which blood tests and urine tests should be completed as part of the screening visit as well as at each subsequent visit for randomised participants.

All laboratory results will be reviewed and reports signed by the delegated trial team medic, and the site team will record in the eCRF whether they were deemed normal, abnormal but not clinically significant or abnormal AND clinically significant. In the latter case the eligibility of participants will be reviewed. Table 3 outlines which blood tests should be carried out at each visit.

Table 3: Blood tests to be carried out at each trial visit.

		Visit									
		1 (Screening)	2 (Baseline)	3	4 (Infusion)	5	6 (Infusion)	7	8	9 (3m FU)	10 (6m FU)
Biochemistry	Urea	X									
	Sodium	X									
	Potassium	X									
	Glucose	X									
	Calcium	X									
	Thyroid stimulating hormone	X									
Haematology	Haemoglobin	X									
	White cell count	X									
	Platelets	X	X		X		X		X	X	X
	Mean red cell volume	X									
Liver function	Bilirubin	X	X		X		X		X	X	X
	ALT	X	X		X		X		X	X	X
	Albumin	X	X		X		X		X	X	X
	Gamma-GT	X	X		X		X		X	X	X
	AST	X	X		X		X		X	X	X
	ALP	X	X		X		X		X	X	X

Exploratory	Ketamine		X*		X*		X*		X	X	X

* On infusion days (visits 2, 4 and 6) blood samples will be taken pre- and post-infusion to assess changes in ketamine levels. Blood samples taken after the infusion will be collected after the participant has recovered from the infusion (2 hours after the infusion finishes). Pre-infusion samples to be taken from the cannula before the infusion. Post-infusion samples to be taken via venepuncture from a different site.

All biochemistry, haematology and liver function tests will be processed at a local Trust laboratory as per Trust policy for processing and analysis. Results should be made available for review by the trial medic and documented in the blood sample eCRF. All exploratory samples (i.e. for ketamine analysis) should be spun and stored in a -80ºC freezer at a local laboratory before being periodically couriered to a HTA licensed central laboratory for analysis, details will be specified in the laboratory manual.

The Table 4 below outlines which urine tests will be performed at site using kits provided by Exeter CTU with results recorded in the eCRFs for all trial visits.

Table 4. Outlines which urine tests are to be performed at each visit.

	Visit									
	1 (Screening)	2 (Baseline)	3	4 (Infusion)	5	6 (Infusion)	7	8	9 (3m FU)	10 (6m FU)
Pregnancy test	X	X		X		X				
Methamphetamine	X	X	X	X	X	X	X	X	X	X
Cocaine	X	X	X	X	X	X	X	X	X	X
THC	X	X	X	X	X	X	X	X	X	X
Benzodiazepines	X	X	X	X	X	X	X	X	X	X
Ketamine	X	X		X		X		X	X	X

Amphetamines	X	X	X	X	X	X	X	X	X	X
Morphine	X	X	X	X	X	X	X	X	X	X
Methadone	X	X	X	X	X	X	X	X	X	X
Alcohol	X	X	X	X	X	X	X	X	X	X

People being actively treated for a current co-morbid substance use disorder (past 12 months), see section 7 will be excluded from the trial. Cannabis and benzodiazepine use are being monitored throughout the trial. However, cannabis consumption leads to THC remaining in the urine for approximately 28 days. Therefore, occasional cannabis use may result in a positive THC result. However occasional cannabis use is not grounds for exclusion as long as participants do not have a cannabis use disorder. Benzodiazepines are used in community detox and for sleep problems. Benzodiazepine use has a relatively long detection window, up to 7 days for long acting. Therefore, benzodiazepine use in detox may lead to a positive urine test. However, use of benzodiazepines in detox is not grounds for exclusion as long as participants do not have a benzodiazepine use disorder.

All urine samples will be analysed on the day of collection and will be disposed of after processing according to local processes for urine disposal. Results should be recorded in the urine sample eCRF.

8.10 Long term follow-up assessments

Randomised participants who have completed the treatment phase of the trial (visits 2-8) will be required to attend a 3-month follow-up visit (visit 9, 90 to 97 days after visit 2), and a 6-month follow-up visit (visit 10, 180-187 days after visit 2); there will also be an optional 12-month follow-up online assessment (see section 8.10.1). Table 2 (page 46) outlines which assessments will be carried out at visits 9 and 10.

8.10.1 Opportunistic 12-month follow-up

We will collect opportunistic data at 12 months (360 days + 7days) post randomisation from participants recruited to the trial in years 1 and 2, to assess long-term effects of KARE therapy on alcohol use, social functioning and mental health. At their 6-month follow-up visit (visit 10), participants will be advised that they will have the opportunity to complete the 12-month online assessment and advised to keep drink diaries until this point. A link to the online assessment will be emailed to

participants 360 days after randomisation for completion. Participants will have been asked to provide optional informed consent for data storage for the purposes of the trial at baseline. Data will be collected on number of days of heavy drinking via TLFB and drink diaries, as well as social functioning (SF-36) and mental health (BDI, change in WHO risk levels).

The site team will call participants prior to the 12-month follow-up window to remind those participants who consented to take part in the opportunistic follow-up about the email link they will receive and re-confirm their email address. If participants are happy to complete the questionnaires they will be emailed a link to provide follow-up data.

8.11 Qualitative assessments

Participants will be invited to take part in an optional qualitative component of the trial. An open-ended survey will be provided to those participants who opt-in to the qualitative aspect of the trial at visit 1 asking about preconceptions around ketamine. Those participants will then be invited to take part in semi-structured interviews over the phone concerning their experiences with the intervention following the final data collection point (6 months/visit 10). They will have 3 months (90 days) to participate.

Data will be analysed using reflexive thematic analysis [62], around 30 participants are likely to be required to reach saturation. Three or four participants will be identified from each site, following asking them at randomisation whether they wish to take part.

8.12 Withdrawal criteria

Participants who withdraw before Visit 2 (Baseline) will be replaced by assigning successive screening IDs to eligible participants, but after completing eligibility checks and breathalyser on visit 2, participants will be randomised and will not be replaced.

Participants have the right to withdraw at any time and there is no obligation to provide reasons for withdrawal. Participants who discontinue any aspect of the trial treatment, would still be invited to complete the follow-up visits at 3 months (visit 9) and 6 months (visit 10), unless they fully withdraw from the trial. A participant cannot choose to discontinue one element of the treatment package, i.e. if they discontinue from IMP treatment they cannot continue with therapy/education or vice versa. Participants wishing to withdraw their consent from the trial should contact a member of their site trial team to make

their wishes known. In addition, the CI and/or PI may discontinue a participant from the trial at any time it is considered necessary for any reason including:

- Ineligibility (either arising during the trial or retrospectively)
- Significant non-compliance with treatment or trial requirements e.g. If the participant misses 2 consecutive infusions, as detailed in section 9.11
- An adverse event which requires discontinuation of the trial medication or results in inability to continue to comply with trial procedures
- Disease progression which requires discontinuation of the trial medication or results in inability to comply with trial procedures
- Consent withdrawn, loss of capacity or detention under Mental Health Act
- Pregnancy, see section 10.6.
- In the case of an overdose with ketamine, the participant will be withdrawn from the trial (see section 10.7)
- Positive urine screen for ketamine after randomisation. Participants would be withdrawn from treatment but invited to continue to 3-month and 6-month follow-up.

However, all efforts will be made to maintain participants in the trial where possible and to continue assessments as intended. If treatment is stopped for longer than 7 days in this trial, then it will not be possible to resume treatment. The reason for participant withdrawal will be recorded in the withdrawal/change in participation eCRF and medical notes (or source data file if no medical notes are available) within 24 hours of the site trial team becoming aware.

Where the participant has/is withdrawn due to an AE, the investigator or delegate should follow the procedures documented in section 10.3 in order to assess the safety of the IMP. It should be made clear to any participant specifically withdrawing consent for further data collection that data already collected will be retained for analysis, and data pertaining to safety will continue to be collected for regulatory reporting purposes and will be included in any safety analysis and the final analysis. Furthermore, if any significant new information becomes available in regard to the treatment they have received in the trial it may be necessary to contact them in the future about this.

If a participant becomes uncontactable and stops engaging with the trial they will be deemed ‘lost to follow-up’. Every effort will be made to attempt to continue collecting full protocol assessments from

those lost to follow-up and/or participants who repeatedly deviate from the protocol. Our PPI team suggested one phone call and a follow up email / letter would be appropriate. All protocol deviations and violations will be recorded and reported to the Sponsor.

All participants who withdraw, or who are lost to follow-up, will still have the option to receive information about the trial, including newsletters and end of trial results unless they opt not to receive them.

The trial may be stopped before completion for the following reasons:

- If the CI and/or Sponsor decide to suspend the trial pending safety review of an emergent issue
- The CI and /or Sponsor decide to stop the trial for safety, administrative or other reasons

All available data from participants who change their participation status following randomisation will be included in the analyses as appropriate.

8.13 End of trial

The end of the trial will be on completion of data cleaning and database lock. ExeCTU will be responsible for notifying sites, the Sponsor and regulatory authorities as well as submitting the end of trial declaration.

Participants invovlement in the trial will cease after their visit 10. There will however be several voluntary opportunities to take part in including: a) joining an online peer support group of fellow participants (sections 8.7 and 14.10), b) taking part in an interview about their trial experiences within 3 months of their visit 10 (section 8.11), and c) an opportunistic 12m online follow-up for those enrolled in the first year of the trial (section 8.10.1).

9 INVESTIGATIONAL MEDICINAL PRODUCT

9.1 Name and description of investigational medicinal product(s)

The product under test will be ketamine hydrocholoride either 0.8mg/kg or 0.05mg/kg; 50mg/mL or 10mg/ml injection vials/ampoules will be used.

9.2 Regulatory status of the drug

Ketamine is a controlled drug (Class B, Schedule 2).

9.3 Product Characteristics

For details of product characteristics refer to the latest summary of product characteristics (SmPC) and the trial pharmacy manual.

9.4 Drug storage and supply

Full details can be found in the trial pharmacy manual. Routine hospital stocks of ketamine will be used for this trial. A drug inventory/dispensing record will be maintained and updated by the authorised unblinded personnel at pharmacy or delegated unblinded site staff on the ward for all drugs provided and dispensed at each trial site. Temperature records will be maintained throughout the trial. Ketamine can be stored at room temperature (0-25ºC). Once the ketamine infusion has been made up by pharmacy or the unblinded team, it should be used as soon as possible. At the end of the trial, the drug inventory/dispensing record should not be destroyed without Sponsor authorisation and a file note should be included in the TMF and pharmacy site file (PSF) about where to locate these records. An unblinded person at each trial site is responsible for all drug supplies. Written documentation is mandatory.

The unblinded persons at the sites will keep adequate records of the receipt, preparation, administration and return, quarantine or destruction of the trial medication. They will conceal the accountability forms to blinded personnel and ensure these logs are maintained and kept in the PSF. All data regarding the trial medication must be recorded on the relevant forms provided by ExeCTU or on local pharmacy accountability forms authorised by ExeCTU. Any dispensed but completely unused infusions (where the infusion syringe/bag has not been opened) will be returned to pharmacy and destroyed in line with site pharmacy procedures. Partially unused infusions will be returned to pharmacy and destroyed according to site pharmacy procedures. Therefore, the local controlled drug policy will be followed at the research

site to ensure that materials are appropriately destroyed. In all instances a record of this destruction will be kept in accordance with relevant SOPs, to document the return and/or destruction of materials at site.

9.5 Preparation and labelling of Investigational Medicinal Product

Preparation and labelling of the IMP should be completed in accordance with Annex 13 of Good Manufacturing Practice (GMP) guidelines. Labelling exemption will apply and site pharmacies/site unblinded personnel are not required to label hospital stock of ketamine (unless specified within Trust policy, please see the pharmacy manual for further details).

Site pharmacies/site unblinded personnel should attach an infusion label (as defined in the pharmacy manual) to the prepared infusion syringes/bags.

9.6 Dosage schedules

[redacted]Three infusions will be administered at weekly intervals, one each at visits 2, 4 and 6. Doses will be made up from a neutral glass vial/ampoule with rubber closure and aluminium flip-off cap containing ketamine hydrochloride. The total amount to be delivered will be calculated on the basis of the participant's screening visit weight.

Site pharmacy / unblinded site staff will order ketamine and dispense per participant, added to saline (0.9%) to make up to 50ml solution in syringes/bags for the syringe/infusion pump to infuse intravenously over 40 minutes. Doses will be administered using a computer-controlled syringe pump if a syringe has been prepared, or a computer-controlled infusion pump if an infusion bag has been prepared.

9.7 Dosage modifications

No dose modification will be permitted in this trial. If intolerable side effects are experienced, the participant will be withdrawn from treatment (see section 8.12).

9.8 Rescue Medication

Sites should have immediate access to rescue medications for the following reactions in this trial:

1. Allergic reaction – if a participant has an allergic reaction to the IMP they should be withdrawn from the trial. Rescue medication and resuscitative equipment should be immediately available for such an event.
2. Intolerable emergence phenomenon – varying reactions to the IMP are expected in this trial, however if emergency phenomena are intolerable to a participant during an infusion the infusion should be stopped in the first instance, these effects should remit very rapidly. Alternatively the co-administration of a benzodiazepine; lorazepam can be administered by the trial medic
3. Nausea – participants will fast for 6 hours before an infusion to reduce the risk of vomiting and pulmonary aspiration. In the case of vomiting, or if nausea is intolerable to the participant, then the trial medics can offer medication (e.g. ondansetron) to ease nausea or the infusion should be stopped, whereupon these symptoms should remit very quickly.

9.9 Known drug reactions and interaction with other therapies

See SmPC and risk section 3. Note that the SmPC relates to anaesthetic dose levels of ketamine, this trial uses lower doses.

9.10 Concomitant medication

Ketamine interacts with the following substances and therefore their concomitant use will not be permitted during active treatment days: barbiturates and/or narcotics, atracurium and tubocurarine, central nervous system (CNS) depressants (e.g. phenothiazines, sedating H1 – blockers or skeletal muscle relaxants), thiopental, thyroid hormones, theophylline and other methylxanthines, sympathomimetics and vasopressin, ergometrine, and drugs that inhibit/induce CYP34A enzyme activity e.g. anti-psychotics.

Due to potential impacts on the primary outcomes taking any other alcohol relapse prevention medication will not be permitted during the period of trial (Visit 2 - Visit 8).

The delegated trial site team will ask participants about concomitant medication prior to confirmation of eligibility and a list of restricted concomitant medications will be sent to the participant's GP at the time of confirming eligibility. Participants that are unable to stop taking restricted medication will be unable to enter the trial. For specifics regarding cannabis use please see section 8.9.2. Participant-reported

concomitant medication reviews will also take place at all trial visits to continue to review eligibility and document concomitant medication use. All concomitant medication use should be recorded in the concomitant medication eCRF and reviewed by a delegated RN or trial medic.

9.11 Trial restrictions

Ketamine is an analgesic agent and participants will be required to fast (nil by mouth excluding water) for six hours prior to infusion and completely (i.e. no water) 2 hours prior. Confirmation from the participant about last consumed food/drink will be required on infusion days and if the window is not met infusions will be delayed.

9.12 Assessment of compliance with treatment

Compliance includes adherence to both to IMP and protocol trial procedures. The trial medication will be administered by the research medic/nurse only in the context of the participant attending the trial site facility. Participants will not be responsible for any trial medication. A member of the site team will ensure that the arrangements for each treatment visit are agreed with the participant. Where necessary, the site team will assist in transportation. If a participant fails to attend a clinic visit for the infusion then the site team will endeavour to contact the participant to identify the reason. Where possible an alternative appointment will be made within the infusion visit window (see Table 2 page 46). If the participant fails to attend a clinic visit for the follow-up day the site team will endeavour to contact the participant to identify the reason and where possible arrange an alternative visit within the follow-up visit window (see Table 2 page 46). All episodes of failure to attend visits will be recorded in the medical notes, eCRF and protocol deviation log (eCRF). If the participant misses 2 consecutive infusions, then they will be withdrawn from treatment and will be invited to attend follow up visits 9 and 10 as part of our intention to treat protocol. Non-compliance to the protocol trial procedures will be documented by the site team and reported to ExeCTU via the eCRF. Persistent non-compliance (attendance <80% for treatment visits i.e. visits 2-8) may lead the participant to be withdrawn from the trial.

10 PHARMACOVIGILANCE

10.1 Definitions

Adverse event (AE)

Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.

Serious Adverse Event (SAE)

A serious adverse event is any untoward medical occurrence that occurs from time of consent up to 30 days post last IMP administration. After this period, investigators are still required to report any SARs that they become aware of until a participant's last visit:

- results in death
- is life-threatening
- requires in-patient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability/incapacity
- consists of a congenital anomaly or birth defect

Other 'important medical events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences.

In addition;

- **Dissociative and psychotomimetic effects, analgesia, dizziness, lack of co-ordination, unsteadiness, impaired memory and impaired concentration are expected following infusion. Persistence of any of these effects two hours after the infusion should be reported as an SAE.**
- **Increased blood pressure. Persistent increased blood pressure e.g. ≥ 220 systolic for 30 minutes should be reported as an SAE**

NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

Serious adverse reactions (SAR)

A serious adverse reaction is an SAE that is suspected as having a causality to IMP, as assessed by the investigator or delegate responsible for the care of the participant.

Suspected unexpected serious adverse reaction (SUSAR)

A SUSAR is a SAR that is not listed as expected for the IMP in the reference safety information (RSI) as assessed by the CI or nominated representative. The RSI for this trial is the summary of product characteristics (SmPC) section 4.8.

Related unexpected serious adverse event (RUSAE)

A RUSAE is an SAE that is related to the therapy/education and not listed in the protocol as an expected outcome.

10.2 Reporting adverse events

For the purposes of this trial any clinically significant AE will be recorded from the time of consent up to 30 days post last IMP administration.

10.2.1 Expected AE's

The following AEs are expected disease related and/or procedural expected events:

- Bruising caused by venepuncture
- Dissociative and psychotomimetic effects, analgesia, dizziness, lack of co-ordination, unsteadiness, impaired memory and impaired concentration following infusion. Persistent effects two hours after the infusion should be reported as an SAE.
- Skin rash caused by the BACtrack Skyn device
- Increased blood pressure. Persistent increased blood pressure e.g. ≥ 220 systolic for 30 minutes should be reported as an SAE.
- Drinking lapse or relapse
- Emotional distress or anxiety caused by the psychological therapy or education sessions

Please note expected AEs should be documented in source data but are not required to be reported via the REDCap eCRF unless they meet the definition of an SAE. All unexpected AEs should be reported in both the source data and REDCap eCRF.

10.3 Reporting serious adverse events

Any event that meets the protocol definition of an SAE must be reported to ExeCTU and the Sponsor **within 24 hours** of the PI, designee or research team becoming aware of the event by completing an SAE eCRF in REDCap. In the even of a death a death eCRF should also be completed in REDCap.

ExeCTU and the Sponsor will be notified by email whenever a new SAE eCRF entry has been completed.

For each SAE the following information will be collected:

- Full details in medical terms with a diagnosis, if possible;
- Event duration (date of onset and date of resolution);
- Seriousness criteria;
- Causality, in the opinion of the PI (or designee);
- Action taken;
- Outcome;

In addition to the above, the following details will be collected for each SUSAR/RUSAE:

- Relevant medical history;
- Concomitant medications;
- Treatment for SUSAR/RUSAE;
- Relevant diagnostic tests.

All SAEs must be reviewed and signed by a Principal Investigator (PI) or designated representative.

It is the PI or designated representative responsibility that all SAEs/SARs/SUSARs/RUSAEs are followed up until the final outcome is reached or up to the end of the trial. All follow-up information should be entered into the eCRF as soon as the PI or designated representative becomes aware of the outcome. Ongoing SAEs/SARs/SUSARs/RUSAEs at the end of the trial will be followed up by the participant's GP and/or the routine clinical care team until discharge.

10.3.1 Reviewing serious adverse events

The Chief Investigator (CI) or designated representative will review all reported SAEs to assess relatedness, and where related, assess expectedness to the IMP against the RSI. All serious events judged as related to the intervention (therapy/education) will be considered unexpected i.e. RUSAE. The CI is not allowed to downgraded a PI's assessment of causality.

Sites should respond as soon as possible to requests for further information by the CI or designated representative required for the final assessment of the SAE.

In the event of a SUSAR or RUSAE, the Sponsor or delegate will take responsibility for unblinding the participant, prior to the submission of the SUSAR to the MHRA and the REC. Investigators will only

receive information on the results of the unblinding if it is judged necessary for the safety of the participant.

10.3.2 Expedited reporting of SUSARs

If an SAE is identified as related to the IMP and unexpected by the CI or designated representative the sponsor will be notified within 24 hours. It will be reported by the Sponsor or delegate to the MHRA and REC within the required expedited reporting timelines. SUSARs that are fatal or life-threatening must be notified to the MHRA and REC within 7 days of the CTU being notified. Other SUSARs must be reported to the REC and MHRA within 15 days after the CTU has learned of them. All other recruiting sites will be informed of the SUSAR by the Sponsor or delegate.

10.3.3 Expedited reporting of RUSAEs

If an SAE is identified as related to the therapy/education and unexpected by the CI or designated representative the Sponsor will be notified within 24 hours. It will be reported by the Sponsor or delegate to the REC within the required expedited reporting timelines. RUSAEs must be reported to the REC within 15 days after the CTU has learned of them. All other recruiting sites will be informed of the SUSAR by the Sponsor or delegate.

10.3.4 Chief Investigator responsibilities

The CI or designated representative are responsible for oversight of the safety of participants in the trial, including an ongoing review of the risk/benefit. The CI will review SAEs causality using their medical judgement and review all SARs for expectedness using the RSI in a timely manner. The CI will assign Medical Dictionary for Regulatory Activities (MedDRA) coding to all reportable safety events.

10.4 Safety reporting

10.4.1 Development Safety Update Report (DSUR)

A DSUR will be provided to the REC and MHRA by the Sponsor or delegate at the end of each reporting year. The CI (or designated representative) in collaboration with the Sponsor (or delegate) will prepare all relevant information for the DSUR. The CI will review the clinical sections and provide

final sign off prior to submission. In the event of a disagreement between local assessment and CI review, local assessments will not be overruled, but the CI may add comments prior to expedited reporting.

10.4.2 TSC

In accordance with the TSC charter, the TSC will periodically review blinded, pooled safety data and liaise with the DMC regarding safety issues.

10.4.3 DMC

In accordance with the DMC charter, the DMC will periodically review unblinded safety data for each treatment group separately to determine patterns and trends of events, or to identify safety issues that would not be apparent on an individual case basis.

10.6 Pregnancy reporting

In the event of a pregnancy occurring during the trial, this must be reported using an ExeCTU pregnancy eCRF within 24 hours of learning of its occurrence. Pregnancies from visit 2 until 30 days post participant last IMP infusion should be reported. If the pregnancy is not known until after this time frame, it should still be reported if conception was during this period. Any pregnancy that occurs during the treatment weeks will result in exclusion from treatment. If pregnancy occurs in a participant's partner, or a participant, a pregnant partner PIS and ICF should be supplied to the pregnant person for consideration. Consent will be sought from the pregnant individual to follow the pregnancy until the end of the pregnancy (including premature termination) to determine the outcome and status of mother and child. Any adverse outcome of pregnancy should be assessed for causality to the treatment received.

Any SAE occurring in association with a pregnancy brought to the investigator's attention after the participant has completed the trial and considered by the investigator as possibly related to the investigational product, must be promptly reported to ExeCTU.

10.7 IMP Overdose

We do not envisage an overdose as infusions are prepared by pharmacy or unblinded research nurses, and then administered by a research nurse/medic within the research site. Accidental administration of 50 times the higher protocol dose constitutes an overdose. In the event of an overdose, the participant should be observed closely for signs of toxicity. Appropriate supportive treatments should be provided if clinically indicated. ExeCTU and the Sponsor should be notified within 24 hours *via* the breach reporting eCRF. Local Trust procedures on incident reporting will also be followed. Overdoses will be observed from drug charts, or an anaesthetic response in the participant. If an SAE is associated with the overdose then this will be fully described in the SAE eCRF. In the case of a ketamine overdose, the participant will be withdrawn from treatment and will be invited to attend follow up visits 9 and 10 as part of our intention to treat protocol.

10.8 Reporting urgent safety measures

The Sponsor, CI, PI and/or TSC may take appropriate urgent safety measures (USM) in order to protect the participants of a clinical trial against any immediate hazard to their health or safety. USMs identified shall take immediate effect and the MHRA should be telephoned within 24 hours to discuss the event with a medical assessor. The REC and MHRA should be notified in writing (substantial amendment) no later than 3 calendar days from the date the measures are taken.

If the CI and the Sponsor consider the USM to affect all participants, all PIs must be informed of the USM.

10.9 The type and duration of the follow-up of participants after adverse reactions.

If a participant has an adverse reaction (AR) during infusion they will be monitored in the research facility until a resolution or stabilisation is reached. If an AR happens while the participant is not in the research facility they will be told to present to A&E at site or the nearest hospital.

10.10 Development safety update reports

The main REC and the MHRA will be provided with Development Safety Update Reports (DSUR) which will be written in conjunction with ExeCTU, the CI and the Sponsor's office. The report will be submitted

within 60 days of the Developmental International Birth Date (DIBD) of the trial each year until the trial is declared ended.

11 STATISTICS AND DATA ANALYSIS

11.1 Sample size calculation

From the Phase II study, the mean number of days of relapse (comparable to heavy drinking; women: relapse: 6.5 units/day, HDD: 5 units/day; men: relapse: 8.1 units/day; HDD: 7.5 units/day) was estimated [redacted], with association standard deviations, using data from participants who completed a minimum of 159 days of TLFB data (maximum 180 days). The upper limit of a one-sided 80% confidence interval for the SD for each group was then determined [redacted] Allowing for 20% attrition, a total of 258 participants are required.

For all participants, a minimum of 180 days of TLFB data will be sought. However, as a key secondary outcome, we will look at percentage days of heavy drinking [redacted]. Using the upper limit of a one-sided 80% confidence interval for the SD for percentage days relapse based on the Phase II study [redacted], and aiming for 90% power and an alpha threshold of 0.05, a total of 224 participants are required, rising to 280 when allowing for 20% attrition. An overall sample size of 280 participants will therefore be sought.

In view of the fact that SDs from the Phase II pilot are being used, we will monitor the SDs for both number and percentage of days of HDD, both overall and by disaggregated groups. We will calculate the SDs when 40 participants [redacted] have reached 180-day follow-up, with the aim of reviewing the sample size using both the pooled SD and SD for each treatment group separately. This sample size review is not a formal Stop/Go criterion for the trial and will be performed in conjunction with the oversight committees.

11.2 Planned recruitment rate

The recruitment period will be 24 months. We intend to include up to ten recruiting centres. Of an estimated population with severe AUD in UK of 1.2M we anticipate ~ 60% will be eligible based on our inclusion criteria, providing a pool of ~720,000 potentially eligible individuals.

With ten sites initiated each would need to recruit n~28 participants – we anticipate higher recruitment based on previous recruitment to the Phase II trial in lead sites: Exeter, Manchester and North London. We anticipate screen failure rate of 30% based on updated inclusion criteria.

We had a lower than anticipated attrition in our Phase II study of 20% - usual rates for attrition from treatment AUD are around 50-72% by the fourth session [68, 69]. We anticipate a similar low rate of attrition in this trial although we have implemented changes based on PPI feedback which our PPI team have suggested will improve retention.

We have based our sample size calculations on the same attrition as in our proof-of-concept study of 20%.

11.3 Statistical considerations

Clinical trial: Statistical analyses will be adherent to the ICH E9 Guideline [70] and the more recent ICH E9 (R1) addendum on estimands [71]. The primary analyses will be conducted following the end of the trial (collection of the final follow-up data for the last participant) and final database lock, data cleaning and data export to the trial statistician, with masked allocation codes. Analyses of the primary and secondary outcomes at the primary follow-up time (6 months) using the treatment policy approach (see below) will be performed by a statistician who is blinded to treatment allocation. Following unblinding of the trial team, subsequent analyses will be performed by an unblinded statistician.

11.3.1 Analysis sets

The primary statistical analysis will include observed data only.

11.3.2 Analyses supporting primary objectives

A detailed statistical analysis plan (SAP) [71] will be delivered during the recruitment, intervention delivery and follow-up phases of the trial, based on the summary of the SAP in the trial protocol, and will be approved by the TSC prior to database lock. Any amendments to the SAP following sign-off, for example to include additional sensitivity analyses as required or to add post hoc analyses, will be documented during the trial.

Participant characteristics will be reported descriptively by treatment group and will be scrutinised for any between group imbalances (a difference of more than 10 percentage points for binary/categorical characteristics or greater than 1 SD difference in means for continuous characteristics). All [redacted] comparisons [redacted] will be reported with a 95% confidence interval and p-value (interpreted using a 0.05 two-sided alpha threshold). The primary analysis for the primary outcome will be a mixed effects linear regression model with a random effect for site.

Secondary outcomes will be reported descriptively at baseline, 3-month and 6-month follow-up (and at 12 months where data are available). Inferential [redacted] comparisons for the secondary outcomes will be performed at 6-month follow-up using similar methods as for the primary outcome (i.e. a mixed effects linear regression or logistic regression as appropriate), with adjustment for baseline scores where applicable. No formal adjustments for multiple testing will be made; the primary outcome will be interpreted first, with secondary outcomes interpreted in the light of multiple testing.

11.3.3 Handling of intercurrent events of primary estimands

Intercurrent events related to adherence to treatment (i.e. discontinuation/withdrawal) will be handled using the treatment policy strategy; the treatment effect is sought irrespective of the occurrence of an intercurrent event. This policy is in alignment with an ITT analysis. Deaths during the trial will be handled using the 'while alive' approach; participant data collected prior to death will be included in the analyses.

A principal stratum approach will be used to target the treatment effect in adherent participants (assuming that adherence status would be identical for a participant irrespective of the treatment group to which they were allocated). A per protocol analysis will compare adherent participants [redacted]

[redacted]. Participants will be considered as adherent if they received all three infusions at their allocated dose plus all their scheduled sessions as allocated. The per protocol approach is in alignment with a principal stratum approach. The resulting estimand therefore applies to the population of people who would be adherent to treatment as offered.

A per protocol analysis will be performed for the primary outcome and all secondary outcomes at 6-month follow-up. There are limited opportunities within the trial for treatment switching [redacted]. There is no possibility for the participants to receive ketamine outside the trial, and participants are requested to refrain from beginning new psychological therapy during the active treatment phase. A participant could only receive the incorrect dose of ketamine if an error occurred in making up or administering the IMP.

11.3.4 Handling of missing data

As a sensitivity analysis for comparison with the treatment policy analysis (i.e. disregarding the intercurrent event of non-adherence to treatment) using observed data only, we will use multiple imputation to impute missing outcome data for the primary outcome and all continuous outcomes at 6 months (i.e. to address the intercurrent event of loss to follow-up). Multiple imputation using chained equations (MICE) will be used; the imputation algorithm will include baseline characteristics that are found to be predictive of missingness of the primary outcome, as well as treatment arm, baseline characteristics included in the primary and secondary analyses, baseline outcome scores, and minimisation variables. Logistic regression will be used to determine characteristics associated with missing primary outcome data (days of heavy drinking at 6-month follow-up). Predictive mean matching will be the method for imputing individual scores; the number of imputed datasets will be determined by the percentage of participants that have missing primary outcome data. Observed and imputed data will be used to perform a sensitivity analysis [redacted] at 6 months using the treatment policy approach. Imputation of missing data is based on the assumption that such data are missing at random (propensity for missingness is not related to the (unobserved) value of the missing data). The estimand derived from analyses of observed and imputed data therefore relates to the same population as that of the estimand derived from the primary analysis using observed data only. In the event of a participant death during the trial, data that would have been collected will be considered as non-existent rather than missing and will not be imputed.

11.3.5 Sensitivity analyses

Should any participant characteristics be found to be unbalanced at baseline and thought to be predictive of outcome, including baseline alcohol use, sensitivity analyses for the primary and secondary outcomes will be performed to adjust for these characteristics.

11.3.6 Additional analyses

As an additional analysis, for the secondary continuous outcomes, we will perform a mixed effect linear regression model (with a random effect on participant) to include all data available at baseline and 3, 6 and 12 months, to investigate whether there is any difference in the patterns observed over time [redacted] (with adjustment as for the regression models including 6-month follow-up data only).

We will examine differential treatment effects by treatment group at varying levels of depressive symptoms at baseline, for the primary outcome treatment policy analysis using observed data only, by adding an interaction term between baseline depressive symptoms and treatment group.

11.3.7 Interim analyses and criteria for the premature termination of the trial

No formal interim [redacted] analyses are planned (although standard deviations for number and percentage of heavy drinking days will be sought for the purpose of a review of the sample size – see Section 11.1). From a safety perspective, adverse events will be monitored regularly by the trial team and trial oversight committees, and any concerns will be addressed. There are two Stop/Go milestones, one with respect to securing ethical approval and the other regarding progress with site opening and participant recruitment.

The first STOP/GO milestone will be ethical approval <6 months post trial start (green), 6-10 months (amber), >10 months (red).

The second STOP/GO milestone will be at the end of the internal pilot phase, this phase will begin at month 11 of the study timeline (Jan 2024) and end 9 months later (Sept 2024). This review will consider 1) opening of sites, with a focus on opening an initial seven sites (although opening of the remaining sites will continue at pace during the latter months of the internal pilot phase); 2) participant recruitment rates. We anticipate that after the nine months of the pilot phase, we will have seven sites open and have recruited ~70 participants. The mean recruitment rate is anticipated to be ~1.46 participants/site/month (for months when sites are open to recruitment) in the internal pilot phase, allowing for staggered site opening and differing sizes of recruiting sites. Proposed green/amber/red thresholds are shown below in Table 5. Screening data and the data for these progression criteria will be monitored by the TMG in the initial months of recruitment and if required, further strategies will be developed, led by input from our patient representatives, to tackle identified barriers by collecting and inspecting reasons for non-participation/lower levels of recruitment than expected. At the end of the internal pilot phase, progress will be reviewed by the TSC, Sponsor and NIHR. Participant recruitment will not be paused during the review of the progression criteria.

The following actions will be taken in response to progress as measured against these criteria, in close consultation with the trial oversight committees, Sponsor and NIHR:

Green: The trial will continue. Refinements to enhance recruitment will be considered and implemented by the trial team.

Amber: The trial team, oversight committees (and others) including the PPI members, will discuss modifications to improve recruitment. The trial will continue if effective modifications to recruitment processes can be agreed and made, with regular reviews.

Red: The trial team, including PPI members, will discuss any mitigating circumstances with the Trial Steering Committee and NIHR. If the trial is deemed not to be feasible, a closure plan will be agreed.

If there is inconsistency in the scoring of the progression criteria e.g. two criteria are green and one amber, then overall the trial will be categorised according to the criterion that is furthest from achieving the progression threshold (e.g if two criteria are green and one amber, the trial will be categorised as amber).

Whilst the internal pilot phase aims to open, at minimum, seven sites to achieve the interim recruitment target after nine months, opening of the remaining sites (aiming for a maximum of 10 sites) will continue throughout the latter months of the internal pilot phase. On progressing to the main trial period, additional

sites may be sought if required, based on the observed recruitment rates during the internal pilot phase, to reach the overall recruitment target within the planned 24-month recruitment window.

Table 5. Progression criteria (after initial 9 months of active recruitment)

Criterion	Green	Amber	Red
% threshold	100%	60%-99%	<60%
Number of sites open to recruitment*	≥7	4-6	<4
Mean recruitment rate/site/month**	≥1.46	0.88 to 1.45	<0.88
Total number of participants recruited**	≥70	42-69	<42

**allowing for staggered site opening*

***calculated over the months a site is open to recruitment*

As well as considering the formal, pre-specified STOP/GO criteria, at the end of the internal pilot phase, the following will also be reviewed:

- Uptake of BACtrack devices by participants and completeness of BACtrack data. Projections will be made around likely uptake of the device and data completeness levels. An assessment will be made by the TMG as to whether sufficient and useable data is present and likely to be produced to facilitate meaningful analysis at the end of the trial. If any barriers to uptake or data completeness are identified, the trial team, including PPI members, will consider strategies to try to improve uptake and data completeness, as appropriate.
- Reasons for exclusions listed on site screening logs to assess whether language barriers are present and if any appropriate improvements to the trial can be made.

Mechanistic study: For the mechanistic study, we will collect depression symptom data (MADRS) and examine relationships with drinking outcomes using mediation analysis based on structural equation modelling.

Moderated mediation analyses will be performed using PROCESS version 3.5 [72] using Model 8, bootstrapping set to 5000 samples and with confidence intervals of 95%. In these analyses, the predictor variable (X) will be the Intervention Condition [redacted] and the outcome (Y) variable will be days of heavy drinking at 6 months follow-up. The moderator (W) will be the family history of alcohol use disorder (Positive vs Negative) which has emerged from recent work in depression as predictive of better treatment outcome (e.g. [73, 74], see [75] for a review) and our own exploratory analyses from the proof of concept trial (see UPLOADS; Morgan et al., in prep). The mediators will be respectively the depressive symptoms as indexed using standard self-report and clinician rated symptom scales (BDI and MADRS) as well as the aggregated indicator from our natural language processing analyses at the post-treatment follow-up in three separate moderated mediation analyses.

We will also use the Automated Social Identity assessment (ASIA), a freely available pattern classifier tool we have developed that relies on computational linguistics and uses a binary classification model to determine which identities are salient in a person at a particular moment. ASIA has been trained to identify ‘depressed’ natural language to 85% accuracy [53, 76].

We will aggregate and analyse natural linguistic data for each treatment week (weeks 1 to 4), and then aggregate responses monthly until the 6-month period (months 2, 3, 4, 5, 6). We will calculate the probability of being ‘depressed’ or ‘recovered’ in each group and use latent growth curve modelling to examine whether trajectories differ with regards to these groups. We will then use Cox regression models to examine whether ASIA identity probabilities are predictive of relapse.

The mechanistic insights from these analyses would be whether:

1. Changes in alcohol use disorder are mediated by earlier changes in depression and anxiety which in turn suggests:
    a. It is important to target ketamine treatment in AUD during the risky window post-detoxification where depressive and anxiety symptoms are highest
    b. Depressive symptom reduction is an early marker of treatment response in AUD
    c. Co-morbid depression and AUD may be particularly indicated for ketamine treatment
2. Family history of alcohol problems are a reliable moderator of treatment response to ketamine in AUD, potential providing an easily indexed pre-treatment predictor of treatment response

3. Natural language indices of depression may be used as a valid and reliable measure of symptoms
4. Self-report, clinician rated and passively collected (natural language) indices of depression may provide different indicators of symptomatology

11.4 Economic evaluation

We will explore the feasibility of collecting appropriate data to inform a future cost-effectiveness analysis of KARE therapy. We will establish methods for estimating intervention resource use and costs, and assess the acceptability of outcome measures suitable for use in cost-effectiveness analyses, these being the EQ-5D-5L [12], and the ICECAP-A [13].

12 DATA MANAGEMENT

12.1 Data collection tools and source document identification

The primary data source will be trial-specific paper and electronic case report forms ((e)CRFs) and laboratory reports. Participants will complete trial questionnaires and this data will be transcribed into the secure, online trial database by blinded trial personnel. The questionnaires will be source data. Research nurses/medics will also collect various physical measurements on each trial participant, which will be documented in the medical notes and then transcribed into the trial database. Participants will be identified by a trial number allocated at the point of consenting which will ensure anonymity of data recorded electronically. SAE data will be recorded directly into the trial database (source data will be medical records).

Sites will be required to answer data queries raised by ExeCTU in a timely manner within the trial database. A data cleaning work instruction will be provided to sites.

Every effort will be made to collect all PROMS data at each visit. However, a minimum set of questionnaires will be required to be completed by participants at the appropriate visits including the ATLFB, BDI and SF-36. If participants decline to answer these questionnaires at the appropriate time points they would not be able to continue in the trial and would be withdrawn from the intervention, see section 8.12. This is due to our key outcome measures being linked to this PROMS data.

12.2 Data handling and record keeping

A Data Management Plan (DMP) will be created and updated throughout the trial as appropriate. Working instructions will be provided to the site teams on record keeping and data entry processes. Electronic systems will be validated, tested and documented before starting recruitment. The DMP and validation documents will be available upon request to ExeCTU.

REDCap by Vanderbilt will be the Electronic Data Capture (EDC) System used for data entry and storage of anonymised participant records and CRF data. REDCap will be hosted securely within University of Exeter's Amazon Web Services (AWS) account. All source data (other than data collected from the BacTrack device) will be securely stored in AWS data centres in the UK with access limited to only authorised staff. The REDCap database will be encrypted at rest. Access to REDCap public facing website via web browser will be encrypted using the appropriate Transport Layer Security (TLS) protocol. Data from the BacTrack devices will be stored on a secure drive at the Psychopharmacology and Addiction Research Centre, University of Exeter. Automated data (BacTrack) will be entered from data files filed with the source data.

The CRFs and trial specific documents held by the site teams will be stored securely with access restricted and limited to delegated research staff. Questionnaire source data will be transcribed into the eCRF. REDCap will keep a record of all changes to and access of the database. The REDCap database, audit log and associate files will be backed up daily and monthly following best practice guidelines.

eCRF will be accessible by the site research team through password protected individual users accounts. Access to eCRF and data read/write/export rights will be managed by specific role based access, ensuring site research team only can only perform functions within REDCap according to their role. The data will be available for download by the trial statisticians and nominated members of ExeCTU over a TLS encrypted protocol. Once downloaded, data will be stored on a password protected network drive at the University of Exeter. At the end of the trial, sites will receive an electronic copy of the eCRFs for their participants at site for archiving purposes.

The CI will ultimately be responsible for data entry and quality. Trial staff as identified on the delegation log will also be responsible for data entry and quality. Data analysis will be performed independently of data entry by the trial statistician. Once all data checks and data are completed, the database will be locked and read only. Users will still be able to view the contents of the database and produce reports.

12.3 Access to Data

Access to the data held at participating sites will be restricted to those who have a relevant purpose to access the data. Access will be granted to authorised representatives from the University of Exeter as the Sponsor, as well as representatives from ExeCTU and regulatory agencies e.g. MHRA, for the purposes of auditing, monitoring and inspection of the trial.

Participants will be asked to consent to representatives of the Sponsor, the University of Exeter or regulatory agencies e.g. MHRA, accessing their data that is relevant to their participation in the trial.

Data entered into the EDC system will be accessed by authorised members of the trial team at participating sites, ExeCTU and regulatory authorities e.g. MHRA. Access will be restricted with individual log-in credentials and site and role restriction applied so that individuals can only access data appropriate to their location and role.

Third parties i.e. central laboratory and BacTrack, will not be able to access the EDC system. Alcohol use data will be transferred to the United States (KHN Solutions Inc) over secure firewalled server for the purposes of monitoring alcohol use in this trial. Participants' personal email addresses will be shared with KHN Solutions Inc. for this purpose. No other identifying data will be transferred. The central laboratory will not require any identifiable information to be sent to analyses samples.

12.4 Archiving

The Sponsor is responsible for arranging appropriate archiving on conclusion of the trial of the TMF and EDC system data.

Participating sites will be responsible for archiving their investigator site files, including paper CRFs and consent forms, following their local NHS Trust archiving procedures. Sites will be required to notify ExeCTU and the Sponsor of their archiving arrangements.

Trial documents will be archived for a minimum of 10 years after the end of the trial in line with the Sponsor's procedures. After 10 years, all personal identifiable data will be securely destroyed upon authorisation from the Sponsor. The anonymised dataset will be stored indefinitely for the purposes of future ethically approved research.

13 MONITORING, AUDIT & INSPECTION

Trial supervision will be established according to the principles of GCP and in-line with the UK Policy Framework for Health and Social Care Research. This will include the establishment of a core project team, TMG, an independent TSC, and an independent DMC. A detailed monitoring plan will be agreed between the CI, ExeCTU and the Sponsor. The monitoring plan will be based on the risk assessment, which will consider the safety, or physical or mental integrity, of the trial participants, and the scientific value of the research. The risk assessment will be reviewed periodically and in response to amendments to the trial protocol.

This Trial Monitoring Plan will detail the timing and content of reports to monitor trial conduct, implementation, and adherence with CONSORT. Procedures will be in place to assess risk on an ongoing basis, with adjustments made accordingly.

Monitoring will be conducted by a combination of remote, central and on-site monitoring led by ExeCTU. Sites will send ExeCTU unredacted copies of consent forms for monitoring purposes. Extra on-site monitoring will be conducted in repsonse to pre-defined triggers, as detailed in the monitoring plan, or if concerns are raised by an individual with knowledge of the trial.

Sites will be expected to cooperate with remote and on-site monitoring procedures by provision of copies of requested documents in a timely manner and the completion of self-audit checklists. In the case of triggered on-site monitoring visits, sites will be expected to provide space for the monitor(s) to work on the Trust premises and provide access to all documents requested in the notification of

monitoring visit letter. The PI or delegated member of the trial team must be available during on-site monitoring visits. The ExeCTU will provide sites with sufficient notice to prepare for a monitoring visit.

The Sponsor and/or regulatory authorities may audit or inspect any aspect of the trial, including ongoing site visits, at any time during the trial.

14 ETHICAL AND REGULATORY CONSIDERATIONS

14.1 Research Ethics Committee (REC) review & reports

The trial will be submitted to, and approved by, a UK Health Departments Research Ethics Committee, the MHRA, and obtain HRA Approval with subsequent appropriate local R&D departments Capacity & Capability Approval for each participating site prior to entering participants into the trial. ExeCTU will provide a copy of the final trial protocol, participant information sheet, consent form, GP letter and all other relevant trial documentation that will be provided to the participants, any advertisements that will be used, and details of any participant compensation.

Any changes in research activity and documentation, except those necessary to remove an apparent immediate hazard to the participant in the case of an urgent safety measure, must in the first instance be reviewed by the Chief Investigator.

All substantial amendments and relevant non-substantial amendments will be discussed by the TMG, the Sponsor and with the PPI group if appropriate. The chief investigator (CM) will be responsible for the final decision on making an amendment to the protocol. The approval of the TSC chairperson will be sought for substantial amendments, as well as the funder where relevant, to the protocol in advance of submitting them to the MHRA, REC and/or HRA, and if necessary, a meeting of the TSC will be convened to discuss the amendment. A full list of all substantial and non-substantial amendments will be provided as part of regular funder reports.

The Sponsor will decide if an amendment is substantial or non-substantial following HRA guidance. All amendments will be submitted to the NHS REC that issued a favourable opinion (if appropriate), the MHRA (if appropriate) and the HRA following the appropriate HRA amendment process in place at the time of submission. Amendments requiring approval may be implemented only after a copy of the

approval letter has been obtained. Amendments will be communicated by the trial manager to R&D departments, PIs and research teams at participating sites as soon as possible upon receipt of approval to do so from the HRA.

Urgent safety measures that result in a substantial amendment may be implemented prior to receiving Sponsor or ethical/regulatory approval. However, in this case, approval will be obtained as soon as possible after implementation.

All SUSAR reports and annual safety updates will be sent to the REC/MHRA in a timely fashion, to facilitate their continuing review of the trial. The REC/MHRA will also be informed about the end of the trial within the required timelines.

The CI or delegate will inform the trial registry of changes to the trial.

An amendment log will be maintained by the trial manager and filed in the TMF. The protocol version history will be recorded in an appendix to the protocol. Research sites will be provided with an updated document version control list where applicable following an amendment.

14.2 Peer review

The trial has been subject to three rounds of independent, international expert peer review by reviewers nominated by NIHR and awarded funding from NIHR.

14.3 Public and Patient Involvement

We have involved service users, carers and the public at all levels of development of this protocol. The proof-of-concept study which this proposal is based on involved a PPI group in the trial design, advising on the development of the therapy and co-creating the materials for use in the trial, including the participant information sheet and other participant-facing information.

Key workstreams for PPI representatives are:

• 2 PPI representatives on the TMG and 2 independent PPI representatives on the TSC.

• Research design and protocol development

• Input on ethical submissions

• Co-production of participant facing information, for example information sheets, advertisements

• Contributing to results generation

• Consideration and interpretation of results with trial team

• Co-producing presentation of results for trial web-platform and dissemination to participants and beyond

• Dissemination

• Co-production of annual regional workshops to stakeholders

• Writing content for web platform on the trial

• Co-creating training and teaching programme

• Co-creating recommendations for treatment and guidelines

• Co-producing results presentation materials in a variety of settings

• Presenting the results with the trial team

• Co-producing the conference with regional workshops

14.4 Regulatory Compliance

The trial will not commence until a Clinical Trial Authorisation (CTA) is obtained from the MHRA and favourable REC opinion. The protocol and trial conduct will comply with the Medicines for Human Use (Clinical Trials) Regulations 2004 and any relevant amendments.

Before any site can enrol participants into the trial, the Principal Investigator or designee will ensure that appropriate approvals from participating organisations are in place.

14.5 Protocol compliance

Protocol compliance will be assessed throughout the trial. Protocol deviations, unplanned non-compliance, or breaches are considered departures from the approved protocol.

Frequently re-occurring deviations are not acceptable and could potentially be classified as a serious breach. Prospective, planned deviations or waivers to the protocol are not allowed under the UK regulations on clinical trials.

Protocol violations should be reported immediately to ExeCTU using the protocol deviations eCRF. Protocol violations that need to be reported include:

- Enrolment of participants outside of the eligibility criteria
- Drug administration errors related to the trial drugs which lead to an SAE (note that other drug administration errors, that do not lead to an SAE, may also constitute a violation)
- Overdose

If the protocol violation is also associated with an event which meets the criteria of an SAE or SUSAR this should also be reported in accordance with section 10.3 of the protocol.

14.6 Notification of Serious Breaches to GCP and/or the protocol

A "serious breach" is a breach which is likely to effect to a significant degree –

(a) the safety or physical or mental integrity of the participants of the trial; or
(b) the scientific value of the trial

Serious breaches may be identified through routine or triggered monitoring, inspection by the regulatory authorities, by chance, or by direct report to ExeCTU and/or the Sponsor by a member of the trial team or other party. The Sponsor will be notified of any suspected serious breaches by a member of the ExeCTU trial team following the ExeCTU SOP. Research sites may notify ExeCTU in the first instance by contacting the trial manager who will onward report the suspected breach to the Sponsor.

The Sponsor representative will decide if the event constitutes a serious breach. The Sponsor will report serious breaches to the appropriate regulatory bodies within 7 days of becoming aware of the event.

In the event of a serious breach, the Sponsor, ExeCTU, and the individuals involved will work together to agree and implement a corrective and preventative action (CAPA) plan and follow up on the plan at agreed intervals to ensure effective implementation.

14.7 Data protection and participant confidentiality

This trial will be conducted in a way that protects the rights and dignity of the participants. We will adhere to the UK GDPR and Data Protection Act 2018 when collecting, processing, sharing, storing reporting and destroying data, all trial data will handled with the strictest confidentiality. Trial data will be reported anonymously so that it will not be possible to identify any individual taking part in the trial.

Each participant will be assigned a unique ID number. Personal identifiable data will be collected and stored separately to research data and will only be accessible to authorised members of the research team. Personal data will only be used for reasons relevant to the research as outlined in the participant information sheets and will be stored for 10 years after the end of the trial before being destroyed.

Data will be managed by the UK Clinical Research Collaboration (UKCRC) registered ExeCTU following UK General Data Protection Regulation. Data will be collected and stored in accordance with UK GDPR and the Data Protection Act (DPA 2018) and ICH GCP E6 R2. Access to the EDC system (REDCap Academic) web interface will be over Hyper Text Transfer Protocol Secure (HTTPS) / Transport Layer Security (TLS) version 1.2 as a minimum and it will be ensured that web traffic to and from the REDCap server is encrypted. We will host REDCap Academic in Amazon Webservices (AWS). Amazon Relational Database Service (RDS) will be encrypted. Amazon RDS encrypted database instances use the industry standard AES-256 encryption algorithm to encrypt the data on the server that hosts the Amazon RDS database instances. The AWS global infrastructure is designed and managed according to security best practices as well as a variety of security compliance standards. AWS provides on-demand access to security and compliance reports and select online agreements through AWS Artefact. Standards include ISO 27001 and ISO 9001.

Only Principal Investigators or their authorised delegates who are suitably qualified and trained will access the participants' medical notes to gather the required information for the trial. Investigators will hold substantive or honorary contracts with the NHS Trust at which the participant is recruited and will therefore be bound by the confidentiality clauses that all NHS staff adhere to.

Data collected at sites on paper such as participant contact information and consent forms will be securely stored and archived at site.

The data controller for the trial is the Sponsor, the University of Exeter.

14.8 Financial and other competing interests for the chief investigator, PIs at each site and committee members for the overall trial management

The KARE psychological therapy is licensed from University of Exeter by Awakn Life Sciences. Professor Morgan, Dr McAndrew and Ms Bethan Marsh receive royalty payments from the annual license fee.

Funding for the trial comes from NIHR with additional funds from Awakn Life Sciences. These funds are provided in accordance with NIHR terms for commercial collaboration and rules for state aid dictating IP and ownership of data rest with University of Exeter for this trial.

No other financial interests are relevant but at the time of writing the protocol not all sites/personnel may have been identified. Further information will be stored in the Trial Master File.

14.9 Indemnity

The University of Exeter as Sponsor of the trial holds clinical trial insurance to provide for the payment of compensation to research participants arising from injury or illness arising from the clinical trial where there is no legal liability. If an injury arises as a result of how the trial has been set up, insurance cover is provided by the University of Exeter's clinical trials policy on a non-negligence basis. If an injury is caused by an NHS member of staff whilst carrying out any medical intervention to the participant in the trial the participant will need to pursue a claim via the NHS indemnity scheme.

Hospitals selected to participate in this clinical trial shall provide clinical negligence insurance cover for harm caused by their employees and a copy of the relevant insurance policy or summary shall be provided to University of Exeter, upon request.

14.10 Post trial care

Following the collection of primary outcomes at six months the participants will receive no ongoing formal care however participants will have the option to enrol in an optional online fortnightly peer support group which will be facilitated by the trial team.

14.11 Access to the final trial dataset

We will store anonymised research data and outputs in the University of Exeter's Open Research Exeter repository (https://ore.exeter.ac.uk/repository/) in order to facilitate open access to, and the impact of, our research. All future research proposals must obtain the appropriate ethical and regulatory approvals.

15 DISSEMINIATION POLICY

15.1 Dissemination policy

University of Exeter owns the data arising from the trial. On completion of the trial the data will be analysed with results also reported on ISRCTN.

All proposed publications will be discussed with the Sponsor prior to publishing other than those presented at scientific forums/meetings. Please refer to University of Exeter publication policy. The trial protocol will be published and eventual findings published in high impact open access journals and communicated at international academic conferences.

A lay summary sheet of results will be prepared for the participants and circulated at the end of the trial and posted on the trial website.

Broader Dissemination Policy: The core trial team will develop training materials, guidelines and recommendations where appropriate from the findings of the trial. The expertise of the core trial team, and their position within a broad geographical spread of NHS services, along with sitting on many non-statutory and statutory alcohol organisations, guideline committees and policy making bodies means we are extremely well placed to cascade these findings out across the UK and realise their impact on alcohol treatment.

In the final year of the project, all the regional workshop groups will be invited to attend a conference in person, with hybrid options available, where the trial and core PPI team will present the findings and seek early input in a series of focus groups and breakout sessions.

Guidelines, Recommendations and Policy Documents: The trial team comprises senior members of the alcohol treatment guidelines group (e.g. NICE guideline for alcohol treatment group, 2011; OHID Alcohol Guidelines Group; British Association of Psychopharmacology Guidelines) and team members are therefore well-placed to support the development of recommendations and guidelines based on the trial findings to support the visibility of this work. We will use our network of stakeholders to develop our recommendations for treatment and core competencies for those delivering KARE therapy.

15.2 Authorship eligibility guidelines and any intended use of professional writers

We will follow the International Committee of Medical Journal Editors authorship criteria for outcome papers:

- Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
- Drafting the work or revising it critically for important intellectual content; AND
- Final approval of the version to be published; AND
- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

An authorship plan will be agreed prior to the drafting of outcome papers. We do not plan to engage the use of professional writers for this trial.

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17. APPENDICIES

17.1 Appendix 1 – Amendment History

Amendment No.	Protocol version no.	Protocol date	Author(s) of changes	Details of changes made
1	1.0	29/JUN/2023	Amy McAndrew	Updates in line with NIHR and CTU review including: - Addition of exploratory analyses details - Removal of the brand of self-breathalsyers to be used - Addition of anxiety measure and objectives - Addition of readiness to change scale - References of a summary PIS changed to FAQ PIS - Addition of family history added to table 2 - Addition of GU assessment to screening review by trial medics - Timeline of progression review - Addition of rescue medication section - Addition of alcohol to table 4 - Re-write of section 10 for clarity and addition of RUSAEs.
2	2.0	29/AUG/2023	Amy McAndrew	Updates in line with ethical resubmission: - Clarification of CI and scientific lead roles - Change of named sponsor representative. - Addition of CTA and REC reference numbers. - Updates to the indemnity section 14.9 - Updates to visit timepoints for the APEQ and Hood mysticism scale. - Updates to annotation in table 2 for vital signs - Update to Dr Cole's email address and removing Dr Brandner and Dr O'Kane's email addresses. - Clarification of core PROMS data - Clarification on demographic data collection. - Update to pregnancy test inclusion criteria timelines.

				- Updates to urine drug testing panel.
3	3.0	26/OCT/2023	Amy McAndrew	Update in line with substantial amendment 1: - TSC roles and responsibilities updated - Updates to blood pressure exclusion criterion. - Addition of ISRCTN number.
4	4.0	24/JAN/2024	Amy McAndrew	Update in line with substantial amendment 2: - Timeframe for KSET, SADQ, 3 things task and informed consent updated. - Addition of new exclusion criterion regarding previous ketamine treatment. - Addition of AST and ALP liver function test (LFT).
5	5.0	20/MAR/2024	Amy McAndrew	Update in line with non-substantial amendment 6: - Addition of ethnicity to pre-screening question set.
6	6.0	21/MAY/2024	Amy McAndrew	Update in line with non-substantial amendment 7: - Addition of option to use infusion bags rather than syringes for infusions.
7	7.0	06/JUN/2024	Amy McAndrew	Updated in line with substantial amendment 3: - Addition of the option to use 10mg/ml vials/ampoules of ketamine - Addition of the option to use an additional label for dispensing vials/ampoules for the creation of the IMP