Full title of trial	A phase II, randomised, double-blind, placebo- controlled, multi-site, parallel group clinical trial to examine ketamine as a pharmacological treatment for alcohol dependence in an alcohol dependent population.
Short title	KARE: Ketamine for reduction of Alcoholic REIapse
Version and date of protocol	Final Version 12, 20 January 2020
Sponsor:	University College London (UCL)
Sponsor protocol number	13/0253
Funder (s) :	Medical Research Council
EudraCT no	2015-000222-11
ACTIVE IMP(s):	Ketamine
PLACEBO IMP(s):	Placebo (Saline)
Phase of trial	Phase II
Sites(s)	Multisite

Chief investigator:

Dr Brigitta Brandner

Consultant Anaesthetist

UCL Centre for Anaesthesia

University College London Hospital

Sponsor Representative:

Samim Patel

Email: samim.patel@ucl.ac.uk

Tel: 020 76799320

Joint Research Office, 1st Floor Maple House,

LONDON NW1 2BU

Email: brigitta.brandner@nhs.net

Tel: 020 3447 3343 fax: 020 3447 9604

149 Tottenham Court Road,

London W1T 7DN.

Postal address:

Joint Research Office, UCL

Gower Street,

London

London WC1E 6BT

Signatures

The Chief Investigator and the JRO have discussed this protocol. The investigators agree to perform the investigations and to abide by this protocol.

The investigator agrees to conduct the trial in compliance with the approved protocol, EU GCP and UK Regulations for CTIMPs (SI 2004/1031; as amended), the UK Data Protection Act (1998), the Trust Information Governance Policy (or other local equivalent), the Research Governance Framework (2005' 2nd Edition; as amended), the Sponsor's SOPs, and other regulatory requirements as amended.

Chief investigator

Dr Brigitta Brandner

Signature Date

Sponsor Representative

Dr Nick McNally, Director of Research Support
UCL

Signature Date

This Protocol template is intended for use with UK sites only.

Contents

List of abbreviations

AE	Adverse Event
ALP	Alkaline phosphatase
ALT	Alanine transaminase
AR	Adverse Reaction
AST	Aspartate aminotransferase
ACQ-NOW	Alcohol Craving Questionnaire
BDI	Beck Depression Inventory
BDNF	Brain-derived neurotrophic factor
BMI	Body Mass Index
BPRS	Brief Psychiatric Rating Scale
CA	Competent Authority
CBT	Cognitive Behavioural Therapy
CI	Chief Investigator
CNS	Central Nervous System
CRF	Case Report Form
CRO	Contract Research Organisation

CTA	Clinical Trial Authorisation
CTIMP	Clinical Trial of Investigational Medicinal Product
DMC	Data Monitoring Committee
DSM	Diagnostic and Statistical Manual of Mental Disorders
DSUR	Development Safety Update Report
EC	European Commission
ECRF	Exeter Clinical Research Facility
ECT	Electro-convulsive therapy
EMEA	European Medicines Agency
EU	European Union
EUCTD	European Clinical Trials Directive
EudraCT	European Clinical Trials Database
EudraVIGILANCE	European database for Pharmacovigilance
GAfREC	Governance Arrangements for NHS Research Ethics
GCP	Good Clinical Practice
GGT	Gamma-GT
GMP	Good Manufacturing Practice
HAM-D	Hamilton Depression Scale
IB	Investigator Brochure
ICF	Informed Consent Form
IDMC	Independent Data Monitoring Committee
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
ISF	Investigator Site File
ISRCTN	International Standard Randomised
LFT	Liver Function Test
MA	Marketing Authorisation
MDD	Major Depressive Disorder

MHRA	Medicines and Healthcare products Regulatory Agency
MS	Member State
Main REC	Main Research Ethics Committee
NHS R&D	National Health Service Research & Development
NMDA	N-methyl-d-aspartate
PI	Principal Investigator
PIS	Participant Information Sheet
POMS	Profile of Mood States
PSI	Psychotomimetic States Inventory
QA	Quality Assurance
QC	Quality Control
QP	Qualified Person for release of trial drug
RCT	Randomised Control Trial
REC	Research Ethics Committee
SAR	Serious Adverse Reaction
SAE	Serious Adverse Event
SCID	Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders
SDV	Source Document Verification
SOP	Standard Operating Procedure
SPC	Summary of Product Characteristics
SSA	Site Specific Assessment
STAI	State-Trait Anxiety Inventory
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMG	Trial Management Group
TSC	Trial Steering Committee
UCLH	University College London Hospitals NHS Foundation Trust
VAS	Visual Analogue Scale
WOCBP	Women of Child-Bearing Potential

Trial personnel

Chief Investigator (CI): Dr Brigitta Brandner

Anaesthetics Department

Podium 3, Maple Link corridor

University College Hospital

235 Euston Road

London

NW1 2BU

e-mail: brigitta.brandner@nhs.net

tel: 020 3447 3343 fax: 020 3447 9604

Sponsor's representative: Samim Patel

Joint Research Office, UCL,

Gower Street,

London, WC1E 6BT.

e-mail: samim.patel@ucl.ac.uk
tel: 020 76799320 fax: 020 3108 2312

Statistician: Dr Fiona Warren

Lecturer in Medical Statistics

University of Exeter

Smeall Building

St Luke's Campus
Exeter
EX1 2LU
e-mail: f.warren@exeter.ac.uk

tel: +44 (0) 1392 722749 fax: +44 (0) 1392 722894

Central laboratories: ABS Laboratories

Mira Doig

ABS Laboratories Ltd

BioPark,

Broadwater Road,
Welwyn Garden City,
AL7 3AX
Hertfordshire
e-mail: info@abslabs.com
Tel: 01707 358669 fax: 0207 916-1989

SCRAM-X Providers: Alere Toxicology

Charter House II
Links Business Park
St Mellons
Cardiff
CF3 0LT
e-mail: james.rowe@alere.com
tel: +44 (0)2920 540 542 fax: 44 (0)8452 991 410

Study Centre: NIHR/Wellcome UCLH Research Facility

University College Hospital
Clinical Research Facility
Ground floor
Elizabeth Garrett Anderson Wing
235 Euston Road
London NW1 2BU
email: generalcrf@uclh.nhs.uk
tel: 0203 447 6036 fax: 020 3447 6094

Study Centre: NIHR Exeter Clinical Research Facility

University of Exeter Medical School
Royal Devon & Exeter Foundation NHS Trust
Barrack Road
Exeter
Devon
EX4 5DW

Email: crf@exeter.ac.uk

Tel: 01392408182

Lead Researcher (PI): Dr Celia Morgan

Centre for Clinical Psychopharmacology

Department of Psychology

Washington Singer Laboratories

Perry Rd

Exeter

EX4 4QG

email: celia.morgan@exeter.ac.uk

tel: 01392 724 649 fax:01392 724 623

Summary

Title:	A phase II, randomised, double-blind, placebo-controlled, multi-site, parallel group clinical trial to examine ketamine as a pharmacological treatment for alcohol dependence in an alcohol dependent population.
Short title:	KARE: Ketamine for the reduction of Alcoholic RElapse
Trial medication:	Ketamine Hydrochloride and Placebo (Saline)
Phase of trial:	Phase II
Objectives:	Primary objectives: 1) To obtain preliminary data on whether ketamine is effective in promoting and prolonging abstinence in alcohol dependent patients following detoxification. 2) To assess safety and tolerability of ketamine in alcohol dependence Secondary objectives: 1) To make an early assessment on likely compliance to a combined ketamine and relapse prevention based cognitive behavioural therapy (CBT) 2) To obtain preliminary data as to whether ketamine alone is as effective as a combined ketamine and psychotherapy treatment.
Type of trial:	Phase IIa/b, double-blind, randomised, parallel group, multi-site trial in an alcohol dependent population
Trial design and methods:	96 recently detoxified alcoholics will be randomised to receive either 3 sessions of ketamine (0.8 mg/kg IV over 40 minutes) or placebo (50ml Saline 0.9% IV over 40 minutes) plus either manualised psychological therapy or psychoeducation control. Patients will be assessed at 3 and 6 months on a range of psychological and biological variables. The primary endpoint is relapse rate at 6 months. Secondary endpoints include 3 and 6 month percentage days abstinence, tolerability (indicated by drop-out), adverse events, depressive symptoms, craving and quality of life. Application/exploitation: The findings would have broad application given the worldwide prevalence of alcoholism and associated medical, psychological and social problems.
Trial duration per participant:	24 weeks

Estimated total trial duration:	30 months
Planned trial sites:	Multi-site
Total number of participants planned:	96
Main inclusion/exclusion criteria:	Main Inclusion Criteria: • 18 to 65 years old; • Meet either a) DSM-5 criteria for moderate/severe alcohol use disorder or b) DSM-IV criteria for alcohol abuse/dependence within the last 12 months; • Currently abstinent from alcohol (breathlyser BAC level 0.00) and negative urine drug screen (participants testing positive for THC who do not have a history or current cannabis dependency may be included; participants testing positive for benzodiazepines and who do not have a history or current dependency for benzodiazepines may be included); • Capacity to give informed consent as defined by GCP guidelines; • Willing to wear SCRAM-X bracelet for active treatment; • Females of childbearing potential and males must be willing to use an effective method of contraception (hormonal or barrier method of birth control; True abstinence) from the time consent is signed until 6 weeks after treatment discontinuation and inform the trial if pregnancy occurs. For the purpose of clarity, True abstinence is when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence, spermicides only, withdrawal or lactational amenorrhoea method for the duration of a trial, are not acceptable methods of contraception; • Females of childbearing potential must have a negative pregnancy test within 7 days prior to being registered for trial treatment and on day of first treatment. Main Exclusion Criteria: • Currently taking any other relapse prevention medication or anti-depressants; • Current uncontrolled hypertension (systolic 140mm Hg or greater and diastolic 90mm Hg or greater); • Currently has BMI outside normal limits <16 or > 35 • Any relevant mental or physical health issues as determined by medically qualified personnel, which may include:

- Current or history of psychosis as identified by DSM-5 or DSM-IV SCID;
- Current or historical diagnosis of schizophrenia in a first degree relative;
- Current co-morbid psychiatric diagnosis excluding depression and anxiety;
- Previous or current diagnosis of substance dependence / severe substance misuse disorder as confirmed by the participant's GP or if the participant has sought professional help for their dependence;
- Clinically relevant history of neuropsychological difficulties. One or more previous medically confirmed seizures, including seizures witnessed by an appropriate clinician, documented evidence from an EEG or a history consistent with a diagnosis of an epileptiform illness;
- Current suicidal ideation, as judged clinically.

- Any medication deemed, by the trial medical professionals, to pose risk combined with ketamine which may include daily prescribed use of;
  a. Barbiturates and/or narcotics
  b. Atracurium and tubocurarine
  c. Central nervous system (CNS) depressants (e.g. phenothiazines, sedating H1 – blockers or skeletal muscle relaxants)
  d. Thiopental
  e. Thyroid hormones
  f. Antihypertensive agents
  g. Theophylline and methylxanthines.
- Liver function tests that assess chronic liver damage (namely bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST)) > 3 times normal levels
- Where there are special warnings or precautions for use according to the SPC where the risk 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. Current diagnosis of:
  a. Acute intermittent porphyria
  b. Dehydration or hypovolemia
  c. Hyperthyroidism
  d. Pulmonary or upper respitatory tract infection
  e. Severe Coronary artery disease, Cerebrovascular accident or cerebral trauma
  f. Known glaucoma or globe injuries

g. Cirrhosis
h. Epilepsy
i. Intracranial mass lesions, hydrocephalus, or presence of head injury (i.e. evidence of lasting impact of head injury that is affecting everyday functioning)

- Not willing to use effective contraception or (females) take pregnancy test;
- Allergic reaction to ketamine;
- >10 previous inpatient detoxifications from alcohol;
- Pregnant or breastfeeding
- Allergies to excipients of IMP or placebo;
- Use of another IMP that is likely to interfere with the study medication within 3 months of study enrolment.

Statistical methodology and analysis:

The primary outcomes are relapse in alcohol use and percentage of days abstinent at 6-month follow-up. Relapse in alcohol use will be analysed descriptively using proportions per arm and as relative risks with 95% confidence intervals for selected comparisons. Percentage of days abstinent will be analysed descriptively and as between-group mean differences with 95% confidence intervals for selected comparisons. The primary analysis will be on an intention-to-treat complete case basis. Secondary analysis will be conducted using a per protocol approach. Sensitivity analyses using multiple imputation methods will be conducted for relapse at 6-month follow-up only. Secondary outcomes will be analysed descriptively on an intention-to-treat complete case basis and reported as between-group mean differences with 95% confidence intervals for ketamine versus non-ketamine participants.

2 Introduction

2.1 Background

Worldwide, alcohol abuse is a burgeoning problem. In the UK alone, nearly 9% of men and 4% of women today meet criteria for alcohol dependence – in all ~ 3.9 million British adults [1]. Alcohol misuse globally accounts for roughly 4% of all deaths and 5% of the burden of disease [2]. Here in the UK 22,000 people die annually because of alcohol misuse, which can produce severe and enduring physical and neurological problems. Costs to the NHS from alcohol abuse are estimated at £2.7 billion annually [2]. Abstinence is key to allow recovery of physical and mental health as well as quality of life, but treatment for alcohol dependence is associated with high relapse rates of around 50% at 3

months, 70% at 6 months [3, 40]. Despite the huge burden on the NHS and UK economy, treating alcohol dependence and prolonging abstinence remains an unmet need.

The end users of our intervention are ultimately alcohol dependent patients. The proposed treatment would be a brief intervention to reduce relapse rates and concurrent depressive symptoms that are rife in alcohol dependent individuals. Benefits of no longer being dependent on alcohol for end-users 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 resulting in an overall increase in quality of life. Considering the high toll alcohol abuse has on the health system [9], benefits would accrue in a reduction in burden on the NHS and its workforce, in alcohol-related deaths and in other non-fatal acute harms. Economic benefits would not only be reflected in a reduction in burden to the NHS but in more frequent and regular engagement in work activities, and a reduction in crime. 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 of time.

2.2 Preclinical data

Ketamine is a lipid soluble molecule that readily crosses the blood-brain barrier following peripheral administration. Preclinical work has demonstrated that ketamine is stored in adipose tissue and then slowly released back into the plasma compartment [7]. The alpha phase of ketamine distribution lasts about 45 minutes, with a half-life of 10 to 15 minutes. The first phase corresponds clinically to the anaesthetic effect of the drug. When administered intravenously for anaesthesia, a sensation of dissociation occurs within 15 seconds and anaesthesia occurs within 30 seconds (in 3-4 minutes for intra-muscular (IM) route). The anaesthetic effects are terminated by a combination of redistribution and hepatic biotransformation to an active metabolite, norketamine [8]. Norketamine has itself been suggested to have some psychotomimetic effects [9]. The terminal half-life of ketamine is about 2-3 hours.

In preclinical models, ketamine has been shown to be highly effective in depression [see 10 for a review]; these include forced swim [11; 1213; - see also 14 for a review), novelty suppressed feeding test [15; 16; 17] and the tail suspension test [12; 19]. Ketamine pre-treatment blocks alcohol seeking in alcohol preferring rats [14; 34], but this effect is reversed by co-administration of rapamycin [13], which blocks increases in synaptogenesis. Similarly the antidepressant effects of ketamine are blocked by this same compound [21]. Thus the mechanism for reduction in alcohol seeking following ketamine may be the same mechanism of the anti-depressant effects of ketamine: an increase in synaptogenesis.

2.3 Clinical data

A review of several studies administering ketamine to 450 healthy humans, found no serious adverse events. Out of the 450 infusions, 9 participants reported adverse mental status events (high levels of hallucinations and dysphoria) during the infusion, all of which ended with discontinuation of the infusion [20]. 3 of these became unresponsive to verbal stimuli and six reported mild distress at the dissociative effects of ketamine.

Over 2000 patients with treatment-resistant depression have been involved worldwide in clinical trials using ketamine as a treatment for depression [46]. These include several with repeated dosing [98; Collins et al. 2010] including one repeated dosing study recently completed in the UK [21; 22].

The first study to draw attention to ketamine as an antidepressant was of 17 treatment-resistant patients with Major Depressive Disorder [MDD; 23]. This placebo-controlled, randomized, crossover study found 71% of the participants to have a greater than 50% reduction in depressive symptoms within 24 hours of ketamine administration, while the same participants showed almost no change in symptoms following the placebo saline injection. Moreover, the response was sustained for the 1-week follow-up in approximately one-third of the participants. There have been several subsequent placebo-controlled crossover studies that showed very similar findings of rapid onset of robust antidepressant activity lasting for several days to weeks after a single subanaesthetic dose of ketamine in the treatment of major depressive episodes associated with both MDD and bipolar disorder [e.g. 94; 21].

Numerous open-label studies and case series provide additional evidence of ketamine's antidepressant effect and further characterize its effects in unique patient populations. Rapid reductions in suicidal ideation in depressed patients who received ketamine have been reported [25]. Other studies have begun to examine the potential benefits of adding ketamine to the anesthetic regimen of patients undergoing ECT [26; 27]. Still other reports have begun to evaluate the potential use of ketamine in palliative care settings, where the drug's pain-reducing effects may provide an additional benefit [28; 29].

Pilot work conducted in the 1980s, found unprecedented reductions in relapse rates in alcoholism following ketamine treatment. Three weekly doses (2.5mg/kg bolus I.M.) of ketamine were given alongside sessions of psychotherapy before and after the administration of the drug to 111 recently detoxified alcohol dependent patients. Of a control group of 100 similar recently detoxified alcohol dependent patients, 24% were abstinent after 1 year compared with 66% of those who had undergone ketamine therapy [5]. A 40% reduction in relapse rate is much greater than anything previously been observed with any other relapse prevention method in alcohol dependence. These preliminary findings have been supported by

case studies of the successful use of ketamine, alongside transpersonal therapy, in the treatment of alcoholism, where 15 patients had 70% abstinence rates at 1 year [30].

Importantly, ketamine has a very favourable safety profile. One concern with this therapy may be that ketamine can also be abused but we have shown that higher subanaesthetic doses of ketamine, such as that proposed in this study, are not rewarding, [68] and recently detoxified alcoholics given ketamine did not go on to abuse the drug [51, 69] and alcohol craving did not increase following ketamine in this group [51]. A clinical trial is underway at Yale University in the US using ketamine for the treatment of depression in alcoholism [31] and the study team have reported the treatment to be well tolerated with no adverse events [32]. Further, as discussed above in section 2.2 there has been no evidence of subsequent drug abuse, or any persisting problems when ketamine was administered to a large sample of psychologically-prepared patients in a supportive research setting [38] and similar absences of subsequent drug abuse have been observed in smaller samples of depressed patients [71].

2.4 Rationale and risks/benefits

The research question is whether ketamine can reduce relapse in alcohol dependence.

Scientific Rationale

Exsiting treatments in alcohol use disorder are of limited efficacy and are poorly adhered to. In the UK only acamprosate and disulfiram are licensed for relapse prevention with naltrexone used but not licensed for this purpose (unlike in the US). Various other antidepressants and anticonvulsants have been trialled (e.g. trazadone, gabapentin) but any effects disappear as soon as treatment is discontinued. While psychosocial interventions are recommended as first line treatments [84], for example couples' therapy, CBT and motivational enhancement therapy; their effects are, at best, modest.

These current pharmacological treatments for relapse prevention have limited efficacy and require daily dosing. Naltrexone has side effects, disulfiram is associated with adverse events and toxicity. Other drugs that have shown some minor efficacy (e.g. gabapentin) cease to be effective as soon as active treatment is discontinued. If this study confirms the long-lasting effect of ketamine on relapse, then it would mean it was 6 times more efficacious than any existing therapy [2]. Ketamine has a significantly better safety profile compared to disulfuram, and as our proposed solution requires only 3 sessions of ketamine-assisted therapy and one extra psychological therapy session, treatment adherance [42] – which has been a problem with all existing pharmacotherapies - would likely be good.

Further, all competing solutions require being maintained on medication for a minimum of 6 months but likely longer, whereas ketamine-assisted therapy requires only 3 weeks making the treatment more tolerable and less stigmatising.

Ketamine has been extraordinarily successful in treating depression [4; 11; 43], such that it has recently been hailed '..a wonder drug…' in the journal Science by some researchers and clinicians [44]. Similarly, pilot work conducted in the 1980s, found unprecedented reductions in relapse rates in alcoholism following ketamine treatment [33].

At the time of the pilot work in alcohol dependence in Russia, any potential biological mechanism was unclear. However the remarkable recent success of isolated doses of ketamine in the treatment of depression [4; 43] suggests that a similar biological mechanism could be in operation in this observed reduction of relapse in alcoholism following ketamine. The proposed biological mechanism behind the anti-depressant effects of ketamine is increased synaptogenesis and recent empirical evidence suggests that blocking synaptogenesis also blocks ketamine-induced reductions in alcohol consumption [45]. We are proposing that ketamine may improve relapse in alcoholism via a three-way mechanism: stimuliating the growth of neurons and synapses; targeting depressive symptoms; and enhancing the uptake of psychological therapy.

Stimulating neurogenesis and synaptogenesis
The birth of new neurons and synapses in the human brain is now widely accepted as an 'ordinary process with extraordinary implications' [52]. For many years neurogenesis and synaptogenesis have been suggested to be fundamentally impaired in depression. Preclinical research [53] and human case studies [54] now suggest that ketamine exerts its anti-depressant effects by stimulating the growth of new synapses and promoting synaptic transmission in the prefrontal cortex.

Recent theoretical accounts have also proposed a role for impaired neurogenesis and synaptogenesis in addiction [52; 55]. These accounts are supported by vast numbers of preclinical studies that suggest that these processes are blocked following administration of addictive substances, in particular alcohol [e.g. 56-61]. Changes in potential indices of neurogenesis, such as serum BDNF, are observed in alcoholics [62], with levels increasing the longer their sobriety [39]. Reducing the numbers of newborn neurons and synapses has been suggested as a means of making the addicted brain less able to learn about non-drug rewards and unable to project into the future [52].

Ketamine pre-treatment blocks alcohol seeking in alcohol preferring rats [46; 66], but this effect is reversed by co-administration of rapamycin [45], which blocks increases in synaptogenesis. Similarly the antidepressant effects of ketamine are blocked by this same compound [53]. Thus the mechanism for reduction in alcohol seeking following ketamine may be the

same mechanism of the anti-depressant effects of ketamine: an increase in synaptogenesis.

Alleviating depressive symptoms

Depression is almost ubiquitous in alcoholism and nearly all alcoholics have depressive symptoms upon entry into detoxification programmes [47]. Conventional anti-depressants have no impact on drinking, which is problematic as depressive symptoms are thought to precipitate relapse [48; 49]. Over 50% of alcoholics will have relapsed 3 months post-treatment [3]. Given the fast-acting and impressive antidepressant profile of ketamine, its impact on early depressive symptoms during this vulnerable period post-detoxifcation may explain why our preliminary data suggest that ketamine is a far more effective treatment than any other relapse prevention medication in alcoholism.

Ketamine also has been found to produce a more robust anti-depressant effect in treatment-refractory depressed individuals with a family history of alcoholism compared to those without [50]. It has been suggested that this is due to genetic variation in density of NMDA-receptors, hence it is possible that ketamine may work more effectively as an antidepressant in alcohol-dependent individuals. When administered to recently detoxified alcoholics, our collaborator (IP) has shown that ketamine can reduce dysphoria [51], supporting our hypothesis that it will be an effective treatment of low mood in this sample.

Enhancing the uptake of psychological therapy

Psychosocial therapies are currently the mainstays of treatment for alcohol dependence but are of limited effectiveness, which may partly be because they depend on the brain's capacity for neuroplastic change [63]. Psychological therapies in alcoholism are also less effective in individuals with cognitive impairment [64]. Undergoing learning based psychological therapy during the period of neurogenesis and synaptogenesis, which commences around two hours after an acute dose of ketamine [53], may facilitate its uptake as the brain is primed to make new connections and learn new information. Increased synaptogenesis has been linked with improved memory [e.g. 65; 69]. Therefore ketamine may enhance the uptake of psychological therapy in the hours following an acute dose by making the brain more receptive to new learning.

The notion that treatments that stimulate neurogenesis and synaptogenesis in this manner may work synergistically with psychological therapies is becoming more accepted [90] and may represent a future paradigm shift in the treatment of mental health problems. Historically, approaches to treating alcoholism that involve psychological therapy and provoke neurogenesis have enjoyed some success [see e.g. 91 for a review] but it is only recently that the biological mechanisms have been elucidated. In order to examine whether enhancing the uptake of therapy is the mechanism by which ketamine is effective in alcoholism we have included a ketamine + 'no therapy' arm in the trial. These data will have considerable implications not only for alcohol dependence, but also

depression as this may suggest a similar psychotherapy plus ketamine approach may enhance the effectiveness of ketamine treatment.

Additional advantages of ketamine: glutamatergic actions
Ketamine also acts as an antagonist of the glutamatergic N-methyl-d-aspartate receptor. Glutamatergic activation and glutamate receptor up-regulation contribute to alcohol dependence and withdrawal [66]. Acute detoxification is associated with a hyperglutmatergic effect that NMDA-receptor antagonists have been shown to normalise [66]. Excess glutamate is known to have toxic effects, and ketamine may protect against some of these adverse effects.

Risks / Benefits

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 much higher doses (1 mg/kg to 4.5 mg/kg over 60 seconds) than our proposed dose of 0.8 mg/kg over 40 minutes, and even at these higher doses ketamine has a very good safety profile [34]. Use of ketamine is indicated with caution in the chronic alcoholic and the acutely alcohol-intoxicated patient. This is because ketamine is metabolised in the liver and hepatic clearance is required for termination of clinical effects. A prolonged duration of action may occur in patients with cirrhosis or other types of liver impairment. For this reason exclusion criteria will be liver function tests (LFTs, specifically bilirubin, ALT, AST) 3 times> the upper limit of normal. These are the same criteria used in the clinical trial for ketamine for depression in alcoholism in the US [31] by our collaborator at Yale. Her current study, and previous work which has administered ketamine to the same population (recently detoxified alcoholics) has shown good tolerability and safety in this group at a similar dose (0.5mg/kg IV over 40 minutes) [35; 36]. Further, breathalyser readings taken at infusion visits will be used to ensure that the visit is terminated where patients are currently intoxicated with alcohol.

The SPC states that dose reductions should be considered in alcoholic patients: our study does intend to use less than the minimum clinical dose of 1mg/kg. The SPC also states that abnormal liver function tests 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. Benefits of no longer being dependent on alcohol for end-users 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, and a reduction in

crime. 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 [41], therefore benefits would also acrue 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. Data therefore suggest that the potential benefits to this group of patients far outweigh the risks.

2.5 Assessment and management of risk

This trial is categorised as TYPE B suggesting that the risk is somewhat higher than the risk of standard medical care. The IMP is licenced in the EU but is being trialled in a new indication

The table below summarises the risks, frequencies and mitigations of the IMP:

Potential risk	**Risk Frequency ***	**Risk Management**
Elevation of blood pressure, respiratory and heart rate	Common	IMP will be administered at site. Vital signs will be monitored throughout the infusion of ketamine. Patients will not leave the site until they are judged 'street ready' by an anaesthetist, all signs of acute intoxication are absent and they will be advised to be collected by a responsible adult or transportation will be arranged for them. At discharge patients will be given a 24 hour contact card for emergencies. Patients with uncontrolled hypertension, eclampsia or pre-eclampsia, severe coronary or myocardial disease, cerebrovascular accident or cerebral trauma will be excluded from the study (see section 5.2). Patients taking thyroid hormones have an increased risk of developing hypertension and tachycardia when given with ketamine and therefore we will exclude these patients (see section 5.2).
Bradycardia, Arrhythmia,	Uncommon	IMP will be administered at site. Vital signs (heart rate, blood pressure, pulse oximetry)

Hypotension		will be monitored throughout the infusion of ketamine. Patients will not leave the site until they are judged 'street ready' by an anaesthetist, all signs of acute intoxication are absent and they will be advised to be collected by a responsible adult or transportation will be arranged for them. At discharge patients will be given a 24 hour contact card for emergencies. Patients with uncontrolled hypertension, eclampsia or pre-eclampsia, severe coronary or myocardial disease, cerebrovascular accident or cerebral trauma will be excluded from the study (see section 5.2). Concomitant use of antihypertensive agents increases risk of hypotension and therefore, patients on antihypertensive agents will be excluded from the study (see section 5.2).
Anaphylactic reaction	Rare	Ketamine will be administered by an anaesthetic registrar or consultant in the Clinical Research Facility at sites with access to resuscitative equipment. Patients will not leave the site until they are judged 'street ready' by an anaesthetist, all signs of acute intoxication are absent and they will be advised to be collected by a responsible adult or transportation will be arranged for them. At discharge patients will be given a 24 hour contact card for emergencies. Patients with a known allergy to the IMP, placebo or any of its excipients will be excluded from the study (see section 5.2). Patients on trial treatment phase who have an allergic reaction to ketamine will be withdrawn from further IMP treatment.
Elevated Intraocular pressure	Not known	Patients with glaucoma or globe injuries will be excluded from the study (see section 5.2).
Diplopia	Common	Patients will agree not to drive or operate heavy machinery on the day of the infusions. They will not leave the site until they are judged 'street ready' by an anaesthetist, all signs of acute intoxication are absent and they will be advised to be collected by a responsible adult or

		transportation will be arranged for them. At discharge patients will be given a 24 hour contact card for emergencies.
Nystagmus, Hypertonia, Tonic clonic movements	Common	These effects are reported with anaesthetic doses but the dose we are using in this trial is much lower than anaesthetic doses and over a much longer period. Whilst in previous studies we have observed nystagmus, we have not observed tonic clonic movements. To mitigate this unlikely risk patients will agree not to drive or operate heavy machinery on the day of the infusions. Patients will not leave the site until they are judged 'street ready' by an anaesthetist, all signs of acute intoxication are absent and they will be advised to be collected by a responsible adult or transportation will be arranged for them. At discharge patients will be given a 24 hour contact card for emergencies.
Prolonged acute effects, impaired hepatic clearance, drug-induced liver damage	Not known	Use of ketamine is indicated with caution in the chronic alcoholic and the acutely alcohol-intoxicated patient. This is because ketamine is metabolised in the liver and hepatic clearance is required for termination of clinical effects. A prolonged duration of action may occur in patients with cirrhosis or other types of liver impairment. 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. Long term ketamine abuse can result in liver damage. However, we are giving just three, small doses. So liver damage is not an expected outcome. Patients with liver function tests (LFTs, specifically bilirubin, ALT, AST) 3 times > the upper limit of normal will be excluded from the study (see section 5.2).
Emergence reactions: Hallucinations, abnormal dreams,	Common	Psychotomimetic symptoms or 'emergence reactions' are a key feature of ketamine administration. The psychological effects of anaesthetic doses vary between pleasant dream like states and vivid imagery to out of

nightmare, confusion, agitation, abnormal behaviour		body experiences and hallucinations. 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 [20]. Patients with schizophrenia given doses of ketamine similar to those administered in this study have been known to have longer lasting psychotomimetic states [38] and for that reason psychosis in the patient and schizophrenia in the patient or a first degree relative are an exclusion criteria for the study (see section 5.2). Emergence phenomena can be reduced in anaesthesia with the co-administration of a benzodiazepine; midazolam can be administered by the anaesthetist if the emergence phenomena are intolerable to the patient. Alternatively the infusion can be stopped and, due to short half-life of ketamine, these effects should remit very rapidly.
Delirium, Flashback, dysphoria, insomnia, disorientation	Rare	This dose is lower than an anaesthetic dose, where risks are rare. 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 [20]. Patients with schizophrenia given doses of ketamine similar to those administered in this study have been known to have longer lasting psychotomimetic states [38] and for that reason psychosis in the patient and schizophrenia in the patient or a first degree relative are an exclusion criteria for the study (see section 5.2). Emergence phenomena can be reduced in anaesthesia with the co-administration of a benzodiazepine; midazolam can be administered by the anaesthetist any symptoms are intolerable to the patient. Alternatively the infusion can be stopped and, due to short half-life of ketamine, these

		effects should remit very rapidly. IMP will be administered at site. Patients will not leave the site until they are judged 'street ready' by an anaesthetist, all signs of acute intoxication are absent and they will be advised to be collected by a responsible adult or transportation will be arranged for them. At discharge patients will be given a 24 hour contact card for emergencies.
Anxiety	Uncommon	If patients find any symptoms intolerable, a benzopdazepine can be co-administered which should reduce anxiety. Alternatively the infusion can be stopped and, due to short half-life of ketamine, these effects should remit very rapidly.
Nausea, Vomiting	Common	Patients will fast for 6 hours before the infusion to reduce the risk of vomiting and pulmonary aspiration. In the case of vomiting, or if nausea is intolerable to the patient then the infusion will be stopped, whereupon these symptoms should remit very quickly.
Ketamine abuse	Not known	Patients with a significant history of substance misuse other than alcohol will be excluded. No previous studies giving ketamine to this patient group found evidence that they subsequently went on to abuse the drug [4; 5].
Respiratory depression, laryngospasm, obstructive airway disorder or apnoea	Rare	These effects occur only with large doses and rapid infusions. Ketamine will be administered at a sub-anaesthetic dose and infused over 40 minutes, in the numerous previous studies using this dosing regimen this adverse effect has never been reported.
Salivary hypersecretion	Rare	Participants will be warned of this potential side effect, which would not be prolonged and for the duration of the infusion only. Increased salivation in this context should not be associated with any further risks. We have not observed this adverse event with our previous sub-anaesthetic ketamine studies, therefore it may be confined to anaesthetic doses, but should there be any increased salivation this will be for the duration of the infusion only.
Erythema,	Common	Mild rash and redness of the skin have been

Rash morbilliform		observed following ketamine, which remit upon cessation of administration of the drug, however these might concern participants if unexpected, therefore we will fully inform participants of this possibility in the information sheet.
Cystitis, Haemorrhagic cystitis	Rare	Ketamine-induced ulcerative cystitis is now a clinical condition observed after prolonged daily or more than daily use of ketamine in abusers. Only one case has been reported in the medical literature following the repeated daily administration of ketamine for chronic pain. As patients in this study will only receive 3 doses of ketamine, spaced at a week apart, we do not anticipate cystitis to be a risk from ketamine administration in the current study, however this will be carefully monitored and we shall ask questions pertaining to cystitis in our recording of adverse events.
Injection site pain, injection site rash	Uncommon	If participants experience this uncommon side effect, local anaesthetic may be given. They will be informed of the potential of a rash and this will be carefully monitored.
Assessment of psychiatric conditions	Inclusion of a participant with a comorbid psychiatric disorder	The SPC for ketamine advises caution in patients with a history of psychosis therefore all participants will be assessed for psychosis using the SCID. For other comorbid psychiatric disorders the research team will ask the participant's medical health professional to notify us. Hence anyone with a current psychiatric disorder apart from depression and anxiety will be excluded.
Urine drug screen	Allowing a cannabis dependent participant to take part in the trial.	People with a previous or current cannabis dependence/severe use disorder diagnosis will be excluded from the trial, as will people with any other substance dependence/severe use disorder diagnosis (apart from alcohol). Therefore, the risk of including a cannabis dependent participant will be minimal. However, occasional cannabis use is comorbid with alcohol use. Cannabis use, like other substance use, will be monitored throughout the trial using a urine drug screen. Cannabis consumption leads to THC remaining in urine for approximately 28 days. Therefore,

		occasional use of cannabis may result in a positive THC urine screen. However, occasional cannabis use is not grounds for exclusion. Therefore, people who are not dependent on cannabis (and do not have a history of it), but do have a positive THC urine drug screen, may be included.
Urine drug screen	Allowing a benzodiazepine dependent participant to take part in the trial.	People with a diagnosis of previous or current benzodiazepine dependence/severe use disorder will be excluded from the trial, as will people with a diagnosis of any other substance dependence/severe use disorder (apart from alcohol). Therefore, the risk of including a benzodiazepine dependent participant is minimal. However, benzodiazepines are used in community and inpatient alcohol detox and for sleep problems. Benzodiazepine use, like other substance use, will be monitored throughout the trial using a urine drug screen. Benzodiazepine use has a relatively long detection window (up to 7 days for long-acting). Therefore, benzodiazepine use in detox may result in a positive benzodiazepine urine screen. However use of benzodiazepines in detox is not grounds for exclusion. Therefore, people who are not dependent on benzodiazepines (and do not have a history of it), but do have a positive benzodiazepine urine drug screen, may be included.

* From SPC of anaesthetic use of ketamine (Appendix E)

RISK OF IMP

Ketamine has a very wide margin of safety: several instances of unintentional anaesthetic administraion of overdoses up to 10 times that required have been followed by prolonged but complete recovery (see SPC).

Use with caution is indicated in patients with acute intermittent porphyria, increased cerebrospinal fluid pressure (as assessed by questionnaire), hyperthyroidism, pulmonary and upper respiratory infection as well a pregnancy therefore to further mitigate risk these are all exclusion criteria for the study (see section 5.2). Several drugs may interact with ketamine (e.g. barbituates, narcotics, CNS depressants) therefore currently daily use of these medications will be an exclusion criteria (see section 5.2).

Psychotomimetic symptoms or ‘emergence reactions’ are a key feature of ketamine administration. The psychological effects of anaesthetic doses vary between pleasant dream like states, vivid imagery to out of body

experiences and hallucinations. 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 [20]. Patients with schizophrenia given doses of ketamine similar to those administered in this study have been known to have longer lasting psychotomimetic states [38] and for that reason psychosis in the patient and schizophrenia in the patient or a first degree relative are an exclusion criteria for the study (section 5.2). Emergence phenomena can be reduced in anaesthesia with the co-administration of a benzodiazepine; midazolam can be administered by the anaesthetist if the emergence phenomena are intolerable to the patient.

WOCBP will be included in this clinical trial as per the ICH M3 (R2) which suggests WOCBP can be included in clinical trials without developmental toxicity in studies where there is intensive control for pregnancy. Any risks will be mitigated by the use of contraceptives and pregnancy testing. Ketamine is indicated for use in caesarean section. A recent Cochrane Review [37] compared ketamine for forceps delivery to other analgesics and found no difference in maternal or neonatal outcomes. However, preclinical data from rats given extremely high doses indicate some neurotoxicity in rats. The current trial will use methods of birth control which result in low failure rates of less than 1% per year (See Inclusion criteria section 5.1), if pregnancy is detected then participants will be immediately excluded.

The summary of product characteristics advises caution in patients with neurotic traits or psychiatric illness (e.g. schizophrenia and acute psychosis). To mitigate risks against this risk and risk of potential suicide the protocol will exclude patients with these conditions as well as those who have suicidal ideation. At screening, the Columbia Suicide Severity Rating Scale will be used to assess suicide ideation. As patients at risk of suicide will be excluded, this tool will not need to be done at every assessment point as we have mitigated this risk from the outset. Additionally we will be monitoring depressive symptoms throughout the trial (Beck Depression Inventory and Hamilton Depression Rating Scale). The population group being studied are alcohol dependent individuals where alcohol use will be the primary disorder and not depression. The IMP (Ketamine) is an anti-depressant drug and has indeed been shown to have efficacy at reducing suicidal ideation in individuals with treatment resistant depression thus we feel the risk of increased suicidal ideation from ketamine is minimal.

All other risks related to trial design and methods
i) Risks from study procedures

The table below summarises the risks and mitigations of all tests above standard care that are being performed:

Intervention	Potential risk	Risk Management
Cannulation and Venepuncture	Cannulation is required for administration of IMP and placebo. Plasma samples will be taken 13 times during the course of this study. Both are accompanied with a risk of discomfort, bruising, excessive bleeding, fainting or feeling lightheaded, hematoma & infection	Cannulation will be performed by an experienced anaesthetist and staff trained in venepuncture. Venepuncture risks will be managed using standard clinical care precautions which include wearing protective clothing, hand and surface hygiene. Risks to participants from venepuncture will be managed using standard clinical care. Non clinical staff performing venepuncture will receive appropriate training. Furthermore, in an effort to mitigate these risks, the participant information sheet (PIS) will make reference to these risks and inform people who have previously suffered complications during venepuncture or who have a fear of needles that they should not take part. Every effort will be made to make participants feel comfortable before, during and after cannulation and venepuncture by encouraging participants to relax and talking through any concerns they have about the procedure. Trust incident reporting will apply and be followed in the event of patient/staff needle stick injury.
SCRAM-X bracelet	Participants will have their alcohol use over active treatment monitored via the SCRAM-X bracelet worn on the ankle. The wearer may not soak in the bath or swim.	Inclusion criteria require patients to be willing to wear the bracelet for active treatment. The researchers who fit the bracelet will be extensively trained in fitting the bracelet

	Wearing the bracelet carries with it a risk of discomfort. It can cause bruising, pain and scars from it rubbing against the skin.	by colleagues at the health monitoring company Alere. Patients will be fully informed of the potential discomfort and the implications of wearing the bracelet in the participant information sheet. . Participants will be trained in how to clean under the bracelet to ensure that the risk of any skin problems is mitigated.
Psychological therapy	Psychological therapy may cause transient distress as the participant discusses sensitive and upsetting material	Participants will be informed that they do not have to discuss material they are not comfortable discussing. Trained psychologists with experience of psychological therapies will administer the therapy and be supervised by a consultant clinical psychologist with over 20 years experience in the field of treatment of alcohol use disorders.

ii) Data risks

Potential data risks include breach of participant confidentiality through inappropriate collection or storing of data. In order to minimise these risks, all researchers are GCP trained. Confidentiality will be ensured using standard procedures (e.g. password protected computers and data storage, all electronic data coded numerically so that individual participants cannot be identified; consent forms will be kept in secure locked cupboards in locked rooms). Any publications will similarly use anonymised data. The trial is occurring at two sites which facilitates data security. We appreciate that data about illicit drug use is sensitive and our security measures are appropriate to this.

The investigator will ensure quality of the study data with respect to inclusion/exclusion criteria, protocol adherence, data collection and storage, and all physical data collected as part of this trial will be entered into a Red Pill database designed by sealedenvelope.com with quality control checks.

The trial will be monitored by an appointed external monitor according to a monitoring plan developed by the sponsor and risk assessment of the trial. These risks will be further minimized by the use of a short trial duration

and finite follow up. Agreements are in place with the laboratories (ABS Laboratories, SCRAM-X and Alere) who will handle data from the study externally to ensure they agree to comply with confidentiality and relevant data protection acts.

Anonymised data collected from the SCRAM-X will be transferred to the UK study centre (Alere) and transferred to the US via a secure firewalled server for collation and then returned to Alere where it will be transferred securely to the study team. The patient information sheet will explain this to the patient and specific consent for anonymised data to go to the US will be sought.

Data collection using the SCRAM-X and of biological samples will be done in accordance with relevant UK confidentiality and data protection acts. Data collected with the bracelet will be entered anonymously into the Microsoft Access database. The patient information sheet will explain the measures taken to protect the patients' identity and collected data.

Biological samples will be labelled using anonymous patient IDs and will be sent by secure courier within the UK to the head analyst at our central laboratory (ABS Laboratories) who have reliably analysed biological samples for many of our previous research projects and is both regulated and accredited.

Consent: Standard procedures will be used whereby participants have a minimum of 24 hours after reading the patient information sheet before deciding whether to take part and giving consent. They will be encouraged to discuss their participation with significant others. All researchers appointed with this project have previous experience taking consent from patients.

Treatment
The participant information sheet will state that the trial design does not allow for switching of participants in the placebo arm to the active arm at the end of the trial. This is because neuropsychological measures are subject to repeated practice effects. However if the active treatment is successful, participants would be informed if a large scale clinical trial is subsequently initiated.

Patient Group
Although we have excluded patients with suicidal ideation or any other current psychiatric diagnosis apart from depression or anxiety, as this is an alcohol dependent population it is possible that they may experience worsening of their mental state during the study duration. If we observe or if patients report any changes in mental state at any of the study visits which we would deem as putting themselves or others at risk then we will refer them back to their medical care provider (e.g. Consultant Addiction Psychiatrist if referred from substance misuse services or GP if self-referral).

3 Objectives

Primary objectives:

1) To obtain preliminary data on whether ketamine is effective in promoting and prolonging abstinence in alcohol dependent patients following detoxification.

2) To assess safety and tolerability of ketamine in alcohol dependence

Secondary objectives:

1) To make an early assessment on likely compliance to a combined ketamine and relapse prevention based cognitive behavioural therapy (CBT)

2) To obtain preliminary data as to whether ketamine alone is as effective as a combined ketamine and psychotherapy treatment.

4 Trial design

4.1 Overall design

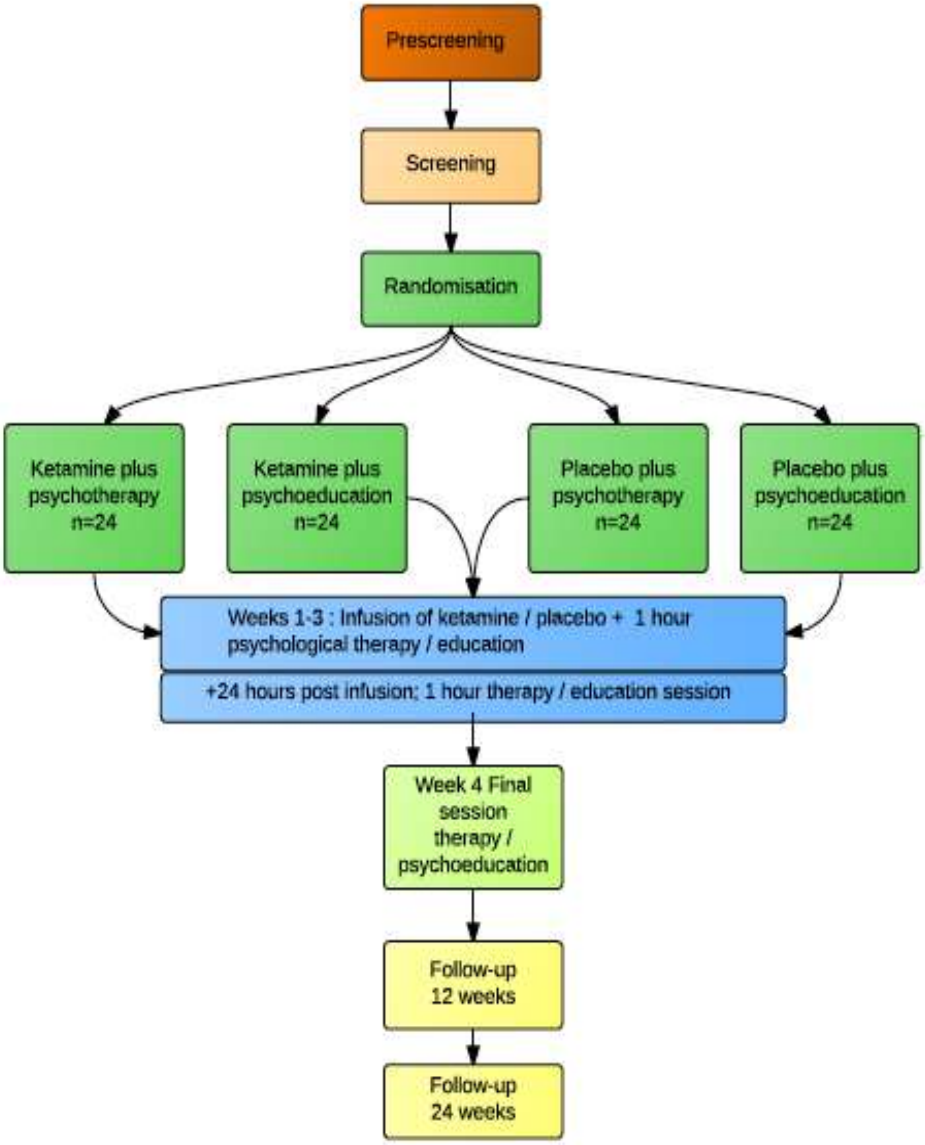
This non-commerical parallel group, placebo-controlled double blind design aims to make a preliminary assessment of the effectiveness of ketamine in promoting and prolonging abstinence in alcohol dependent patients (Fig. 1). *Why this design was chosen:* A parallel group design is chosen as a crossover would not be feasible with the long time-scales of the study, and given marked carry-over effects that occur in substance-use reduction studies. Three weekly doses of ketamine were chosen as this protocol showed effectiveness in the preliminary studies [33]. This approach has been chosen, rather than a full-scale trial as it is important to confirm the preliminary findings in alcohol dependence. We have chosen to assess outcomes at 3 months and 6 months as from examining other pharmacological and non-pharmacological trials, the largest change in drinking behaviour occurs in the first 3 months and then tails off [40]. However we will follow up again at 6 months to index maintenance of the treatment effect (balancing against the issues of retention of patients in the trial).

For the purpose of this study, Relapse: 5 drinks (drink=13g) in men (8.1units) and 4 drinks (6.5 units) in women on any single occasion and Lapse is defined as ‘any other episode of alcohol consumption’.

Blinding to the IMP: The trial design will be double blinded. This has been chosen so as to reduce any bias from the power of suggestion of which treatment the patient is received by both the researchers and the patient. The pharmacy or delegated unblinded personnel at both sites will prepare

the syringe for infusion in a blinded fashion so that the administering anaesthetist, psychological researcher and patient are all blind to treatment allocation.

Figure 1: Schematic of overall trial design from recruitment to end of follow up



5 Selection of Subjects

5.1 Inclusion criteria

1. 18 – 65 years old
2. Meet either a) DSM-5 criteria for moderate/severe alcohol use disorder or b) DSM-IV criteria for alcohol abuse/dependence (see Appendix A) within the last 12 months
3. Currently abstinent from alcohol (breathlyser BAC level 0.00) and negative urine drug screen (participants testing positive for THC who do not have a history or current cannabis dependency may be included; participants testing positive for benzodiazepines who do not have a previous or current diagnosis of benzodiazepine dependence/severe use disorder may be included)
4. Capacity to give informed consent as defined by GCP guidelines
5. Willing to wear SCRAM-X bracelet for active treatment
6. Females of childbearing potential and males must be willing to use an effective method of contraception (hormonal or barrier method of birth control; True abstinence) from the time consent is signed until 6 weeks after treatment discontinuation and inform the trial if pregnancy occurs. For the purpose of clarity, True abstinence is when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence, withdrawal, spermicides only or lactational amenorrhoea method for the duration of a trial, are not acceptable methods of contraception.
7. Females of childbearing potential must have a negative pregnancy test within 7 days prior to being registered for trial treatment and on day of first treatment.

5.2 Exclusion criteria

1. Currently taking any other relapse prevention medication or anti-depressants
2. Current uncontrolled hypertension, systolic 140mm Hg or greater and diastolic 90mm Hg or greater
3. Currently has BMI outside normal limits <16 or > 35
4. Any relevant mental or physical health issues as determined by medically qualified personnel, which may include:
    a. Current or history of psychosis as identified by DSM-5 or DSM-IV SCID
    b. Current or historical diagnosis of schizophrenia in a first degree relative

c. Co-morbid current psychiatric diagnosis excluding depression and anxiety.

d. Previous or current diagnosis of a susbtance dependence / severe substance misuse disorder as confirmed by the participant's GP or if the participant has sought professional help for their dependence

e. Clinically relevant history of neuropsychological difficulties

f. One or more previous medically confirmed seizures including seizures witnessed by an appropriate clinician, documented evidence from an EEG or a history consistent with a diagnosis of an epileptiform illness

g. Current suicidal ideation, as judged clinically

5. Any medication deemed, by the trial medical professionals, to pose risk combined with ketamine which may include daily prescribed use of:

   a. Barbiturates and/or narcotics

   b. Atracurium and tubocurarine

   c. Central nervous system (CNS) depressants (e.g. phenothiazines, sedating H1 – blockers or skeletal muscle relaxants)

   d. Thiopental

   e. Thyroid hormones

   f. Antihypertensive agents

   g. Theophylline and methylxanthine

6. Liver function tests that assess chronic liver damage (namely bilirubin, ALT, AST) > 3 times normal levels

7. Where there are "Special warnings and precautions for use" according to the SPC and 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. Current diagnosis of:

   a. Acute intermittent porphyria

   b. Dehydration or hypovolemia

   c. Hyperthyroidism

   d. Pulmonary or upper respitatory tract infection

   e. Severe Coronary artery diesase, Cerebrovascular accident or cerebral trauma

   f. Known glaucoma or globe injuries

g. Cirrhosis

h. Epilepsy

i. Intracranial mass lesions, hydrocephalus, or presence of head injury (i.e. evidence of lasting impact of head injury that is affecting everyday functioning)

8. Not willing to use effective contraception or (females) take pregnancy test
9. Allergic reaction to ketamine
10. >10 previous inpatient detoxifications from alcohol
11. Pregnant or Breastfeeding
12. Allergies to excipients of IMP and placebo
13. Use of another experimental investigational medicinal product that is likely to interfere with the study medication within 3 months of study enrolment.

6 Recruitment

The patients will be primarily recruited through Participant Identification Centres. These centres will be the substance misuse and addiction psychiatry services in Central, North West, South London as well as Devon, Dorset, Wiltshire, Somerset and Bristol who will refer potential participants to the research team. Avon and Wiltshire PIC will also distribute their “Everyone Included” letter, a research opportunity letter, to potentially eligible participants. The principal and co -investigators will work to raise awareness and educate all addiction service providers about the study. Based on previous experience, we expect that recruitment of suitable patients will primarily occur by being identified by their Doctor, nurse or other professional in the clinic or service they are attending. Patients will also be recruited from primary care (GP practices) with the aid of Clinical Commissioning Groups (CCGs) in the South West and London. PICs will be provided with a recruitment flyer that can be distributed amongst staff that are advertising the trial to potential participants to help them remember the key aspects of the trial, e.g. basic inclusion/exclusion criteria, and facilitate discussion. If interested, the patient/user will be given a REC approved invitation to participate letter, giving a brief description of the study and the contact details of the study team. Patients may contact the study team themselves, or complete the return slip and agree that their name and contact number can be given to the research fellows. The research team will then ensure the patient receives the Patient Information Sheet, via post, email or via the study team and follow up the patient with a telephone call to further discuss the study and conduct a pre-screening assessment (see section 7.4).

The research fellow / assistant psychologist will then contact the individual interested in participating via phone and discuss the trial and answer any queries they may have. If they would like to participate, the researcher will

then go through the prescreening questionnaire to establish whether the patient appears eligible to attend for a full screening appointment. If the patient appears eligible, the researcher will arrange to see them at the clinical research facility. If a potentially eligible patient is identified prior to detoxification from alcohol, an appointment will be made for after their detoxification. At the initial visit with the researcher and a medical doctor, the trial will be explained, written informed consent obtained, their eligibility assessed and baseline 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 and the GP will be requested to inform us if they have any concerns about the patient participating in the trial. Once eligibility is confirmed, a date will be made for them to attend the study centre for their first treatment visit.

We will also set up a study website to accompany the study, where patients can register their interest and we will publicise the trial through forums and social networking, relevant charities such as Foundation 66, Alcohol Concern, 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 Research Ethics Committee.

7 Study procedures and schedule of assessments

7.1 Informed consent procedure

It is the responsibility of the Investigator, or a person delegated by the Investigator to obtain written informed consent from each subject prior to participation in the trial, following provision of the trial participant's information sheet (PIS) and an adequate explanation of the aims, methods, anticipated benefits and potential hazards of the study. The person taking consent will be GCP and protocol trained, suitably qualified and experienced, and will have been delegated this duty by the CI/PI on the delegation log.

At least 24 hours will be given for consideration by the patient before taking part. The PI or delegate will record when the patient information sheet (PIS) has been given to the patient. The Investigator or designee will explain the patients 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 trial. A second signed Informed Consent form will be given to the participant. The other original signed form will be retained at the study site in the site file and a copy placed in the medical notes. If new safety information results in significant changes in the risk/benefit assessment, the consent form will be reviewed and updated if necessary and subjects will be re-consented as appropriate. Re-consenting can be delegated to trial psychologists who have completed GCP training, protocol training and informed consent

training. All trial psychologists including research assistants and postdoctoral research associates can be delegated this task.

7.2 Randomisation procedures

A blocked design for randomisation will be used to allocate patients using a 1:1:1:1 ratio for the 4 respective groups. Randomisation will be performed by a specialist company (www.sealedenevelope.com) who will hold the randomisation list and provide 24/7 internet access for unblinding services. Early drop-outs (during screening and the baseline week up until randomisation) will be replaced. Once patients have been randomised at week 0 they will not be replaced regardless of compliance or dropout status and will be analysed as part of the intention to treat analysis. After randomisation, the site research team will be given a unique trial randomisation code via email from sealedenvelope.com. This code corresponds to an envelope at the site which contains the treatment allocation. These envelopes will be provided by the trial statistician at the start of the trial and are kept in a secure location by allocated partially unblinded staff. The trial statistician will be provided the treatment allocation codes prior to the start of the trial to prepare the envelopes. Separate envelopes will be provided for the delegated staff preparing the IMP (containing the IMP treatment allocation) and the psychology staff (containing the psychological treatment allocation). To protect the blind, pharmacy or delegated unblinded staff preparing the IMP at site will be notified separately via email of the randomisation code. An additional e-mail is sent to the psychology team at site who can refer to the correct envelope to determine the psychological treatment allocation. Randomisation details of patients will be entered on a trial Subject Log and will follow the instructions set out in a Standard Operating Procedure (SOP) on randomisation. Data review will take place when half the target samples have been randomised. Upon randomisation, patients will be given a study specific patient card which will have study title, IMP details, patient ID and contact details of the out of hours contact in cases of emergency.

7.3 Unblinding

Emergency Unblinding

The study 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 patient 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 at www.sealedenevelope.com

Authorised members of the research team will have administrative rights to the unblinding system and a nominated individual will be available 24 hours a day.

In the event a code is required to be unblinded a formal request for unblinding will be made by the Investigator/treating health care professional to the authorised individual.

If the person requiring the unblinding is a member of the Investigating team then a formal request to the authorised individual will be made who will then log in to the sealed envelope web-based system to obtain the unblinded information.

If the person requiring the unblinding is not the CI then that health care professional will notify the Investigating team (via the 24 hour telephone number on the patient contact card) that an unblinding is required for a trial subject and an assessment to unblind should be made in consultation with the clinical and research teams. Unblinding will take place if in the opinion of a treating physician a patient's health is compromised or an SAE has occurred that requires unblinding. The treating physician has the ultimate decision and right to unblind the patient.

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

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

The CI/PI will document the breaking of the code and the reasons for doing so on the CRF/data collection tool, in the site file and medical notes. It will also be documented at the end of the study in any final study report and/or statistical report.

The CI/Investigating team will notify the JRO (acting on behalf of the Sponsor) 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.

Subject always to clinical need, and where possible, other members of the research team will remain blinded.

The CI (or appointed clinical cover team, consisting of a group of anaesthetists and psychiatrists) will be contactable via telephone / text /

email for out of hours procedures and unblinding. Please refer to 'Unblinding SOP' for further details.

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 agencies.

- An authorised member of the JRO 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 SOP on unblinding.
- The Sponsor will provide the unblinded information on the e-SUSAR website form.
- Unblinded information in the SUSAR reports will not be forwarded to the trial team and kept in the JRO sponsor file.
- SUSAR reports will be disseminated to Investigators at site, but the report will remain blinded.

7.4 Screening Period

Identification and Pre-screening (within 12 weeks of Screening visit):

Pre-screening assessment will be carried out by delegated members of the research team. Initial approaches to participants will be made only by the members of the appropriate clinical teams and referred to the research team (see section 5). A telephone assessment by the research team will be made to conduct the following:

- Discuss the trial.
- Further confirm initial eligibility using the inclusion and exclusion criteria in section 5, and whether the patient will be called for a full screening visit.
- Complete REC approved pre-screening questionnaire on medical history and dependency history to further assess initial eligibility.
- Book screening visit to those who pass the initial eligibility and still express interest in participating.

Screening Visit (Visit 1 Day 28 to 1 days before visit 2 (baseline) visit):

Formal screening will take place at this screening visit as set out in Appendix B and listed below. The methods of the assessments are explained in section 7.9. Consent will be taken from the patient prior to the assessments at this visit (see section 7.1).

Following screening and eligibility determination, those still meeting criteria for inclusion in the study can be fitted with the SCRAM-X bracelet anytime between the screening visit and visit 2. A date for visit 2 will be arranged, within 28 days of the screening date.

The visit schedule is set out below and as a chart in Appendix B:

I. Trial Discussion
II. Informed Consent
III. Medical history
IV. Physical Examination (repeat screens of height and weight may be conducted if initial results do not fall within boundaries described in 5.2 but patient meets other criteria for eligibility)
V. SCID
VI. Vital Signs (repeat screens of blood pressure may be conducted if initial results do not fall within boundaries described in 5.2 but patient meets other criteria for eligibility)
VII. Bloods to assess eligibility (U&Es, LFTs, FBC; repeat screens may be conducted every 7days if initial results do not fall within boundaries described in 5.2 but patient meets other criteria for eligibility, see Appendix B and section 7.9.2 for details of the tests that will be used).
VIII. Eligibility Determination
IX. Urine Drug Screen (repeat screens may be conducted if initial results do not fall within boundaries described in 5.2 but patient meets other criteria for eligibility, see Appendix B and section 7.9.2 for details of the tests that will be used)
X. Pregnancy test in WOCBP (urine test)
XI. Breathalyser (repeat breathalyser screens may be conducted if initial result does not fall within boundaries described in 5.1 but patient wishes to continue with detoxification and return once they are abstinent)
XII. Routine SCRAM-X fitting (unless study team deem this not possible)
XIII. Concomitant medication review
XIV. Alcohol and Drug Use History
XV. BDI
XVI. HAM-D
XVII. Columbia Suicide Severity Rating Scale
XVIII. Reasons for drinking questionnaire
XIX. STAI
XX. ACQ-NOW

XXI. BPRS

XXII. PSI

XXIII. Alcohol Timeline Follow Back

If more than 28 days pass between the screening visit and visit 2 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 Appendix B.

I. Refresher Trial Discussion

II. Updated Medical history

III. Physical Examination

IV. SCID

V. Vital Signs

VI. Bloods to assess eligibility (U&Es, LFTs, FBC; repeat screens may be conducted every 7days if initial results do not fall within boundaries described in 5.2 but patient meets other criteria for eligibility, see Appendix B and section 7.9.2 for details of the tests that will be used.)

VII. Eligibility Determination

VIII. Urine Drug Screen (see Appendix B and section 7.9.2 for details of the tests that will be used)

IX. Pregnancy test in WOCBP (urine test)

X. Breathalyser

XI. Concomitant medication review

XII. Updating Alcohol and Drug Use History

XIII. BDI

XIV. HAM-D

XV. Columbia Suicide Severity Rating Scale

XVI. BPRS

XVII. PSI

XVIII. Alcohol Timeline Follow Back

XIX. SCRAM-X checks (if already attached) / alternative SCRAM-X fitting (unless study team deem this not possible)

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

I. Breathalyser (If the initial breathalyser reading is >0, patients who wish to continue with detoxification and return once they are abstinent will be re-consented appropriately),

II. Inflated blood pressure with no evidence of uncontrolled hypertension, e.g. due to situational anxiety or recent alcohol withdrawal,

III. Elevated LFTs,

IV. BMI outside of trial limits,

V. Positive urine drug screen due to recreational drug use, when there is no evidence of a current substance dependence.

7.5 Baseline assessments (Visit 2, 1 to 28 days after screening):

The methods of the assessments are described in detail in section 7.9.

I. Vital Signs (see Appendix B and section 7.9.2 for details of the tests that will be used). Vital signs will be continuously monitored throughout the infusion 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 participants recovery.

II. Bloods, blood samples for BDNF and ketamine will be obtained pre-IMP/placebo administration and post IMP administration (see Appendix B and section 7.9.2 for details of the tests that will be used.)

III. Full eligibility determination

IV. Urine Drug Screen (see Appendix B and section 7.9.2 for details of the tests that will be used.)

V. Pregnancy test in WOCBP (urine test)

VI. Breathalyser

VII. Randomisation

VIII. IMP/placebo Administration (see section 7.6)

IX. SCRAM-X checks (if already fitted) / alternative SCRAM-X fitting (where routine fitting at screening not completed)

X. Relapse Prevention Based Cognitive Behavioural Therapy

XI. Adverse Events Review

XII. Concomitant medication review

XIII. BDI

XIV. HAM-D

XV. POMS

XVI. STAI

XVII. ACQ-NOW

XVIII. BPRS

XIX. PSI

XX. Alcohol Timeline Follow Back

XXI. Fagerstrom Nicotine Dependence

XXII. Craving VAS

XXIII. SF-12

XXIV. Prose Recall

XXV. Delay Discounting (monetary choice questionnaire)

XXVI. Stop Signal Reaction time

XXVII. Working memory (digit span WAIS-IV)

XXVIII. Adverse Effect VAS(e.g. nausea, intoxication, anxiety, memory : 20 mins before infusion and every 20 mins for next 2 hours)

XXIX. Pattern Recognition Memory Test

7.6 Treatment procedures (visits 2 (i.e. baseline; 1 to 28 days after screening), visit 4 (4 to 21 days after visit 2) and 6 (4 to 21 days after visit 4))

IMP Dosing Patients will receive 3 x weekly infusions of ketamine (Ketalar®) (0.8mg/kg made up to 50ml with saline over 40 minutes) or 3 x weekly infusion of placebo (0.9% saline over 40 minutes). The drug/ placebo will be prepared in a blinded fashion by pharmacy (who are unblinded) or delegated unblinded site staff on the ward at site and will be administered by the research anaesthetist at the Clinical Research Facility at sites who will remain blinded.

S+ Ketamine hydrochloride packaged as: Ketalar ® for Injection. The total amount to be delivered will be calculated on the basis of the patient's weight (0.8 mg/kg). Site pharmacy will order ketamine and dispense per patient, added to saline (0.9%) to make up to 50ml in syringes for the infusion pump. For patients allocated the placebo, site pharmacy will prepare a 50ml saline (0.9%) solution in syringes for the infusion pump. Doses will be administered using a computer controlled infusion pump. Participants will be given the option of whether they'd like to listen to non-vocal instrumental music during the infusion to block out environmental noise.

Relapse Prevention Based Psychological Therapy: 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). The aim of these 7 sessions is to help to develop an enjoyable and meaningful life without alcohol. It focuses around two broad themes. The first theme relates to relapse prevention, i.e. skills and strategies to reduce the likelihood of relapse and maintain abstinence. The second theme focuses on promoting well-being and deals with issues such as purpose, meaning and life enjoyment, along with skills for coping with life's day-to-day problems and stresses.

Session 1: This session focusses on introducing the concepts of high risk situations and triggers as well as on planning your activities.

Session 2: This session focusses on recognising high risk situations and planning effective coping responses. In addition we identify essential resources for sobriety.

Session 3: The aim of this session is to develop further understanding of the role of thinking in drinking and how thinking biases can lead to unhelpful feelings and behaviour. In this session we also work on developing effective problem solving skills.

Session 4: The aim of this session is to develop general skills to recognise urges and craving and to plan an effective response. In this session we also introduce relaxation techniques and the concept of mindfulness.

Session 5: The aim of this session is to identify early warning signs of possible relapse. We also introduce the Demand Control Support model of stress to enhance insight into stress and ways of managing stress.

Session 6: This session focusses on lapse management and developing emergency plans aimed at preventing full relapse and we work on enhancing life enjoyment and satisfaction.

Session 7: In the final session we look at roles and identities and introduce another mindfulness practice. We then develop a plan for the next three months

Education control will be a 7 session educational programme educating patients about the risks of alcohol use and the effects of alcohol on the body (the supporting documents will also provide more detail).

7.7 Subsequent assessments

Visit 3 (1 to 5 days after visit 2), visit 5 (1 to 5 days after visit 4), 7 (1 to 5 days after visit 6)

I. Vital Signs

II. Bloods (see Appendix B and section 7.9.2 for details of the tests that will be used.)

III. Urine Drug Screen (See Appendix B and section 7.9.2 for details of the tests that will be used.)
IV. Breathalyser
V. SCRAM-X checks
VI. Relapse Prevention Based Cognitive Behavioural Therapy
VII. Adverse Events Review
VIII. Concomitant medication review
IX. HAM-D
X. POMS
XI. ACQ-NOW
XII. BPRS
XIII. Craving VAS
XIV. Prose Recall Task
XV. Adverse Effects VAS

Visit 4 (4 to 21 days after visit 2) & visit 6 (4 to 21 days after visit 4) (Infusion Days)

I. Vital Signs, vital signs will be continuously monitored throughout the infusion and until the participant has recovered. This monitoring will be recorded on a standard observation chart and will be 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. Bloods, blood samples for BDNF and ketamine will be obtained pre-IMP/placebo administration and post IMP administration (see Appendix B and section 7.9.2 for details of the tests that will be used.)
II. Urine Drug Screen (See Appendix B and section 7.9.2 for details of the tests that will be used.)
III. Pregnancy test in WOCBP (urine test)
IV. Breathalyser
V. IMP/ placebo Administration
VI. SCRAM-X checks
VII. Relapse Prevention Based Cognitive Behavioural Therapy
VIII. Adverse Events Review
IX. Concomitant medication review
X. BDI
XI. HAM-D
XII. POMS

XIII. STAI
XIV. ACQ-NOW
XV. BPRS
XVI. PSI
XVII. Alcohol Timeline Follow Back
XVIII. Craving VAS
XIX. Prose Recall
XX. Adverse Effects VAS (e.g. nausea, intoxication, anxiety, memory : 20 mins before infusion and every 20 mins for next 2 hours)
XXI. Pattern Recognition Memory Test

Telephone reminders (Week 3; Week 11; Week 23)

1. In between the last three visits, the patients will be telephoned to remind them of their appointment and confirm attendance.

Visit 8 (4 to 21 days after visit 6), 9 (11 to 13 weeks after visit 2), 10 (23 to 25 weeks after visit 2)

I. SCID for visits 9 and 10 only
II. Vital Signs for visit 8 only
III. Bloods (see Appendix B and section 7.9.2 for details of the tests that will be used),
IV. Urine Drug Screen (See Appendix B and section 7.9.2 for details of the tests that will be used.)
V. Breathalyser
VI. SCRAM-X removal (visit 8 only)
VII. Relapse Prevention Based Cognitive Behavioural Therapy for visit 8 only
VIII. Adverse Events Review
IX. Concomitant medication review
X. Alcohol and Drug use History
XI. BDI
XII. HAM-D
XIII. POMS
XIV. STAI
XV. ACQ-NOW
XVI. BPRS
XVII. PSI

XVIII. Alcohol Timeline Follow Back
XIX. Drink diary
XX. Fagerstrom Nicotine Dependence
XXI. Craving VAS
XXII. SF-12
XXIII. Prose Recall
XXIV. Delay Discounting (monetary choice questionnaire)
XXV. Stop Signal Reaction time
XXVI. Working Memory (digit span WAIS-IV)
XXVII. Adverse Effects VAS
XXVIII. Pattern Recognition Test

7.8 Table of study assessments

Appendix B has a table listing all the study assessment per visit..

7.9 Methods

7.9.1 *Non laboratory procedures*

Medical History: The medical history will be taken by the researcher from the patient and by referring to medical notes to measure eligibility.

The assessment days at which questionnaire and neurocognitive measures will be administered can be found in section 7. Below is a list of questionnaire and neurocognitive measures and their state of validation:

Validated Interviews and Questionnaires:

- The Structured Clinical Interview for DSM-IV/DSM-5 Disorders (SCID) is used to confirm a diagnosis of alcohol dependence and the absence of current psychiatric diagnoses which are listed as exclusion criteria (e.g. schizophrenia). This diagnostic schedule is widely used. It lasts 20-30 minutes.
- 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 Hamilton Depression Inventory (HAM-D) is a 21 item clinician rated depression scale.
- The Columbia Suicide Severity Rating Scale is a 6 item interview used to assess suicidal ideation and behaviour and will be used to verify the exclusion criteria of subjects with suicide ideation.

- The State form of the Spielberger Trait Anxiety inventory (STAI) questionnaire (20 items) will be used to measure anxiety throughout the study.
- The Profile of Mood States 2 (POMS 2) Short Form will be used for the quick assessment of affective states (Anger-Hostility; Confusion-Bewilderment; Depression-Dejection; Fatigue-Inertia; Tension-Anxiety; Vigour-Activity; Friendliness).
- The Fagerstrom Test of Nicotine Dependence (FTND) – A five item scale to index nicotine dependence.
- The Brief Psychiatric Rating Scale (BPRS) is a clinician rated assessment of current psychotic symptoms based on a short interview.
- The Psychotomimetic States Inventory (PSI) is a self-rated scale of transient psychotic symptoms.
- SF-12 is a short scale that measures social functioning.
- A semi-structured interview detailing the patient's alcohol and drug use history will also be used.
- 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).
- A drink diary will be given to each participant to take home in between Visits 8, 9 and 10. Participants will be asked to record their alcohol consumption every day in between study 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.

Validated Neurocognitive measures:

- Delay discounting (e.g. monetary choice questionnaire): this is a task that measures an individual's preference for immediate small award over a long term bigger gain.
- Prose recall task: this looks at episodic memory by testing participants recall of a short news broadcast.

- Stop signal task: Stop signal reaction time examines response inhibition, participants have to inhibit prepotent responses to stimuli on the screen when they see a cue or 'stop signal'.
- Working memory task (e.g. digit span WAIS-IV): Working memory measures an individual's ability to maintain and manipulate small amounts of information.
- Pattern recognition memory task (BPS-O Task) is a memory task that taps hippocampal functioning and requires participants to distinguish between perceptually similar items that they have seen before and those they have not.

Questionnaires that are not validated:

- The Pre-Screening questionnaire has been developed to assess suitability for inclusion into the trial.
- Adverse Effects Visual Analgoue Scale (VAS) has been developed to measure adverse events during the ketamine infusion and treatment.
- Craving VAS: a one item visual analogue scale will be used to assess craving for alcohol anchored at one end with 'No desire to drink alcohol' and the other 'Very strong desire to drink alcohol'.

Breathalyser tests will be used at each visit for the following reasons:

- Screening & re-screening – To assess eligibility
- Baseline visit (1st infusion) – To assess eligibility/ensure safety of IMP administration/ensure patient is able to complete cognitive tasks and questionnaires, as well as engage with therapy/education
- Visit 3, 5, 7 & 8 – To ensure patient is able to complete cognitive tasks and questionnaires, as well as engage with therapy/education
- Visit 4 & 6 (2nd & 3rd infusion) – To ensure safety of IMP administration/ensure patient is able to complete cognitive tasks and questionnaires, as well as engage with therapy/education
- Visit 9 & 10 - To ensure patient is able to complete cognitive tasks and questionnaires

Once randomised, if a patient attends for any visit and does not blow 0 on the breathalyser the visit will be terminated (either for the primary purpose of safety on infusion visits or of data integrity on non-infusion visits) and the patient invited to re-attend to complete the visit within the allocated visit window.

Concomitant Medication: All prescription medication, over-the-counter medication, vitamins, and/or herbal supplements will be recorded on case report forms (CRFs).

Vital Signs: Resting pulse, pulse oximetry and blood pressure (BP) measurements will be measured at each visit phase for safety monitoring. Vital signs will be continuously monitored throughout the infusion 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 participants recovery.

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 and neurological system to a level of detail that would be expected for a patient due to receive anaesthesia.

7.9.2 *Laboratory procedures*

In order to assist the identification of pathology and confirm physical health and eligibility for inclusion in the study the following blood tests will be performed: biochemistry (urea, sodium, potassium, glucose, calcium, thyroid stimulating hormone) haematology (haemoglobin, white cell count, platelets, mean red cell volume); liver function (Bilirubin, ALT, AST, Total Protein, Alkaline Phos, Albumin, Globulin, Gamma-GT). The following liver function tests will be used to assess eligibility: bilirubin, ALT, AST. The following urine drug screen will be performed [extended panel: methamphetamine, cocaine, THC, benzodiazepines, tricyclic antidepressants, barbituates, phencyclidine,, amphetamines, morphine, methadone] (urine test cup/dip test). An additional urine drug screen test for ketamine will be done on the screening visit and on visits 2, 4, 6, 8, 9 and 10. Urine pregnancy tests (urine test) will be done on the screening visit and on infusion visits.

The laboratory results will be reviewed and reports signed by the Investigator who will record in the CRF whether they are normal, abnormal but not clinically significant or abnormal AND clinically significant. In the latter case the eligibility of participants will be reviewed.

The following samples will be processed at Local Labs for screening:

- Biochemistry (urea, sodium, potassium, glucose, calcium, thyroid stimulating hormone)
- Haematology (haemoglobin, white cell count, platelets, mean red cell volume);
- Liver function (Bilirubin, ALT, AST, Total Protein, Alkaline Phos (ALP), Albumin, Globulin, Gamma-GT)

The following urine tests will be performed at site using provided kits with results recorded in the medical notes/source data (urine test cup/ dip stick test) at screening visit and on Visits 2, 4 and 6:

- Urine Drug Screen (extended panel: methamphetamine, cocaine, THC, benzodiazepines, tricyclic antidepressants, barbituates, phencyclidine, ketamine, amphetamines, morphine, methadone) (urine test cup/dip test)
- Pregnancy test (urine test)

The following urine drug screens will be performed at site using provided kits with results recorded in the medical notes/source data (urine test cup/ dip stick test) at Visits 3, 5 and 7:

- Urine Drug Screen (extended panel: methamphetamine, cocaine, THC, benzodiazepines, tricyclic antidepressants, barbituates, phencyclidine, amphetamines, morphine, methadone) (urine test cup)

The following urine drug screens will be performed at site using provided kits with results recorded in the medical notes/source data (urine test cup/ dip stick test) at Visits 8, 9 and 10:

- Urine Drug Screen (extended panel: methamphetamine, cocaine, THC, benzodiazepines, tricyclic antidepressants, barbituates, phencyclidine, ketamine, amphetamines, morphine, methadone) (urine test cup)

The following samples will be processed and analysed at local labs for all subsequent follow up visits:

- Liver function (Bilirubin, ALT, AST, Total Protein, Alkaline Phos (ALP), Albumin, Globulin, Gamma-GT)

The following samples will be processed and analysed for subsequent visits according to the study specific SOP at an HTA licensed, accredited Central Laboratory:

- BDNF
- Ketamine,

The Laboratory SOP provides the details on sample handling, processing, storage and shipment for those samples going to the central laboratory. On infusion days (visits 2, 4 and 6) blood samples will be taken to pre- and post-infusion to assess changes in BDNF and ketamine levels. Blood samples taken after the infusion will be collected after the participant has recovered from the infusion.

7.10 Definition of end of trial

The end of the trial will be the last follow-up visit of the participant at 23 to 25 weeks post visit 2.

7.11 Discontinuation/withdrawal of participants and 'stopping rules'

All efforts will be made to maintain participants in the study where possible and to continue assessments as intended. However, there are circumstances under which treatment may be discontinued and/or participants withdrawn from the trial.

7.11.1 *Discontinuation from treatment*

The investigator may discontinue a patient from treatment if it is considered necessary for any reason including:

- Ineligibility (either arising during the study or retrospective)
- Significant protocol deviation e.g. if treatment is stopped for longer than 21 days (All protocol deviations and violations will be recorded and reported to the sponsor)
- Significant non-compliance with treatment or study requirements e.g. If the participant misses 2 consecutive infusions, as detailed in section 9.12
- An adverse event which requires discontinuation of the study medication or results in inability to continue to comply with study procedures
- Disease progression which requires discontinuation of the study medication
- Pregnancy
- In the case of an overdose (see section 10.5.5)

Where treatment is discontinued, participants will be invited to attend follow up visits 9 & 10 on the basis of our planned intention to treat analysis which assumes (and formally tests: see section 13.3.4) that data are missing at random.

The reason for participant treatment discontinuation will be recorded in the case report form (CRF).

7.11.2 *Withdrawal from the trial*

Participants have the right to withdraw at any time. Participants who formally withdraw from the study at any point will not receive any further contact from the study team. Participants who withdraw before Visit 2 (Baseline) will be replaced by assigning successive screening IDs to eligible subjects, but after completing randomisation on visit 2 participants will not be replaced due to the planned intention to treat analysis.

In addition the investigator may withdraw a participant from the study at any time if it is considered necessary for any reason including:

- Ineligibility (either arising during the study or retrospective)
- Significant protocol deviation
- Significant non-compliance with treatment or study requirements
- An adverse event which results in inability to continue to comply with study procedures
- Disease progression which results in inability to comply with study procedures
- Consent withdrawn, loss of capacity or detention under Mental Health Act
- Failure to respond to contact attempts from the study team
- Pregnancy

The reason for participant withdrawal will be recorded in the case report form (CRF).

7.11.3 *Stopping rules*

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

8 Name and description of all drugs used in the trial

8.1 Treatment of subjects

Investigational product/treatment
Participants will receive the following:

1. 3 x weekly infusions of IV ketamine hydrochloride (Ketalar®) at a dose of 0.8mg/kg over 40 mins, or
2. 3 x weekly infusion of placebo (50ml Saline 0.9%) over 40 mins.
3. Ketamine is packaged as: Ketalar® glass vial with rubber closure and aluminium flip-off cap containing. Exipients with known effects: Each 1 ml contains 2.6 mg of sodium. The total amount to be delivered will be calculated on the basis of the patient's weight (0.8 mg/kg). Site pharmacy will order ketamine and dispense per patient, added to saline (0.9%) to make up to 50ml solution in syringes for the infusion pump to infuse intravenously. Doses will be administered using a computer controlled infusion pump.

Placebo will be 50 ml saline (NaCl) 0.9% in syringes for the infusion pump.

8.2 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, antihypertensive agents, theophylline and other methylxanthines.

Due to potential impacts on the primary outcomes taking any other relapse prevention medication or anti-depressants will not be permitted during the period of study (Visit 2 - Visit 8).
Other concomitant medication use will be recorded in the CRF.

9 Investigational Medicinal Product

9.1 Name and description of investigational medicinal product(s)

The product under test will be three weekly doses of ketamine hydrocholoride (Ketalar®) at a dose of 0.8mg/kg I.V. over 40 minutes. Ketalar® 10mg/ml or 50mg/mL Injection vials will be used. Ketamine is a Controlled Drug (Schedule 4, Part 1). Placebo will be saline (0.9%) given I.V. over 40 mins.

Doses will be made up from Ketalar® neutral glass vial with rubber closure and aluminium flip-off cap containing ketamine hydrochloride. The Marketing License holder is Pfizer.

9.2 Name and description of each NIMP

N/A No NIMPs to be used in this trial

9.3 Summary of findings from non-clinical studies

Please refer to the Summary of Product Characteristics (SPC) and Section 2.1.

9.4 Summary of findings from clinical studies

Please refer to the Summary of Product Characteristics (SPC) and Section 2.3.

9.5 Summary of known and potential risks and benefits

See Section 2.4 and 2.5 and Summary of Product Characteristics.

9.6 Description and justification of route of administration and dosage

Ketamine will be administered at a dose of 0.8mg/kg IV over 40 mins using an infusion pump. The original study of ketamine for relapse prevention in alcoholics used a high IM bolus dose (2.5mg/kg), however our collaborator Evgeny Krupitsky suggested the use of a lower dose in alcohol dependence (1.2mg/kg IM) which data from a small sample (n=15) suggests was also effective. The lowest dose of ketamine that is likely to be effective is clearly preferable to minimise psychotomimetic effects which may reduce treatment tolerability and increase risk of drop-out. The proposed dose is higher than that routinely used in patients with treatment refractory depression (usually 0.5mg/kg IV see 43 for a review) but well within the range of doses that increase synaptogenesis in preclinical studies (up to 30 mg/kg IP). Similar doses have also been used successfully in treatment resistant depression (1.0mg/kg IM: 95). The reasons for use of this higher dose is that, given the better bioavailability of ketamine IV, this dose roughly equates to the lowest effective IM bolus dose in alcohol dependent patients used by our collaborator EK. The conversion of IM to IV dose was based on extrapolation of pharmacokinetic (PK) data [96; 97] as well as consultation with Professor Anthony Absalom (Cambridge / Groningen) who has investigated the PK profile of ketamine. We have opted for an IV route of administration as the effects are more easily controlled by the clinician, i.e. the duration of effects are shorter, and there is less variability in Cmax [99]. Placebo will be 50ml saline (0.9%) given IV over 40 mins using an infusion pump.

9.7 Dosages, dosage modifications and method of administration

Patients will be administered three doses of 0.8 mg/kg ketamine IV or three doses of the placebo (50ml Saline 0.9%) given IV over 40 mins through computer controlled infusion pump. As dose will be tailored to weight of participants, the site pharmacy or delegated unblinded site staff on the ward will prepare individualised doses according to the randomisation and patient individual weight.

9.8 Preparation and labelling of Investigational Medicinal Product

Preparation and labelling of the investigational medicinal products should be completed in accordance with Annex 13 of Good Manufacturing Practice (GMP) guidelines. Labelling exemption will apply and a dispensing labelling (as defined in the SoDA) will be used.

The prepared IMP and Placebo will be labelled with the approved templates provided by the sponsor.

9.9 Drug accountability

Routine hospital stocks of ketamine and saline 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 study site. At the end of the study, one copy of the drug inventory/dispensing record should be sent to the sponsor, one kept in the central study file and one in the site files. An unblinded person at each study 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 or destruction of the study medication. They will conceal the accountability forms to blinded personnel and ensure these logs are maintained and kept in the pharmacy file at site. All data regarding the study medication must be recorded on the relevant forms provided by the sponsor or local pharmacy accountability forms. Any dispensed but completely unused infusions (where the infusion bag has not been opened) at the London site will be returned to pharmacy and destroyed in line with site pharmacy procedures. Partially unused infusions at the London site cannot be accepted by pharmacy. Therefore the local controlled drug policy will be followed at the Clinical Research Facility to ensure that materials are appropriately destroyed. Completely unused or partially unused infusions at the Exeter site cannot be accepted by pharmacy and are therefore destroyed at the Clinical Research Facility. 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.

9.10 Source of IMPs including placebo

The IMP will be sourced from routine hospital stock and their handling and management will be subject to standard procedures of the pharmacy. Sourcing of IMP is also discussed in the Summary of Drug Arrangements.
The following IMPs and placebo can be used from routine hospital stock and their handling and management will be subject to standard procedures of the Pharmacy:

- IMP (Ketamine): Ketalar®
- Placebo (Saline 0.9 %) hospital stocks and any brand can be used as long as they are licensed for use within the UK.

9.11 Dose modifications

No dose modification will be permitted. If intolerable side effects are experienced, the subject will be withdrawn from IMP treatment (see also section 7.11).

9.12 Assessment of compliance

Compliance includes both adherences to IMP and Protocol study procedures. The trial medication will be administered by the research anaesthetist only in the context of the patient attending the Clinical Research Facility. Patients will not be responsible for any trial medication. A member of the research team will ensure that the arrangements for each treatment visit are agreed with the participant and their carer. Where necessary, the researcher will assist in transportation. If a participant fails to attend a clinic visit for the infusion then the researcher will endeavour to contact the patient to identify the reason. Where possible an alternate appointment will be made within the infusion visit window (see Appendix B). If the participant fails to attend a clinic visit for the follow-up day the researcher will endeavour to contact the patient to identify the reason and where possible arrange an alternative visit within the follow up visit window (see Appendix B). All episodes of failure to attend will be recorded in the medical notes, CRF and protocol deviation log. 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. Noncompliance to the Protocol study procedures will be documented by the investigator and reported to the Sponsor as agreed. Persistent noncompliance (<80%) may lead the patient to be withdrawn from the study.

9.13 Post-trial IMP arrangements

There is no plan to allow continued treatment with ketamine.

10 Recording and reporting of adverse events and reactions

10.1 Definitions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.
Adverse Reaction (AR)	Any untoward and unintended response in a subject to an investigational medicinal product which **is related** to any dose administered to that subject. *This includes medication errors, uses outside of protocol (including misuse and abuse of product)*
Serious adverse event (SAE), serious adverse reaction (SAR) or unexpected serious adverse reaction	Any adverse event, adverse reaction or unexpected adverse reaction, respectively, that: • results in death, • is life-threatening, • requires hospitalisation or prolongation of existing hospitalisation, • results in persistent or significant disability or incapacity, or • consists of a congenital anomaly or birth defect
Important Medical Event	These events may jeopardise the subject or may require an intervention to prevent one of the above characteristics/consequences. Such events should also be considered 'serious'.
Unexpected adverse reaction	An adverse reaction the nature and severity of which is not consistent with the information about the medicinal product in question set out: (a) in the case of a product with a marketing authorization, in the summary of product characteristics for that product, (b) in the case of any other investigational medicinal product, in the investigator's brochure relating to the trial in question.
SUSAR	Suspected Unexpected Serious Adverse Reaction

10.2 Recording adverse events

All adverse events will be recorded in the medical records and CRF only following consent.

If the investigator suspects that the subjects' disease has progressed faster due to the administration of the IMP, then he will record and report

this as an unexpected adverse event. Adverse events that are known to the IMP when used in its licensed indication (listed in Appendix C, or events that are disease related or related to procedures as listed in section 10.3.3) will only be recorded in the medical notes, however serious AEs will be recorded in the CRF and SAE log.

Clinically significant abnormalities in the results of objective tests (e.g. liver function, biochemistry) will also be recorded as adverse events. If the results are not expected as part of disease or IMP, these will also be recorded as unexpected. All adverse events will be recorded with clinical symptoms and accompanied with a simple, brief description of the event, including dates as appropriate. All adverse events will be recorded until 6 months post-treatment. All Serious Adverse Events will be reportable to the Sponsor from IMP administration up to 30 days post last IMP administration.

10.3 Assessments of Adverse Events

Each adverse event will be assessed for the following criteria:

10.3.1 Severity

Category	Definition
Mild	The adverse event does not interfere with the volunteer's daily routine, and does not require intervention; it causes slight discomfort.
Moderate	The adverse event interferes with some aspects of the volunteer's routine, or requires intervention, but is not damaging to health; it causes moderate discomfort.
Severe	The adverse event results in alteration, discomfort or disability which is clearly damaging to health.

10.3.2 Causality

The assessment of relationship of adverse events to the administration of IMP is a clinical decision based on all available information at the time of the completion of the case report form. The following categories will be used to define the causality of the adverse event:

Category	Definition
Definitely	There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out.
Probably	There is evidence to suggest a causal relationship, and the influence of other factors is unlikely.
Possibly	There is some evidence to suggest a causal relationship (e.g. the event occurred within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant events).
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the patient's clinical condition, other concomitant treatments).
Not related	There is no evidence of any causal relationship.

Not Assessable	Unable to assess on information available.

10.3.3 *Expectedness*

Category	Definition
Expected	An adverse event that is consistent with the information about the IMP listed in the SPC **or clearly defined in this protocol.**
Unexpected	An adverse event that is classed in nature as serious and which is not consistent with the information about the IMP listed in the SPC.

The reference document to be used to assess expectedness against the IMP and placebo is the SPC. The protocol and SCRAM-X bracelet brochure will be used as the reference document to assess disease related and/or procedural expected events.

The following Adverse Events 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 ketamine infusion
- Skin rash caused by the SCRAM-X bracelet
- Drinking relapse

10.3.4 Seriousness

Seriousness as defined for an SAE in section 10.1.

Collection, recording and reporting of adverse events (including serious and non-serious events and reactions) to the sponsor will be completed according to the sponsor's SOP (INV/S05).

10.4 Procedures for recording and reporting Serious Adverse Events

All serious adverse events will be recorded in the hospital medical notes and the CRF, and the sponsor's AE log. The AE log will be reported to the sponsor at least once per year. The Chief or Principal Investigator will complete the sponsor's serious adverse event form and the form will be faxed to the sponsor on 020 3108 2312 or preferably emailed on sae@ucl.ac.uk, within 24 hours of his / her becoming aware of the event. The Chief or Principal Investigator will respond to any SAE queries raised by the sponsor as soon as possible. All SUSARs must be notified to the

sponsor immediately (within 24 hours) according to the sponsor's written SOP. Reporting to the sponsor will be completed as per the sponsor's SOP and using the UCL SAE form (INV/S05).

10.5 Notification of deaths

All deaths, including deaths deemed unrelated to the IMP, if they occur earlier than expected will be reported to the sponsor within 24 hours of site being made aware of the event.

10.5.1 *Reporting SUSARs*

The sponsor will notify the main REC and MHRA of all SUSARs. SUSARs that are fatal or life-threatening must be notified to the MHRA and REC within 7 days after the sponsor has learned of them. Other SUSARs must be reported to the REC and MHRA within 15 days after the sponsor has learned of them. The procedure for unblinding in the event of a SUSAR is documented in section 7.3.

10.5.2 *Development Safety Update Reports*

The sponsor will provide the main REC and the MHRA with Development Safety Update Reports (DSUR) which will be written in conjunction with the trial team 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. This will be done in accordance with the sponsor's SOP (SPON/S17).

10.5.3 *Annual progress reports*

An annual progress report (APR) will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the trial is declared ended. The chief investigator will prepare the APR.

10.5.4 *Pregnancy (If applicable)*

We intend to record and notify pregnancies to the sponsor (using the sponsor's SOP). Any pregnancy that occurs during the treatment weeks will result in exclusion from treatment.

In the event of a pregnancy occurring during the study, this must be reported using a sponsor pregnancy reporting form.

To ensure subject's safety, each pregnancy must be reported to the sponsor within 24 hours of learning of its occurrence. The pregnancy must be followed to determine the outcome (including premature termination) and status of mother and child.

Pregnancy complications and elective terminations for medical reasons must be reported as an AE or SAE. Spontaneous abortion must be reported as an SAE to the CI and Sponsor within 24 hours of learning of its occurrence.

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

10.5.5 *Overdose*

We do not envisage an overdose as drugs are prepared by pharmacy and then administered by the anaesthetist at the Clinical Research Facility. Accidental administration of 50 times the protocol dose constitutes an overdose. In the event of an overdose and protocol deviation then the sponsor will be notified (and this information will be placed in the deviation log) and trust policy on incident reporting will be followed. Overdoses will be observed from drug charts, or an anaesthetic response in the patient. If an SAE is associated with the overdose then this will be fully described in the SAE report form. We will use intention to treat analysis in the case of an overdose. In the case of an overdose, the patient 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.

10.5.6 *Reporting Urgent Safety Measures*

If any urgent safety measures are taken the PI/Sponsor shall immediately and in any event no later than 3 days from the date the measures are taken, give written notice to the MHRA and the relevant REC of the measures taken and the circumstances giving rise to those measures. The guidance on the MHRA website will be used for details on clinical trials safety reporting.

10.6 The type and duration of the follow-up of subjects after adverse events.

If a patient has an adverse reaction during infusion they will be monitored in the Clinical Research Facility until a resolution or stabilisation is reached. If an SAE happens while the subject is not in the research facility they will be given the number of an on-call anaesthetist and told to present to A&E at site (preferably) or the nearest hospital. Any SUSAR related to the IMP will need to be reported to the Sponsor irrespective of how long after IMP administration the reaction has occurred.

10.6.1 *Notification of Serious Breaches to GCP and/or the protocol (SPON/S15)*

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 subjects of the trial;

or

(b) the scientific value of the trial.

The sponsor of a clinical trial shall notify the licensing authority in writing of any serious breach of:

(a) the conditions and principles of GCP in connection with that trial;

or

(b) the protocol relating to that trial, as amended from time to time, within 7 days of becoming aware of that breach.

The sponsor will be notified immediately of any case where the above definition applies during the trial conduct phase. The sponsor’s SOP on the ‘Notification of violations, urgent safety measures and serious breaches’ will be followed.

11 Data management and quality assurance

11.1 Confidentiality

All data will be handled in accordance with the UK Data Protection Act 1998. The Case Report Forms (CRFs) will not bear the subject’s name or other personal identifiable data. The subject’s initials, date of birth and patient ID, will be used for identification.

11.2 Data collection tools and source document identification

Data to be collected can be found in sections 7.5 and 7.7. Every effort will be made to maximise completeness of data. Trial data will be collected in an Electronic Case Report Form hosted on sealedenvelope.com, prepared using their “Red Pill” service (www.sealedenvelope.com/redpill). Source data documents will be defined at site prior to the start of the trial.

Full details of source data and documentation will be identified in a separate source document identification list but in summary will comprise of the following:

- Patient Clinical Record (medical notes)
- Trial specific source data worksheets and trial specific logs

- Laboratory test print outs
- Questionnaires and measurement scales
- Encrypted memory stick containing computer tasks data files and SCRAM-X data

Data to be recorded in the source data first and then transcribed into the CRF:

- Patient demographics; age, date of birth and initials
- Medical history including drug use, alcohol use, smoking
- Physical examination
- Patient eligibility assessment
- Allergies
- Concomitant medication
- Study IMP treatment
- Therapies: Psychoeducation Therapy, Relapse-prevention based CBT
- Clinical Assessment measurements: Vital signs, Blood and urine screen. On infusion visits (visits 2, 4 and 6) continuous monitoring of vital signs will occur through the infusion until the participant has recovered. This monitoring will be recorded on a standard observation chart and will be 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.
- Adverse Events (refer to section 10)
- Assessment tools:
    - Pattern Recognition Test
    - Stop Signal Reaction Time
    - Delay Discounting (monetary choice questionnaire)
    - Working Memory (digit span WAIS-IV)
    - Prose Recall
    - SCRAM-X checks
    - BPRS
    - PSI
    - Adverse events VAS
    - Craving VAS
    - Fagerstrom smoking
    - Timeline follow Back
    - Drink diary
    - Reasons for drinking questionnaire
    - Columbia Suicide Severity Rating Scale
    - BDI
    - HAM-D
    - POMS

- STAI
- SF-12
- ACQ-NOW

The following data to be collected in the source documents but will not be collected in the CRF:

- Adverse events that are expected for the IMP and which are not serious and listed in section 10

Questionnaires and measurements scales to determine adverse effects/treatment adherence will be delivered in clinics by fully trained staff to ensure completeness. In cases where there are some missing data, the patient will be asked those questions on the telephone (a member of the Investigator Team will call him/her).

It will be the responsibility of the Lead Researcher to ensure the accuracy of all data entered into the CRF. The delegation log will identify all those personnel with responsibilities for data collection and handling, including those who have access to the trial database.

11.3 Data handling and analysis

A bespoke password protected “Red Pill” database designed by sealedenvelope.com (limited to nominated staff recorded on the delegation log by the CI) will be used for data entry and storage of anonymised patient records and CRF data. This database will be hosted on a secure server at sealedenvelope. All source data (other than data collected from the SCRAM-X bracelet) will be securely stored at site with access limited to only authorised staff. Data from the SCRAM-X bracelet will be stored on a secure drive at the Psychopharmacology and Addiction Research Centre, Washington Singer Laboratories. Automated data (SCRAM-X, pattern recognition task, stop signal task) will be kept on an encrypted memory stick with the source data.

The CRF and trial specific documents held by the researcher will be stored securely with access restricted and limited to nominated research staff recorded on the delegation log and in accordance with the data protection act 1998, UCL Information Security Policy and Trust Information Governance Policy. Electronic and questionnaire source data will be stored in a password protected Microsoft Access database. The Red Pill database will keep a record of all changes to and access of the database. All data and audit log files from the Red Pill eCRF are backed up daily to tape within the data-centre with a two week retention period. Since the databases and log files are cumulative (no deletion), it is not necessary to keep backups beyond this retention period. In addition all data and log files are replicated immediately and continuously to a remote server for off-site storage.

The CRF will be accessible by the research team through access codes on the password protective electronic database site (the detailed arrangements will be in the data management SOP). The data will be available for download by the trial statistician and nominated members of the study team over a CTPS encrypted protocol. Once downloaded, data will be stored on a password protected networked drive at the University of Exeter. At the end of the study, sites will file copies of the eCRFs for their patients on an encrypted memory stick for archiving purposes.

The CI will be ultimately responsible for data entry and quality. Trial staff as identified on the delegation log will also be responsible for data entry and quality. Single data entry with quality control checks will be used in the eCRF. Once data has been entered a visual check between what has been entered and the CRF/source data will be made by another member of the research team. Validity checks will be made using dates of testing days against each patient ID. Data stored within the Access database will be entered using Teleform software and then verified by the data manager.

Data analysis will be performed independently of data entry by the trial statistician.

Data will be stored and backed up daily by through the Red Pill service. The drives will be backed up frequently, allowing for data retrieval in the event of data loss. Data transfer and storage will be in accordance with the UK Data Protection Act 1998 as well as UCL Information Security Policy and Trust Information governance policy. Once all data checks and data are completed, the database will be locked and read only. Users can still view the contents of the database and produce reports. The database will also be accessed centrally by the study statistician (on a read only basis) for data analysis and access of the database will be logged in the data transfer log kept in the TMF or the database will be sent by Professor Celia Morgan to the statistician electronically as read only through a secure process of password protected encryption and this will be documented in the data transfer log kept in the TMF.

12 Record keeping and archiving

Archiving will be authorised by the Sponsor following submission of the end of study report. The Chief Investigator will be responsible for the secure archiving of essential trial documents and the trial database as per their trust/university policy. All essential documents will be archived for a minimum of 25 years after completion of trial. The investigator or a delegate at site is responsible for the secure archiving of essential site trial documents as per local trust policy arrangements. Destruction of essential documents will require authorisation from the Sponsor.

13 Statistical Considerations

Dr Fiona Warren is the trial statistician who will be responsible for all statistical aspects of the trial from design through to analysis and dissemination.

13.1 Outcomes

13.1.1 Primary outcomes

Relapse rates at 6 months

Percentage Days Abstinent at 6 months

13.1.2 Secondary outcomes

- Number of days of continuous abstinence at 3 months (Time-line follow back)
- Percentage days abstinent at 3 months (timeline follow-back)
- State mood (Profile of Mood states)
- Depression (Beck Depression Inventory; Hamilton Depression Scale)
- Anxiety (Speilberger Trait Anxiety Inventory)
- Psychotic symptoms (Brief Psychiatric Rating Scale; Psychotomimetic States Inventory)
- Cigarette smoking (Fagerstrom Smoking)
- Craving (Visual Aanalogue Scales)
- Quality of Life (SF-12)
- Episodic Memory (Prose Recall)
- Delay Discounting (monetary choice questionnaire)
- Response Inhibition (Stop Signal Reaction time)
- Working Memory (digit span WAIS-IV)
- Hippocampal Functioning (Pattern Recognition Test)
- Adverse Effects (Adverse Effects VAS)
- Alcohol Craving Questionnaire - short-form (ACQ-NOW)

13.2 Sample size and recruitment

13.2.1 Sample size calculation

As this is a proof of concept study we wish to include the minimum number of subjects, and must balance considerations of feasibility, including

recruitment, whilst providing a reliable early indicator of efficacy that would warrant continuing to a larger trial.

Our justification of sample size of n=96:

Following randomisation the patient allocation will be n=24 per cell. Drop-out rates will be minimised with incremental payment schedules as we have used in previous studies where we have achieved high retention rates in difficult populations (e.g. [93]). It is anticipated that wearing the SCRAM-X bracelets may also reduce drop-out rates as they are designed to increase compliance with treatment programmes in offending populations (Compliance Monitoring Systems, LLP). However, we have adopted a very conservative estimated 50% drop-out. If this level of drop-out is observed, that will leave n=12 in each individual cell, with a total of n=24 patients having been administered ketamine and n=24 placebo.

With n=24 people in each drug arm we will be able to estimate a decrease in the relapse rate from 50% in patients given placebo to 25% (90% CI: 3% to 47%) in patients given ketamine.

A decrease of 25% in relapse would be clinically important, and lower than that observed in the preliminary work ([33]: 42%); it would clearly suggest that further investigation is warranted. Our confidence intervals are relatively broad as this is a proof of concept study and we wish to minimize the numbers of subjects involved.

13.2.2 Planned recruitment rate

The recruitment period will be 4 years. Approximately 540 patients every 12 months pass through the detoxification services in the NHS trusts we will recruit from, therefore we consider the recruitment of these 96 individuals over 24 months to be achievable.

13.3 Statistical analysis plan

13.3.1 Summary of baseline data and flow of patients

We will assess the comparability of the randomised groups including each factor including demographics and the baseline assessments described in section 7. We plan to produce a consort flow diagram (http://www.consort-statement.org/).

13.3.2 Primary outcome analysis

There are two primary outcomes: (i) proportion relapsed (recommenced using alcohol) at 6-month follow-up; and (ii) percentage of days abstinent at 6-month follow-up (the denominator being 175 days) .The proportion of relapsed participants at 6-month follow-up will be reported as a percentage for each arm, as well as for the ketamine arms combined and

the psychotherapy arms combined. Although no formal power calculations for a between-group analysis have been performed, the proportion of relapsed participants at 6-month follow-up will be expressed as a relative risk (RR) with a 95% confidence interval for the following comparisons: (i) all ketamine participants versus all non-ketamine participants; (ii) ketamine + psychotherapy participants versus ketamine + non-psychotherapy participants; and (iii) ketamine + psychotherapy participants vs. placebo + no psychotherapy participants. These analyses are purely exploratory and should be viewed with caution both in the light of lack of power and multiple testing. Percentage of days abstinent at 6-month follow-up will be reported descriptively in the same way by arm and combination of arms; additionally, the between-group mean differences and 95% confidence intervals will be reported for the comparisons set out above; again, these analyses should be regarded as exploratory. The primary analysis will be an intention-to-treat (ITT) complete case analysis including all randomised participants. A secondary analysis will be conducted including only those participants deemed to have completed to a sufficient degree their allocated interventions, that is, a per protocol analysis. All analyses will be performed by a statistician who is blinded to the treatment allocations and will be performed using Stata v.13.

13.3.3 Secondary outcome analysis

There are 15 secondary outcomes (section 13.1.2); all of these outcomes will be reported descriptively on an ITT complete case basis; additionally, the between-group mean differences and 95% confidence intervals will be reported on an exploratory basis for the primary comparison (all ketamine participants versus all non-ketamine participants). Also, as a feasibility outcome, attrition will be reported as a proportion (with 95% confidence interval) overall and by arm.

13.3.4 Sensitivity and other planned analyses

All participants will be in a state of detoxification at recruitment, hence in the event of loss to follow-up, it is not appropriate to make an assumption that the participant had or had not relapsed at 6 months. To address the issue of missing data due to loss to follow-up, a sensitivity analysis will be performed using multiple imputation methods, for relapse at 6-month follow-up only, making the assumption that all missing data were missing at random.

13.4 Randomisation methods

See Section 7.2 for a full description of randomisation methods, block design will be used.

13.5 Interim analysis

As an interim analysis with regards to trial continuation, attrition among participants receiving ketamine only will be determined; the trial will be discontinued if more than 21/24 (88%) of participants who were randomised to ketamine are lost to follow-up at 3 months. Only aggregate data will be provided to the statistician at 3-month follow-up to ensure that treatment arm allocation will remain concealed. Due to the short duration of follow-up, no interim analyses for the primary or secondary outcomes are planned. From a safety perspective, adverse events will be monitored by the trial team and any concerns will be addressed.

13.6 Other statistical considerations

A full statistical analysis plan (SAP) will be presented to the TMG prior to commencing the analyses. Any amendments to the SAP will be recorded, with the nature of the amendment, the date of amendment and date approved by the TMG.

14 Name of Committees involved in trial

A trial management group (TMG) will be put in place for this trial which consists of the Project Manager, CI, Lead Researcher, Co-Investigators, Trial Anaesthetist, Trial Statistician, Research Associate and Research Assistant. The terms of reference and current members of this committee will be held in the Trial Master File and can be provided upon request.

15 Direct Access to Source Data/Documents

The investigator(s)/ institution(s) will permit trial-related monitoring, audits, REC review, and regulatory inspection(s), providing direct access to source data/documents. Trial participants are informed of this during the informed consent discussion. Participants will consent to provide access to their medical notes.

16 Ethics and regulatory requirements

The sponsor will ensure that the trial protocol, patient information sheet, consent form, GP letter and submitted supporting documents have been approved by the appropriate regulatory body (MHRA in UK) and a main research ethics committee, prior to any patient recruitment.

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 amendments, will be submitted by the CI to the sponsor who will assess if the amendment is substantial or non-substantial. Substantial amendments to the protocol and other trial

related essential documents as assessed by the sponsor will be submitted in writing to the appropriate REC, Regulatory Authority and Trust Research & Development (R&D) for approval prior to implementation of amended documents.

Before the site can enrol patients into the trial, the Chief Investigator/Principal Investigator or designee must apply for NHS permission from their Trust Research & Development (R&D) and be granted written permission. It is the responsibility of the Chief Investigator/ Principal Investigator or designee at each site to ensure that all subsequent amendments gain the necessary approval. This does not affect the individual clinician's responsibility to take immediate action if thought necessary to protect the health and interest of individual patients (see section 10.5.6 for reporting urgent safety measures).

Within 90 days after the end of the trial, the CI/Sponsor will ensure that the main REC and the MHRA are notified that the trial has finished. If the trial is terminated prematurely, those reports will be made within 15 days after the end of the trial. The CI will supply the Sponsor with a summary report of the clinical trial, which will then be submitted to the MHRA and main REC within 1 year after the end of the trial.

17 Monitoring requirement for the trial

A trial specific monitoring plan will be established for studies. The trial will be monitored with the agreed plan.

18 Finance

This trial is being funded by the Medical Research Council.

19 Insurance

University College London holds insurance against claims from participants for injury caused by their participation in the clinical trial. Participants may be able to claim compensation if they can prove that UCL has been negligent. However, as this clinical trial is being carried out in a hospital, the hospital continues to have a duty of care to the participant of the clinical trial. University College London does not accept liability for any breach in the hospital's duty of care, or any negligence on the part of hospital employees. This applies whether the hospital is an NHS Trust or otherwise.

Participants may also be able to claim compensation for injury caused by participation in this clinical trial without the need to prove negligence on the part of University College London or another party. Participants who sustain injury and wish to make a claim for compensation should do so in writing in the first instance to the Chief Investigator, who will pass the claim to the Sponsor's Insurers, via the Sponsor's office.

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 College London, upon request.

20 Publication policy

All proposed publications will be discussed with Sponsor prior to publishing other than those presented at scientific forums/meetings. Please refer to UCL publication policy.

21 Statement of compliance

The trial will be conducted in compliance with the approved protocol, the UK Regulations, EU GCP and the applicable regulatory requirement(s).

22 References

1. Health and Social Care Information Centre Statistics on Alcohol: England 2011;2012. 2012 [Available from: http://www.hscic.gov.uk/pubs/alcohol11].

2. World Health Organisation, Global Status Report on Alcohol and Health 2011, 2011.

3. McLellan, A.T., et al., . JAMA, 2000. 284(13): p. 1689-95.

4. Zarate, C.A., Jr., et al Arch Gen Psychiatry, 2006. 63(8): p. 856-64.

5. Krupitsky, E.M. and A.Y. Grinenko,. J Psychoactive Drugs, 1997. 29(2): p. 165-83.

6. Curran, G.M., et al.,. J Subst Abuse Treat, 2000. 19(3): p. 259-65.

7. Martin, D. and Lodge, D., Neuropharmacology, 1985(24): p. 999-1003.

8. Goodman & Gillman, Pharmacology and Therapeutics 2003

9. Linderfors, N, et al., Brain Res 1997 759: 205-12

10. Krystal, J.H., Sanacora, G., Duman, R.S., Biol. Psychiatry, 2013 (73): p. 1133– 1141.

11. Burgdorf J, Zhang XL, Nicholson KL, et al. Neuropsychopharmacology. 2013(38): p. 729–742.

12. Koike, H., Iijima, M., and Chaki, S. Pharmacol. Biochem. Behav. 2013 (107): p. 20–23.

13. Yang, C et al Front, Med 2012 6: 411-5

14. Browne CA & Lucki, I Front Pharmacol 2013 4:161

15. Iijima M, Fukumoto K, Chaki S. Behav Brain Res 2012(235): p. 287-92.
16. Carrier, N., and Kabbaj, M.Neuropharmacology 2013(70): p, 27–34.
17. Li N, et al. Science. 2010(329): p. 59–964.
18. Koike H, Iijima M, Chaki S. Behav Brain Res. 201(224): p. 107–111.
19. Bechtholt-Gompf AJ, Smith KL, John CS, Kang HH, Carlezon WA Jr, Cohen BM, Ongür D. Psychopharmacology (Berl). 2011(215): p. 689–95.
20. Perry, EB et al., Psychopharmacology 2007 192: 253-260
21. ReD-Kite ISRCTN 89575054
22. Diamond PR., Farmery AD., Atkinson S., Haldar J., Williams N., Cowen PJ., Gedder JR., McShane R. J Psychopharmacol 2014(6): p. 536–544
23. Zarate C Jr,Machado-Vieira R, Henter I,et al. Harv Rev Psychiatry 2010(18): p. 293-303
24. DiazGranados, N., Ibrahim, L., Brutsche, NE, Newberg, A, Kronstein, P., Khalife, S, et al., Arch Gen Psychiatry 2010 67: 793-802
25. Price RB, Nock MK, Charney DS, Mathew SJ. Biol Psychiatry. 2009;(66(5)): p. 522–526.
26. Kranaster L, Kammerer-Ciernioch J, Hoyer C, Sartorius A. Eur Arch Psychiatry Clin Neurosci. 2011(261): p. 575–582.
27. Erdill, F., Ozgul, U., Clak, C., Cumurcu, B., Durmus, M. J ECT 2015 Feb 25 (PMID 25719444)
28. Kerr CL, Windeyer C, Boure LP et al. Am J Vet Res 2007(68): p, 1287–1293
29. Irwin SA, Iglewicz A. J Palliat Med 2010(13): p. 903–8.
30. Kolp, E., Krupitsky, E., Young, M.S., Jansen, K., Friedman, H., O'Connor, LA, International Journal of Transpersonal Studies 2007 26: 1-17
31. Clinical trials.gov identifier: NCT01551329
32. Petrakis, personal communication
33. Krupitsky, E. M., & Grinenko, A. Y. Journal of Psychoactive Drugs, 1997(29): p, 165–183.
34. Morgan CJ & Curran HV, Addiction 2012 107: 27-38
35. Krupitsky EM, Burakov AM, Dunaevsky IV, Romanova TN, Slavina TY, Grinenko AY. J Psychoactive Drugs. 2007(39): p. 13–19.
36. Petrakis IL. Journal of Clinical Psychopharmacology 2006(26, Suppl. 1): p. 3–12.
37. Nikpoor, P. & Bain, E., Cochrane Database Syst Rev 2013 9: CD008878

38. Lahti AC, Weiler MA, Tamara Michaelidis BA, Parwani A, Tamminga CA. 2001(25): p. 455–467

39. Herrera, D.G., et al. Proc Natl Acad Sci U S A, 2003. 100(13): p. 7919-24.

40. Chick, J., et al.,. Alcohol Alcohol, 2000. 35(2): p. 176-87.

41. Health and Social Care Information Centre, Statistics on Alcohol: England, 2013.

42. Harris, A.H., et al., Psychol Serv, 2013.

43. Aan Het Rot, M., et al., Biol Psychiatry, 2012. 72(7): p. 537-47.

44. Duman, R.S. and G.K. Aghajanian,. Science, 2012. 338(6103): p. 68-72.

45. Sabino, V., et al., Behav Brain Res, 2013. 247: p. 9-16.

46. Clinicaltrials.gov. 2013.

47. Hasin, D.S., et al.,. Arch Gen Psychiatry, 2005. 62(10): p. 1097-106.

48. Pettinati, H.M.,. Biol Psychiatry, 2004. 56(10): p. 785-92.

49. Mason, B.J., et al. JAMA, 1996. 275(10): p. 761-7.

50. Luckenbaugh, D.A., et al.,. Bipolar Disord, 2012. 14(8): p. 880-7.

51. Krystal, J.H., et al.,. Arch Gen Psychiatry, 1998. 55(4): p. 354-60.

52. Chambers, R.A., Drug Alcohol Depend, 2013. 130(1-3): p. 1-12.

53. Li, N., et al., Science, 2010. 329(5994): p. 959-64.

54. Denk, M.C., et al.,. Am J Psychiatry, 2011. 168(7): p. 751-2.

55. Mandyam, C.D. and G.F. Koob, Trends Neurosci, 2012. 35(4): p. 250-60.

56. Helfer, J.L., et al.,. Brain Res, 2009. 1294: p. 1-11.

57. Hernandez-Rabaza, V., et al.,. Addict Biol, 2010. 15(4): p. 413-23.

58. Nixon, K., et al.. Neurobiol Dis, 2008. 31(2): p. 218-29.

59. Stevenson, J.R., et al. Neuropsychopharmacology, 2009. 34(5): p. 1209-22.

60. Nixon, K. and F.T. Crews. J Neurosci, 2004. 24(43): p. 9714-22.

61. Crews, F.T., K. Nixon, and M.E. Wilkie. Alcohol, 2004. 33(1): p. 63-71.

62. Zanardini, R., et al., Alcohol Clin Exp Res, 2011. 35(8): p. 1529-33.

63. Grosjean, B. Am J Psychother, 2005. 59(3): p. 181-97.

64. Bates, M.E., J.F. Buckman, and T.T. Nguyen. Neuropsychol Rev, 2013. 23(1): p. 27-47.

65. Birch, A.M., N.B. McGarry, and A.M. Kelly, Hippocampus, 2013. 23(6): p. 437-50.

66. Krystal, J.H., et al., Pharmacol Ther, 2003. 99(1): p. 79-94.

67. Hashimoto, K., E. Shimizu, and M. Iyo, Brain Res Brain Res Rev, 2004. 45(2): p. 104-14.

68. Morgan, C.J., et al., Psychopharmacology (Berl), 2004. 172(3): p. 298-308.

69. Krupitsky, E.M., et al., Neuropsychopharmacology, 2001. 25(6): p. 936-47.

70. Perry, E.B., Jr., et al., Psychopharmacology (Berl), 2007. 192(2): p. 253-60.

71. aan het Rot, M., et al., Biol Psychiatry, 2010. 67(2): p. 139-45.

72. Hunt, W.A., L.W. Barnett, and L.G. Branch, J Clin Psychol, 1971. 27(4): p. 455-6.

73. Vaillant, G.E., Addiction, 2003. 98(8): p. 1043-51.

74. Groot, Y.C., et al., J Int Neuropsychol Soc, 2002. 8(5): p. 645-54.

75. Shallice, T., Philos Trans R Soc Lond B Biol Sci, 1982. 298(1089): p. 199-209.

76. Verbruggen, F., G.D. Logan, and M.A. Stevens,. Behav Res Methods, 2008. 40(2): p.

479-83.

77. Gandek, B., et al., J Clin Epidemiol, 1998. 51(11): p. 1171-8.

78. Spielberger, C.D. and P.R. Vagg, J Pers Assess, 1984. 48(1): p. 95-
79. Bohn, M.J., D.D. Krahn, and B.A. Staehler, Clin Exp Res, 1995. 19(3): p. 600-6.

80. Chick, J., et al., Alcohol Alcohol, 2000. 35(6): p. 587-93.

81. Griffiths, A., et al Addiction, 2012. 107(10): p. 1809-16.

82. Gueorguieva, R. and J.H. Krystal, Arch Gen Psychiatry, 2004. 61(3): p. 310-7.

83. Krupitsky, E., et al., J Subst Abuse Treat, 2002. 23(4): p. 273-83.

84. Collaborating Centre for Mental Health (2011); The NICE guideline on diagnosis,

assessment and management of harmful drinking and alcohol dependence.

85. Morgan, CJA, Muetzelfeldt, L., Curran HV, Addiction 2010 105:121-133

86. Morgan, CJA, Schafer, G, Freeman, T, Curran HV, 2011

Neuropsychopharmacology 35 (9), 1879-1885

87. Wilson B., Cockburn J.,& Baddeley A. (1985) The Rivermead Behavioural Memory Test.

Bury St Edmunds: Thames Valley Test Company

88. Beck A. T., Steer R. A.,& Brown G. K. (1996) Manual for the Beck Depression

Inventory–II. San Antonio, TX: Psychological Corporation.

89. Cocks, K & Torgerson, D.J. 2013 J Clin Epidemiology 66:197-201

90. Harmer, C. Cowen, P. 2013 Phil Trans R. Soc: B Phil. Trans. R. Soc. B 368: 20120407

91. Krebs, T. & Johansen, 2012 Y. J Psychopharm 26:994-1002

92. Kolp, E. et al., 2006 Human Psychol 34: 399-422

93. Morgan, CJA et al., 2010 Addiction 105: 121-133

94. Zarate CA, Jr, Brutsche NE, Ibrahim L, Franco-Chaves J, Diazgranados N, Cravchik A, et al. Biol Psychiatry. 2012(71): p. 939–946

95. Zanicotti, CG, Perez, D., Glue, P J Palliat Med 2012 15:400-3

96. Clements JA, Nimmo WS, Grant, IS. J Pharm Sci 1982 71:539-542

97. Clements JA, Nimmo WS. Br J Anaesth 1981 53: 27-30

98. Murrough, JW et al. Biol Psychiat 2013 74: 250-256

99. Grant, IS, Nimmo, WS, Clements JA Br J Anaesth 1981 53: 805-810

Appendix A: DSM IV and 5 criteria for alcohol abuse/dependence and moderate/severe alcohol use disorder

DSM–IV			DSM–5	
Any 1 = ALCOHOL ABUSE	Recurrent alcohol use resulting in a failure to fulfill major role obligations at work, school, or home (e.g., repeated absences or poor work performance related to alcohol use; alcohol-related absences, suspensions, or expulsions from school; neglect of children or household.	1	Alcohol is often taken in larger amounts or over a longer period than was intended. (See DSM–IV, criterion 7.)	The presence of at least 2 of these symptoms indicates an **Alcohol Use Disorder (AUD).** The severity of the AUD is defined as: **Mild:** The presence of 2 to 3 symptoms **Moderate:** The presence of 4 to 5 symptoms **Severe:** The presence of 6 or more symptoms
	Recurrent alcohol use in situations in which it is physically hazardous (e.g., driving an automobile or operating a machine when impaired by alcohol abuse).	2	There is a persistent desire or unsuccessful efforts to cut down or control alcohol use. (See DSM–IV, criterion 8.)	
	Recurrent alcohol-related legal problems (e.g., arrests for alcohol-related disorderly conduct). ****This is not included in DSM–5****	3	A great deal of time is spent in activities necessary to obtain alcohol, use alcohol, or recover from its effects. (See DSM–IV, criterion 9.)	
	Continued alcohol use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the alcohol (e.g., arguments with spouse about the consequences of intoxication, physical fights).	4	Craving, or a strong desire or urge to use alcohol. ****This is new to DSM–5****	
Any 3 = ALCOHOL DEPENDENCE	Tolerance, as defined by either of the following: a) A need for markedly increased amounts of alcohol to achieve intoxication or desired effect b) Markedly diminished effect with continued use of the same amount of alcohol	5	Recurrent alcohol use resulting in a failure to fulfill major role obligations at work, school, or home. (See DSM–IV, criterion 1.)	
	Withdrawal, as manifested by either of the following: a) The characteristic withdrawal syndrome for alcohol b) Alcohol is taken to relieve or avoid withdrawal symptoms	6	Continued alcohol use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of alcohol. (See DSM–IV, criterion 4.)	
	Alcohol is often taken in larger amounts or over a longer period than was intended.	7	Important social, occupational, or recreational activities are given up or reduced because of alcohol use. (See DSM–IV, criterion 10.)	
	There is a persistent desire or unsuccessful efforts to cut down or control alcohol use.	8	Recurrent alcohol use in situations in which it is physically hazardous. (See DSM–IV, criterion 2.)	
	A great deal of time is spent in activities necessary to obtain alcohol (e.g., driving long distances), use alcohol, or recover from its effects.	9	Alcohol use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by alcohol. (See DSM–IV, criterion 11.)	
	Important social, occupational, or recreational activities are given up or reduced because of alcohol use.	10	Tolerance, as defined by either of the following: a) A need for markedly increased amounts of alcohol to achieve intoxication or desired effect b) A markedly diminished effect with continued use of the same amount of alcohol (See DSM–IV, criterion 5.)	
	Alcohol use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance (e.g., continued drinking despite recognition that an ulcer was made worse by alcohol consumption).	11	Withdrawal, as manifested by either of the following: a) The characteristic withdrawal syndrome for alcohol (refer to criteria A and B of the criteria set for alcohol withdrawal) b) Alcohol (or a closely related substance, such as a benzodiazepine) is taken to relieve or avoid withdrawal symptoms. (See DSM–IV, criterion 6.)	

Appendix B: Schedule of Study Procedures

	Pre-Screening	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
		1 to 28 days before visit 2	Only to be run if 28 days elapses between screening and visit 2	1 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 21 days after visit 6	11 to 13 weeks after visit 2	23 to 25 weeks 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
Vital Signs [b]		X	X	X	X	X	X	X	X	X		
Bloods [c, d]		X [c]	X	X [d]	X [d]	X [d]	X [d]	X [d]	x [d]	X [d]	X [d]	X [d]
Eligibility determination	X	X	X	X								
Urine Drug screen		X [e]	X	X [e]	X [f]	X [e]	X [f]	X [e]	X [f]	X [e]	X [e]	X [e]
Pregnancy Test I WOCBP		X	X	X		X		X				
Breathalyser		X	X	X	X	X	X	X	X	X	X	X
Randomisation				X								
SCRAM-X fitting		X [g]	X [g]	X [g]								
IMP/Plac administration				X		X		X				
SCRAM-X checks			X	X	X	X	X	X	X	X		
Relapse-prevention based CBT				X	X	X	X	X	X	X		
Adverse Events review				X	X	X	X	X	X	X	X	X
Concomitant Medication review		X	X	X	X	X	X	X	X	X	X	X
Alcohol and Drug Use		X	X							X	X	X

History												

	Pre-Screening	**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
		1 to 28 days before visit 2	Only to be run if 28 days elapses between screening and visit 2	1 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 21 days after visit 6	11 to 13 weeks after visit 2	23 to 25 weeks after visit 2
BDI		X	X	X		X		X		X	X	X
HAM-D		X	X	X	X	X	X	X	X	X	X	X
Columbia Suicide Severity Rating Scale		x	X									
POMS				X	X	X	X	X	X	X	X	X
Reasons for Drinking Questionnaire		X										
STAI		X		X		X		X		X	X	X
ACQ-NOW		X		X	X	X	X	X	X	X	X	X
BPRS		X	X	X	X	X	X	X	X	X	X	X
PSI		X	X	X		X		X		X	X	X
Alcohol Timeline Follow Back		X	X	X		X		X		X	X	X
Drink diary										X	X	X
Fagerstrom Nicotine Dependence				X						X	X	X
Craving VAS				X	X	X	X	X	X	X	X	X
SF-12				X						X	X	X
Prose Recall				X	X	X	X	X	X	X	X	X

Delay Discounting (monetary choice questionnaire)				X						X	X	X
Stop Signal Reaction Time				X						X	X	X
Working Memory (digit span WAIS-IV)				X						X	X	X
Adverse effects VAS +				X	X	X	X	X	X	X	X	X
Pattern Recognition Memory Test				X		X		X		X	X	X

Performed by Research Fellow, Nurse or Assistant

Performed by Anaesthetist

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

a) Physical – Height, weight, An examination of cardiovascular, respiratory, GI 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, AST, Total Protein, Alkaline Phos (ALP), Albumin, Globulin, gamma-glutamyl transpeptidase (GGT)), Biochemistry (urea, sodium, potassium, glucose, calcium, thyroid stimulating hormone).
d) Bloods (Study): BDNF; ketamine; Liver function (Bilirubin, ALT, AST, Total Protein, Alkaline Phos (ALP), Albumin, Globulin, gamma-glutamyl transpeptidase (GGT)).
e) Urine Drug screen (Screening, infusion days and F-UP visits) - (methamphetamine, cocaine, THC, benzodiazepines, tricyclic antidepressants, barbituates, phencyclidine,amphetamines, morphine, methadone, ketamine).
f) Urine Drug screen (Non-infusion days, treatment phase) – (methamphetamine, cocaine, THC, benzodiazepines, tricyclic

antidepressants, barbituates, phencyclidine, amphetamines, morphine, methadone).

g) SCRAM-X device can be fitted at any one of these visits.

Appendix C: Known Adverse Effects of Ketamine when used in an anaesthetic setting

The following Adverse Events have been reported:

MedDRA System Organ Class	**Frequency†**	**Undesirable Effects**
Immune system disorders	Rare	Anaphylactic reaction*
Metabolism and nutrition disorders	Uncommon	Anorexia
Psychiatric disorders	Common	Hallucination, Abnormal dreams, Nightmare, Confusion, Agitation, Abnormal behaviour
	Uncommon	Anxiety
	Rare	Delirium* Flashback*, Dysphoria*, Insomnia, Disorientation*
Nervous system disorders	Common	Nystagmus, Hypertonia, Tonic clonic movements
Eye disorders	Common	Diplopia
	Not Known	Intraocular pressure increased
Cardiac disorders	Common	Blood pressure increased, Heart rate increased
	Uncommon	Bradycardia, Arrhythmia
Vascular disorders	Uncommon	Hypotension
Respiratory, thoracic and mediastinal disorders	Common	Respiratory rate increased
	Uncommon	Respiratory depression, Laryngospasm
	Rare	Obstructive airway disorder*, Apnoea*
Gastrointestinal disorders	Common	Nausea, Vomiting
	Rare	Salivary hypersecretion*
Hepatobiliary disorders	Not known	Liver function test abnormal, Drug-induced liver injury**

Skin and subcutaneous tissue disorders	Common	Erythema, Rash morbilliform
Renal and urinary disorders	Rare	Cystitis*, Haemorrhagic cystitis*
General disorders and administration site conditions	Uncommon	Injection site pain, Injection site rash

† Common (⩾1/100 to <1/10); Uncommon (⩾1/1,000 to <1/100); Rare (⩾1/10,000 to <1/1,000); Not known (frequency cannot be estimated from the available data)

* AE frequency estimated from post-marketing safety database

** Extended period use (>3 days) or drug abuse