Does in-bed **Cycl**ing delivered within 48 hours of mechanical ventilation, r**E**duce the occurrence of **D**elirium in critically ill patients **(FRECycl-D):** A mixed-methods **F**easibility **R**andomised controlled trial.

STATISTICAL ANALYSIS PLAN

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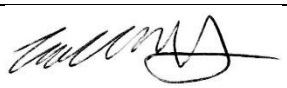
SAP oversight	Trial Statistician	Jade Chynoweth	University of Plymouth Medical Statistics Fellow		16JUN2025
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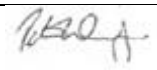
SAP oversight (mechanistic sub-study)	Professor of Health Sciences & Bioengineering	Professor Peter Worsley	University of Southampton.		03/07/2025
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ABBREVIATIONS

ABGs	Arterial Blood Gas
AE	Adverse event
BMI	Body Mass Index
CAM-ICU	The Confusion Assessment Method for the Intensive Care Unit
CCI	Charlson Comorbidity Index
CFS	Clinical Frailty Scale
CI	Chief Investigator
CI	Confidence Interval
CRP	C-Reactive Protein
COS	Core Outcome Set
CT	Computed Tomography scan
DOB	Date of birth
eCRF	electronic Case Report Form
ELISA	Enzyme-Linked Immunosorbent Assay
FAM-CAM	Family Confusion Assessment Method
FSS-ICU	Functional Status Score for the Intensive Care Unit
GCP	Good Clinical Practice
HRA	Health Research Authority
ICU	Intensive Care Unit
IL	Interleukin
IQR	Interquartile Range
ISF	Investigator Site File
IMV	Invasive Mechanical Ventilation

MCID	Minimum Clinically Important Differences
MRI	Magnetic Resonance Imaging
MOCA	Montreal Cognitive Assessment
6MWT	6 Minute Walk Test
NHS	National Health Service
NIHR	National Institute for Health and Care Research
NIRS	Near-Infra-Red Spectroscopy
NRES	National Research Ethics Service
PAG	Public Advisory Group
PenCTU	Peninsula Clinical Trials Unit
PES	Plain English Summary
PI	Principal Investigator
PIS	Participant/Consultee Information Sheet
PPIE	Patient and Public Involvement and Engagement
QALYs	Quality Adjusted-Life Years
QoL	Quality of Life
RCT	Randomised Controlled Trial
R&D	NHS Trust Research & Development Department
REC	Research Ethics Committee
rSO2	Regional cerebral oxygenation
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction

SD	Standard Deviation
SF-36	Short Form 36
SOFA	Sequential Organ Failure Assessment
SOP	Standard Operating Procedure
UHP	University Hospitals Plymouth NHS Trust
VBGs	Venous Blood Gases

1.0 INTRODUCTION

1.1 BACKGROUND

Delirium is a severe neuropsychiatric clinical state.[1] It presents as an acute onset of cognitive deficits such as inattention, and fluctuant levels of consciousness from near-coma to severe agitation.[2] Moreover, patients commonly experience psychotic symptoms.[3] Delirium is associated with increased mortality and morbidity e.g., long-term cognitive decline (at 3-and-12- months), poor memory, hallucinations, attention difficulties and patient-reported poor quality of life (QoL) following ICU discharge.[4,5] A systematic review of international studies estimated substantial economic costs were associated with delirium.[6] Therefore, there is a global drive to increase delirium research to relieve the persistent burden of long-term cognitive impairment as a consequence of delirium.[7] Patients admitted to an intensive care unit (ICU), requiring invasive mechanical ventilation (IMV), have the highest incidence of delirium (50-80%) in the ICU.[1,8] From 2022-23, there were 189,141 ICU admissions in the UK, and of these 80,902 patients (43%) received IMV within 24 hours of admission.[9] Early mobilisation is “a type of intervention within rehabilitation that facilitates the movement of patients and expends energy with a goal of improving patient outcomes”.[10] Preliminary evidence suggests early mobilisation is associated with reduced delirium in the ICU in groups receiving similar sedation regimens.[11,12] To date, the effectiveness of this has not been fully investigated.[13] Moreover, there are many barriers to IMV patients receiving early mobilisation.[14,15] The high incidence of delirium in IMV patients may be the result of the lack of early mobilisation.

1.2 Rationale: Feasibility Trial

Currently, the origin of delirium is unclear. However, there are multiple potential causes that may explain the pathophysiology behind the neurological dysfunction leading to delirium e.g., hypoxia and inflammation.[1,16-19] Moreover, there are a number of predisposing (age, cognitive impairment) and precipitating (IMV, immobilisation) factors for the development of delirium.[20] Evidence shows ICU patients are exposed to more than 10 of these risk factors.[1] Best practice guidelines suggest a multi-component approach comprising of pharmacological and non-pharmacological interventions to prevent and manage delirium in the ICU e.g., the ABCDEF Bundle.[21] Early mobilisation is a component of the bundle. However, evidence demonstrating the effectiveness of early mobilisation (as a stand-alone intervention) to reduce and/or prevent delirium is lacking.[13] A recent updated systematic review and meta-analysis suggested that in-bed cycling may address some of the barriers such as IMV to mobilising critically ill patients.[22] Findings demonstrated that in-bed cycling may improve physical function at ICU and hospital discharge and potentially reduce length of ICU and hospital length of stay. However, none of the outcomes included delirium. Due to the low certainty evidence, the authors suggested more high-quality trials are needed to investigate the effectiveness of this method of early mobilisation. Moreover, qualitative research alongside trials may importantly demonstrate the acceptability and/or value of research investigating complex interventions.[23]

1.3 Rationale: Mechanistic sub-study

Mechanisms of bioenergetic insufficiency have been described as potential causes for the development of delirium.[1] These include the cerebral metabolic insufficiency hypothesis where in high-risk patients (e.g., patients requiring IMV due to respiratory failure), delirium may be caused by brain dysfunction following a failure to meet the brain's energy demands. For example, hypoxaemia may induce brain hypoxia and therefore brain dysfunction. A systematic review identified associations between low levels of regional cerebral oxygenation (rSO_2) in patients diagnosed with delirium compared to non-delirious patients in the ICU.[24] Moreover, evidence suggests severe systemic inflammation may result in a neuroinflammatory response leading to the development of delirium in the 'vulnerable brain'. Preliminary data has demonstrated that biomarkers of systemic inflammation, astrocyte and glial activation have been associated with delirium duration, delirium severity and in-hospital mortality in patients admitted to the ICU.[1,25] The aim of the mechanistic sub-study is to explore the impact of early (≤48 hours following MV) in-bed cycling upon cerebral

oxygenation and, systemic inflammation and neuroprotection. These data will be used to describe the physiological response to the intervention and potential associations with clinical outcomes i.e., delirium. Public representatives suggested that these findings could generate more knowledge about delirium and the role of early mobilisation in preventing and/or reducing delirium in the ICU.

2.0 Objectives: Feasibility Trial

Primary objectives

To evaluate the feasibility of early (≤ 48 hours following IMV) in-bed cycling to reduce delirium in IMV patients. Semi-structured interviews will be carried out with the key stakeholders (trial participants, their relatives and carers) to determine the acceptability of the research procedures e.g., the intervention.

Secondary objectives

A variety of clinical outcomes have been selected to explore how delirium can be recorded in IMV patients (see section 6.1). These data will contribute towards the selection of the primary outcome measure for the future definitive trial. Moreover, a selection of patient-focused outcomes to measure quality of life will be carried out (see section 6.1). These will be used to inform the decision for the selected measure of health-related quality of life to complete the Quality Adjusted Life Years (QALYs) assessment as part of the Health Economic evaluation for the full RCT.[26] The relevant core outcome sets (COS) have guided the choice of delirium and functional outcome measures.[27,28]

2.1 OBJECTIVES: MECHANISTIC SUB-STUDY

To explore the impact of early in-bed cycling upon brain oxygenation, systemic inflammation and neuroprotection in patients requiring IMV and to describe potential associations between these, clinical outcomes (e.g., delirium duration, delirium severity) and long-term outcomes (e.g., cognition, presence of delirium). No single biomarker has been associated with the precipitation of and/or predisposition of delirium.[25] Therefore, a panel of biomarkers related to systemic inflammation, neuroprotection and astrocyte activation have been selected with consideration of the current evidence and expert opinion for the purposes of this research (see section 6.1).[25]

3.0 STUDY METHODS

A multi-site feasibility RCT including a mechanistic sub-study and an embedded qualitative interview study. The results of this feasibility trial will be evaluated alongside the PRECIS-2 tool to guide the future design (e.g., pragmatic vs explanatory) for the future definitive trial.[29]

3.1 TRIAL DESIGN

Intervention

Following written obtained consent/consultee agreement, participants enrolled in the trial will be randomised in a 1:1 ratio to receive either early (within ≤ 48 hours following IMV) in-bed cycling in addition to standard care or standard care alone. The intervention group will involve in-bed cycling five days per week for a maximum of 14 days or until out-of-bed mobilisation commences (whichever comes first) in addition to standard ICU care. Out-of-bed mobilisation is defined as 'any activity where the patient sits over the edge of the bed (dangling), stands, walks, marches on the spot or sits out of bed'.[30] If the patient is readmitted to the ICU within 90 days of randomisation, they should recommence the in-bed cycling intervention in the ICU up until day-14 (in total) or out-of-bed mobilisation starts (whichever comes first).

Comparator

Standard care only. Across the UK, early mobilisation initiated within four days of ICU admission is unusual. Generally, non-cycling exercise is initiated in IMV patients e.g., assisted-limb movement. Currently, the participating sites do not use in-bed cycling within 48 hours of IMV. If the patient is readmitted to the ICU within 90 days of randomisation, they should recommence standard care in the ICU up until day-14 (in total) or out-of-bed mobilisation starts (whichever comes first).

Participating sites will follow and record a targeted sedation protocol for the intervention and comparator group using the Richmond Agitation Sedation Score (RASS -4 to +2) to minimise confounding factors.

The mechanistic sub-study (single site)

Intervention group

Following written obtained consent/consultee agreement, continuous rSO_2 using the NIRS INVOSTM 7100 device (CE marked with class IIB medical device status) will be measured (as per intended purpose). The Chief Investigator will place one soma sensor on the left and one on the right side of the participants forehead. Each infrared sensor is connected to the device

for recording data. These data will be collected via each sensor (left and right) continuously at baseline, during in-bed cycling and at recovery to provide real-time estimated values of brain tissue oxygenation for the first three days from randomisation. The percentage of continuous rSO2 will be recorded at baseline (resting state), during (intervention/standard care) and on recovery.

Arterial blood gases (ABGs) and venous blood gases (VBGs) will measure oxygen indices and blood lactate levels. ABGs and VBGs will be taken from an intravenous catheter and arterial catheter (in place as part of routine ICU care). The Chief Investigator will take ABGs and VBGs 10 minutes before commencing in-bed cycling whilst the participant is at rest, every 10 minutes during in-bed cycling and 10 minutes after in-bed cycling for the first three days from randomisation.

The additional (venous) blood samples will be collected by the Chief Investigator whilst the participant is in a resting state (i.e., not cycling in-bed) at days 0,3,5. The UHP pathology laboratory will support the collection, spinning and freezing of all blood samples to spin in a centrifuge (at 1600g and 18 °C), transport into five aliquots (500 microlitres per aliquot) per sample and freeze at -80° within four hours of taking the sample as standard practice. A volume of 10 millilitres of blood serum will be taken from each participant at each time point. The samples will be kept in the UHP pathology laboratory until the end of the study. At this point, a courier service will transport samples to the Birmingham Clinical Immunology Service diagnostic laboratory to measure sample concentrations using Enzyme-Linked Immunosorbent Assay (ELISA), a standard clinical assay and a fluidic-based assay run on the Luminex platform analyses standardised methods.[31]

Comparator group

For the first three days from randomisation, the Chief Investigator will collect resting (baseline) rSO_2 (as described above). The Chief Investigator will take blood samples from participants (VBGs, ABGs) for the first three days at comparable timepoints to the intervention group. Additional (venous) blood samples will be collected from the participant whilst at rest on days 0,3, and 5. These will be used to analyse an identical biomarker profile and to provide between group differences.

3.2 Randomisation

Eighty-four consenting participants will be randomised using permuted block-randomisation in a 1:1 ratio, stratified according to site (Derriford hospital, Torbay hospital, Blackpool hospital), to either the intervention group or the comparator group. These processes will use the randomisation module in the REDCap database provided by the Peninsula Clinical Trials Unit (PenCTU). The Chief Investigator will follow-up all participants in both groups at 90-days from randomisation (via telephone or in-person).

Due to the nature of the intervention, participants and the research team will not be blinded to the intervention. Moreover, the Chief Investigator as part of their doctoral training programme, will complete all data collection at 90-day follow-up for both groups. Therefore, blinding of outcome assessments will not be possible.

3.3 Sample Size

The aim of this multi-site feasibility RCT is to provide estimated rates of feasibility outcomes (recruitment, retention, fidelity). For a feasibility RCT designed with 80% power and one-sided 5% alpha, a sample size of 84 participants will be recruited within 18 months across all sites (42 per group). This equates to recruiting 1.16 participants per week. Moreover, the sample size will allow for a loss to follow-up due to mortality (approx. 30%).[32] The sample size calculations have been guided by best practice recommendations for determining sample size using a Red, Amber, Green (RAG) system, revised and agreed upon in consultation with the PenCTU and expert opinion in relation to the trial methodology and population of interest (see table 1. Appendix 1).[33] Moreover the proposed RAG criteria were revised in consultation with the PenCTU and expert opinion to ensure known levels of recruitment uptake, participant retention and intervention fidelity in trials carried out in the ICU across the UK were taken into consideration. The agreed RAG criteria are outlined in Table 2 below.

TABLE2. RAG criteria

	Green (Go – proceed with RCT)	Amber (Amend – proceed with changes)	Red (Stop – do not proceed unless changes are possible)
Proposed recruitment rate (%)	>20%	10-20%	<10%
Retention rate (%)	≥85%	65-85%	<65%
Intervention fidelity (%)	≥75%	50-75%	<50%

The RAG system will guide progression to a definitive trial of effectiveness. These criteria will be consulted across the length of the feasibility trial by the key stakeholders (Chief Investigator, PI, PenCTU, R&D, Trial Steering Committee) and considered alongside the qualitative interview study results.[23,33] This estimated sample size aims to ensure areas of uncertainty are tested. Moreover, the estimated sample size will ensure an appropriate sample population for the mechanistic sub-study and qualitative interviews are achieved.

3.4 Framework

The feasibility methodology of this trial is limited to a descriptive interpretation of results. Therefore, data will not be analysed using a hypothesis testing framework (e.g., the superiority framework) for statistical analysis which defines a clear statement of belief (e.g., treatment A is better than treatment B).

3.5 Statistical Interim Analysis & Stopping Guidance

No formal statistical interim analyses are planned therefore the RAG criteria will not be used to inform stopping guidance for this feasibility study.

3.6 Timing of Final Analysis

The end of the study period is defined as the date at which the last participant has completed follow-up at 90 days from randomisation. Once the trial database is locked, the participants' data will be exported into SPSS for the Chief Investigator to complete the statistical analysis. All outcomes will be analysed by the Chief Investigator at the end of the trial period.

3.7 Timing of Outcome Assessments

Table three (appendix 2), outlines the data and specific outcome measures collected at the relative timepoint (screening, baseline), day 0-14 (from randomisation), day 30 (from randomisation), day 90 (from randomisation)).

4.0 STATISTICAL PRINCIPLES

This feasibility study will use a preliminary assessment of the data to inform a definitive trial. Therefore, data will be descriptively analysed and presented for the feasibility trial data. Hypothesis testing will be carried out for exploratory purposes of the biological data in the

mechanistic sub-study only. The statistical analysis plan (SAP) will guide the analysis and reporting of the trial data. Baseline demographic, clinical characteristics and missing data will be presented to indicate between group differences. Medians (interquartile range, range) will be reported for ordinal data, mean (standard deviation, range) for continuous data and raw count (number, %) for nominal data. Frequency distribution plots will be used to test for normality. Parametric descriptive analysis will be carried out for normally distributed data e.g., means, standard deviations (SD) and ranges for continuous outcomes where the distribution appears approximately normally distributed. Descriptive analysis will be completed where there is approximately no normal distribution e.g., medians, IQR, ranges for continuous outcomes and raw count (%) for categorical outcomes will be presented.

Multiple precipitating and predisposing factors such as sedation have been identified for the development of delirium in the ICU.[20] These may be considered as potential confounding factors. Potential confounding factors will be descriptively reported in both groups e.g., sedation, death.

4.1 Confidence Intervals

The outcomes of this trial are exploratory due to the feasibility methodology. Hypothesis testing will not be used for analysis of the main trial data therefore findings will not be interpreted as definitive results. Ninety-five percent CIs will be used to describe variability of feasibility outcomes. Group comparison of 95%, 85% and 75% CIs will assess outcomes for potential signal effect (secondary outcomes, mechanistic outcomes only). The CIs of the potential primary outcome (delirium) will be plotted across baseline (ICU admission), day 14, day 30 and day 90 timepoints. The CIs will be used by the key stakeholders to explore the potential Minimum Clinically Important Differences (MCID).[34] This may provide an estimation of the range of possible treatment effects. These data will inform the chosen primary outcome measure of delirium in an IMV population, appropriate sample size (section 6.7) and progression criteria for the future definitive RCT (section 5.6).[35,-37] Moreover the standard deviation will be calculated for the primary outcome at each timepoint (baseline, day 14, day 30, day 90) in order to determine the sample size of the future definitive trial.

4.2 Non-Compliance and Protocol Deviations

All protocol non-compliance, deviation and/or withdrawal will be recorded by the research team as per Good Clinical Practice (GCP), in the electronic Case Report Form (eCRF). A withdrawal will be defined as participant withdrawal from the trial in full. Where participants

wish to continue in the trial but withdraw from aspects of the trial this will be described according to the adherence criteria (see below). If the trial protocol were not delivered e.g., due to staff availability, this will be described within the adherence criteria. Where participants are withdrawn from the trial due to death, this will be described as the number and percentage of deaths between each randomised group. A serious breach of protocol is defined as frequent protocol deviations. All protocol non-compliance, deviation and/or withdrawal data will be reported to the Trial Steering Committee (TSC) and Trial Management Group (TMG). Where a serious breach of protocol is identified by the TSC and TMG, these will be reported by the Sponsor to the Research Ethics Committee.

4.3 Adherence

Adherence to the intervention protocol of the randomised groups will be monitored across the full trial period. Adherence will be defined as the number and percentage of participants who completed the allocated trial protocol where they were eligible at the present time. This will be described across each time point i.e., day 0-14, day 30 and day 90 from randomisation. See tables 4-8 (appendix 3) for details.

4.4 Analysis Populations

An Intention to Treat (ITT) analysis of the descriptive statistics will be carried out. Missing data will not be imputed. Outcomes with missing data will not be included in the ITT. Therefore, a per protocol analysis will be completed as a sensitivity analysis. [35,36] The sensitivity analysis will in part, analyse participants who tolerated the intervention in full versus control (including those participants who did not tolerate the intervention in full). This will explore potential phenotypes of patients who may benefit/not benefit from the intervention. Safety data will be summarised for all participants enrolled in both groups across the length of the trial. These data will include pre-defined adverse events (AEs) related to the intervention and serious adverse events (SAEs).

5.0 TRIAL POPULATION

5.1 Screening Data

All patients admitted to the Derriford, Torbay and Blackpool trial sites will be screened by the local site ICU clinical team and research team (Chief Investigator, PI, research nurses) for eligibility in the FRECycl-D trial using strict inclusion and exclusion criteria detailed below.

5.2 ELIGIBILITY

Inclusion Criteria:

- Adults (aged 18 years and above)
- Unplanned ICU admissions
- IMV initiated within ≤48 hours of ICU admission.
- Expected to remain on IMV >24 hours.

Exclusion Criteria:

- Contra-indications to mobilisation
- Known or suspected cognitive impairment and/or learning difficulties.
- Plan is for palliation / withdrawal of treatment.
- Immobile prior to ICU admission
- Body weight over the device safety limit (≥135 Kg)
- BMI <18.5 kg/m^2
- Planned ICU admission.
- Pregnancy
- Prisoners

5.3 RECRUITMENT

Data concerning participant flow through the trial from screening to follow-up will be reported using the CONSORT 2010 statement as per figure 1 (appendix 4).[38]

In particular, the following data will be collected and provided, where applicable:

- Number of patients screened for eligibility
- Number of patients identified as eligible to participate in the trial
- Number of patients (percentage of eligible) ineligible (with reasons where available)
- Number of patients (percentage of eligible) declined to participate (with reasons where available)
- Number of patients (percentage of eligible) consented to participate
- Number of participants (percentage of consented) who completed baseline assessments (day 0)
- Number of participants (percentage of consented) who did not receive the intervention.(with reasons where available)

- Number of participants (percentage of consented) who did not tolerate the intervention in full (with reasons where available).
- Number of participants (percentage of consented) who completed in-hospital follow up (day 30)
- Number of participants (percentage of consented) who complete 90-day follow up
- Number of participants (percentage of consented) lost to follow-up
- Number of participants (percentage of consented) that fully withdrew from the trial
- Number of participants (percentage of consented) included in final analysis.

5.4 Withdrawal/Follow-up

This study is a feasibility RCT therefore participant discontinuation, withdrawals (in-bed cycling, mechanistic study, qualitative study, trial protocol) and follow-up will be recorded as per the primary objectives. Reasons for discontinuation/withdrawal will be documented. See the FRECycl-D trial protocol version 8.0 (11.06.2025). These data will be presented in the Consort flow diagram (Figure 1, Appendix 4).

5.5 Baseline Characteristics

Baseline demographic and clinical characteristics will be summarised to evaluate between group differences and describe the sample population (*see SOP 014 and the FRECycl-D trial protocol version 8.0, 11.06.2025*). The baseline characteristics that will be collected are presented in Table 9 below.

TABLE 9. BASELINE CHARACTERISTICS
DATA TYPE
Age (years)
Biological sex
Ethnicity
Comorbidities (Charlson Comorbidity Index)
Dependency Prior to ICU admission (Clinical Frailty Scale)
Body Mass Index (BMI) (kg/m^2)
Reason for ICU admission
Severity of illness (SOFA score)

6.0 ANALYSIS

The data collected in the FRECycl-D trial will be analysed by the Chief Investigator using descriptive statistics with support from the Peninsula Clinical Trials Unit (PenCTU). No hypothesis testing will be carried out due to the feasibility trial methodology.[39] However, exploratory analysis of the mechanistic outcomes will be conducted strictly for hypothesis generating purposes to inform future trial design.[34,40] These data will be analysed by the Chief Investigator with support from Associate Professor Adrian Shields (Birmingham Immunology Service) and Professor Peter Worsley (University of Southampton).

6.1 Outcome Definitions

Feasibility outcomes

The following feasibility outcomes will be described by site and in total.

- Recruitment rate (% of participants enrolled *vs* % of participants eligible),
- Retention rate (% of enrolled participants who completed the intervention protocol in full excluding deaths),
- Intervention fidelity (% intervention sessions completed).

The acceptability of the intervention and research processes e.g., selected outcome measures, will be qualitatively analysed.

Secondary outcomes

The following clinical and patient-focused outcomes will be described between randomisation groups per site and in total. The selection of the outcomes defined below have been guided by the relevant core outcome sets for trials investigating delirium and physical function in critically ill patient populations.[27,28]

- Occurrence of delirium

The CAM-ICU assessment of delirium in the ICU will be completed twice daily as per standard practice. These data will be collected from day-0 to day-14 and the total up to day-30 (unless discharged from ICU). The CAM-ICU assessment is a validated and sensitive delirium monitoring tool commonly used in standard ICU practice.[41] The tool comprises of four assessment features (feature 1: mental status; feature 2: inattention; feature 3: altered levels of consciousness; feature 4: disorganised thinking). The CAM-ICU defines delirium as 'positive' or 'negative'. A positive delirium score is defined as feature 1 and feature 2 and either features 3 or 4 present (*see figure 2, appendix 5 for details*). The occurrence of delirium will

be described as the number/% of participants with a CAM-ICU positive score from day-0 to day-14 and the total up to day-30. However, the tool excludes patients with RASS scores of -4 and -5. Therefore, the number/% of participants with 'unable to assess CAM-ICU due to RASS -4/-5' will be presented. Analysis of all delirium outcome data will take into account death and coma to avoid confounding findings. These data will be descriptively presented.

- Delirium free days

Delirium free days will be defined as the number of days/% of participants who were CAM-ICU negative on day-0 to day-14 and the total up to day-30. These data will take into account death and coma to avoid confounding findings.

- Duration (days) of Delirium

The duration of delirium will be described as the number of days/% of participants who were CAM-ICU positive from day-0 to day-14 and the total up to day-30.

- Severity of Delirium

The CAM-ICU-7 delirium tool is a valid and sensitive tool used to assess delirium severity in the ICU.[42] The CAM-ICU-7 assessment will be completed once per day from day-0 to day-14 from randomisation. The CAM-ICU-7 scores participants from 0-7 (0-2: no delirium, 3-5: mild to moderate delirium, and 6-7: severe delirium). However, the tool excludes patients with RASS scores of -4 and -5. Therefore, the number/% of participants with 'unable to assess CAM-ICU-7 due to RASS -4/-5' will be presented. See figure 3 (appendix 6
) for a detailed description.

- Time to delirium resolution

Time to delirium resolution is a composite outcome defined as a measurement of the time delirium commenced and the time delirium finally resolved. Therefore, the total number of days from the first delirium positive score to the last delirium negative score will be calculated. This will be measured using the CAM-ICU (day-0 to day-14, day-30) and the Family Confusion Assessment Method (FAM-CAM) on day-90.[43] The FAM-CAM is a sensitive tool completed by caregivers used to detect delirium in combination with valid delirium assessment tools such as the CAM-ICU.

- Physical function

The Functional Status Score for the ICU (FSS-ICU) is a valid ordinal measure of physical function in the ICU.[44] The FSS-ICU assesses patients across five functional categories (rolling, supine-to-sit transfers, unsupported sitting, sit-to-stand, ambulation). Each category is scored from 1 (total dependence) to 7 (complete independence). A score of 0 is given to a patient if

they are unable to perform a task due to physical limitations or medical status. The scores for each category provide a total FSS-ICU score ranging from 0 to 35. The FSS-ICU score will be measured on day-14 from randomisation or when out-of-bed mobilisation begins (whichever comes first).

- ICU and hospital length of stay

ICU length of stay is defined as the total length of ICU stay in days from ICU admission to ICU discharge. Hospital length of stay is defined as the total length of stay in days from ICU discharge to hospital discharge. These will be presented individually e.g., ICU length of stay and as a total length of stay e.g., ICU length of stay and hospital length of stay.

- Ventilator free days

Ventilator free days will be defined as the number of days without invasive mechanical ventilation from the date of extubation between day-0 and up to day-30 from randomisation.

- Sedation free days

Sedation free days will be defined as the number of days without infusions of sedation agents from day-0 up to day-30 from randomisation.

- Deaths

The number/% of deaths will be calculated per group (intervention, comparator), per site and in total per group. This will provide comparison of between group mortality rates (%). These data will be collected by the local site clinical and research teams.

- Adverse events (AEs)

Safety monitoring will be completed across the length of the trial from day-0 to day-14 from randomisation or when out-of-bed mobilisation begins (whichever comes first).

These data will be collected by the local site clinical and research teams.
The definitions of AEs are defined in section 5 of the trial protocol (*version 7.0, 29.04.2025*).

Follow-up outcomes

At day-90 from randomisation, a number of outcome measures will be carried out with participants in both groups (intervention, comparator) via telephone and in-person. The choice of the outcome measures has been guided by the relevant core outcome sets for trials investigating delirium and physical function in critically ill patient populations.[27,28]

- Physical function

The 6-minute walk test (6MWT) is a reliable and valid tool used to measure physical exercise capacity following critical illness.[45,46] This is the longest distanced walked (measured in meters/% predicted) by participants at follow-up within a timed 6-minutes.

- Quality of Life (QoL)

I. The EQ-5D-5L is a valid questionnaire used to measure health-related QoL across 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression.[47] Each dimension is scored across five levels (1=no problems, 5=severe problems). It has been licensed by the EuroQol Research Foundation for the purposes of this study. The Chief Investigator will complete the questionnaire via telephone with trial participants. The score will be calculated for each domain and in total to provide an index score.

II. Following recommendations from public representatives who were previous ICU patients diagnosed with delirium and a relative, a proxy version of the EQ-5D-5L questionnaire will be completed. The proxy EQ-5D-5L is a valid questionnaire used to measure health-related QoL.[48] It has been licensed by the EuroQol Research Foundation for the purposes of this study. The Chief Investigator will complete the questionnaire with relatives or carers of trial participants via telephone. The score will be calculated for each domain and in total.

III. 36 item Short Form Survey Instrument (SF-36) is a valid and reliable tool used to measure QoL in ICU patients.[49] The tool includes questions related to functional status, emotional and social well-being and overall evaluation of health within eight domains. The Chief Investigator will complete the questionnaire with trial participants via telephone. The total score will be calculated.

- Pain (SF-36)

IV. Section 21 and 22 of the SF-36 survey will be used to describe the trial participants reported pain at day-90 from randomisation. The Chief Investigator will collect these data as described above. The total score will be calculated.

- Cognition

  The Montreal Cognitive Assessment (MOCA) is a valid screening tool used to detect mild cognitive impairment.[50] The MOCA instrument screens cognitive domains such as attention and concentration, executive functions, memory, language, visuoconstructional skills, conceptual thinking, calculations, and orientation. The maximum score is 30 where a score of ≥26 is defined as normal. The MOCA has been licensed for purposes of this study. The assessment will be carried out by the Chief Investigator trained in the use of the MOCA assessment in-person with trial participants at day-90 from randomisation.

- Presence of delirium after ICU discharge (FAM-CAM)
  The FAM-CAM is a sensitive tool completed by caregivers to detect delirium in combination with valid delirium assessment tools such as the CAM-ICU. The presence of delirium is determined by the presence of assessment features (acute onset or fluctuating course, inattention and, either disorganized thinking or altered consciousness). The FAM-CAM delirium detection tool will be carried out at day-90 from randomisation by the Chief Investigator as previously described above.

Mechanistic sub-study outcomes

The Chief Investigator will collect a variety of data from all enrolled participants in both groups using the NIRS device, ABGs and VBGs across the first three days from randomisation. Additional venous blood samples will be collected at days 0,3,5 from randomisation. These data will be used to describe between group comparisons of regional cerebral oxygenation, systemic inflammation and neuroprotection as previously outlined. Missing data will not be imputed. Where there are missing data, these will be reported alongside justification e.g., feasibility of data collection. This will importantly inform the future study design. The biological data will be reported using the REMARK checklist as per the EQUATOR network guidelines.[51]

- Regional cerebral oxygenation (rSO2): Regional cerebral oxygenation will be measured using Near-Infrared Spectroscopy (NIRS). NIRS is a non-invasive, inexpensive tool that provides continuous real-time monitoring of brain tissue oxygenation.[52] The device (INVOSTM 7100) emits and detects infrared light from diodes within the soma sensors placed on the participants forehead. This measures rSO2, calculated by the signal ratio of oxyhaemoglobin to total haemoglobin (assuming a 25% arterial circulation and 75% venous circulation of the brain tissue beneath the sensors). The rSO2 (%) value is an indicator of oxygen delivery and oxygen utilisation of the brain tissue under the soma sensors. It is commonly used clinically as a non-invasive measure of cerebral perfusion during cardiac surgery.[53,54] Moreover, it has demonstrated comparable findings with neuroimaging techniques such as MRI and CT.[53]
- Venous Blood Gases (VBGs) and Arterial Blood Gases (ABGs): VBGs and ABGs are used in standard ICU care to monitor patients' metabolic status, respiratory function, and acid-base balance. This allows health professionals to identify and treat

conditions such as hypoxaemia. Comparison of ABGs and VBGs will provide important information regarding the regulation of cerebral perfusion and energy utilisation. Oxygen indices measured using ABGs and VBGs will be presented alongside blood glucose, blood lactate levels and the rSO2 between randomised groups to demonstrate trial participants responses to the intervention and minimise confounding factors of the NIRS data.

- Additional venous blood samples: The CI will collect additional venous blood samples (10 millilitres per timepoint) from enrolled participants on days 0,3 and 5 from randomisation. The UHP pathology laboratory will support the collection, spinning, freezing and transportation of samples. At the end of the study period, the Birmingham Clinical Immunology Service diagnostic laboratory, will measure sample concentrations of a panel of biomarkers (ELISA, a standard clinical assay and fluidic based assay on a Luminex platform). The following biomarkers have been selected with consideration of the current evidence and expert opinion:
- Interleukin- 6 (IL-6)
- C-Reactive Protein (CRP)
- Interleukin-10 (IL-10)
- Interleukin-8 (IL-8)
- Serum protein S-100B

6.2 Analysis Methods

Analysis of feasibility outcomes

In addition to the feasibility measures previously defined, data collected to describe the intervention and standard care groups will be summarised. This will present between group differences, per site and in total. Please see table 19 (Appendix 12) for details.

Analysis of secondary outcomes

The following secondary outcomes will be analysed between randomised groups according to the specific timepoints. These data will present the average value of all outcomes across/up to each time point. See Table 10-11 (appendix 7).

Analysis of follow-up outcomes

Outcomes to measure quality of life, delirium, pain, cognition and physical function will be collected at day 90 from randomisation (Table 12-13, appendix 8). These will be reported by participants in both randomised groups. Relatives or carers of participants in both groups will complete a proxy version of the EQ-5D-5L health related quality of life questionnaire. These data will be summarised according to each randomisation group. The acceptability of the questionnaires and assessments used will be evaluated in the qualitative interview study.

Analysis of mechanistic outcomes

Baseline characteristics will be summarised for between group comparison (see Table 9). The STRING bioinformatics tool (version 12.0) will be used to search for protein-protein interactions (known and predicted).[62] This will outline potential confounding factors in the analysis of the selected panel of biomarkers. The biological data will be descriptively analysed according to the type of data (e.g., continuous, categorical). This will ensure appropriate interpretation of results following exploratory hypothesis testing and accurate between group comparison.[34-36]

The mean and SD of rSO2, oxygen indices, blood glucose and blood lactate levels will be presented at the relevant timepoints (baseline, every 10 minutes during the intervention, 10 minutes after the intervention and comparable timepoints in the standard care group) per day. These values will be plotted according to the pre-specified timepoints and day of observation (days 1-3) to present between group differences (Table 14-15, appendix 9).

The additional venous blood samples will be analysed within a single run. This will minimise sample variation and therefore provide more accurate comparisons of these data. A description of the data for the human tissue samples, will include haemolysis of samples, volume of samples collected, the time points at which the samples were collected, the assay specific formats, process flow and principles to ensure accurate interpretation, validity of the results and minimise confounding factors e.g., haemolysis.

As previously described the selected biomarkers each have unique roles and signalling pathways. Moreover, they may act both locally and globally. Furthermore, their individual concentration levels in the blood may upregulate or downregulate each other depending on the stimulus e.g., oxidative stress, exercise. Therefore, between group differences (mean, SD) will be made with reference to the individual selected biomarkers (see Table 11-12,

appendix 10) and as a panel of biomarkers according to each time point (day-0, day-3, day-5).

One-way analysis of variance will be used to analyse individual biological variables for comparison between timepoints (day 0,3,5). Multivariant analysis will identify potential correlations between the biological data (e.g., panel of biomarkers, rSO2, oxygen indices) across the pre-specified timepoints. This may also highlight potential errors or deficiencies of the identified biomarker values e.g., an absence of CRP in relation to IL-6 may suggest an error in the methods of measuring concentration levels or the (rare) presence of IL-6 deficiency.[58]

The strength of potential correlations between the biological outcomes across the pre-specified timepoints will be calculated for both groups using the appropriate method according to the distribution of data (e.g. Spearman rank correlation coefficient (*r*)) alongside their CI (75%, 85%, 95%). Multiple regression will analyse how much these variables affect each other with reference to the pre-specified timepoints and how much the outcome (delirium occurrence, delirium severity, mortality), is affected. The subject to variable ratio will be taken into account alongside these data to ensure appropriate interpretation. An area under the Receiver Operator Characteristic (ROC) curve will demonstrate between group differences of the biological variables and potential associations with clinical outcomes e.g., CAM-ICU positive and CAM-ICU negative scores. This will present the sensitivity and specificity of the response to the intervention.[36] Moreover, subgroup analysis e.g., delirium occurrence, severity of illness may identify potential responders/non-responders to the intervention.

6.3 Missing Data

Missing data are anticipated to be low. These data will be summarised in both randomisation groups at each relevant time point. This may outline potential inadequacies of the selected outcome measures. Analysis of data will be compared to the qualitative interview data to evaluate potential strategies to improve the research process including the minimisation of missing data for the future definitive trial. Where missing data are identified for any outcome measures, imputation will not be carried out.

6.4 Harms

Predefined safety events related to the intervention and serious adverse events will be reported to evaluate the intervention and research processes. These safety events will be monitored across the course of the trial from the time of obtained consent to day-14 or when out of mobilisation starts. Adverse events (AEs) that are not serious and/or not related to the intervention will be recorded in the patient's medical notes (see the trial protocol *version 8.0, 11.06.2025,* SOP 014). AEs related to the intervention and SAEs will be summarised (number, %) according to each group. The per protocol analysis will include AEs related to the intervention and SAEs between groups and compared to the participants' clinical outcomes. Comparison of these findings with the sensitivity analysis of intervention versus comparator (including participants who did not complete the intervention in full) will be made. This may provide a clinically useful description of findings.

6.5 Progression to a definitive trial

Data according to the RAG criteria previously described will be summarised and discussed with the TSC to determine if progression to a definitive RCT is indicated. Where recruitment, retention and intervention fidelity are within the green RAG criteria, progression to a definitive trial will be indicated. For example, if >20% (*n*=16.8) of the target sample size are recruited overall in the trial; ≥85% of those consented completed the trial (excluding deaths) and ≥75% of consented participants completed the intervention protocol in full. If data are within the amber parameters for recruitment, retention and intervention fidelity, these would indicate to proceed towards a definitive trial however, with relevant changes. The qualitative interview study will evaluate the intervention and research processes from the perspectives of the participants, their relatives and/or carers in the intervention arm. These data will provide insight into potential areas of improvement e.g., the selected outcome measures and intervention protocol. The RAG system and the qualitative interview study data will inform the implementation strategy for the future definitive trial.

6.6 Definitive trial sample size

Between randomised group differences of the selected delirium outcome measures (occurrence, duration in days, delirium free days and severity of delirium) will be analysed at day-0, day-14, day-30 and day-90 using CIs at different intervals (95%, 85%, 75%) and overall SD to identify evidence of signal efficacy (see table 5). These data will inform the

choice of the selected primary outcome measure for the definitive trial. The CI upper limits of the selected primary outcome will be used to inform the sample size. Moreover, between group differences using the CIs will guide the choice for the appropriate measure of health-related quality of life as part of the Health Economics evaluation in the future RCT.

6.7 Statistical Software

The Chief Investigator will perform the statistical analysis using SPSS (version 28.0 or later).

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8.0 APPENDICES

Appendix 1: Sample size calculation.

The sample size for this two-arm feasibility trial with random 1:1 allocation (intervention:comparator), one-sided 5% alpha, 80% power and the key feasibility objectives was initially guided by Lewis et al., 2021 (with specific reference to table 1). See table 1 below for details.[33]

Table 1.

Feasibility objective	Red zone upper limit	Green zone lower limit	Required sample size	Number of screened patients who are eligible to be randomised.
Recruitment uptake	20%	35%	57	200
Retention (number of eligible participants randomised)	65%	85%	34 (total randomised)	
Intervention fidelity (number of participants randomised to the intervention arm).	50%	75%	27 (intervention arm only)	

The largest value (57) (rounded up to 58) across the feasibility objectives was discussed in consultation with the PenCTU and expert opinion. To answer the research question in relation to feasibility, assessment of the retention rate with a confidence interval of ± 8.5% and an estimated rate of 80% was additionally considered. The required minimum sample size of 84 participants (42 per randomised group) for the FRECycl-D trial was agreed upon by all key stakeholders previously described, with reference to the trial methodology and population of interest. The target sample size calculation has taken into account the mortality rate for critically ill patients.

Appendix 2: Timeline of data collection

TABLE 3. DATA COLLECTED AT EACH TIMEPOINT					
	Timepoint				
	Screening	**Baseline (ICU admission)**	**Day 0-14**	**Day 0-30**	**Day 90**
Eligibility Screen	✓				
Informed consent/agreement	✓				
Patient contact details	✓				
Randomisation	✓				
Demographics		✓			
Medical history		✓			
Feasibility data		✓	✓	✓	✓
Secondary outcomes		✓	✓	✓	✓
Mechanistic data			✓		
AE/SAE data			✓	✓	✓
Interview			✓	✓	✓
Follow-up					
QoL, (EQ-5D-5L, SF-36, proxy-EQ-5D-5L)					✓
Pain, (SF-36)					✓
Physical function, (6MWT).					✓
Cognition, (MOCA)					✓
Delirium, (FAM-CAM)					✓
Time to delirium resolution					✓

Appendix 3: Tables 4-8. Trial protocol adherence

Table 4: Delirium assessment			
Intervention (delirium assessment excl. death)	**Day 0-14 (n/%)**	**Day 15-30 (n/%)**	**Reason/Description e.g.,** • Patient factors (patient unavailable/other procedure, declined) • Therapist factors (staff availability, sickness, annual leave) • Staff factors (staff availability, sickness, annual leave) • Equipment factors (device malfunction)
CAM-ICU:			
Patients identified as eligible for assessment (RASS >-3).			
Patients identified as ineligible			
Patient eligibility unknown			
Eligible patients declined assessment			
Eligible patients not assessed			
Eligible patients assessed			
CAM-ICU-7 (excluding weekends)			
Patients identified as eligible for assessment (RASS >-3).		NA	
Patients identified as ineligible			
Patient eligibility unknown			
Eligible patients declined assessment			
Eligible patients not assessed			
Eligible patients assessed			

Table 5: Intervention and FSS-ICU		
Intervention	**Day 0-14 (n/%)**	**Description where relevant e.g.,**
In-bed cycling (excl. weekends):		

Patients identified as eligible for intervention.		• Patient factors (patient unavailable/other procedure, declined) • Therapist factors (staff availability, sickness, annual leave) • Staff factors (staff availability, sickness, annual leave) • Equipment factors (device malfunction)
Patients identified as ineligible		
Patient eligibility unknown		
Eligible patients declined/unavailable for intervention		
Eligible patients not assessed for intervention		
Eligible patients who did not complete the intervention in full		
Eligible patients completed the intervention in full		
FSS-ICU (excl. weekends):		
Patients identified as eligible for intervention.		
Patients identified as ineligible		
Patient eligibility unknown		
Eligible patients declined/unavailable for intervention		
Eligible patients not assessed for intervention		
Eligible patients who did not complete the intervention in full		
Eligible patients completed the intervention in full		

Table 6: Near-Infrared Spectroscopy, ABGs and VBGs (Intervention group)		
Intervention	**Day 0-3 (n/%)**	**Description where relevant e.g.,** • Patient factors (patient unavailable/other procedure, declined) • Therapist factors (staff availability, sickness, annual leave) • Staff factors (staff availability, sickness, annual leave) • Equipment factors (device malfunction)
Near Infrared Spectroscopy (excl. weekends):		
Patients identified as eligible for intervention.		
Patients identified as ineligible		
Patient eligibility unknown		
Eligible patients declined/unavailable for intervention		
Eligible patients not assessed for intervention		
Eligible patients who did not complete the intervention in full		
Eligible patients completed the intervention in full		
Arterial blood gases (excl. weekends):		
Patients identified as eligible for intervention.		
Patients identified as ineligible		
Patient eligibility unknown		
Eligible patients declined/unavailable for intervention		
Eligible patients not assessed for intervention		
Eligible patients who did not complete the intervention in full		

Eligible patients completed the intervention in full		
Venous blood gases (excl. weekends):		
Patients identified as eligible for intervention.		
Patients identified as ineligible		
Patient eligibility unknown		
Eligible patients declined/unavailable for intervention		
Eligible patients not assessed for intervention		
Eligible patients who did not complete the intervention in full		
Eligible patients completed the intervention in full		
Patients identified as eligible for intervention.		

Table 7: Additional venous blood samples (Intervention group)

Intervention	**Day 0 (n/%)**	**Day 3 (n/%)**	**Day 5 (n/%)**	**Description where relevant e.g.,**
Additional venous blood samples (excl. weekends):				• Patient factors (patient unavailable/other procedure, declined) • Staff factors (staff availability, sickness, annual leave)
Patients identified as eligible for intervention.				
Patients identified as ineligible				
Patient eligibility unknown				
Eligible patients declined/unavailable for intervention				

Eligible patients not assessed for intervention				• Equipment factors (line blocked, unavailable due to medications, no available line)
Eligible patients who did not complete the intervention in full				
Eligible patients completed the intervention in full				
Patients identified as eligible for intervention.				

Table 8: Follow-up outcomes (intervention group)

Intervention	**Day 90 (n/%)**	**Description where relevant e.g.,** • Patient factors (patient unavailable/other procedure, declined) • Therapist factors (staff availability, sickness, annual leave) • Staff factors (staff availability, sickness, annual leave) • Equipment factors (device malfunction)
FAM-CAM (excl. death):		
Patients identified as eligible		
Patients identified as ineligible		
Patient eligibility unknown		
Eligible patients declined/unavailable for intervention		
Eligible patients not assessed for intervention		
Eligible patients who did not complete the intervention in full		
Eligible patients completed the intervention in full		
MOCA (excl. death):		
Patients identified as eligible		
Patients identified as ineligible		

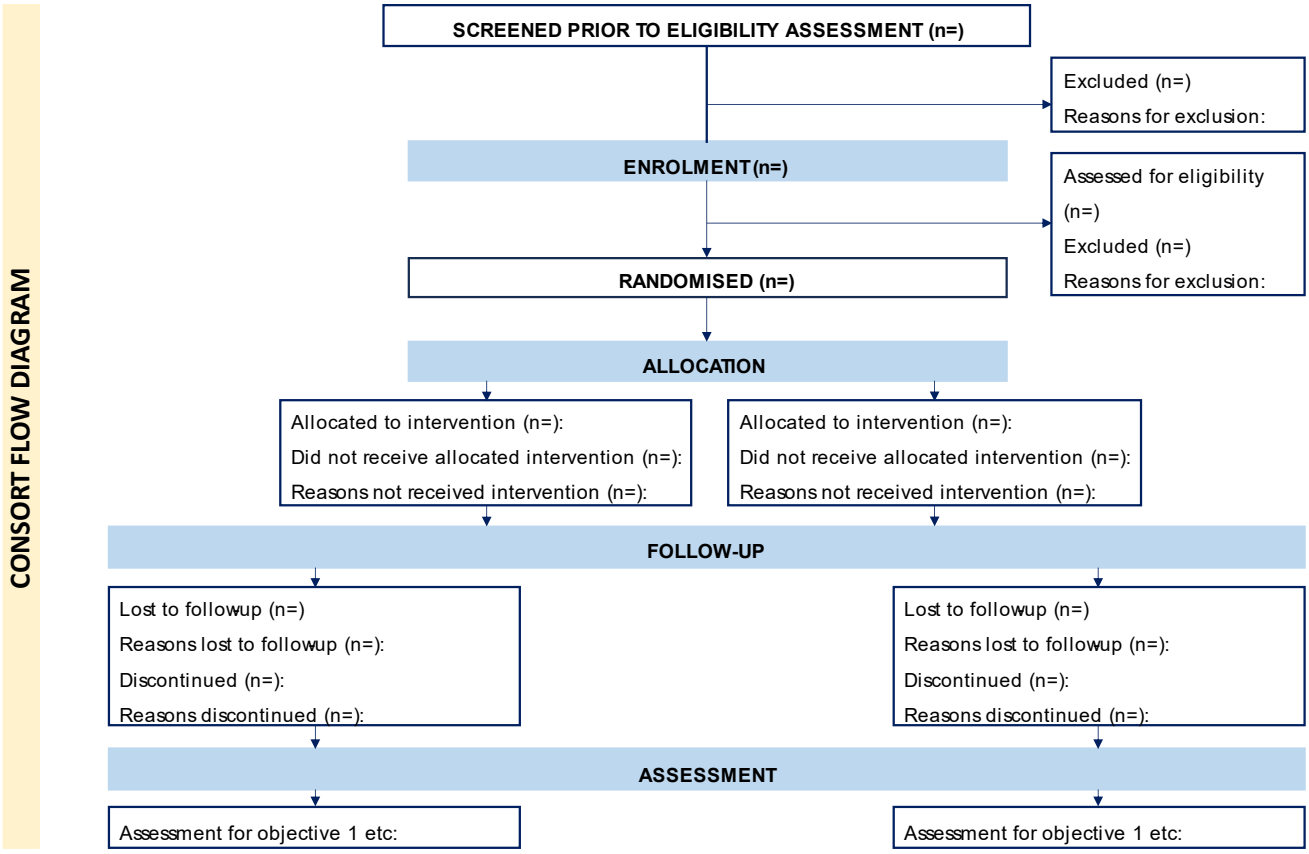
Patient eligibility unknown		
Eligible patients declined/unavailable for intervention		
Eligible patients not assessed for intervention		
Eligible patients who did not complete the intervention in full		
Eligible patients completed the intervention in full		
Time to delirium resolution (excl. death):		
Patients identified as eligible		
Patients identified as ineligible		
Patient eligibility unknown		
Eligible patients declined/unavailable for intervention		
Eligible patients not assessed for intervention		
Eligible patients who did not complete the intervention in full		
Eligible patients completed the intervention in full		
EQ-5D-5L (excl. death):		
Patients identified as eligible		
Patients identified as ineligible		

Patient eligibility unknown		
Eligible patients declined/unavailable for intervention		
Eligible patients not assessed for intervention		
Eligible patients who did not complete the intervention in full		
Eligible patients completed the intervention in full		
SF-36 (excl. death):		
Patients identified as eligible		
Patients identified as ineligible		
Patient eligibility unknown		
Eligible patients declined/unavailable for intervention		
Eligible patients not assessed for intervention		
Eligible patients who did not complete the intervention in full		
Eligible patients completed the intervention in full		
SF-36-Pain (excl. death):		
Patients identified as eligible		
Patients identified as ineligible		

Patient eligibility unknown		
Eligible patients declined/unavailable for intervention		
Eligible patients not assessed for intervention		
Eligible patients who did not complete the intervention in full		
Proxy EQ-5D-5L (excl. death):		
Patients identified as eligible		
Patients identified as ineligible		
Patient eligibility unknown		
Eligible patients declined/unavailable for intervention		
Eligible patients not assessed for intervention		
Eligible patients who did not complete the intervention in full		
6MWT (excl. death):		
Patients identified as eligible		
Patients identified as ineligible		
Patient eligibility unknown		
Eligible patients declined/unavailable for intervention		

Eligible patients not assessed for intervention		
Eligible patients who did not complete the intervention in full		

Appendix 4: Figure 1. Trial participant flow



Appendix 5: FIGURE 2. The Confusion Assessment Method for the Intensive Care Unit (CAM-ICU).

Feature 1: Acute Onset or Fluctuating Course	Score	Check here if Present
Is the patient different than his/her baseline mental status? OR Has the patient had any fluctuation in mental status in the past 24 hours as evidenced by fluctuation on a sedation/level of consciousness scale (i.e., RASS/SAS), GCS, or previous delirium assessment?	Either question Yes →	☐
Feature 2: Inattention		
Letters Attention Test (See training manual for alternate **Pictures**) Directions: Say to the patient, *"I am going to read you a series of 10 letters. Whenever you hear the letter 'A,' indicate by squeezing my hand."* Read letters from the following letter list in a normal tone 3 seconds apart. **S A V E A H A A R T** or **C A S A B L A N C A** or **A B A D B A D A A Y** **Errors are counted when patient fails to squeeze on the letter "A" and when the patient squeezes on any letter other than "A."**	Number of Errors >2 →	☐
Feature 3: Altered Level of Consciousness		
Present if the Actual RASS score is anything other than alert and calm (zero)	RASS anything other than zero →	☐
Feature 4:Disorganized Thinking		
Yes/No Questions (See training manual for alternate set of questions) 1. Will a stone float on water? 2. Are there fish in the sea? 3. Does one pound weigh more than two pounds? 4. Can you use a hammer to pound a nail? **Errors are counted when the patient incorrectly answers a question.** **Command** Say to patient: "Hold up this many fingers" (Hold 2 fingers in front of patient) "Now do the same thing with the other hand" (Do not repeat number of fingers) *If the patient is unable to move both arms, for 2nd part of command ask patient to "Add one more finger" **An error is counted if patient is unable to complete the entire command.**	Combined number of errors >1→	☐

Overall CAM-ICU Feature 1 plus 2 and either 3 or 4 present = CAM-ICU positive		
	Criteria Met →	☐ CAM-ICU Positive (Delirium Present)
	Criteria Not Met →	☐ CAM-ICU Negative (No Delirium)

Appendix 6: FIGURE 3. The CAM-ICU-7 Delirium Severity Scale

CAM-ICU		
Items	**Grading**	**Score**
1. Acute Onset or Fluctuation of Mental Status Is the patient different than his/her baseline mental status? OR Has the patient had any fluctuation in mental status in the past 24 hours as evidenced by fluctuation on a sedation/level of consciousness scale (i.e., RASS/SAS), GCS, or previous delirium assessment?	0 absent 1 present	
2. Inattention Say to the patient, "*I am going to read you a series of 10 letters. Whenever you hear the letter 'A,' indicate by squeezing my hand.*" Read letters from the following letter list in a normal tone 3 seconds apart. SAVEAHAART (Errors are counted when patient fails to squeeze on the letter "A" and when the patient squeezes on any letter other than "A")	0 absent (correct ≥ 8) 1 for inattention (correct 4-7) 2 for severe inattention (correct 0-3)	
3. Altered Level of Consciousness Present if the Actual RASS score is anything other than alert and calm (zero)	0 absent (RASS 0) 1 for altered level (RASS 1, −1) 2 for severe altered level (RASS >1, < −1)	
4. Disorganized Thinking Yes/No Questions 1. Will a stone float on water? 2. Are there fish in the sea? 3. Does one pound weigh more than two pounds? 4. Can you use a hammer to pound a nail? Errors are counted when the patient incorrectly answers a question. Command: Say to patient "Hold up this many fingers" (Hold two fingers in front of patient). "Now do the same with the other hand" (Do not repeat number of fingers) An error is counted if patient is unable to complete the entire command.	0 absent (correct ≥ 4) 1 for disorganized thinking (correct 2, 3) 2 for severe disorganized thinking (correct 0, 1)	
	Total Score	

Appendix 7: Table 10. Summary statistics of outcomes at day 0-14 and day 30 follow up

Table 10: Outcomes (Day 0-14 and Day 30)						
Secondary Outcome	**Both groups Mean (SD)**		**Intervention Mean (SD)**		**Standard care Mean (SD)**	
Timepoint:	**Day 0-14**	**Day 0-30**	**Day 0-14**	**Day 0-30**	**Day 0-14**	**Day 0-30**
Occurrence of delirium (CAM-ICU)						
Delirium free days (CAM-ICU)						
Duration (days) of Delirium (CAM-ICU)						
	Both groups Mean (SD)		**Intervention Mean (SD)**		**Standard care Mean (SD)**	
Timepoint:	**Day-0-14**		**Day-0-14**		**Day-0-14**	
Severity of Delirium (CAM-ICU-7)						
	Both groups Mean (SD)		**Intervention Mean (SD)**		**Standard care Mean (SD)**	
Timepoint:	**Day-14/out-of-bed mobilisation**		**Day-14/out-of-bed mobilisation**		**Day-14/out-of-bed mobilisation**	
Physical function (FSS-ICU)						
	Both groups N (%) Range		**Intervention N (%) Range**		**Standard care N (%) Range**	
Timepoint:	**Day-0-30**		**Day-0-30**		**Day-0-30**	

Ventilator free days (days)			
Sedation free days (days)			
Daily Richmond Agitation Sedation Scale (RASS)			
Adverse events			
Deaths			

Table 11. Between group difference and CIs for outcomes at day 0-14 and day 30 follow up

Table 11: Between group differences (Day 0-14 and Day 30 outcomes)								
Outcome	**Between group difference**		**75% CI**		**85% CI**		**95% CI**	
Timepoint:	**Day 0-14**	**Day 0-30**	**Day 0-14**	**Day 0-30**	**Day 0-14**	**Day 0-30**	**Day 0-14**	**Day 0-30**
Occurrence of delirium (CAM-ICU)								
Delirium free days (CAM-ICU)								
Duration (days) of Delirium (CAM-ICU)								
	Between group difference		**75% CI**		**85% CI**		**95% CI**	

Timepoint:	**Day-0-14**	**Day-0-14**	**Day-0-14**	**Day-0-14**
Severity of Delirium (CAM-ICU-7)				

Appendix 8: Table 12. Summary statistics of outcomes at day-90 follow-up

Table 12: 90-day follow-up			
	Both groups Mean (SD)	**Intervention Mean (SD)**	**Standard care Mean (SD)**
Timepoint:	**Day-90**	**Day-90**	**Day-90**
QoL (EQ-5D-5L,			
Proxy EQ-5D-5L)			
SF-36,			
Pain (SF-36)			
Cognition (MOCA)			
Presence of delirium after ICU discharge (FAM-CAM)			
Time to delirium resolution (days)			
ICU and hospital length of stay (days)			

Table 13. Between group differences and CIs of outcomes at day-90 follow-up

Table 13: Between group differences (90-day follow-up)			
	Both groups CI (75%,85%,95%)	**Intervention CI (75%,85%,95%)**	**Standard care CI (75%,85%,95%)**
Timepoint:	**Day-90**	**Day-90**	**Day-90**
QoL (EQ-5D-5L,			
Proxy EQ-5D-5L)			

SF-36,			
Pain (SF-36)			
Cognition (MOCA)			
Presence of delirium after ICU discharge (FAM-CAM)			
Time to delirium resolution (days)			
ICU and hospital length of stay (days)			

Appendix 9: Table 14-15. Example of rSO2 analysis.

TABLE 14: Between group differences of regional cerebral oxygenation (rSO2)								
Time point	Between group difference	Intervention				Standard care		
	Mean rSO2 (SD)	Mean rSO2 (SD)	Mean rSO_2 (SD) Left sensor	Mean rSO2 (SD) Right sensor		Mean rSO2 (SD)	Mean rSO_2 (SD) Left sensor	Mean rSO2 (SD) Right sensor
Day-0								
Baseline (rest)								
During intervention								
Recovery								
Maximum								
Minimum								
Difference								
Day-1								
Baseline (rest)								
During intervention								

Recovery								
Maximum								
Minimum								
Difference								
Day-2								
Baseline (rest)								
During intervention								
Recovery								
Maximum								
Minimum								
Difference								

**Standard Deviation (SD)*

TABLE 15: Between group differences of regional cerebral oxygenation (rSO2)								
Time point	Between group difference	Intervention				Standard care		
	rSO_2 (CI 75%, 85%, 95%)	rSO_2 (CI 75%, 85%, 95%)	rSO_2 (CI 75%, 85%, 95%) Left sensor	rSO_2 (CI 75%, 85%, 95%) Right sensor		rSO_2 (CI 75%, 85%, 95%)	rSO_2 (CI 75%, 85%, 95%) Left sensor	rSO_2 (CI 75%, 85%, 95%) Right sensor
Day-0								
Baseline (rest)								
During intervention								
Recovery								
Maximum								
Minimum								
Difference								
Day-1								
Baseline (rest)								
During intervention								
Recovery								
Maximum								

Minimum								
Difference								
Day-2								
Baseline (rest)								
During intervention								
Recovery								
Maximum								
Minimum								
Difference								

* *Confidence Interval (CI)*

Appendix 10: Table 16-17. Example of cytokine analysis

TABLE 16: Between group differences of cytokine measures									
Intervention						Standard care			
Biomarker: IL-6	Mean (SD)	Median (IQR)	Minimum	Maximum		Mean (SD)	Median	Minimum	Maximum
Day 0									
Day 3									
Day 5									

**Standard Deviation (SD), Interquartile Range (IQR).*

TABLE 17: Between group differences of cytokine measures							
Intervention					Standard care		
Biomarker: IL-6	CI (75%)	CI (85%)	CI (95%)		CI (75%)	CI (85%)	CI 95%)
Day 0							
Day 3							
Day 5							

** Confidence Interval (CI).*

Appendix 11: Table 18. Summary of baseline Characteristics

Table 18: Baseline characteristics			
Characteristic	**Both groups (n/%)**	**Intervention (n/%)**	**Standard care (n/%)**
Age			
Sex at birth: Male Female Unknown			
Ethnicity: Asian or Asian British • Indian • Pakistani • Bangladeshi • Chinese • Any other Asian background Black, Black British, Caribbean or African • Caribbean • African • Any other Black, Black British, or Caribbean background Mixed or multiple ethnic groups • White and Black Caribbean • White and Black African • White and Asian • Any other Mixed or multiple ethnic background White • English, Welsh, Scottish, Northern Irish or British • Irish • Gypsy or Irish Traveller			

• Roma • Any other White background Other ethnic group • Arab • Any other ethnic group			
Comorbidities **Charleston Comorbidity Index)**			
Dependency Prior to ICU admission (Clinical Frailty Scale): 1. Very fit 2. Fit 3. Managing well 4. Living with very mild frailty 5. Living with mild frailty 6. Living with moderate frailty 7. Living with severe frailty 8. Living with very severe frailty 9. Terminally ill			
Body Mass Index (BMI) (kg/m^2)			
Reason for ICU admission: Pneumonia Respiratory failure Surgical Trauma Traumatic brain injury Liver failure Renal failure Neurological disorder			
Severity of illness (SOFA score)			

Appendix 12: Table 19. Summary of feasibility outcomes

Table 19: Feasibility outcomes				
Feasibility outcome	**All sites (n/%)**	**Site 01 (n/%)**	**Site 02 (n/%)**	**Site 03 (n/%)**
Recruitment (participants enrolled vs eligible): Patients screened for eligibility Patients identified as eligible Patients identified as ineligible Patient eligibility unknown Eligible patients declined participation Eligible patients consent to participation Eligible patients enrolled				
Retention (excluding deaths) Enrolled participants who completed baseline assessments Enrolled participants who completed follow-up assessments up to day 30. Enrolled participants who completed follow-up assessments at day 90. Enrolled participants lost to follow-up (excl. deaths) Enrolled participants fully withdrawn from the trial Enrolled participants included in final analysis				
Intervention fidelity (intervention sessions completed in full).				

Enrolled participants who did not receive the intervention Enrolled participants who did not tolerate the intervention in full Enrolled participants who completed the intervention in full				

Appendix 13: Table 20. Completeness of data collection

Table 20: Data completeness			
Timepoint	Both groups (n/%)	Intervention (n/%)	Standard care (n/%)
Day 0-14			
Baseline data			
CAM-ICU			
CAM-ICU-7			
Intervention			
Standard care			
FSS-ICU outcome			
ABGs			
VBGs			
NIRS (rSO2)			
Additional venous blood samples			
Day 0-30			
Number of delirium free days			
Duration of ICU delirium (days)			
ICU date of admission			
Hospital date of discharge			

Number of ventilator free days			
Number of sedation free days			
Day 90			
EQ-5D-5L questionnaire			
EQ-5D-5L proxy questionnaire			
SF-36 questionnaire			
FAM-CAM outcome			
6MWT outcome			
Time to delirium resolution			
ICU LOS			
Hospital LOS			