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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: Clinical feasibility study protocol

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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 C Bellamy, joint clinical lead
- Dr Nicholas D Richards, Principal Investigator
- Professor Simon J Howell, Primary Supervisor
- Dr Ruben Mujica-Mota, Health Economics lead
- Dr Samuel Relton, Statistical lead
- Fiona Tingerides, Critical Care Pharmacy lead

Introduction

Background and rationale

Mechanical ventilation is a common intervention in Intensive Care Unit (ICU), with approximately 43.8% (88,259) of all patients admitted to ICU across the United Kingdom (UK) between April 2022 and March 2023 requiring mechanical ventilation.[1] Worldwide estimates from 2010 were that 20 million patients worldwide require invasive mechanical ventilation each year.[2] For most patients, medical sedation is a requirement for mechanical ventilation. Optimising sedation and analgesia is fundamental to the management of critically ill patients. Agent selection is a balance of risks and benefits. 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 and may be detrimental in certain population groups.[3-7]

A significant consequence of sedatives, in particular benzodiazepines significantly increase the risk of delirium in ICU.[8, 9] 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, post-traumatic stress disorder (PTSD), and increases mortality.[10, 11]

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.[12] Owing to its ability to stimulate the sympathetic nervous system, preserving heart rate and blood pressure, whist avoiding respiratory suppression, ketamine has become increasingly popular as an anaesthetic agent for emergency surgical procedures in hypotensive patients.[13, 14]

Although having been available in clinical practice for 50 years, and becoming licensed for major depressive disorder (MDD) treatment in 2019,[15] ketamine by continuous infusion remains a rarely used sedative to facilitate mechanical ventilation in UK practice.[16] A review of the literature revealed a paucity of high-quality evidence with very few well-designed prospective studies.[17] 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.

Given that psychological symptoms such as depression or PTSD following ICU admission are also common, ketamine's ability to rapidly provide antidepressant effects may be beneficial in post-ICU MDD when used as a sedative on ICU. [18-20]. Publications investigating the link between ketamine use on ICU (for analgesia, sedation, or otherwise) and depressive symptoms following or during ICU admission currently remain limited to case reports.[21] [22]

A large prospective randomised controlled trial (RCT) is required to provide robust evidence with regards to continuous ketamine sedation. However, given implementing ketamine sedation is likely to represent a complex intervention involving a novel sedation regime, significant barriers to implementation and integration into routine practice may exist. This study will address the first step by investigating the feasibility of conducting a future multi-centre, randomised trial of ketamine sedation on ICU.

Trial setting and design

The study is set in adult critical care and is a single-centre, single-arm, prospective, feasibility study of continuous ketamine infusions for primary sedation in patients undergoing mechanical ventilation on the intensive care unit (ICU).

This study is a clinical trial of an investigational medicinal product (CTIMP) and has been approved by the Medicines and Healthcare products Regulatory Agency (MHRA) (CTA 18166/0242/001-0001) and the Health Research Authority and Health and Care Research Wales (HRA and HCRW) (22/EE/0186). The study is registered on ISRCTN (ISRCTN13274002). The current version of the protocol (V1.1, 11/07/2024) is included in the supplementary materials.

Objectives

Primary objective

The primary objective is to establish the feasibility of using continuous ketamine infusions for sedation and the collection of potential key future endpoints to inform a

subsequent randomised controlled trial. This includes measures informing implementation trial methods, including: feasibility, deliverability, and quality of data collection procedures.

This will help distinguish between intervention failure and implementation failure, for example:

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 and ability to collect data).
3. Understanding 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.

Implementation trial method objectives:

This feasibility study will investigate the processes involved in delivering the intervention as intended, and to identify barriers and facilitators to intervention, 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 ketamine sedation.
- 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:

- Exploratory assessment of clinical efficacy markers through monitoring patient-based outcomes and clinical effects relating to the investigational medicinal product (IMP) throughout the patient's ICU stay, hospital stay, and at 90-day follow-up.

Patient and public involvement

PPI work has been carried out through previous ICU patient focus groups held in conjunction with the NIHR Biomedical Research Centre (BRC), Leeds. Six focus group participants described their experiences as patients in ICU, revealing a high incidence of negative recalled experiences, particularly with regards to delirium and sedation. Participants were asked to provide their thoughts on the rationale, acceptability, and design of the proposed study. All participants felt that the intervention was acceptable, even given the negative reputation of ketamine, and that they would be willing to receive a ketamine-based sedation regime if they were in ICU. This PPI work also helped refine design aspects such as plain English summaries, and considerations when gaining assent from relatives.

The study has also undergone 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)*' who confirmed this to be an area of high importance for patients and their relatives, and as having potential to significantly impact patient experience and outcomes.

Methods

Participants, interventions, and outcomes

Eligibility criteria

Table 1: Inclusion and Exclusion Criteria

INCLUSION CRITERIA	
1.	Patient requiring mechanical ventilation in an ICU
2.	Aged 18 or over
3.	Within 48 hours of starting mechanical ventilation in an ICU
4.	Requiring sedation with any agent
5.	Expected to require a total of 48 hours of mechanical ventilation or more in ICU
6.	Expected to require a further 24 hours of mechanical ventilation or more at the time of eligibility in the opinion of the responsible clinician
EXLUSION 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[29]*) 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. Guilain-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 a 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 mechanical ventilation 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.[23]

**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[24] 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.

The inclusion and exclusion criteria are in keeping with recent ICU sedation studies and were designed using a combination of expert opinion, retrospective review of the trial site patient population, literature review, and regulatory requirements.

Recruitment and screening

Patients requiring mechanical ventilation will be screened using the SHOCK-ICU eligibility checklist as soon after identification as possible to avoid delays in enrolment and initiation of IMP. Screening will continue for up to 48 hours post initiation of mechanical ventilation. Periods of mechanical ventilation occurring prior to admission, e.g. in operating theatres or emergency department will not count towards the 48-hour eligibility time, except mechanical ventilation occurring at an external ICU. Screening may occur multiple times during the 48 hours if appropriate.

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.

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.

Should a participant regain capacity during the study period, they will be asked to provide retrospective consent. This will occur as soon as practically possible upon identification of regaining capacity.

Participants, their legal representative, or their professional representative are free to withdraw from the study without reason at any point. Refusal to participate or withdrawal from the study will not impact any other aspects of care.

The consent process is illustrated in **Figure 1** in the appendix.

Interventions

Patients will commence intravenous infusion of open-label study drug according to a weight-based dose regimen (see **supplementary materials**). Dosing will be based on actual body weight unless BMI >40 Kg $M^{2\ -1}$, in which case an adjusted body weight (ABW) will be used.[25]

Clinical staff will transition patients to achieve sedation with the IMP as quickly as clinically feasible and safe, to replicate routine practice. Alfentanil will be used for analgesia alongside the IMP and titrated using clinical judgement to replicate standard care.

Patients will be titrated to achieve the default sedation target of most awake and comfortable state unless otherwise clinically indicated (Richmond Agitation Sedation Scale -2 to +1).

All participants should undergo regular attempts to wean from sedation and mechanical ventilation as appropriate and according to local ICU guidelines and standard of care procedures.

Endpoints

The endpoints used to assess the study objectives are detailed in **Table 1**. The potentially important clinical efficacy measurements are detailed in **Supplementary material - Table 2**. The proposed clinical efficacy measurements are derived 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 accurate collection is possible.

Table 2: 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 adverse events (AEs) / significant AEs (SAEs), adverse reactions (ARs), suspected unexpected serious AR (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

Sample size

As this is a feasibility study, a formal power calculation is not suitable. Estimated sample sizes were tested using Lewis and colleagues' method of hypothesis testing of feasibility outcomes based on progression criteria via the authors published application SS-Progress (https://ss-progress.shinyapps.io/ss_progress_app/).[26, 27] Based on this method, 59 potential participants would need to be screened and 30 participants would need to be enrolled to power assessments of progression criteria at both participant and intervention level with a power of ≥92% (see Figure 4 in the supplementary material). Therefore, the study aims to enrol 30 participants.

Assignment of intervention

Allocation / Blinding

This is an open-label, non-randomised study.

Data collection, management, and analysis

Data collection methods

Data will be collected using SHOCK-ICU case report forms (CRF) at baseline, daily until off mechanical ventilation for >48h, ICU discharge, and 90-days.

Statistical analysis

Simple descriptive statistics (frequencies, percentages) will be used to assess the study endpoints and used to inform predefined progression criteria for the study protocol.

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 and Intensive Care National Audit and Research Centre (ICNARC).

Progression criteria will be assessed according to the predetermined thresholds set out in Table 4 in the supplementary materials.

Monitoring

A trial specific monitoring and reporting plan has been agreed with the sponsor and regulatory bodies, including of AEs, SAEs, ARs, SUSARs, and urgent safety measures.

Ethics

Research ethics approval

The trial will be conducted in accordance with the UK Policy Framework for Health and Social Care Research 2018, the Medicines for Human Use (Clinical Trials) Regulations 2004 and subsequent amendments, Data Protection Act 2018, 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 study been approved by the Medicines and Healthcare products Regulatory Agency (MHRA) (CTA 18166/0242/001-0001) and the Health Research Authority and Health and Care Research Wales (HRA and HCRW) (22/EE/0186). The study is registered on ISRCTN (ISRCTN13274002).

Confidentiality

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.

Dissemination Plans

Data depositing

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 and will be archived using the LTHT approved external archiving service for at least 25 years after completion or discontinuation of the study.

Publications

The results will be submitted for publication in relevant peer reviewed literature and for presentation at meetings. 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 and the investigators.

Conflicts of Interest

NR (principal investigator) is in receipt of the Intensive Care Society Road to Research Award to fund activities relating to this study.

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Supplementary Material

Figure 1: SHOCK-ICU Consent Process

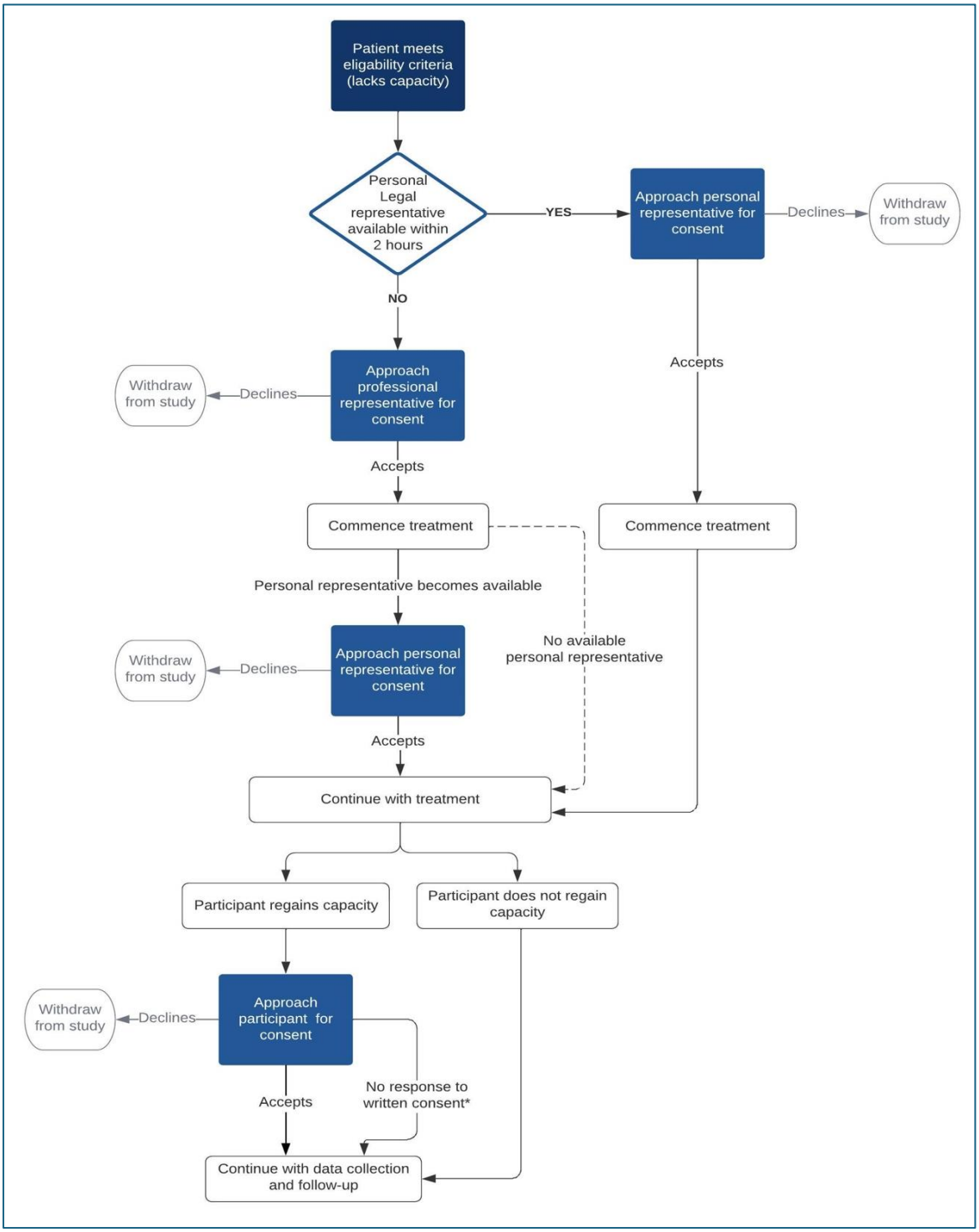

Figure 2: Weight-based Sedation Regime (Initial management)

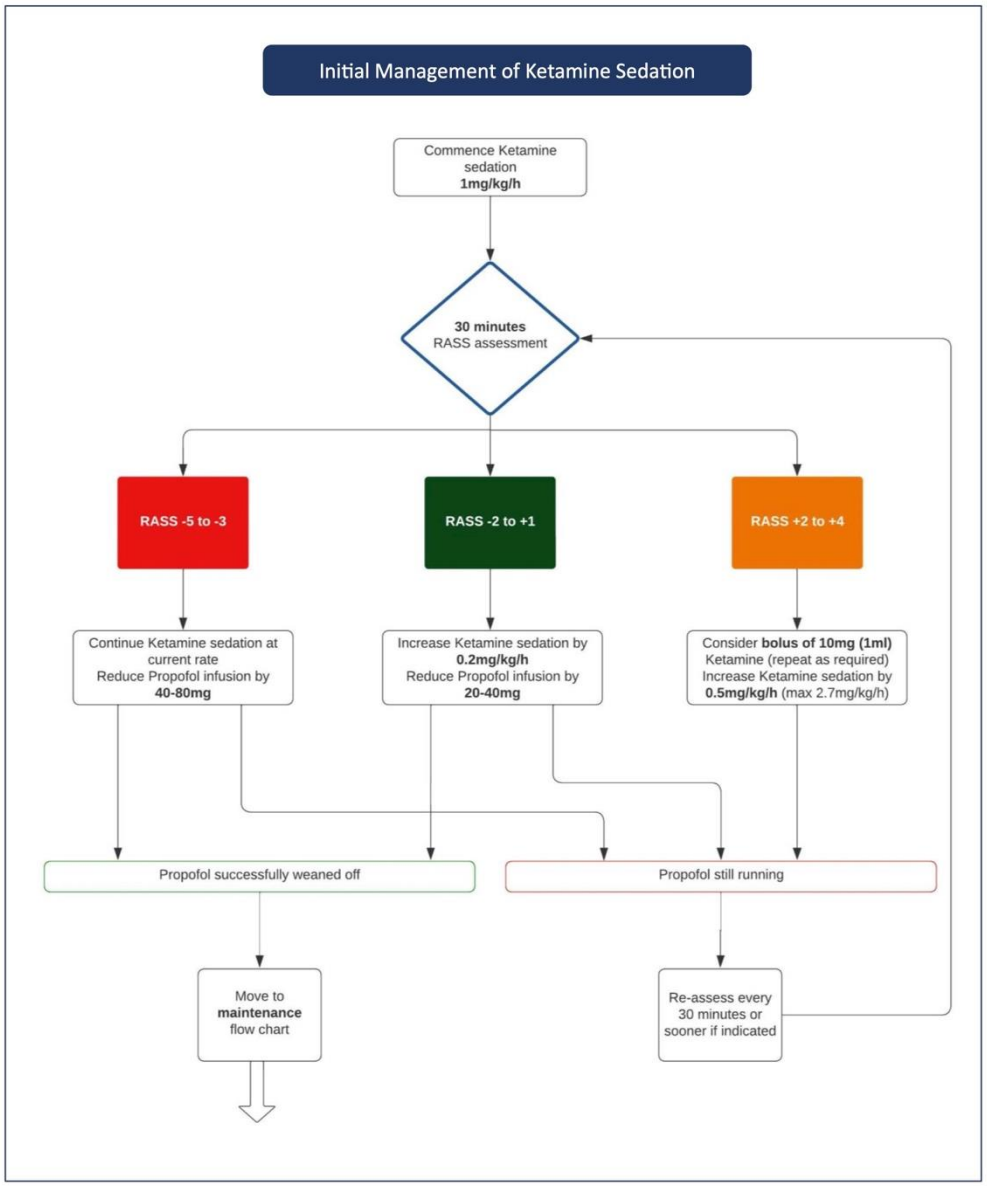

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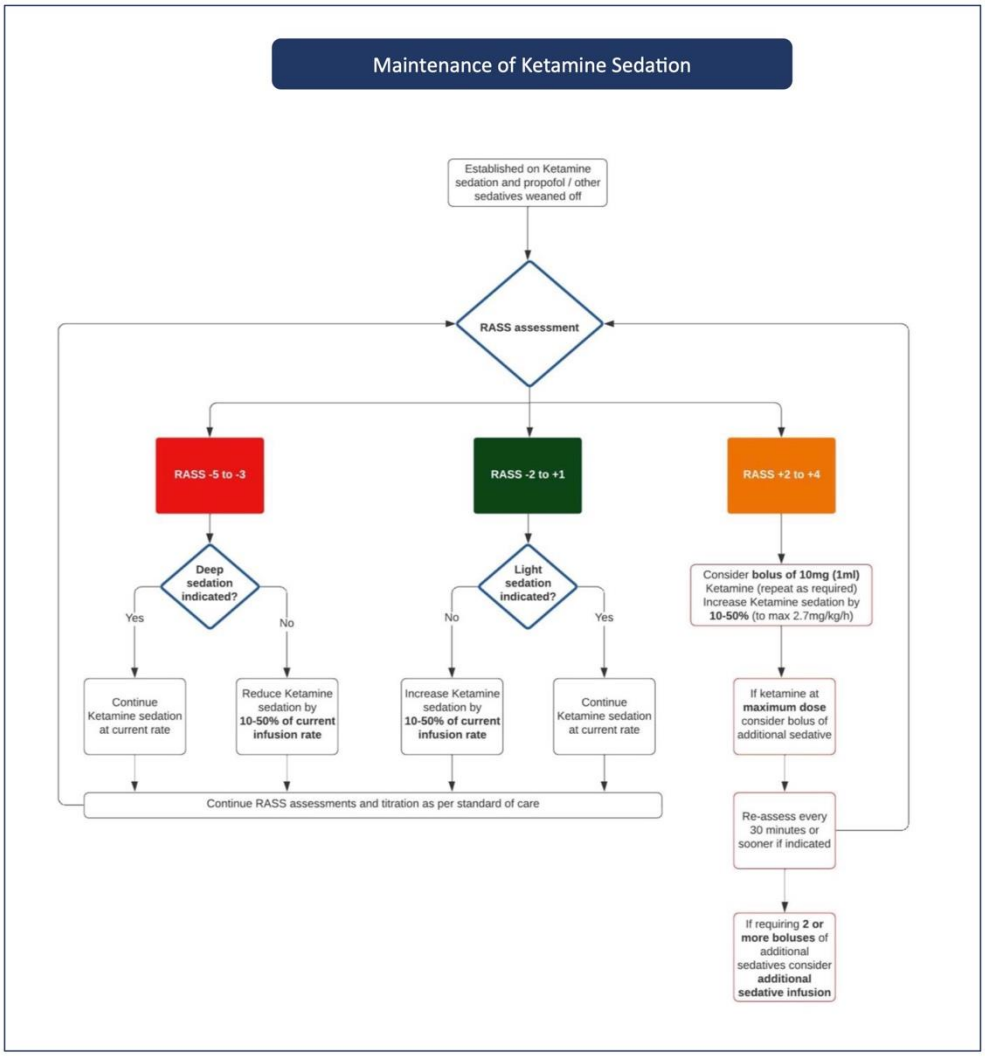
Figure 3: Weight-based Sedation Regime (maintenance)



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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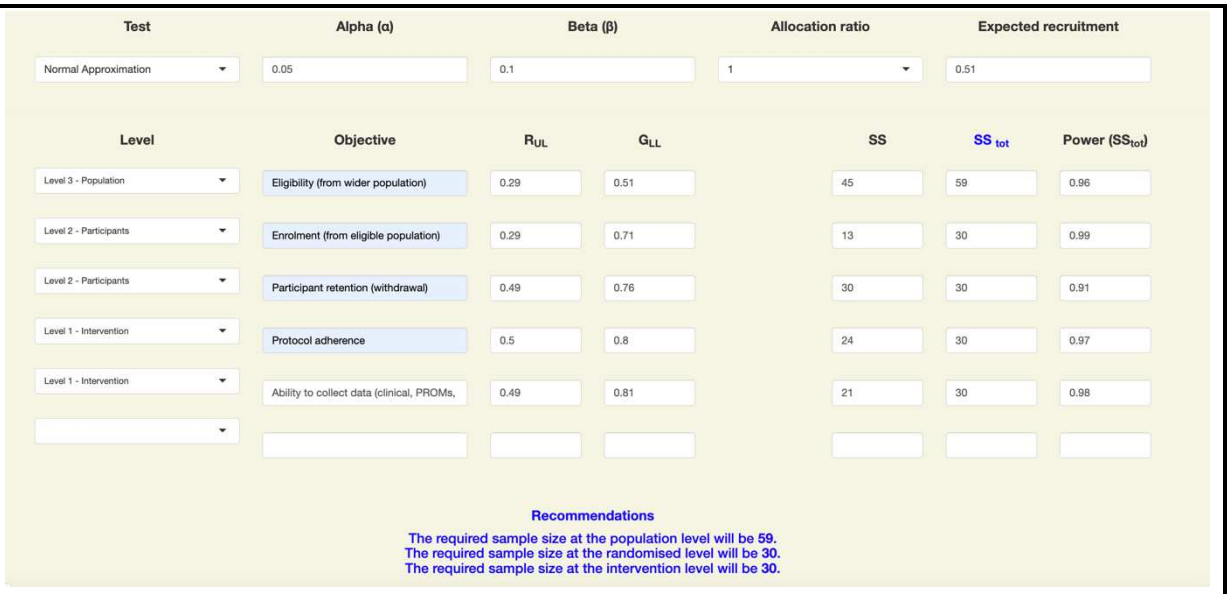
Figure 4: Sample Size Calculations



Test	Alpha (α)	Beta (β)	Allocation ratio	Expected recruitment
Normal Approximation	0.05	0.1	1	0.51

Level	Objective	R_{UL}	G_{LL}	SS	SS_{tot}	Power (SS_{tot})
Level 3 - Population	Eligibility (from wider population)	0.29	0.51	45	59	0.96
Level 2 - Participants	Enrolment (from eligible population)	0.29	0.71	13	30	0.99
Level 2 - Participants	Participant retention (withdrawal)	0.49	0.76	30	30	0.91
Level 1 - Intervention	Protocol adherence	0.5	0.8	24	30	0.97
Level 1 - Intervention	Ability to collect data (clinical, PROMs,	0.49	0.81	21	30	0.98

Recommendations

The required sample size at the population level will be **59.**
The required sample size at the randomised level will be **30.**
The required sample size at the intervention level will be **30.**

Sample size calculation using SS Progress App (available from https://ss-progress.shinyapps.io/ss_progress_app/) created by Lewis and colleagues.[26, 27]

Table 3: 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 mechanical ventilation >48h
Requirement for 'rescue' sedation and indication	Daily from start of IMP until off mechanical ventilation >48h
Requirement for muscle relaxant and indication	Daily from start of IMP until off mechanical ventilation >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 mechanical ventilation >48h
Incidence and indication for deep sedation	Daily from start of IMP until off mechanical ventilation >48h
Duration of mechanical ventilation, time to extubation from cessation of IMP	End of study period
Requirements for tracheostomy	Daily from start of IMP until off mechanical ventilation >48h
Incidence of unplanned extubation or decannulation, requirements for re-intubation or decannulation	Daily from start of IMP until off mechanical ventilation >48h
Incidence of significant hypotension, hypertension, bradycardia, tachycardia, or arrhythmias* and details of each	Daily from start of IMP until off mechanical ventilation >48h
Requirement for vasopressors	Daily from start of IMP until off mechanical ventilation >48h
Cumulative, peak, trough bolus, and average dose of vasopressors	Daily from start of IMP until off mechanical ventilation >48h

Incidence delirium	Daily from start of IMP until off mechanical ventilation >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 mechanical ventilation >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).

Table 4: Progression Criteria

Aspect of the trial		Threshold	Progression
Population level	Eligibility (% of screened patients meeting eligibility)	>50%	Go
		30-50%	Amber
		<30%	Stop
Participant level	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
Intervention level	Protocol adherence	>80%	Go
		50-80%	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