SHOCK-ICU Protocol v1.1

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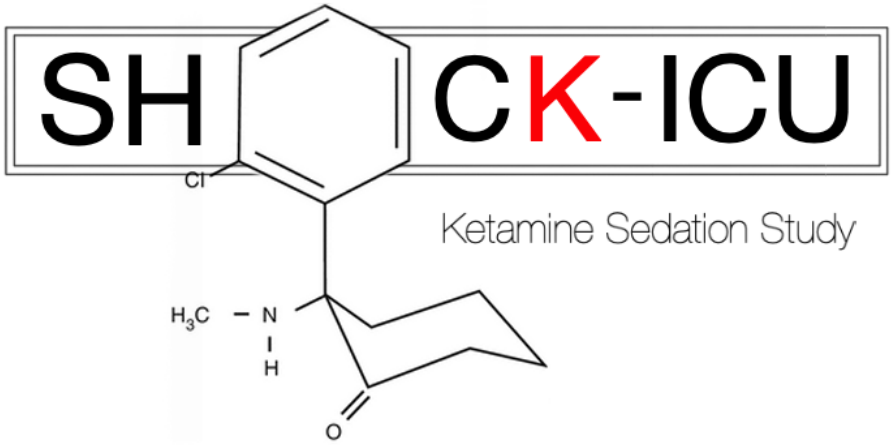

The **S**edative and **H**aemodynamic Effects **O**f **C**ontinuous **K**etamine Infusions on **I**ntensive **C**are **U**nit Patients (**SHOCK-ICU**): Investigating key outcomes, resource utilisation, and staff decision-making.

Workstream 2: Feasibility study

Sponsors	Leeds Teaching Hospitals NHS Trust Research & Innovation Centre St James's University Hospital Beckett Street Leeds, LS9 7TF Tel 0113 2060483 leedsth-tr.sponsorqa@nhs.net
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Signatures

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

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

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

For and on behalf of the Trial Sponsor:

Date:

Signature: ..../...../.....

Name (please print): .....

Position: .....

Chief Investigator:

Date:

Signature: ..../...../.....

Name (please print): .....

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List of abbreviations

Abbreviation	Definition
ACCM	The American College of Critical Care Medicine
ADR	Adverse drug reaction
AE	Adverse event
AKI	Acute Kidney Injury
ALT	alanine transaminase
AR	Adverse reaction
BNF	British National Formulary
CAM-ICU	Confusion Agitation Method for delirium in ICU
CI	Chief Investigator
CNS	Central Nervous System
CO	Cardiac Output
CRF	Case Report Form
CTIMP	Clinical Trial of Investigational Medicinal Product
CVVHD	Continuous Veno-Venous Haemodialysis
EQ-5D-5L	Health Related Quality of Life Questionnaire
GCP	Good Clinical Practice
GP	General Practitioner
HADS	Hospital Anxiety and Depression Scale
HRQoL	Health Related Quality of Life
ICD10	International Classification of Diseases 10th Revision
ICE	Integrated Clinical Environment
ICE-Q	Intensive Care Experience Questionnaire
ICH GCP	International Conference on Harmonisation - Good Clinical Practice
ICNARC	Intensive Care National Audit and Research Centre
ICP	Intracranial Pressure
ICU	Intensive Care Unit
ID	Identification
IES-R	Impact of event scale – revised
IMP	Investigational Medicinal Product
INR	International Normalised Ratio
IRAS	Integrated Research Application System
IV	Intravenous
LTHT	Leeds Teaching Hospitals NHS Trust

MAP	Mean Arterial Pressure
MDD	Major depressive disorder
MHRA	Medicines and Healthcare products Regulatory Agency
MRC	Medical Research Council
MV	Mechanical Ventilation
NHS	National Health Service
NIMP	Non-Investigational Medicinal Product
NMDA	N-methyl D-aspartic acid
O2	Oxygen
PCL-5	Post-Traumatic Stress Disorder Checklist
PEEP	Peak end expiratory pressure
PI	Principle investigator
PICO	Population Comparison Intervention Outcome
PIS	Patient Information Sheet
PLICS	Patient Level Costing
PPM	Patient Pathway Manager
PRIS	Propofol infusion syndrome
PS	Pressure support
PTSD	Post-Traumatic Stress Disorder
QA	Quality Assurance
RASS	Richmond Agitation Sedation Scale
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
RIS	Relative information sheet
RRT	Renal Replacement Therapy
RSI	Reference Safety Information
SAE	Significant Adverse Event
SAR	Significant Adverse Reaction
SBP	Systolic Blood Pressure
SHOCK-ICU	The Sedative and haemodynamic effects of continuous ketamine Infusions on Intensive Care Unit patients
SJUH	St James's University Hospital
SmPC	Summary of Product Characteristics
SOFA	Sequential Organ Failure Assessment
SOP	Standard Operating Procedure
SPG	Symmetrical Peripheral Gangrene

STROBE	Strengthening the Reporting of Observational Studies in Epidemiolog
SUSAR	Suspected unexpected serious adverse reaction
SVR	Systemic Vascular Resistance
TMF	Trial Master File
UK	United Kingdom
UKCPA	United Kingdom Clinical Pharmacist Association
USM	Urgent Safety Measure

Trial Summary

I. Summary

Trial Title	The Sedative and Haemodynamic Effects of Continuous Ketamine Infusions on Intensive Care Unit Patients (SHOCK-ICU): Investigating key outcomes, resource utilisation, and staff decision-making. *Workstream 2: Feasibility study*		
Study Acronym	SHOCK-ICU		
Clinical Phase	Feasibility		
Trial Design	Prospective cohort feasibility study		
Trial Participants	Adult ICU patients within 48 hours of starting mechanical ventilation (MV), expected to require at least 24 hours further MV at screening.		
Planned Number of Participants	30	**Planned Number of Sites**	1
Treatment Duration	Variable: From within 2 hours of commencing MV until 48 hours without invasive ventilation		
Follow-up Duration	90 days		
Planned Trial Period	24 months		
Primary Aim	To generate feasibility data and to highlight potentially important clinical and patient centred outcomes that may become key endpoints in subsequent trials.		
Primary Objectives	To undertake both process and scientific assessments of ketamine sedation, which will inform progression criteria for future studies.		
Exploratory Outcomes	To assess early markers of efficacy by monitoring patient-based outcomes and clinical effects relating to the IMP throughout the ICU stay, hospital stay, and at 90-day follow-up.		

Eligibility Criteria	1. Requiring mechanical ventilation on ICU 2. Aged 18 years or older 3. Within 48hrs of starting mechanical ventilation 4. Requiring sedation 5. Expected to require more than 48hrs of mechanical ventilation 6. Expected to require a further 24hrs of mechanical ventilation at time of eligibility		
IMP(s)	Ketamine	**NIMP(s)**	Alfentanil
IMP Formulation, Dose, and Route of Administration	Ketamine Hydrochloride via IV Infusion prepared as 10mg/ml in normal saline, with a starting dose of 1mg/kg/h and titrated within a dose range of 0-2.7mg/kg/h		
Key words	Ketamine, sedation, intensive care, delirium		

II. Role of Trial Sponsor

The sponsorship responsibilities for Clinical Trials of Investigational Medicinal Products (CTIMPs) are regulated by the Medicines for Human Use (Clinical Trials) Regulations 2004 (as amended).
This protocol details which responsibilities have been delegated to the CI or PI.

III. Roles and Responsibilities of Trial Management Group

The Trial Management Group (TMG) will comprise of the following persons:

- Dr James Beck, chief investigator and joint clinical lead
- Professor Mark Bellamy, joint clinical lead
- Dr Nicholas Richards, Principal Investigator
- Professor Simon Howell, Primary Supervisor
- Dr Ruben Mujica-Mota, Health Economics lead
- Dr Samuel Relton, Statistical lead
- Fiona Tingerides, Critical Care Pharmacy lead

The TMG will be responsible for the day-to-day running of the study, protocol adherence, and safeguarding of participants and data. The TMG will meet regularly throughout the study period.
As this is a small scale, low risk feasibility study, there will be no steering committee at this stage.

IV. Protocol Contributors

Key contributors:

- Dr Nicholas Richards – primary author and study design
- Professor Mark Bellamy – Co-author and joint clinical / Intensive Care lead
- Dr James Beck – Co-author and joint clinical / Intensive Care lead
- Professor Simon Howell – Co-author and Academic lead
- Dr Ruben Mujica-Mota – Health economics input
- Dr Samuel Relton – Statistical input
- Fiona Tingerides – Critical care pharmacy input
- Helen Thorp – Clinical trials pharmacy input

Patient, Public and Carer Involvement and Engagement (PPIE)
PPIE work has been carried out with previous SJUH ICU patient focus groups held in conjunction with the NIHR Biomedical Research Centre (BRC), Leeds, and through external PPI review from the national ICU charity '*ICU Steps*' and the '*National Institute of Academic Anaesthesia Patient, Carer and Public Involvement and Engagement (NIAA PCPIE)*'.

1. Introduction

1.1 Background

Mechanical ventilation (MV) is a common intensive care intervention (approximately 20 million patients per annum worldwide). Patients sick enough to require MV experience high mortality and morbidity. MV accounts for much intensive care unit (ICU) resource utilisation.[1]

For most patients, medical sedation is a requirement for MV; optimising sedation and pain-relief (analgesia) is fundamental to the management of critically ill patients. Agent selection is a balance of risks and benefits. International guidance has been aimed at improving outcomes[2] owing to reported associations between deep sedation and negative prognostic markers.[3] There is also new evidence suggesting that current sedatives may in fact be detrimental in certain population groups.[4, 5]

Providing adequate sedation, minimising agitation and delirium, maintaining comfort, reducing pain, and improving outcomes have been identified as top priorities for ICU research by both patients and clinicians.[6]

Most traditional sedatives (including propofol, benzodiazepines, and alpha-2-agonists) are associated with multiple significant and potentially problematic adverse effects, (commonly hypotension, bradycardia, and prolonged mechanical ventilation). The predominant mechanism resulting in hypotension is attenuation of external stimulation, reduced sympathetic tone, and vasodilation.[7]

Sedatives, in particular benzodiazepines significantly increase the risk of delirium in ICU.[2, 8]
ICU delirium causes significant distress for both patients and their relatives, increases the work burden for ICU staff, and puts patients at significant risk of serious complications (e.g. accidental removal of endotracheal tubes, tracheostomies, and venous catheters), increased risk of developing psychological symptoms such as depression and post-traumatic stress disorder (PTSD), and even up to a threefold increase in 6-month mortality.[9, 10]

In a 2016 survey of ICUs in the UK, propofol combined with either alfentanil or fentanyl was the most common sedation-analgesia regime; 92.2% of units reported propofol as first line agent.[11] A third of units reported using other non-ketamine sedative agents either 'frequently' or 'very frequently', including benzodiazepines (29.4%), clonidine (35.3%), and dexmedetomidine (11.8%).

Ketamine is an N-methyl D-aspartic acid (NMDA) receptor antagonist that has been used since the 1970s to provide cataleptic, amnesic, analgesic, and dose dependant anaesthetic effects.[12]

Ketamine has been particularly successful in military[13] and pre-hospital[14] settings owing to its ability to stimulate the sympathetic nervous system, preserving heart rate and blood pressure, whist avoiding respiratory suppression[15], as a result ketamine has become increasingly popular as an anaesthetic agent for emergency surgical procedures in hypotensive patients.[16]

Ketamine was also licensed for MDD treatment in 2019 after several studies, reviews, and meta-analyses concluded intravenous ketamine provided rapid antidepressant effects in treatment-resistant MDD and PTSD, with documented duration of improvement ranging from a few days to weeks following administration.[17-21]

Given that psychological symptoms such as depression or PTSD following ICU admission are common, ketamine's ability to rapidly provide antidepressant effects that are sustained beyond the acute pharmacological effects may be of benefit when used as a sedative in the context of post-ICU MDD. However, there are currently no peer-reviewed publications investigating the link between ketamine use on ICU (for analgesia, sedation, or otherwise) and depressive symptoms following or during ICU admission.

Although having been available in clinical practice for 50 years, ketamine by continuous infusion remains a rarely used sedative to facilitate MV.[11]

Reluctance in its use is likely multifactorial and may relate to lack of clinical familiarity (as demonstrated in two surveys of UK sedation practices),[11, 22] perceived contraindications such as raised intracranial pressure (ICP), and possible side effects such as '*emergence reactions*'. Emergence reactions are psychomotor symptoms experienced by some patients when waking from ketamine anaesthesia. The reported incidence of these reactions varies from 5% to 30%.[23]

A review of the literature revealed a paucity of high-quality evidence with very few well-designed prospective studies.[24] However, despite the lack of well-designed, well-powered studies, the reported findings suggest a range of potential patient benefits, including improved sedation and pain scores, reduced concomitant sedative infusions, reduced opioid requirement, and haemodynamic stability.

There were reassuring findings relating to the safety of ketamine sedation with low numbers of ADRs or SAEs reported. Reports of reduced incidence of delirium with no reports of emergence reactions go some way to alleviate apprehensions around unwanted psychomimetic phenomena.

The low incidence of adverse effects was not restricted to particularly low-dose or short-duration regimes, with doses and durations of ketamine ranging significantly across studies.

However, these results must be interpreted with caution given the poor quality of included studies and small sample sizes. Additionally, the retrospective nature of

many of the studies increases the risk of recall bias, inclusion bias, and reporting bias.

In summary, ketamine represents a novel alternative to traditional sedation; however, there are currently multiple gaps in the literature surrounding its use. The available data indicates that continuous ketamine infusions on ICU appear safe and well tolerated and may convey some benefits to patients at the doses and durations investigated, however these results must be interpreted with caution given the poor quality of included studies and small sample sizes.

Early results suggest multiple potential benefits to mechanically ventilated critically ill patients, including an improved haemodynamic profile, improved sedation, and lower incidence of delirium. Patients may also benefit from the rapid antidepressant effects of ketamine.

A large prospective randomised controlled trial (RCT) is required to provide robust evidence with regards to continuous ketamine sedation, however significant barriers to implementation and integration into routine practice may exist.

This study will investigate the feasibility of using ketamine sedation on ICU, as well as exploring clinical and patient-centred outcomes that may become key endpoints in future trials, assessing safety, and preliminary cost-effectiveness data.

2. Study Design

2.1 Hypothesis

The use of ketamine as a continuous sedative infusion will maintain adequate sedation and comfort in mechanically ventilated patients on the intensive care unit, whilst providing potential haemodynamic and psychological benefits.

2.2 'PICO' Question

Population: Adult ICU patients requiring MV and sedation.
Intervention: Sedation with continuous infusion of ketamine + alfentanil analgesic.

Comparison: No direct comparison (single arm), overall rates of adverse events, mortality, and length of stay will be compared to published literature and available published clinical data from study unit.
Outcomes: Feasibility data (process and scientific assessments).

2.3 Type of Study

This is a single-arm, prospective, feasibility study of continuous ketamine infusions for primary sedation in patients undergoing mechanical ventilation (MV).

2.4 Assessment of Risk

This has been judged to be a Type A trial according to the 2011 Medical Research Council (MRC), Department of Health (DH), and Medicines and Healthcare products Regulatory Agency (MHRA) joint project titled: Risk-adapted Approaches to the Management of Clinical Trials of Investigational Medicinal Products.[25] Type A is defined as "no higher than the risk of standard medical care".

The IMP is a licensed product in the UK but will be used outside of its Marketing Authorisation (MA). Ketamine is licensed for the induction and maintenance of anaesthesia and is used safely and effectively for both adults and children.[26, 27]
Ketamine is currently used in some ICUs across England as an "off-label" sedative[11] as well as in other aspects of the management of critically unwell patients, including as a bronchodilator in severe or refractory asthma, for analgesia, in the management of agitation and delirium, and in the management of traumatic brain injury and raised intracranial pressure.[12, 28]
Animal studies have shown the lethal dose of ketamine (LD_{50}) to be over 100 times the effective dose (ED_{50}) value, making overdose "*difficult or even impossib*le"[29].

As continuous infusions of ketamine for sedation is a relatively novel idea, there is not an abundance of safety data, however the current available evidence for the use of a ketamine as a continuous sedative infusion in critically unwell patients is summarised in the 2023 review by Richards et al[24]. Over half of authors (51.9%) included commented on the safety of ketamine; 85.7% of these authors reported no significant adverse reactions or events.
Umunna et al[30] reported an ADR rate of 13.3%, which was lower than the incidence of adverse drug reactions of remifentanil (40%), morphine (30%), dexmedetomidine (40.6%), and midazolam (28.7%). Groetzinger et al[31] only

found a 7.7% incidence of ADRs, which again is significantly lower numbers of adverse drug reactions (ADRs) compared to other sedatives.

In addition to evidence suggesting ketamine in this context to be safe, it will be used in a clinical setting where patients are continuously monitored and the staff are trained and experienced with sedative medications, including ketamine. It will be used within the licensed dose range and current clinical evidence suggests it is safe and well-tolerated with lower or similar rate of adverse events compared to standard of care.[24] There is no reason to suspect a different safety profile to its licensed indication for maintenance of anaesthesia.

All aspects of this study have been designed with participant safety as a priority, including the dosing schedule, requirement for monitoring, inclusion/exclusion criteria, and trial design.

3. Study Objectives and Endpoints

3.1 Aims

The aim of this project is to generate feasibility data and to highlight potentially important clinical and patient centred outcomes that may become key endpoints in subsequent trials.

3.2 Objectives

The objectives of this study are to undertake both process and scientific assessments of ketamine sedation, which will inform progression criteria for future studies.

3.2.1 Primary Objective

The primary objective is to establish the feasibility of using continuous ketamine infusions for sedation to inform a subsequent randomised controlled trial.
Given the complexity of the clinical setting, patient population, and ICU sedation, it is essential to develop an understanding of how this intervention may be implemented in a future larger study. Feasibility data will help distinguish between intervention failure and implementation failure; this includes:

1) Establishing the extent to which the intervention is implemented as intended (implementation fidelity)
2) Exploring feasibility of using proposed clinical markers of efficacy and patient reported outcomes (data completeness / ability to collect data)

3) Exploring clinical staff experience and reported barriers and facilitators to implementation (organisational, logistical, cultural)
4) Monitoring protocol deviations in order to affect changes prior to further studies

Process assessment objectives

The aim of the process assessment is to investigate the processes involved in delivering the intervention as intended, and to identify barriers and facilitators to intervention.

Evaluation of key aspects of the study process, including:

- Expected recruitment, refusal, and follow-up rates
- Ability to collect data from standard of care
- Ability to collect patient reported outcome measures
- Staff feedback on delivery of IMP
- Reliability of data collection

Scientific assessment objectives

Identification of prospective clinical and patient-centred endpoints as well as early indicators of efficacy and safety, for example:

- Level of safety and adverse events
- Exploratory assessment of clinical efficacy markers

3.2.2 Explorative Objectives

Explorative objectives are to investigate the efficacy of ketamine infusions by monitoring patient-based outcomes and clinical effects relating to the IMP throughout the patient's ICU stay, hospital stay, and at 90-day follow-up.

During the three-month follow-up will collect 90-day mortality, readmission status, anxiety and depression, post-traumatic stress, employment status, and health-related quality of life (HRQoL) in order to assess the feasibility of collecting these data points at the time points of interest.

3.3 Endpoints

In order to assess the study process, the following endpoints will be investigated:

- Expected recruitment, refusal, and follow-up rates
    - Recruitment and refusal rates
    - Withdrawal and follow-up rates
    - Withdrawal and refusal reasons
- Ability to collect data measurements:

    - Standard of care data completeness for clinical markers of interest (see *proposed clinical efficacy measures* below)
    - Ability to collect patient reported outcome measures at ICU discharge and 90-days (see *patient reported outcome measures* below)
    - Ability to collect health economic data including cost of IMP, patient level costing data (via PLICS), and employment status
- Staff feedback measurements:
    - Anonymous multiple choice feedback questions regarding ability to carry out study tasks, provide intervention, and care for patients
- Reliability measurements:
    - Correct / accurate recording and formatting of representative sample of CRFs (validity)
    - Completeness of representative sample of CRFs (completeness)

To assess the scientific objectives, the following endpoints will be investigated:

- Level of safety and adverse event measurements:
    - Incidence of AEs /SAEs, ARs, SUSARs
- Exploratory assessment of clinical efficacy markers
    - See below for full list of *proposed clinical efficacy measurement* endpoints collected

So as to assess the ability to collect data, we have identified potentially important clinical efficacy measurements from either routinely collected ICU medical and nursing data or based on the scientific premise of the study. These measurements have the potential to become key endpoints or yield key results in subsequent larger RCTs, and therefore it is useful to assess firstly if it is possible to collect these, and secondly what is required in order to record these accurately.
The proposed clinical efficacy measurements are derived from routinely collected medical and nursing data for patients admitted to ICU who require sedation and MV. No additional tests or assessments are required, except for patient reported outcome measures and health economic data collected at ICU discharge and 90-Day follow-up, which would not routinely happen. It is key aspect of the study to assess the feasibility of collecting these data at both timepoints as this will inform future study design.

The endpoint for this feasibility study is if these data points are possible to collect at the timepoints of interest, and the completeness of the standard of care data, not the specific values, however the feasibility of collecting these data as this will inform future study design.
The full list of proposed clinical efficacy measurements and exploratory outcome measurements, along with their timings, can be found in **Table 2** below.

Table 1 Study endpoints, measurement methods, and timings

Endpoint	Measurement	Timing
Study process measurements		
Recruitment and refusal rates	Frequencies and percentages	Continuously during study period and at the end of the study period
Withdrawal and follow-up rates	Frequencies and percentages	Continuously during study period and at the end of the study period
Withdrawal and refusal reasons	Frequencies and percentages	Continuously during study period and at the end of the study period
Ability to collect data measurements:		
Standard of care data completeness for proposed clinical efficacy markers	Frequencies and percentages	At the end of the study period
Ability to collect PROMs at ICU discharge and 90-day follow-up	Frequencies and percentages	At the end of the study period
Ability to collect health economic data during study period	Frequencies and percentages	At the end of the study period
Staff feedback measurements:		
Feedback on ability to provide intervention and care for study participants	Anonymous categorical data via Google forms	At the end of the study period
Reliability measurements:		
Correct / accurate recording and formatting of representative sample of CRFs (validity)	Frequencies and percentages	At the end of the study period
Completeness of representative sample of CRFs (completeness)	Frequencies and percentages	At the end of the study period
Level of safety and adverse event measurements:		
Incidence of AEs /SAEs, ARs, SUSARs	Numerical and categorical data	Continuously from enrolment until ICU discharge
Exploratory assessment of clinical efficacy measurements:		

Ability to collect proposed clinical efficacy measurements (see ***Table 2*** for full list of measurements and timings)	Frequencies and percentages	At the end of the study period
Ability to collect exploratory outcome measurements (see ***Table 2*** for full list of measurements and timings)	Frequencies and percentages	At the end of the study period

Table 2 Proposed Clinical Efficacy and Exploratory Outcome Measurements and Timings

Outcome	Timing
Proposed clinical efficacy measurements	
Mortality	Daily during study period, ICU discharge, and 90-days
Age	Baseline
Sex	Baseline
Ethnicity	Baseline
Baseline SOFA score	Baseline
Diagnosis	Baseline
Length of ICU stay	ICU discharge
Duration of sedation	End of study period
Cumulative, peak, trough, bolus, and average dose of IMP and NIMP	Daily from start of IMP until off MV >48h
Requirement for 'rescue' sedation and indication	Daily from start of IMP until off MV >48h
Requirement for muscle relaxant and indication	Daily from start of IMP until off MV >48h
Ability to collect IMP, NIMP, and sedation data	End of study period
Incidence of RASS target set / RASS scores recorded	End of study period
Number of RASS scores in range, total number of RASS scores recorded	Daily from start of IMP until off MV >48h
Incidence and indication for deep sedation	Daily from start of IMP until off MV >48h
Duration of MV, time to extubation from cessation of IMP	End of study period
Requirements for tracheostomy	Daily from start of IMP until off MV >48h
Incidence of unplanned extubation or decannulation, requirements for re-intubation or decannulation	Daily from start of IMP until off MV >48h
Incidence of significant hypotension, hypertension, bradycardia, tachycardia, or arrhythmias* and details of each	Daily from start of IMP until off MV >48h
Requirement for vasopressors	Daily from start of IMP until off MV >48h

Cumulative, peak, trough bolus, and average dose of vasopressors	Daily from start of IMP until off MV >48h
Incidence delirium	Daily from start of IMP until off MV >48h, and ICU discharge
Ability to collect delirium data	End of study period
Duration of delirium	End of study period
Incidence of AEs /SAEs, ARs, SUSARs	Continuously from enrolment until ICU discharge
Incidence of new RRT requirements	Daily from start of IMP until off MV >48h
Exploratory measurements:	
Post-traumatic stress disorder score	ICU discharge and 90-days
Anxiety and depression score	ICU discharge and 90-days
Readmission status	90-days
Employment status	90-days
Health related quality of life	90-days
IMP costs	End of study period
Patient-level costing (PLICS)	End of study period

*Heart rate and blood pressure monitoring will conform to ICU standard of care for patients receiving sedation and mechanical ventilation.
The following definitions will be used to identify incidences of hypotension, hypertension, bradycardia, tachycardia, or arrythmias:
Significant hypotension:
A decrease in systolic blood pressure by >30mmHg from enrolment
Or
An increase in or new vasopressor / inotrope requirement to maintain systolic blood pressure >90mmHg or MAP ≥65mmHg.

Significant hypertension:
An absolute systolic blood pressure >180mmHg (excluding patients with a history of hypertension or taking antihypertensives prior to enrolment)
Or
Initiation of any new antihypertensive medications (excluding patients on antihypertensives prior to admission).

Significant bradycardia:
A decrease in heart rate from enrolment >30bpm (excluding patients with HR ≥100bpm at enrolment), or an absolute heart rate <50bpm,

Significant tachycardia:
An increase in heart rate from enrolment >30bpm (excluding patients with HR <50bpm at enrolment), or a new absolute heart rate >120bpm.

Arrhythmias:

Any new tachydysrhythmia as documented by the medical or nursing team that was not present at the time of enrolment (excluding patients with known paroxysmal arrhythmias with recurrence of known arrhythmia).

4. Study Population

4.1 Target Population

The target population are patients admitted to ICU requiring MV and sedation and expected to survive >24 hours and continue to require MV for >48 hours.

4.2 Number of Participants

As this is a feasibility study, a formal power calculation is not suitable. The data collected in this study will aid with statistical power calculations in future studies. Current guidance suggests that a sample size of 30 is adequate for a study of this nature[32] and should be possible in the timeframe.

The prospective cohort will be compared to a historical routinely collected data from SJUH ICU and data from published literature, so that initial findings such as adverse events, length of stay, and mortality can be compared.

5. Study Activities

5.1 Identifying Participants

Patients will be screened and identified by clinical ICU teams at St James's University Hospital (SJUH), Leeds, working in conjunction with the research teams (twice daily at morning and evening handover).
Anonymised reasons for screening / eligibility failure will be recorded using the Eligibility, Approach, and Consent Log in order to aid future trial development.

5.1.1 Inclusion Criteria

1. Requiring mechanical ventilation on ICU
2. Aged 18 years or older
3. Within 48hrs of starting mechanical ventilation
4. Requiring sedation
5. Expected to require more than 48hrs of mechanical ventilation
6. Expected to require a further 24hrs of mechanical ventilation at time of eligibility

5.1.2 Exclusion Criteria

1. Acute brain injury (hypoxic, traumatic, ischaemic, haemorrhagic) at time of screening
2. Acute central nervous system infection (including meningitis and encephalitis) at time of screening
3. Acute liver failure (Hyper-acute, acute, or sub-acute liver failure as defined by O'Grady et al[33]*) at time of screening
4. Acute liver injury (ALT >400iu/L ± INR>1.5 in absence of other causes)** at time of screening
5. Acute myocardial infarction or known severe coronary or myocardial disease at time of screening
6. Allergy to ketamine or any of its formulation excipients, or allergy to alfentanil
7. Continuous neuromuscular paralysis at time of screening
8. Decision to provide only palliative or end-of-life care by clinical team at time of screening
9. Drug induced / malignant hyperpyrexia at time of screening
10. Enrolled in another CTIMP or any ICU study at time of screening
11. Home ventilation (including overnight non-invasive ventilation / CPAP)
12. Liver transplant recipient at any point in participant's medical history
13. Long-term medical condition resulting in the participant lacking capacity prior to current illness, and who is not expected to ever regain capacity to provide consent to participate after cessation of sedation
14. Neuromuscular junction disorder as admitting or contributing diagnosis (e.g. Guillain-Barre, myasthenia gravis etc.) at time of screening
15. Patient not expected to survive >24 hours at time of screening
16. Patient known to be taking / prescribed ergometrine or memantine (severe interaction with IMP)
17. Post cardiac arrest where there is clinical concern of acute hypoxic brain injury at time of screening
18. Pregnancy***, up to 6 weeks post-partum (following delivery), suspected eclampsia / pre-eclampsia, or breast feeding / expressing milk
19. Previously enrolled into SHOCK-ICU
20. Psychosis or any mental health illness requiring treatment at time of screening
21. Raised intra-ocular pressure (suspected, confirmed, or history of****)
22. Severe hypertension (systolic blood pressure >180mmHg) at time of screening

23. Tachyarrhythmia (ventricular and supraventricular) at time of screening excluding atrial fibrillation with rapid ventricular response or sinus tachycardia in the context of a precipitating cause e.g. sepsis
24. Transferred from another ICU in which MV occurred for >6 hours
25. Prisoner or detained in police custody prior to admission

* O'Grady jaundice to encephalopathy time intervals: Hyper-acute = <7 days, acute = 8-28 days, sub-acute = 5-12 weeks.[33]
**These tests should be performed and recorded in the medical notes as part of the standard of care for ICU patients. Any potential participants in this category without liver function tests from the previous 7 days at the time of eligibility screening will be excluded from participation.
*** Any woman of childbearing potential (as defined by Clinical Trials Facilitation and Coordination Group[34] i.e., fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilisation includes hysterectomy, bilateral salpingectomy and bilateral oophorectomy) lacking capacity with a possibility of being pregnant should have a pregnancy test performed and recorded in the medical notes as part of the standard of care for ICU patients. Any potential participants in this category without a valid negative pregnancy test at the time of eligibility screening will be excluded from participation.

**** It is not a requirement to measure intraocular pressure specifically (beyond any clinical reason to outside of the study). Any patient with a documented history of raised intra-ocular pressure or on long-term treatment will be excluded.

5.2 Eligibility

Patients will be screened for eligibility using the specific SHOCK-ICU checklist. A qualified medical professional should carry this out as soon after identification as possible to minimise delay in initiation of IMP.

Screening will continue for up to 48 hours post initiation of MV, and periods of MV occurring prior to admission, e.g. in operating theatre or emergency department will not count as a part of the 48-hour eligibility time constraint, unless transferred from an external ICU. Screening may happen multiple times during the 48 hours if appropriate, e.g. if initially the patient required continuous paralysis, but this was stopped within 48 hours of MV commencing.

Protocol waivers are not acceptable as no person must conduct a clinical trial otherwise than in accordance with the protocol.

5.3 Consenting Participants

5.3.1 Informed Consent

At the point of enrolment patients will lack the capacity to consent because they will be receiving sedative medications. Assent will be obtained in accordance with UK law either through a personal legal representative (usually the next of kin) or if a personal representative is unavailable, then a professional legal representative will be consulted.

A professional legal representative constitutes a person not connected with the conduct of the study, who is either the primary doctor responsible for the potential participant's medical treatment, or a person nominated by the relevant healthcare provider.
The consent process is illustrated in the form of a flow diagram (see **Figure 1**).

5.3.2 Consenting those who lack capacity

In critical care research where patients lack capacity to consent to participation, it is common practice to approach a personal legal representative to provide a declaration of agreement.

Given the time-critical nature of enrolment and treatment (earlier intervention may correlate with preferable outcomes) consent is required within 2 hours of confirmation of eligibility. This time frame is designed to maximise the potential benefit and is in keeping with other current ICU sedation studies.

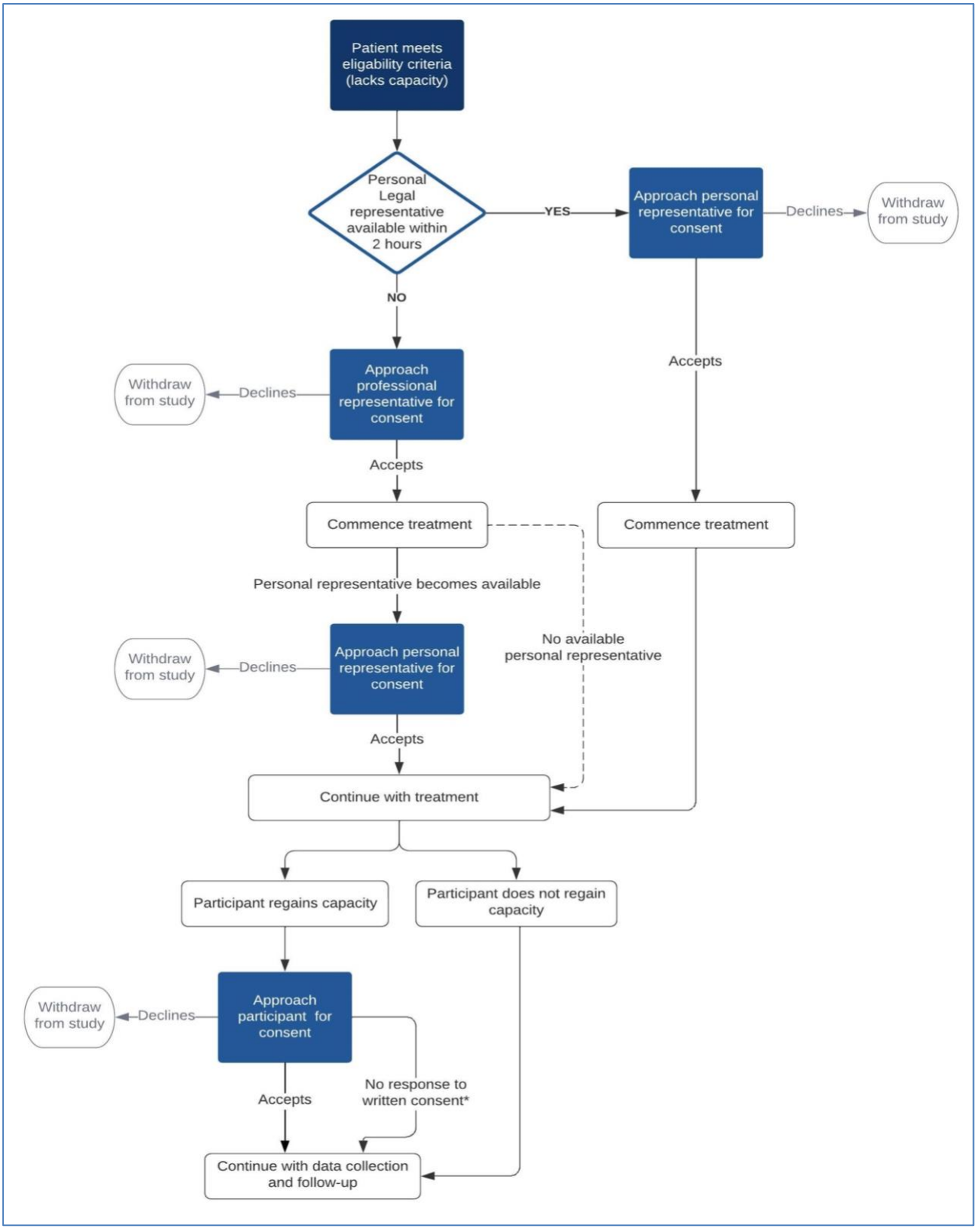
If a personal legal representative is present at the time of eligibility confirmation or within the 2-hour window, they will be provided with the Personal Legal Representative Information Sheet and given opportunity to ask questions of the team. If consent is given on the patient's behalf, then they will be recruited to the study.

If a participant's personal legal representative is not present at the time of eligibility screening, nor the 2 hours post confirmation, then a professional representative who is immediately available will be asked to provided consent on the patient's behalf. The professional legal representative will be given a copy of the Professional Legal Representative Information Sheet and provided the opportunity to ask questions.

All participants enrolled into the study, or their legal representative will receive an Information Sheet.

Should the patient's personal legal representative and a professional legal representative not be available immediately following eligibility screening or the 2 hours post confirmation of eligibility then the patient will be excluded from participation in the study.

Figure 1: SHOCK-ICU Consent Process



5.3.3 Participants that regain capacity

Should a participant regain capacity during the study period, they will be approached by an authorised member of the research team and asked to provide retrospective consent. This will occur as soon as practically possible upon identification of regaining capacity.

A participant information sheet (PIS) will be provided along with the opportunity to ask questions or discuss the study with a member of the research team.

Should the participant provide informed consent, they will continue in the study as planned. If they however do not provide consent, then they will be withdrawn from the study and follow-up, but data collected up to the point of withdrawal will be retained and used in analysis.

Participants that revoke consent on regaining capacity will not be replaced, however rate of withdrawal and, where possible, withdrawal reasons will be recorded in order to aid future trial development.

It is anticipated that most study participants discharged from ICU will have regained capacity whilst on ICU, and therefore will have been approached for informed consent. For those leaving ICU without regaining capacity, the personal or professional legal representative consent will stand until the participant is identified as having capacity, or 90-days have passed. Reasonable attempts will be made to identify when participants discharged from ICU without regaining capacity have subsequently regained capacity, either through looking at the medical notes, face-to-face encounters on the ward, or if discharged from hospital then telephone call to the participant or their registered next of kin. Once identified as having regained capacity, participants will be approached for informed consent as soon as practically possible.

If a participant that has been discharged from hospital has not been able to provide consent prior to hospital discharge, a PIS and consent form will be posted to the participant in an attempt to gain written consent prior to 90-day follow-up.

The participant will be asked to return the signed consent form if they wish to remain in the study or contact the study team if they wish to be withdrawn. If the participant does not return the signed consent form but does not ask to be withdrawn from the trial, the then the professional / personal legal representative consent will remain valid, and the patient will remain in the study and an attempt will be made to contact the participant for 90-day follow-up.

If a participant that has been discharged from hospital has not returned a written consent form or requested to be withdrawn by 90-day follow-up then a second consent form and PIS will be posted at 90-days.

If a participant is deemed to still lack capacity at 90-days, then the professional/personal legal representative consent will stand. No further attempts to contact that participant for informed consent will be made beyond 90 days.

Very occasionally participants may be discharged or leave against medical advice before the research team have had opportunity to approach them for retrospective consent. In these circumstances, the research team will make reasonable efforts to contact the participant through contact details provided in the medical notes.

Participants who, prior to their current illness, lacked capacity to consent through a long-term medical condition and who are not expected to ever regain capacity to be able to consent following cessation of sedation, will be excluded from the study.

5.3.4 Incentives and Reimbursement

There will be no financial incentive or reimbursement for patients, legal representatives, or professional representatives for taking part in this study.

5.5 Intervention

Patients will commence intravenous infusion of open-label study drug according to a weight-based dose regimen (see **Appendix 2**) as early as possible post-enrolment, and within a maximum of two hours.

The intervention will be prescribed by the treating clinical team and will be administered by the bedside clinical nursing staff, as is usual practice in ICU. Clinical staff will transition patients to achieve sedation with the study agent (IMP) as quickly as clinically feasible and safe, to replicate the way these drugs would be used in routine practice. Alfentanil will be used for analgesia alongside the IMP and titrated using clinical judgement to replicate standard care.

Once established, additional sedatives (including propofol) will only be used as a bolus in emergency situations to maintain safety, when the maximum ketamine dose is reached, or because side effects limit dose escalation.

In the unlikely event that a participant remains sedated beyond 90 days then they will transition onto the treating clinical team's sedative of choice and there will be no further intervention as part of the study.

5.5.1 Ketamine

The use of continuous ketamine infusions will follow the regimens used in recent trials[35] and will be calculated on a weight based (mg/kg/h) basis and titrated to effect. A review of the literature revealed an overall average sedation dose of 1.05mg/kg/h, or 2.03mg/kg/h when used as primary sedation.[24]
Dosing will be based on actual body weight, unless the participant has a BMI >40Kg/M^2, in which case an adjusted body weight (ABW) will be used in keeping with recommendations from recent evidence on dosing of ketamine in obese patients.[36]

Ketamine is available in 500mg in 10mls concentrations. 1000mg (2x500mg vials) will be diluted with 80mls of 0.9% sodium chloride, providing an intervention concentration of 10mg/1ml. This concentration is within the accepted concentration range for use on ICU according to the UK Clinical Pharmacy Association (UKCPA) minimum volume for infusion guide[37] and Medusa-NHS injectable Medicines guide, both of which state a maximum preparation of 50mg/ml for use in ICU.

See **Section 6.1.4** for full dosage information.

5.5.2 Blinding

This will be an open-label study with no blinding for clinicians or researchers.

5.6 Management during Intervention

5.6.1 Sedation Targets

Patients will be titrated to achieve the default sedation target of most awake and comfortable state unless otherwise clinically indicated by the ICU teams. If there is no indication for deeper sedation, then the least awake level should be Richmond Agitation Sedation Scale of -2 (brief eye contact in response to voice). RASS of -2 to +1 is widely regarded as light sedation and considered best practice.

Sedation levels should be continuously monitored and if clinically appropriate then efforts to decrease sedative infusions should be made to allow the patient to achieve a state of being most awake but comfortable and safe with a minimum of RASS -2. Bedside nurses will be asked to record the RASS 4-hourly throughout

their shift, and a bedside algorithm will guide the titration of either propofol or ketamine depending on the RASS e.g. if the RASS <-2 then nurses will be required to down titrate the infusion accordingly.

Patients that experience inadequate sedation, or become agitated, will receive additional propofol as required, but only once the maximum tolerated dose of intervention drug is reached. All supportive and additional treatments are as per standard of care procedures, including opioid infusions (alfentanil most commonly) for analgesia as clinically indicated at the discretion of clinical teams.

5.6.2 Vasopressor use

The trust policy for initiation of vasopressors can be found in **Appendix 3**.

Treatment with vasopressors should follow the basic principles:

1. Full assessment and adequate fluid resuscitation
2. Aim for euvolaemia
3. Do not continue to give fluids if no response to fluid challenge
4. Set patient specific MAP target (usually ≥65mmHg if maintains urine output and stability of acidosis / lactate)
5. Initiate a noradrenaline variable rate infusion as first line vasopressor therapy
6. Noradrenaline should then be titrated to achieve the patient's target MAP
7. When noradrenaline reaches dose of >0.5micrograms/kg/min then reassess patient and consider adding in second vasoactive agent (usually vasopressin or terlipressin), consider steroids, and consider dobutamine in heart failure patients

5.6.3 Weaning from MV

All participants should undergo regular attempts to wean from sedation and MV as appropriate and according to local ICU guidelines and standard of care procedures. When possible, patients should be ventilated using a 'spontaneous mode' and regular attempts to reduce ventilator support e.g. peak end expiratory pressure (PEEP), pressure support (PS), and Fraction of Inspired Oxygen (FiO_2), should be made by the clinical staff. Regular or protocolised sedation holds are not a requisite however should be considered if clinically appropriate. The requirement for intubation and sedation should be continually assessed, and readiness for extubation considered.

5.7 Withdrawal of Participants

Participants, their legal representative, or their professional representative are free to withdraw from the study at any point. An investigator may also withdraw participants if appropriate. If withdrawal occurs, then the primary reason for withdrawal will be documented in the SHOCK- ICU Study Withdrawal form.
There are three options for withdrawing:

i. Withdrawal from all aspects of the study including all data collected up to the time of withdrawal and follow-up
ii. Cessation of study medication and follow-up but continued use of data collected up to that point
iii. Withdrawal from intervention only with permitted use of data collected up to time of withdrawal and continued participation in 90-day follow-up

Patients who are withdrawn during the intervention and participants who do not provide consent to remain in the trial after regaining capacity will not be replaced. However, rates of withdrawal will be monitored, especially in relation to withdrawal following deferred consent when this approach is used. If withdrawal rates are high a strategy to address this will be agreed to ensure adequate numbers of participants and to improve rates in further trials.

Safety data including suspected unexpected serious adverse reactions (SUSAR), serious adverse events (SAE), and serious adverse reactions (SAR) will continue to be recorded for participants who have withdrawn consent following IMP administration. SUSAR reporting will continue until the end of the study period (see **Section 10.5**).

Should any new information arise regarding the IMP that is deemed significant to participants, it may be necessary to contact participants including those who have withdrawn consent.

5.7.1 Stopping Criteria

Small sample size precludes accurate assessment of significant clinical events; therefore, there are no predefined statistical stopping criteria for this study.

6. Investigational Medicinal Product (IMP)

6.1 Ketamine

Ketamine is a medicinal product that is licenced in the UK for induction and maintenance of both long and short anaesthetics, pain relief, and as an analgesic in diagnostic manoeuvres and procedures. It's use as ICU sedation is "off-label" but is considered by clinical experts to constitute no greater risk than standard of care (see section **2.4 Assessment of Risk**).

Ketamine is used safely and effectively for the induction and maintenance of anaesthesia in both adults and children[26, 27] and is currently used in some ICUs across England as an "off-label" sedative.[11]
Current available evidence for the use of a ketamine as a continuous sedative infusion in critically unwell patients is summarised in the 2023 review by Richards et al.[24]

Ketamine is a water and lipid soluble N-methyl D-aspartic acid (NMDA) receptor antagonist that has been used since the 1970s to provide cataleptic, amnesic, analgesic, and dose dependant anaesthetic effects.

Ketamine displays both lipophilic and hydrophilic properties and is rapidly distributed throughout the body including the central nervous system (CNS) giving a time to onset of 1 to 5 minutes and a distribution half-life of 7 to 11 minutes. Ketamine is biotransformed into firstly norketamine and ultimately hydroxynorketamine in the liver, 90% of which is excreted in urine.

Ketamine provides sympathetic nervous system stimulation resulting in preserved cardiovascular and respiratory function. The resulting increase in heart rate and blood pressure mean that ketamine has generally become the anaesthetic drug of choice in severely injured trauma patients with hypotension for example in military and pre-hospital settings.

More diverse effects of ketamine include providing enhanced analgesia through opioid receptor agonism, anti-inflammatory effects in sepsis by suppressing nitric oxide synthase, bronchodilatory properties without respiratory depression, neuroprotective properties, tumour inhibition through regulation of carcinoma cell pathways, tumour necrosis factor-alpha and interleukin-6, as well as having a prolonged antidepressant effect.

Side effects include delirium, hallucinations, emergence reactions, tonic-clonic movements, nausea and vomiting, tachycardia and tachyarrhythmias, hypersalivation, and cystitis.

6.1.1 IMP Formulation, packaging and storage

Ketamine 50mg/ml solution for injection or infusion in 10ml single-use vials will be used from commercially available hospital stock. Any licensed brand may be used depending on availability.

Storage and handling of ketamine will be in line with the manufacturer's recommendations and current LTHT practices. For further details refer to the ketamine Summary of Product Characteristics (SmPC).[38]

6.1.2 Labelling

Ketamine will be used in accordance with the conditions set out in Regulation 46 (2) of the Medicines for Human Use (Clinical Trials) Regulations 2004 (and amended in 2006). No special trial labelling requirements apply. Therefore, ketamine 500mg in 10ml vials will be NHS commercial stock supplied and managed in accordance with standard LTHT policy for prescription only medications.

6.1.3 Storage

Ketamine is a Schedule 2 Controlled Drug and will be stored in the original container at room temperature in the ICU Controlled Drugs cupboard. The product does not require any special temperature storage conditions. Routine ward temperature monitoring, recording and reporting procedures will be followed.

6.1.4 Prescribing Preparation and administration

Infusions will be prescribed on standard LTHT ICU Intravenous Infusion Charts.
Ketamine is currently available in 500mg in 10mls preparations. 2x 500mg/10ml vials (1000mg) will be diluted with 80mls of 0.9% sodium chloride for infusion, providing an intervention concentration of 10mg/ml.

The dose of continuous ketamine infusions will follow the regimens used in recent trials. The rate (ml/h) will be calculated on a weight based (mg/kg/h) basis and titrated to effect.
Dosing will be based on actual body weight, unless the participant has a BMI >40kg/m^2, in which case an adjusted body weight (ABW) will be used in keeping

with recommendations from recent evidence on dosing of ketamine in obese patients.[36]
ABW will be calculated accounting for the participants ideal body weight (IBW) and their actual body weight, using the following formula:

$$ABW = IBW + 0.25 \times (\text{actual body weight} - IBW)$$[39]

Ideal bodyweight will be calculated using the Devine formula.[40]
There will be no loading dose or bolus at the start of the infusion and the starting dose will be 1mg/kg/h.

Infusions will be titrated up or down (usually in increments or decrements of 10-50% from current rate) between a maximum dose of 2.7mg/kg/h and a minimum of 0mg/kg/h, according to participant's sedation level, agitation, and response to IMP, replicating current practice. Boluses of 1ml (10mg) may be delivered via the infusion pump in order to maintain participant or staff safety where up titration of sedation may not have desired effect within the necessary timeframe.

If an accurate actual weight is not available, then an estimated weight may be used until an actual weight is recorded to reflect standard practice for weight-based dosing on ICU. In this instance, an actual weight should be recorded at the earliest clinically appropriate timepoint.

Example:
An 80kg patient would be commenced on 1mg/kg/h (80mg/h). This would equate to an infusion rate of 8ml/h (10mg/ml). This would be prepared as 80mls 0.9% NaCl combined with 20ml of 500mg/10ml ketamine.
If the patient remained on 1mg/ml, one 100ml preparation containing 1000mg of ketamine would last 12.5 hours.

6.2 Drug Accountability Records

Trial specific accountability records will not be kept for the IMP in this trial.
All issues of ketamine vials will be recorded in the ward Controlled Drug Record book. Prescriptions will be written by a medically qualified practitioner or nurse prescriber from the participant's usual clinical team. These will be recorded on LTHT ICU infusion prescription charts, and hourly rates of infusions will be documented on the standard ICU nursing charts. These will constitute source data, which will subsequently be documented on the SHOCK-ICU CRF.

6.3 Participant Compliance

The clinical team will control the administration of the IMP whilst the participant is sedated, therefore compliance by the participant will not be relevant.

6.4 Adverse Drug Reactions

6.4.1 Ketamine

A list of adverse effects of ketamine can be found in the SmPC.[38]

6.5 Overdose

Ketamine has a wide margin of safety; several instances of unintentional administration of overdoses of ketamine (up to 10 times that usually required) have been followed by prolonged but complete emergence from anaesthesia, with few or no other complications of overdose to note.[41, 42] Animal studies have shown a wide therapeutic range with a lethal dose (LD_{50}) of around 100 times the intravenous therapeutic dose,[43] making lethal overdoses extremely unlikely.

The clinical team will control the administration of the IMP whilst the participant is sedated, therefore intentional or accidental overdose by the participant will not be relevant.

Dosing algorithms will provide guidance on titration of dosing and maximum rates of infusion to reduce the risk of iatrogenic overdose.

For the duration of time the participant is receiving the IMP they will be closely monitored on an ICU by a clinical team with appropriate expertise in administering the IMP as well as managing adverse effects and overdose, therefore any suspicion of overdose will be managed as per standard care.

6.6 Other Medications

6.6.1 Non-Investigational Medicinal Product (NIMP)

All participants will continue to receive alfentanil as per standard care. This will be titrated according to clinical judgement to replicate how it is normally used. There will be no change to dose ranges, formulation, concentration, or route of administration as part of this study.

6.6.2 Contraindicated Medications

Members of the research team will not be required to record concomitant medications. It will however be a requirement of eligibility screening to review the recorded medications in the participants medical notes to check for known severe interactions.

British National Formulary (BNF) lists severe interactions between ketamine and ergometrine (risk of hypertension), and ketamine and memantine (CNS side effects).[44] All potential participants taking these medications will be identified at screening and excluded from the study. Although unlikely, should there be a clinical need to commence these medications after the patient is enrolled, they will be removed from the study and not receive further doses of the IMP.

If after up-titration to the maximum dose ketamine does not adequately control sedation, then propofol may be introduced to maintain sedation and comfort. If participants were then to become heavily sedated propofol should be reduced before down titration of ketamine.

In the event of acute agitation, participants may receive boluses of IMP, propofol, or other sedatives to maintain safety.

6.6.3 Cautionary Medications

Ketamine is to be used with caution in combination with medicines with an increased risk of hypertension, hypotension, or with CNS depressive effects, for example sedatives, anaesthetic agents, antihypertensives, and antipsychotics. A list of cautionary medications can be found in the SmPC (see "4.5 Interaction with other medicinal products and other forms of interaction").[38]

These risks are present when prescribing any sedative medications on ICU, and clinical staff are experienced in identifying and managing these risks and therefore this will be managed using the clinical judgement of the treating clinical team, as per the standard of care.

7. Data Collection and Management

All data will be collected using paper case report forms (CRFs).

7.1 Study Assessments

Table 3 Study Assessments

	Pre-Enrolment	pre-IMP starting	Daily until off MV for >48h	At ICU Discharge (± 7 days)	At 90-day follow-up (±7 days)
Eligibility screening, confirmation of eligibility, and consent	X				
Baseline data collection including ability to collect ventilation and sedation details, past medical history, BMI, admission diagnosis, SOFA score, requirement of RRT, Delirium status		X			
IMP Administration			X		
Daily data collection during ICU stay including ability to collect ventilation details, sedation details (incl. IMP & RASS), CAM-ICU, CVS details (incidence of hypotension, hypertensions, bradycardia, tachycardia, and vasoactive medication details including vasopressor requirements), RRT requirement, ADRs			X		
Ability to collect delirium incidence (CAM-ICU) at baseline and 2x per day until ICU discharge		X	X	X	
Adverse Event data			X	X	

Retrospective patient consent				X	X
ICU and hospital discharge status, readmission status				X	X
Mortality			X	X	X
Ability to collect PROMs (HADS, PCL-5)				X	X
Ability to collect health economic data (EQ-5D-5L, employment status, and observational economic data)					X
Anonymous staff feedback data			X		

7.1.1 Screening and Baseline Data

Participants will be screened against the study inclusion and exclusion criteria; eligibility will be recorded directly on the CRF and in the medical notes in keeping with MHRA guidance.

Eligibility must be confirmed by a medically qualified doctor. Statements confirming eligibility may be entered into the medical notes by any healthcare professional so long as it is evident that the decision has been made by a medically qualified doctor. No additional tests, investigations, or procedures are required beyond standard of care in order to confirm eligibility.

Anonymous screening and eligibility data will be collected and used to generate a trial CONSORT diagram, as well as to monitor reasons for screening failure.

Consent / assent will be sought according to the process outlined in the study protocol. Consent to participate will be recorded directly on the Consent Form, as the data source. If assent / consent is declined, reason for this will be recorded (if available) in the Eligibility, Approach, and Consent Log.

After confirmation of eligibility and consent to participate, baseline data including date of birth, age, sex, participants' past medical history / comorbidities, smoking status, admission details and diagnosis, ventilation and sedation details, CAM-ICU, and SOFA scores will be collected using the SHOCK-ICU Baseline Data CRF.

7.1.2 Daily Data Collection

Data will be collected daily using the SHOCK-ICU Daily Data CRF. The primary purpose of this is to assess the feasibility and completeness of using routine

information in keeping with what you would expect to be recorded during an ICU admission, including: ventilation and sedation details, CAM-ICU, cardiovascular parameters and vasopressor use, and requirement of RRT. Any adverse events occurring during the intervention period will also be recorded.

Daily data collection CRFs will also include qualitative aspects to aid with process assessments (see **Section 8.4.2**). Clinical staff providing care for enrolled patients will be encouraged to provide daily feedback on experienced barriers or enablers to the intervention and study activities.

Daily data will be collected until 48 hours without MV (extubation or tracheostomy without ventilator support), which is defined as ventilation through an endotracheal tube or ventilation through a tracheostomy either in mandatory mode, CPAP with PEEP >5cmH_2O, or pressure support of ≥5cmH_2O) or 90 days have elapsed. The average duration of MV on ICU is 3-5 days (ICNARC).
If participants should require sedation and MV again following 48 hours free from MV, they will not be eligible to be re-enrolled into this study.

The presence of delirium as indicated by a positive CAM-ICU score will be assessed at ICU discharge. Adverse events including mortality will continue to be recorded until ICU discharge.
Clinical staff providing care for enrolled patients will be asked to answer simple anonymous multiple-choice questions using Google Forms, as well as encouraged to provide daily feedback on experienced barriers or enablers to the intervention and study activities. No personal data from staff will be collected.

7.1.3 ICU Discharge Data

Participant status at discharge (alive; dead; transfer to other ICU; discharged to ward / community / home) will be recorded along with date / time of discharge, and date / time of final extubation on the SHOCK-ICU ICU Discharge Data CRF. If there is a delay in discharging a participant from ICU that is unrelated to their medical condition, for example bed pressures elsewhere in the hospital, then discharge date will be taken as the date the medical team declared the participant ready for discharge from ICU.

Hospital anxiety and depression scale (HADS) and post-traumatic stress disorder checklist (PCL-5) scores will also be collected at this point. These scores will be recorded directly onto source data worksheets and not recorded in the medical

notes. An important outcome in this study is if it is possible to collect PROMs at this timepoint.

There will be a one-week visit window for the ICU discharge data collection to allow for participant and researcher unavailability.

7.1.4 90-day Follow-up Data

Participants will be followed up for 90-days post enrolment. Survival status will be confirmed prior to contacting participants. Participants will be contacted either by telephone or face-to-face (if remains in-patient) and asked to complete the SHOCK-ICU 90-day Follow-up data collection – this includes 90-day survival / discharge status, readmission status, HADS, PCL-5, health related quality of life (EQ-5D-5L), recalled EQ-5D-5L, and employment status. These data points will be recorded directly onto source data worksheets and not recorded in the medical notes. An important outcome in this study is if it is possible to collect PROMs at this timepoint.

There will be a two-week visit window for the follow-up appointment to allow for participant and researcher unavailability (90±7 days).

7.1.5 Survival Status

Survival will be collected up to 90 days post-enrolment.

7.1.6 Health Economic Data Collection

Observational health economic data will be collected daily whilst receiving IMP, then at ICU discharge and 90-day follow-up.

7.2 Data Management

All data will be managed according to the Data Management Plan, developed in line with Sponsor SOP (**QRES 07: Researchers Guide to Data Management**), recorded in separate Sponsor approved template (**CTT58**) and filed in the TMF. The Chief Investigator (CI) and the research department of Adult Critical Care, Leeds Teaching Hospitals NHS Trust will have overall responsibility for data management and quality. All source data will be collected in patient-specific source data worksheets/patient medical records and next transcribed onto paper CRFs maintained in the TMF. There is no plan for data to be entered into any electronic database. Descriptive statistics will be used only to summarise feasibility and safety results.

7.2.1 Access to Data

Direct access will be granted to the Sponsor and the regulatory authorities to permit trial-related monitoring, audits and inspections in line with participant consent.

7.2.2 Personal Data

By enrolling in the study, participants / representatives agree to have the following personal information collected from participants:

- Participant name
- Address, email address, and phone number (for 90-day follow-up)
- Date of birth
- NHS number
- Relevant medical information / history

Personal data will be stored securely on an encrypted Participant ID Log on an encrypted NHS account. At the end of the trial, the Participant ID Log will be archived for 25 years as per LTHT policy on archiving. No identifiable information will feature in any publication / dissemination of results.

No personal data will be recorded from staff members during the study. Staff feedback will be collected through an anonymous Google Form.

7.2.3 Transfer of Data

Anonymous data collected or generated by the study may be transferred to external organisations to be used for further research and or analysis in accordance with the UK Policy Framework for Health and Social Care Research.

7.2.4 Long-Term Data Storage, Archiving, and Retention

Archiving will be authorised by the Sponsor following submission of the End of Trial report. Long-term storage and archiving will occur in accordance with MHRA guidance. Essential documentation will be archived using the LTHT approved external archiving service. Documentation will be retained for at least 25 years after completion or discontinuation of the study. Full details of study Essential Documentation can be found in the Data Management Plan.

Source Data forming part of the medical records will remain with the medical records at the end of the study. Participants' medical records will be clearly labelled that they have taken part in a clinical trial and that the records cannot be destroyed for 25 years after the end of the trial.

Destruction of any essential documents will require authorisation from the Sponsor.

7.3 Source Data Documentation

'Source data' is defined as all original records and certified copies of original records. This will include all clinical records, both electronic and physical, observation records, HADS and PCL-5 patient questionnaires, and study documentation that would be required for the reconstruction and evaluation of the study. The anticipated source data and their locations for this study are detailed in the study Data Management Plan.

Internal source validation checks will be conducted and a representative sample (10%) of CRFs will be compared to the source data for accuracy and integrity.

7.4 Case Report Forms

All data will be collected using paper CRFs.

7.5 Trial Master File and Investigator Site File

7.5.1 Trial Master File

A Trial Master File (TMF) will be set up and kept by research team. This will be readily available at all reasonable times for inspection by the licensing authority or by persons appointed by the Sponsor for trial auditing.
The TMF will contain copies of all essential trial documentation, initial approvals, correspondences, and supporting documentation.
An example list of documents to be included in the TMF is provided below:

- Current protocol and all historical versions
- Blank copies of Patient / Relative Information Sheet, Assent / Consent Form, and GP letter
- Blank example CRF
- All original signed assent / consent forms
- Sponsor approvals and correspondences
- MHRA / REC approvals and correspondences
- General correspondences and meeting minutes
- Staff delegation log
- Screening / Eligibility and Participant ID logs
- Protocol breaches and deviations
- IMP SmPC and accountability logs
- Data Management Plan and Source Data Location Sheet

- Monitoring, audit, and inspection documentation
- Annual reports
- Newsletters
- End of Trial and archiving documentation
- Completed study documents including consent forms, CRFs, and source data worksheets

The Chief Investigator and Sponsor will ensure that the TMF is retained for at least 25 years after the conclusion of the trial (see **Section 7.2.3**).

7.5.2 Investigator Site File

As this is a single site study, the TMF will also serve as the Investigator Site File.

7.6 Monitoring, Audit, and Inspection

The Sponsor reserves the right to audit the site involved in the trial and authorisation for this is given via the study contract or agreement. The site may be monitored or audited by the Sponsor QA Office or their representative, and will be subject to inspection by the MHRA (in order to ensure compliance with ICH-GCP).

In all instances, the Investigator and research team should allow direct access to trial documentation to facilitate these activities. Quality Assurance Investigators will promptly notify the Sponsor Quality Assurance Office of the following within the required timeframe:

- Serious breaches of GCP
- Urgent safety measures
- Protocol violations
- Any amendments to the trial
- Any changes to the Clinical Trial Risk Assessment (form A)
- Any other issues as stated in the study contract or agreement

8. Statistics and Data Analysis

8.1 Sample Size

As this is a feasibility study, a formal power calculation is not suitable. The data collected in this study will aid with statistical power calculations in future studies. Current guidance suggests that a sample size of 30 is adequate for a study of this nature[32] and should be possible in the timeframe.

8.2 Proposed Analysis

Feasibility assessments:

- Scientific Assessment
- Process Assessment

8.2.1 Scientific Assessment

During this study we will identify important clinical and patient-centred endpoints as well as early indicators of efficacy and safety, for example:

- Level of safety and adverse events
- Exploratory assessment of clinical efficacy markers

Descriptive statistics including of baseline characteristics and study population.
Incidence of clinical events, including adverse drug reactions, AEs, SAEs, and SUSARs will be compared to published data in peer reviewed literature as well as available records from the study ICU, including the use of data collected by Intensive Care National Audit and Research Centre (ICNARC).

Findings will be presented in accordance with STROBE guidelines.[45]

8.2.2 Process assessment

As part of the feasibility assessment of this intervention, we will undertake a process assessment. The aim of the process assessment is to investigate the processes involved in delivering the intervention as intended, and to identify barriers and facilitators to intervention.
Given the complexity of the clinical setting, patient population, and ICU sedation, it is essential to develop an understanding of how this intervention may be implemented in a future larger study. Process assessment will help distinguish between intervention failure and implementation failure.

Simple descriptive statistics (frequencies, percentages) will be used to assess the study endpoints (see **3.3 Endpoints**) and used to inform predefined stop, amber, go criteria for the study protocol (see **Section 8.2.3**).

8.2.3 Progression Criteria

Predefined progression criteria have been produced as recommended by the CONSORT 2010 extension to pilot and feasibility guidelines,[46] and can be found in Table 4 below.

The progression criteria have been produced using criteria and cut-offs cited in the ICU literature and reflect the process assessment being undertaken. We will employ and *STOP*, *AMBER*, and *GO* method. *STOP* indicates that progression to

full trial would not be feasible without major changes to the protocol or design, *AMBER* indicates that minor changes to the protocol or design may be required and *GO* indicates that no changes are necessary to progress to the next stage.

Table 4 Progression Criteria

Aspect of the trial	Threshold	Progression
Eligibility (% of screened patients meeting eligibility)	>50%	Go
	30-50%	Amber
	<30%	Stop
Consent and enrolment (% of eligible patients consented and enrolled)	>70%	Go
	30-70%	Amber
	<30%	Stop
Withdrawal (% of patients withdrawn during study period)	<25%	Go
	25-50%	Amber
	>50%	Stop
Protocol adherence	>70%	Go
	50-70%	Amber
	<50%	Stop
Ability to collect proposed clinical efficacy markers (% data completeness)	>80%	Go
	50-80%	Amber
	<50%	Stop
Ability to collect PROMs (% data completeness)	>80%	Go
	50-80%	Amber
	<50%	Stop
Ability to collect health economic data (% data completeness)	>80%	Go
	50-80%	Amber
	<50%	Stop

9. Health Economics

9.1 Health Economic Evaluation

As this is a feasibility study, a full health economic analysis cannot be undertaken, and formal estimation of the cost-effectiveness will not be carried out. During the feasibility stage, clinical and observational costing data will be collected in conjunction with the available Patient-Level Costing (PLICS) data.

Data collected will include IMP acquisition costs, incidence of adverse events and complications, and ICU and hospital length of stay and mortality.

Patient reported outcome measures such as the EQ-5D-5L Euroqol tool (www.euroqol.org) for estimating Quality of Life Years (HRQoL) will also be collected to assess feasibility of use in future more detailed economic analyses.

Existing health economic literature will be screened for suitable models, which will be populated with the findings from the feasibility study.

Deterministic and probabilistic sensitivity analyses will be used to identify variables likely to significantly impact on cost-utility, warranting further investigation in larger analyses.

10. Pharmacovigilance

10.1 Definitions

The ICU research team at Leeds Teaching Hospitals NHS Trust (LTHT) will be responsible for the detection and recording of the events defined below:

- **Adverse event (AE)** – any untoward medical occurrence in a clinical trial participant that does not necessarily have a causal relationship with the IMP
- **Adverse reaction (AR)** – any untoward and unintended response to the IMP that is related to any dose administered to that participant
- **Serious adverse event (SAE) / Serious adverse reaction (SAR)** – any AE or AR that at any dose:
    - Results in death of the trial participant
    - Is life threatening (an event where the participant was at risk of death at the time of the event, rather than an event that potentially could have caused death if it were more severe)
    - Requires unplanned inpatient hospitalisation or prolongation of existing hospitalisation
    - Results in persistent or significant disability or incapacity
    - Consists of a congenital anomaly or birth defect
    - Results in any other significant medical event not meeting the above criteria
- **Suspected unexpected serious adverse reaction (SUSAR)** – a serious adverse reaction where the nature and severity are not defined as expected within the document containing the trial-specific Reference Safety Information (RSI).

The RSI for this study including full details of the contraindications and side effects that have been reported following administration of the IMP can be found in Section 4.8 of the SmPC approved for use in this study.[38]

10.2 Identification and Recording of AEs and SAEs

AEs and SAEs will be recorded from the time of enrolment until discharge from ICU. It is anticipated that the majority of patients will be discharged from ICU prior to 90-days.

AEs and SAEs will not be recorded between ICU discharge and 90-day follow-up. IMP administration will occur solely on ICU during MV and ketamine has a short half-life and high clearance rate,[47] and patients will typically spend several additional days in ICU after successful weaning from MV. The IMP is expected to be completely cleared from participants prior to ICU discharge and therefore the occurrence of new side-effects or adverse events relating to the IMP occurring after discharge from ICU are highly unlikely and will not be recorded. Death of participants following ICU discharge is an important clinical endpoint and will be recorded.

There will be a risk-adapted approach to safety reporting. The study involves sedating critically ill patients in ICU and therefore it is anticipated that participants may experience events that would be consistent with an AE or SAE as part of their critical illness or that are well recognised, defined potential side effects of ketamine.

Sedation-related adverse events and well recognised, defined potential side effects of ketamine, are collected daily during the intervention period and are important exploratory endpoints in the trial. These events do not need to be routinely recorded as AEs or SAEs unless the severity or frequency is unexpected. A full list of known side effects of the IMP and associated frequencies can be found in the SmPC.[38]
Deterioration or worsening of symptoms that are expected due to participants' underlying condition will only be recorded as an AE and in the medical notes if judged to have unexpectedly worsened during the study or related to participation in the study.

Identification and assessment of these events will be the responsibility of the ICU clinical and research teams (participants likely to be incapacitated for the majority of the intervention period), and will be screened for by reviewing participant notes, laboratory tests, and other investigations carried out as part of their ICU

care. There will be no additional investigations undertaken for the purpose of detection of AEs or SAEs.

All relevant AEs occurring after enrolment will be recorded on the SHOCK-ICU AE Log and the medical notes. When an AE / SAE is considered relevant by the clinical or research teams, it will be the responsibility of the PI / CI to review all the relevant documentation and assess seriousness, causality severity, and expectedness (see **Section 10.3** below). Data to be collected includes IMP dose received, date of event, type of event, treatment required, and outcome.

10.2.1 AEs and SAEs that do not Require Recording

All identified AEs / SAEs will be assessed, recorded, and reported as appropriate to the level of severity / seriousness. In the following specific circumstances,

AEs that will not require recording:

- Known adverse effects of IMP detailed in the SmPC[38] unless severity or frequency is unexpected, including:
    - Hallucinations, abnormal dreams, nightmares, confusion, agitation, abnormal behaviour, anxiety, delirium, insomnia, disorientation, dysphoria, flashbacks
    - Increased blood pressure, tachycardia, bradycardia, arrhythmias, hypotension
    - Increased respiratory rate, respiratory depression, laryngospasm, apnoea, obstructive airway disorder
    - Nausea, vomiting
- Complications of ICU procedures excluding those arising from administration of IMP (e.g. extravasation injury).
- Requirements for interventions relating to admitting diagnosis e.g. surgery.
- Worsening of or complications relating to admitting diagnosis thought to be unrelated to participation in the study.
- New infections.
- Death thought not to be related to the IMP / participation in study (mortality is a key clinical endpoint and will still be recorded).

10.3 Assessments of AEs and SAEs

The ICU clinical and research teams will assess seriousness, causality, severity, and expectedness.

10.3.1 Assessment of Seriousness

Seriousness will be assessed using the criteria in **Section 10.1**.

10.3.2 Assessment of Causality

Investigators in conjunction with the clinical ICU teams will judge AEs and SAEs to be:

- **Unrelated** – the event is not considered to be related to the IMP.
- **Unlikely related** – on balance of probability, the event is not considered likely to be related to the IMP
- **Possibly related** – The event, underlying medical condition, or concomitant medications make it possible that the AE / SAE has a causal relationship to the IMP.
- **Probably related** – The event probably has a causal relationship with the IMP (this may be an expected reaction / event or not)

Causality assessments will be made by one or more medically qualified doctors, using medical and scientific judgement as well as knowledge of the subject concerned and the reference safety information.

Where non Investigational Medicinal Products (NIMPs) e.g. rescue/escape drugs are given: if the AE is considered to be related to an interaction between the IMP and the NIMP, or where the AE might be linked to either the IMP or the NIMP but cannot be clearly attributed to either one of these, the event will be considered as an AR. Alternative causes such as natural history of the underlying disease, other risk factors and the temporal relationship of the event to the treatment should be considered and investigated.

10.3.3 Assessment of Expectedness

If an event is considered to be an AR, then there will be an evaluation of expectedness taking into consideration the relevant published safety information for the IMP concerned (e.g. SmPC).

An AR will be judged as either:

- **Expected** – the AR is consistent with recognised effects of the IMP in the SmPC.
- **Unexpected** - the AR is not consistent with recognised effects of the IMP in the SmPC.

10.3.4 Assessment of Severity

Investigators in conjunction with the clinical ICU teams will judge AEs and SAEs to be one of the following severities:

- **Mild** – the event is easily tolerated by the participant, causing minimal / no discomfort and or disruption.
- **Moderate** – the event is causing some discomfort and interference with daily life / clinical effect.
- **Severe** – the event causes significant discomfort / distress and or clinical effect.

10.4 Reporting of AEs and SAEs

Reporting of SAEs will be done according to the Sponsor's guidance (**SOP QCRES_01 *(current)***).

All AEs / SAEs will be recorded both in the CRF and the medical notes. AEs will be assessed for seriousness, severity, and causality, the outcome of which will be documented in the medical notes and the CRF.

All adverse events meeting criteria for 'serious adverse event' (see **Section 10.1**) will be reported to the Sponsor within 24 hours of awareness by sending the '**CTT21: SAE Report**' form to **leedsth-tr.sponsorqa@nhs.net**.
Email reports of SAEs must include the following in the subject line:

- R&I number
- Trial short name
- SAE / SUSAR notification

Incidents and near misses will also be reported both through the Datix system.
Where appropriate an investigation will take place according to LTHT policy (see **SOP-CLIN-25-1.0**).

10.5 Reporting of SUSARs

Reporting of SUSARs will be done according to the Sponsor's guidance (**SOP QCRES_01 *(current)***).

If there is a serious adverse reaction where the nature of the event is not defined as expected within the reference safety information, this constitutes a Suspected Unexpected Serious Adverse Reaction (SUSAR) and required expedited reporting.

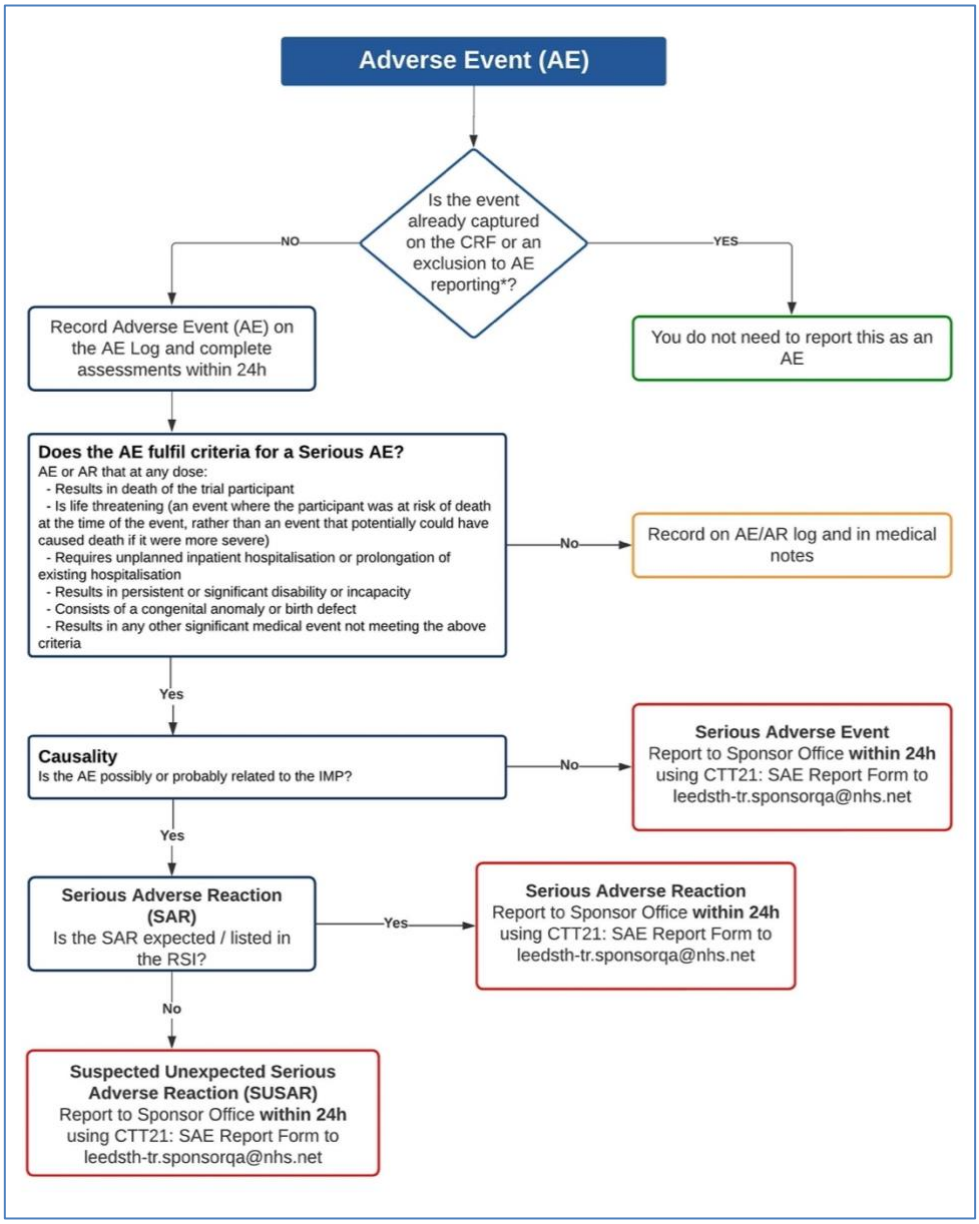
Upon identification of a SUSAR, the CI / PI or named delegate must report the SUSAR via email (**leedsth-tr.sponsorqa@nhs.net)** immediately and always within 24 hours using '**CTT21: SAE Report Form**'.

It is the responsibility of the Sponsor to report the SUSAR to the MHRA / REC as appropriate within the required timeframes.

The active period for collecting SUSARs will begin at initial IMP administration and continue until ICU discharge.

Due to the fact that IMP administration will occur solely on ICU during MV and ketamine has a short half-life and high clearance rate,[47] and patients will typically spend several additional days in ICU after successful weaning from MV, the IMP is expected to be completely cleared from participants prior to ICU discharge and therefore the occurrence of new side-effects or adverse events relating to the IMP occurring after discharge from ICU are highly unlikely. Should the research team be made aware of any new SUSARs following ICU discharge (including in participants that have withdrawn from the study) then these will be reported as described above.

Figure 1 - AE Assessment and Reporting Process



*** Exclusions to AE reporting:**

- Known adverse effects of IMP detailed in the SmPC unless severity or frequency is unexpected, including:
  - Hallucinations, abnormal dreams, nightmares, confusion, agitation, abnormal behaviour, anxiety, delirium, insomnia, disorientation, dysphoria, flashbacks
  - Increased blood pressure, tachycardia, bradycardia, arrhythmias, hypotension
  - Increased respiratory rate, respiratory depression, laryngospasm, apnoea, obstructive airway disorder
  - Nausea, vomiting
- Complications of ICU procedures excluding those arising from administration of IMP (e.g. extravasation injury).
- Requirements for interventions relating to admitting diagnosis e.g. surgery.
- Worsening of or complications relating to admitting diagnosis thought to be unrelated to participation in the study.
- New infections.

Death thought not to be related to the IMP / participation in study (mortality is a key clinical endpoint and will still be recorded).

10.6 Urgent Safety Measure

An Urgent Safety Measure (USM) is an action that the Sponsor or Investigator may take in order to protect the subjects of a clinical trial against any immediate risk to their health or safety.
An USM may be identified as the result of reporting an SAE or SUSAR, which may prompt the urgent implementation of a new protocol measure or amendment to prevent future occurrence or recurrence.

Examples of when an Urgent Safety Measure may be required are as follows:

- Serious adverse reactions with an unexpected outcome (*e.g. death*).
- An increase in the frequency of a serious adverse reaction that is judged to be clinically important.
- A serious adverse event associated with the trial procedures that may be prevented by changing the procedures.
- Lack of efficacy of an investigational medicinal product (IMP) used for the treatment of a life-threatening illness.
- A major safety issue identified from other studies (clinical or non-clinical) or from other usage of the IMP.

Once an Urgent Safety Measure is identified, the Chief Investigator is responsible for notifying the MHRA within 24 hours. This is initially by telephone to the MHRA's Clinical Trial Unit on 0203 080 6456.

The CI or PI must also contact the Sponsor Office and complete **Section A** of form **CTT07 - LTHT / UoL Notification of Urgent Safety Measure** available from the LTHT R&I website.

Copies of all UK related safety information supplied to MHRA must also be emailed in parallel to the main Research Ethics Committee, accompanied by a CTIMPs Safety Report form, which can be found of the HRA website.

Deviations from or changes to the protocol may be implemented by the Trial Management Group / Sponsor to avoid an immediate threat to participant safety without prior approval from the REC / MHRA. These changes must be discussed with the Sponsor and MHRA and a written notification and description of the amendment submitted within 3 days. 10.7 Developmental Safety Update Reports / Annual Safety Reports

An annual safety report describing the general progress of the study, SAE listings, and any other relevant safety data will be submitted to the MHRA, REC, and Sponsor within 60 days of the one-year anniversary of the Clinical Trial Authorization being granted.

The annual report should follow the format of a Developmental Safety Update Report (DSUR), and the associated REC annual safety report will be submitted in parallel. Annual Progress Reports should be submitted annually to the REC (which gave the favourable opinion), starting 12 months after the date on which the favourable opinion was given. An electronic copy of the progress report must be emailed to the REC and Sponsor within 30 days of the end of the reporting period.

11. Governance

All staff members involved in the delivery and conduct of this study must comply with the LTHT / UoL **SOP-GOV-11-2.0 The Governance of Clinical Trials involving CTIMPS or Medical Devices**.

Regular departmental research team meetings will be held, and minutes taken to monitor study progress and issues arising.

11.1 Ethical Considerations

The trial will be performed in accordance with the recommendations guiding physicians in biomedical research involving human participants, adopted by the 18th World Medical Association General Assembly, Helsinki, Finland, June 1964, amended at the 48th World Medical Association General Assembly, Somerset West, Republic of South Africa, October 1996 (website: http://www.wma.net/en/30publications/10policies/b3/index.html).

The trial will be conducted in accordance with the UK Policy Framework for Health and Social Care Research 2018, the applicable UK Statutory Instruments, which include the Medicines for Human Use (Clinical Trials) Regulations 2004 and subsequent amendments and the Data Protection Act 2018 and The Human Tissue Act 2008 and Human Tissue (Scotland) Act 2006 (if applicable) and Guidelines for Good Clinical Practice (GCP). This trial will be carried out under a Clinical Trial Authorisation in accordance with the Medicines for Human Use (Clinical Trials) regulations. The protocol will be submitted to and approved by the REC prior to circulation.

11.2 Good Clinical Practice

All staff involved in clinical trials must undertake a Good Clinical Practice course as part of their induction to understand the above regulations. Training should be renewed every 2 years and all current and previous certificates retained in personal training folders.

It will be the responsibility of the research team to maintain the documented evidence of the training status of staff members involved. The study delegation log must be kept up to date in line with Good Clinical Practice.

All doctors, research nurses and administrative staff involved in clinical trials must be made aware of the most recent versions of the Declaration of Helsinki and Medicines for Health (Clinical Trials) Regulations which cover the conduct of clinical trials in the UK.

11.3 Investigator Responsibilities

The Investigator is responsible for the overall conduct of the study and compliance with the protocol as well as the below responsibilities. Delegation to other members of the research team may occur but this must be recorded on the Delegation Log and signed by all those named prior to undertaking any study-related tasks.

11.3.1 Study Site Staff

It is the investigator's responsibility to ensure that all staff assisting with the study are familiar with the protocol, the IMP, and their trial related duties. Regular teaching sessions will be held to inform the clinical nursing staff, research teams, and ICU doctors are informed prior to the start of the trial.

All staff involved with any aspect of the trial, or named on the delegation log must hold an up-to-date GCP training certificate.

11.3.2 Data Recording

The Principal Investigator (PI) is responsible for the quality of data recorded in the CRF.

11.3.3 Confidentiality and Data Protection

All research data collected as part of the study will be anonymised and stored securely according to legal requirements. Any personal data collected will be stored separately from clinical data.

Clinical information will not be released without the prior written consent of the participant.

All Investigators and study site staff involved with this study must comply with the requirements of the appropriate data protection legislation (including the General Data Protection Regulation and Data Protection Act) with regard to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles. Access to collated identifiable participant data will be restricted to individuals from the research team treating the participants, representatives of the Sponsor and representatives of regulatory authorities. Computers used to collate the data will have limited access measures via usernames and passwords.

Dissemination of findings will contain no participant identifiable information.

12. Study Conduct

12.1 Protocol Amendments

Any changes in research activity, except those necessary to remove an immediate hazard to a participant or researcher e.g., an urgent safety measure, must be approved by the Trial Management Group.

Changes to the protocol must be approved by the Sponsor using the appropriate internal amendment form (**CTT05**) prior to being submitted to the appropriate Research Ethics Committee and MHRA regulatory authorities for approval.

This process will be conducted in accordance with the LTHT SOP **QCRES_03_Researchers guide to Notification of Amendments for UoL LTHT Sponsored CTIMPs**.

12.2 Protocol Non-compliance

12.2.1 Definitions

Protocol non-compliances are any change, diversion, or departure from the study design, procedures defined in the protocol, or Sponsor SOPs.

They can be classified as serious (violation) or non-serious (deviation):

- **Deviation** – any non-compliance that does not significantly affect the subject's rights, safety, or well-being, or key study outcomes.
- **Violation** – a deviation that may potentially significantly impact the completeness, accuracy, and / or reliability of the study data, or that may significantly impact a subject's rights, safety, or well-being.

12.2.2 Assessing, Categorising, and Recording Protocol Violations and Deviations

A Protocol Deviation Assessment Plan (PDAP) has been produced and will be maintained as a living document throughout the study. Anticipated potential protocol deviations have been listed but this in not exhaustive and will be added to as required during the study period.

Protocol non-compliances will be described as organisational level or protocol level. Organisational level refers to non-compliances that breach organisational wide policies, protocols, and SOPs. Protocol level non-compliances refer to those affecting the study procedures defined within the protocol but should not duplicate or contradict organisational non-compliances.

Non-compliances will be categorised based on the element of the study affected, for example: informed consent, inclusion / exclusion, intervention, trial procedures, prohibited concomitant medications, safety reporting, and discontinuation. Non-compliances will then be classified based on severity as either a deviation or a violation (see definitions above).

Examples of serious non-compliances (protocol violations) that may occur in this study include (but are not restricted to):

- IMP initiated prior to informed consent.
- Participant not retrospectively consented once regained capacity.
- Participant incorrectly entered the study.
- Received wrong IMP formulation / dose / route / frequency.
- Received wrong study IMP.
- Received additional sedatives without clinical indication (e.g. safety).
- Received contra-indicated co-prescribed medication.
- Participant received study medication that was deemed unacceptable due to contamination / temperature excursion / expiry date.
- No dose adjustment of IMP based on clinical parameters (Sedation level out of target range >4h).
- Missed safety or efficacy endpoint data collection / recording.

- Procedures / data collection relating to participant safety or efficacy occurring outside of specified time window e.g., follow-up.
- SAEs / SUSARs not reported within 24h.
- Participant continued IMP after withdrawal from study.

12.2.3 Management of Deviations and Violations

All protocol non-compliances, deviations, or suspected breaches must be appropriately recorded in the Log within the PDAP and reported to the Sponsor. Protocol deviations and violations will be reported no later than 3 working days after identification.

The research team will complete form **CTT20: UoL / LTHT CTIMP Protocol Deviations, Violations and Potential GCP Breaches** and send this via email (leedsth-tr.sponsorqa@nhs.net) to Sponsor QA for review.

Deviations and violations will be reviewed in order to identify violations not previously included in the PDAP and to assess whether frequency or volume of deviations PDs should trigger reclassification to violation.

12.3 Urgent Safety Measures

Deviations from or changes to the protocol may be implemented by the Trial Management Group to avoid an immediate threat to participant safety without prior approval from the REC / MHRA (see **Section 10.6**).

12.4 End of Trial Definition

The end of trial will be defined as the date of the last participant's last data item.
The Trial Management Group or Investigators may stop the trial prematurely due to clinical or administrative reasons.
End of trial procedures will be followed according to most up-to-date version of the LTHT SOP **QCRES_08 Researchers Guide to LTHT / UoL End of Trial Procedures** and MHRA guidance.
Once the end of study has been reached (see definition above), the end of trial form will be completed and submitted to the approving ethics committee and MHRA through the Integrated Research Application System (IRAS) within 90 days (or 15 days if premature termination).

A final research report will be submitted via IRAS within 12 months of the end of the study.

No participant will continue to receive the IMP following the end of the trial.

12.6 Insurance and Indemnity

Leeds Teaching Hospitals NHS Trust will act as the Sponsor for the trial. Insurance and indemnity for trial participants and NHS trial staff is covered within the NHS Indemnity Arrangements for clinical negligence claims in the NHS, issued under cover of HSG (96)48. There are no special compensation arrangements, but trial participants may have recourse through the NHS complaints procedures.

Leeds Teaching Hospitals NHS Trust is independent of any pharmaceutical company, and as such it is not covered by the Association of the British Pharmaceutical Industry (ABPI) guidelines for participant compensation.

13. Reporting and Dissemination of Findings

13.1 Authorship

Data generated from this study, subsequent analyses, manuscripts, and other outputs belong to the Study Team and the Chief Investigator.

Authors must demonstrate at least one of the following: substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND drafting the work or revising it critically for important intellectual content; AND final approval of the version to be published; AND agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

13.2 Dissemination of Findings

The results of the pilot will be presented at intellectual meetings e.g., the Intensive Care Society State of the Art meeting and the European Society of Intensive Care Medicine international meeting.

Write-ups will be submitted for publication in Critical Care peer reviewed literature. Material will be included in a thesis to be submitted to University of Leeds. Summaries of the trial will be made available to the participants (unless otherwise specified) and the investigators.

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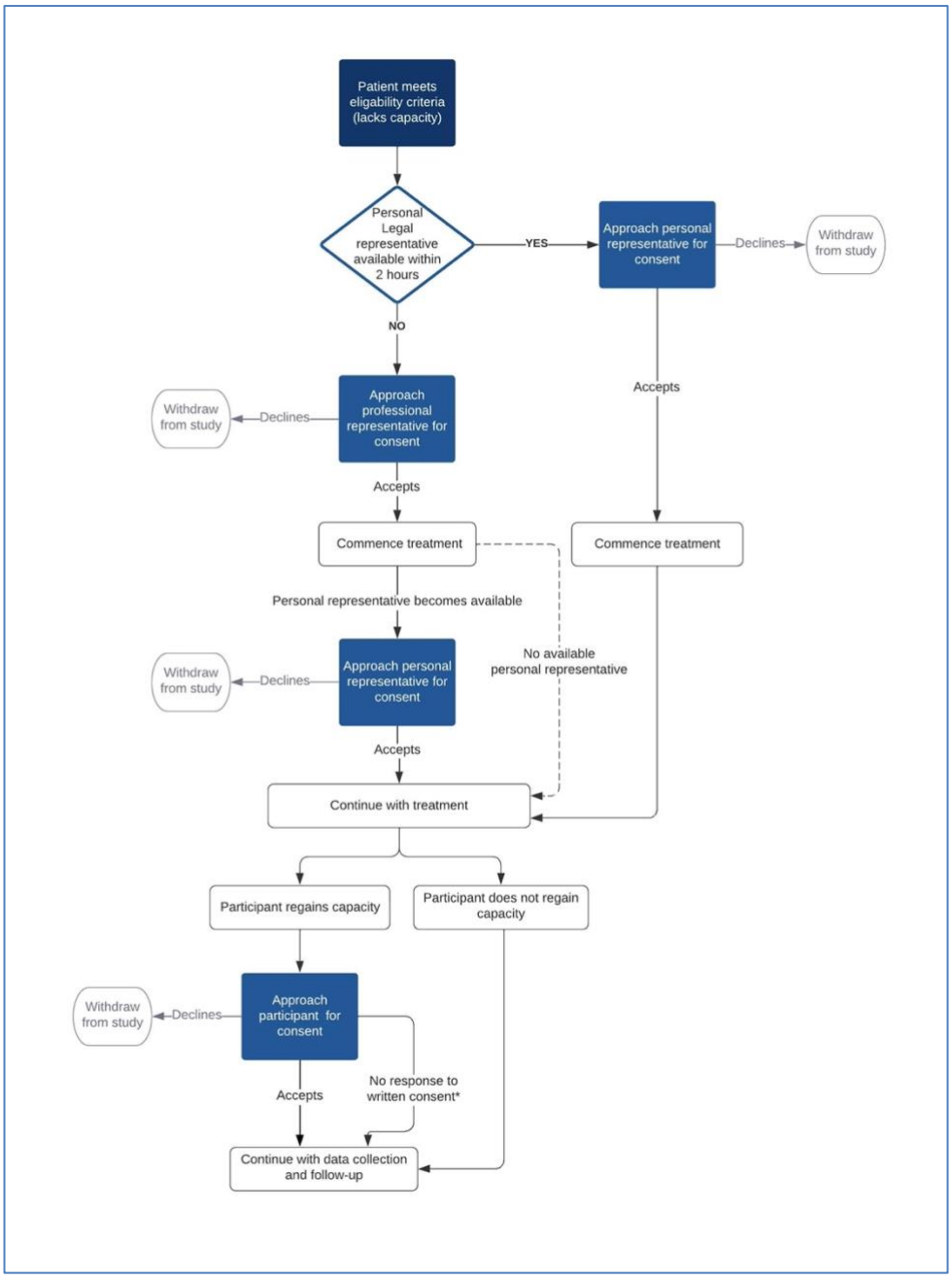
Appendix 1 – SHOCK-ICU: Consent Process



Appendix 2 – Weight-Based Ketamine Sedation Regime

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SHOCK-ICU
Ketamine Sedation Study

The Sedative and Haemodynamic Effects Of Continuous Ketamine Infusions on Intensive Care Unit Patients (SHOCK-ICU)

Weight-Based Ketamine Sedation Regime

- Dilute 2x 500mg/10ml vials (1000mg) with 80mls of 0.9% sodium chloride for infusion, providing an intervention concentration of **10mg/ml**.
- All participants will start on ketamine sedation at a rate of **1mg/kg/h**.
  If an accurate actual weight is not available, then an estimated weight may be used until an actual weight is recorded. An actual weight should be recorded at the earliest clinically appropriate timepoint. For participants with a **BMI >40kg/m²** then adjusted bodyweight must be calculated using the f**ormula on reverse.**
- The starting rate (mL/h) can be calculated as: **mL/h = starting dose / 10**
- After commencing ketamine sedation wean propofol according to flow charts.
- Titrate ketamine doses in increments of **10-50%** of current dose, according to target RASS, participant's sedation level, agitation, and response to ketamine.
- The maximum dose for any participant is **2.7mg/kg/h**. See table overleaf for example weight-based dosing.
- Boluses of 1ml (10mg) may be delivered via the infusion pump and repeated as necessary in order to maintain participant or staff safety where up-titration of sedation may not have desired effect within the necessary timeframe. **These must be recorded on the ICU chart**.
- Additional sedatives (including propofol) may be commenced/used as a bolus in emergency situations to maintain staff or patient safety, when a participant has reached the maximum dose of ketamine without satisfactory response, or if side-effects limit dose escalation. If requiring **2 or more boluses** of additional sedative, **consider commencing an infusion of additional sedative**.

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Example Dosing Based on Actual Body Weight:

	Actual weight (KG)													
	50	**55**	**60**	**65**	**70**	**75**	**80**	**85**	**90**	**95**	**100**	**105**	**110**	**115**	**120**
Starting dose (mg/h)	50	55	60	65	70	75	80	85	90	95	100	105	110	115	120
Starting rate (mL/h)	5	5.5	6	6.5	7	7.5	8	8.5	9	9.5	10	10.5	11	11.5	12
Max dose (mg/h)	135	148.5	162	175.5	189	202.5	216	229.5	243	256.5	270	283.5	297	310.5	324
Max rate (mL/h)	13.5	14.85	16.2	17.55	18.9	20.25	21.6	22.95	24.3	25.65	27	28.35	29.7	31.05	32.4

Adjusted Body Weight (ABW)* formula:

ABW = IBW + 0.25 x (actual body weight - IBW)

*For use in participants with BMI >40kg/m^2

Relevant cautions and Side-effects*

Common:
- Hallucinations, abnormal dreams, confusion, agitation
- Tachycardia
- Increased respiratory rate
- Nystagmus, abnormal eye movements, abnormal limb movements
- Erythema, rash morbilliform

Uncommon / rare:
- Anaphylaxis
- Arrhythmias / bradycardia / hypotension
- Apnoea
- Hypersalivation
- Haemorrhagic cystitis

***For full list please see study Reference Safety Information**

Trouble shooting

If you have urgent issues or concerns, then please ask a senior member of the medical or nursing team as soon as possible.

Agitation / tachycardia / high RR:
- Assess RASS and follow **initial management / maintenance flow charts**
- Consider other causes of agitation or tachycardia e.g. pain, delirium, awareness, ventilator dyssynchrony, underlying pathology
- Consider bolus of 10mg (1ml) ketamine or additional rescue sedatives if concerns over staff/patient safety
- Manage according to clinical assessment / local policy

Hypersalivation
- If problematic consider atropine / glycopyrronium

Arrhythmias
- Assess for **life threatening features** – if present manage as per ALS / local guidelines. If absent, investigate and mange as per unit guidelines.

If any adverse effects are noted or suspected, please document in the medical notes and notify the research team

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SHOCK-ICU Protocol v1.1

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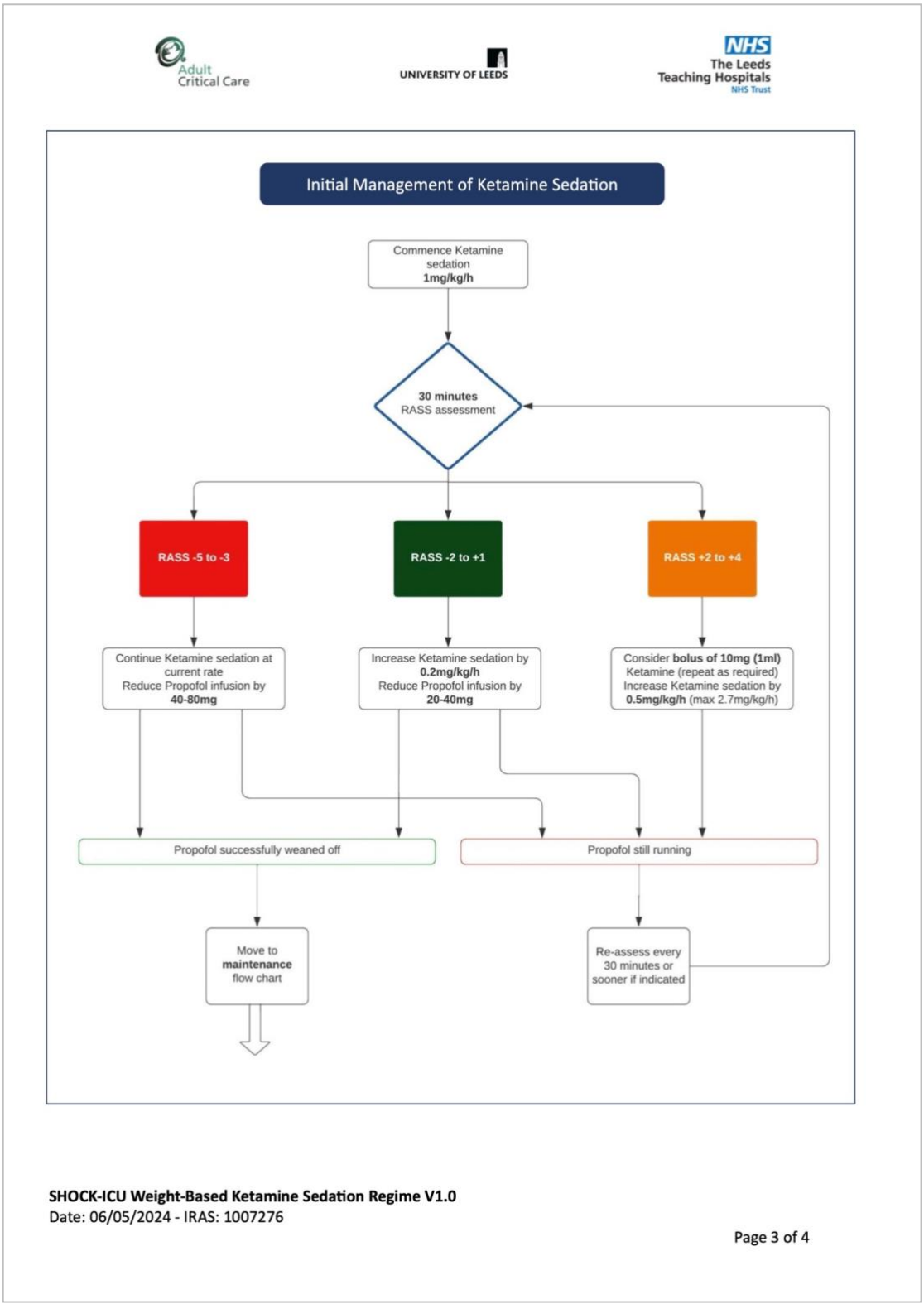

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SHOCK-ICU Protocol v1.1

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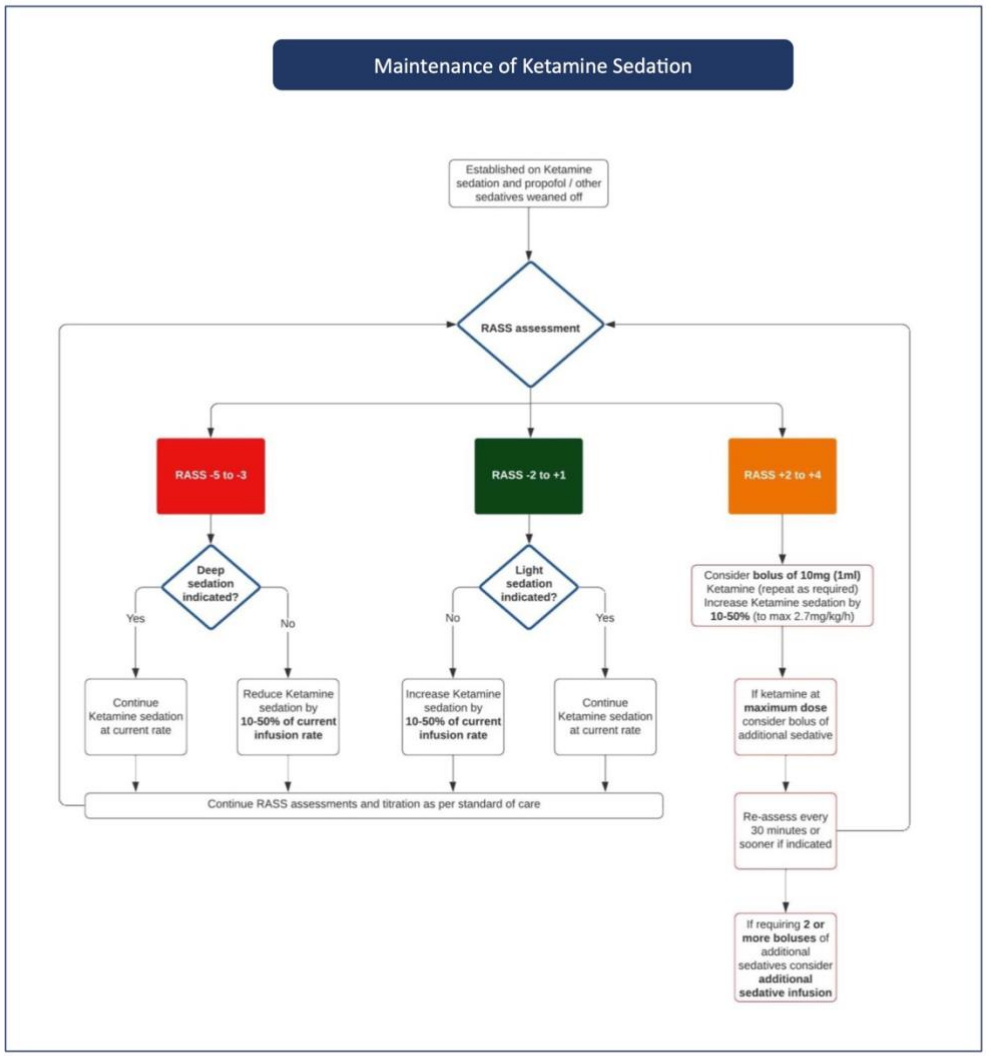

Please contact a member of the SHOCK-ICU research team if you have any queries. If you have urgent issues or concerns, then please ask a senior member of the medical or nursing team as soon as possible.

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Appendix 3 – LTHT Vasopressor Guidelines