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Mobilisation in the EveNing to TreAt deLirium (MENTAL): protocol for a mixed-methods feasibility randomised controlled trial

David McWilliams ,[1,2] Elizabeth King,[3] Peter Nydahl ,[4] Julie Lorraine Darbyshire,[5] L Gallie,[6] Dalia Barghouthy,[7] C Bassford,[7] Owen Gustafson [8]

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For numbered affiliations see end of article.

Correspondence to
Dr David McWilliams;
david.mcwilliams@uhcw.nhs.uk

ABSTRACT

Introduction Delirium is common in critically ill patients and is associated with longer hospital stays, increased mortality and higher healthcare costs. A number of risk factors have been identified for the development of delirium in intensive care, two of which are sleep disturbance and immobilisation. Non-pharmacological interventions for the management of intensive care unit (ICU) delirium have been advocated, including sleep protocols and early mobilisation. However, there is a little published evidence evaluating the feasibility and acceptability of evening mobilisation.

Methods and analysis Mobilisation in the EveNing to TreAt deLirium (MENTAL) is a two-centre, mixed-methods feasibility randomised controlled trial (RCT). Sixty patients will be recruited from ICUs at two acute NHS trusts and randomised on a 1:1 basis to receive additional evening mobilisation, delivered between 19:00 and 21:00, or standard care. The underpinning hypothesis is that the physical exertion associated with evening mobilisation will promote better sleep, subsequently having the potential to reduce delirium incidence. The primary objective is to assess the feasibility and acceptability of a future, multicentre RCT. The primary outcome measures, which will determine feasibility, are recruitment and retention rates, and intervention fidelity. Acceptability of the intervention will be evaluated through semi-structured interviews of participants and staff. Secondary outcome measures include collecting baseline, clinical and outcome data to inform the power calculations of a future definitive trial.

Ethics and dissemination Ethical approval has been obtained through the Wales Research and Ethics Committee 6 (22/WA/0106). Participants are required to provide written informed consent. We aim to disseminate the findings through international conferences, international peer-reviewed journals and social media.

Trial registration number NCT05401461.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The study will evaluate the impact of evening mobilisation on sleep and incidence of delirium in intensive care units.
⇒ Qualitative and quantitative approaches will be used to comprehensively assess study outcomes and to inform a main trial and whether or not it would be feasible.
⇒ The outcomes to be assessed by the study are relevant to patients, intensive care clinicians and commissioners.
⇒ The recruitment and randomisation of study participants from two sites will increase the generalisability of findings.
⇒ A potential limitation would be the acceptability of the intervention to both patients and staff, which may limit intervention fidelity.

INTRODUCTION

Delirium is a common complication for patients admitted to intensive care units (ICUs), with an incidence of around 30% in the general ICU population[1] and up to 80% in those receiving mechanical ventilation.[2] Those who develop delirium experience disturbance in attention, awareness and cognition, resulting in reduced orientation to the environment, hallucinations and high levels of distress. Development of ICU delirium is associated with up to threefold increases in-hospital mortality and length of stay,[3 4] placing considerable burden on caregivers and healthcare services, and increasing healthcare costs.[5] In the longer term, delirium is associated with ongoing functional disability, requiring specialist rehabilitation services or residential care.[6] Up to 71% of patients mechanically ventilated with a positive diagnosis of delirium experience persisting cognitive impairment at 12 months,[7] with around a third severely impaired with deficits comparable with patients following moderate traumatic brain injury.[8]

The identification, treatment and prevention of delirium are major public health

priorities and feature as one of the James Lind Alliance top three research priority areas for intensive care.[9]

Approximately 40% of ICU survivors have not returned to work at 12 months following hospital discharge due to their health,[10] with persistent physical and functional limitation present for months or even years following hospital discharge. Much of this is due to post-intensive care syndrome (PICS), defined as new or worsening physical, cognitive or mental impairments in a patient following critical illness or intensive care.[11] One of the main contributing factors to the development of PICS is delirium, characterised as a disturbance of consciousness, the presence of inattention, disorganised thinking and a fluctuating course.[12] Apart from its long-term effects, delirium is associated with longer hospital stays, increased mortality,[1 13 14] as well as higher healthcare costs.[5]

Despite the high prevalence, without active monitoring, delirium goes undetected in up to 72% of cases.[15] Consequently, national guidelines recommend daily monitoring of sedation scores and delirium assessment in all patients admitted to ICU.[16] While this has led to an improvement in identification of ICU acquired delirium, at present there is a lack of robust evidence to guide clinicians in how to prevent it from developing in the first place.

Rationale for the trial

Multiple risk factors have been identified for the development of ICU-acquired delirium.[10] While a number of these are irreversible (older age, sepsis, alcoholism), strategies and bundles of care have been developed under the umbrella term 'non-pharmacological interventions'.[17] Bundles include elements such as regular reorientation of patients, noise reduction, sleep protocols and early mobilisation.[16] Evidence to support specific interventions is lacking. A recent systematic review and meta-analysis was unable to support their use due to limited or low-quality evidence.[17] Targeted research is needed to evaluate potentially reversible risk factors for the development of delirium.

The intervention component of the Mobilisation in the EveNing to TreAt deLirium (MENTAL) mixed-methods feasibility randomised controlled trial (RCT) is focused on two specific risk areas for development of ICU delirium, namely sleep disturbance and immobilisation.

Sleep disturbance is common in critically ill patients, and may lead to impairment of cognition. Patients in ICU sleep for an average of only 2 hours per day (with <6% of this rapid eye movement) and polysomnography demonstrates severely disrupted sleep.[18] Over half of patients who develop delirium report reversal of day–night rhythms, with patients sleeping more during the day and nocturnal exacerbation of delirium symptoms.[19] Current strategies, therefore, focus on normalising the day/night cycle, with lights on and off at correct times, and encouraging nighttime sleeping rather than during the day.

Bed-rest and delays in mobilisation cause substantial physical and psychological harms for people treated in ICUs.[20–22] When implemented, programmes of early mobilisation have been effective in improving a number of these outcomes, including reductions of 30%–50% in the incidence and duration of delirium.[23–25] Typically, mobilisation occurs during the day due to working patterns of therapy staff,[26] with patients often sleeping directly afterwards due to the intensity of the workload and lower physical reserves.[27] We hypothesise that the provision of mobilisation in the evening may therefore promote more natural overnight sleep, in turn reducing the likelihood of patients developing delirium.

The MENTAL mixed-methods feasibility RCT has been designed with the primary aim of assessing the acceptability of the intervention, and recruitment, randomisation and follow-up rates to inform the design of a future adequately powered multicentre trial.

The primary objectives of the feasibility study are:

- Proportion of patients agreeing to take part out of all those invited (recruitment rate).
- Proportion of participants who complete the intervention (retention rate).
- Percentage of intervention sessions completed (intervention fidelity).
- Intervention acceptability to participants and service providers.

The secondary objectives are:

- To evaluate a range of clinical and patient-reported outcome measures to aid selection of the most appropriate primary outcome measure for a definitive trial, with estimates of variance for sample size calculation and health economic evaluations of any future definitive trial.

METHODS AND ANALYSIS

General design

MENTAL is a two-centre, mixed-methods, feasibility RCT with 1:1 randomisation into either intervention or usual care. Qualitative interviews will be conducted with participants in the intervention arm and ICU staff delivering the intervention. The trial is being sponsored by the University Hospitals Coventry and Warwickshire NHS Trust and is being conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice.

Participants, interventions and outcomes

Study setting

This study is being undertaken in two general adult ICUs in the UK (University Hospital Coventry and Warwickshire, Coventry and John Radcliffe Hospital, Oxford) which have a proven track record in ICU research.

Eligibility criteria

Written informed consent is obtained from participants prior to any study procedures taking place (online supplemental file 1). Eligible patients with altered consciousness caused by illness and therapeutic sedation will lack capacity to consent. In this instance, we will approach a personal consultee or an independent registered medical practitioner if no personal consultee is available. Once

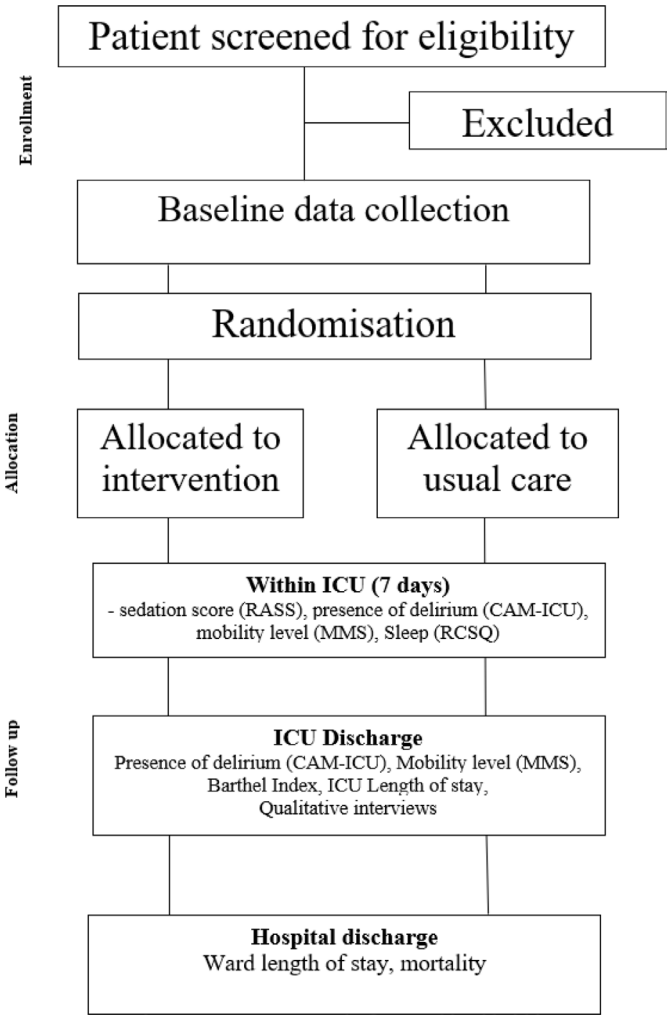

Figure 1 Flow of participants through the study. CAM-ICU, Confusion Assessment Method for the Intensive Care Unit; ICU, intensive care unit; MMS, Manchester Mobility Score; RASS, Richmond Agitation and Sedation Score; RCSQ, Richards-Campbell Sleep Questionnaire.

the participant has recovered from their incapacity, they will be approached to obtain permission to continue in the study. Patients eligible for the study must comply with all of the following before randomisation:

- Aged ≥18 years.
- Able to respond to verbal stimulus (Richmond Agitation Sedation Scale (RASS) ≥−3).
- Expected to remain in ICU for ≥24 hours.

Patients are excluded if they meet any of the following criteria:

- Death expected within the next 72 hours.
- Immobility prior to admission.
- Mobilisation contraindicated (eg, spinal injury).
- Delirium diagnosis during this ICU admission.
- Acute or subacute severe neurological deficit or injury.
- Severe psychiatric illness (not including depression) or developmental problems.
- Suspected or confirmed drug or alcohol intoxication/overdose or withdrawal.

The inclusion and exclusion criteria are designed to include participants who reflect a general population of patients requiring ICU support that may develop delirium, who are able to participate in mobilisation, and exclude patients who are unable to mobilise or are at risk of cognitive impairment unrelated to delirium. Our inclusion criteria are intentionally broad to ensure we also capture patients who are invasively ventilated and/or receiving additional organ support. In the instance where a patient is sedated and therefore does not meet the required RASS score for inclusion, they will continue to be screened daily until sedation has been stopped, and eligibility will then be reassessed.

Intervention

In the intervention arm participants will receive an additional mobilisation session between 19:00 and 21:00 delivered by a dedicated mobilisation team that includes trained ICU physiotherapists. Mobilisation will be defined as a score of ≥2 on the Manchester Mobility Score (MMS) (sit on the edge of the bed or higher). Participants will also be offered the opportunity to engage in activities which may be part of their normal evening routines (eg, brushing teeth, reading or watching television). The intervention will begin on day one of admission or the first evening following recruitment, and will be carried out for up to a maximum of seven consecutive evenings. The intervention will be terminated if (a) the patient's condition deteriorates irretrievably and physiotherapy is no longer appropriate, (b) after seven evenings, or (c) when the patient is discharged from the ICU. The intervention will not continue at secondary wards or units. The evening mobilisation will be delivered in addition to any input from the MDT during normal daily working hours and will not replace any standard therapy.

Usual care

Usual care consists of routine ward-based care delivered during normal working hours (between 08:00 and 17:00), including mobilisation and rehabilitation interventions, and activities of daily living. In the evening, lighting on both units is routinely lowered at around 21:00 and alarm volumes reduced with the aim to reduce light and sound exposure overnight.

Participant and staff interviews

A semi-structured interview to assess intervention acceptability will be undertaken with a subset of participants in the intervention arm. We will also interview nursing and physiotherapy staff that were involved with the delivery of the intervention. Participants in the intervention arm will be interviewed as close to ICU discharge as is reasonably practical. Staff may be interviewed at any time during, or shortly after, the intervention period at their site. All interviews will follow a topic guide which will be developed and piloted with input from the patient contributors. The interview content will follow a narrative framework approach, aiming to explore the participants

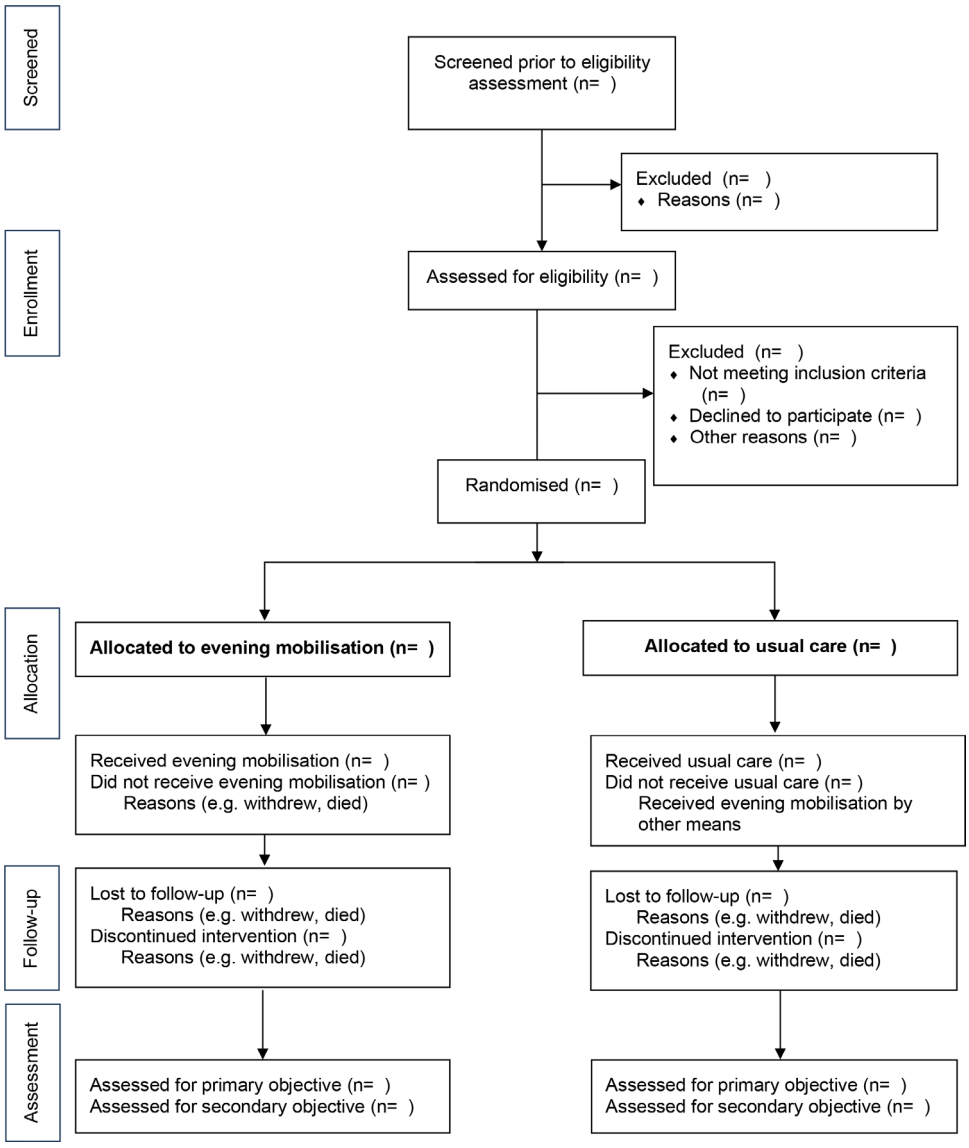

Figure 2 Consolidated Standards of Reporting Trials pilot and feasibility trials flow schematic.

and providers experiences of receiving and delivering the intervention, barriers to engagement or delivery, and ideas for improving the intervention. It is envisaged the interviews will last approximately 20–30 min.

Participant timeline

The participant timeline is highlighted in figure 1.

Outcome measures

Primary outcome measures:

- Recruitment rate, overall and by centre.
- Retention rate, defined as the proportion of participants allocated to the intervention that undertake evening mobilisation.
- Intervention fidelity, measured by the percentage of evening mobilisation sessions completed.
- Acceptability of the intervention to participants and service providers.

Secondary outcome measures:

Measures that will be used in the future full-scale trial will also be collected at baseline, 7 days, ICU and hospital discharge. The proposed primary outcome for the definitive trial is the incidence of delirium assessed as a positive Confusion Assessment Method for the Intensive Care Unit (CAM-ICU). The CAM-ICU is a valid, reliable instrument for delirium detection[28] and has been routinely conducted in the centres for several years.

- Duration of delirium (counted at 12-hour periods; the end of delirium is defined when patients are delirium-negative for 24 hours or discharged to the ward).
- Sleep quality calculated as an average and change over time (using the Richards-Campbell Sleep Questionnaire (RCSQ)).
- Mortality (ICU and hospital).
- Duration of mechanical ventilation.
- Length of ICU stay.
- Length of hospital stay.

Table 1 Timing of visits and data collection

Baseline (prerandomisation)	Confirmation with inclusion and exclusion criteria Date and time of consent Patient demographics (age, sex, ethnicity, height, weight) Relevant clinical history (depression, anxiety, dementia, comorbidities) Primary admission diagnosis SOFA score Presence of sedation and RASS
Daily for 7 days or until ICU discharge	Presence of sedation and RASS Mode of ventilation Frequency and level of mobilisation (MMS) Sleep score (RCSQ) Mobilisation related complications Presence and duration of delirium (CAM-ICU)
ICU discharge	Presence and duration of delirium (CAM-ICU) Duration of mechanical ventilation Frequency and level of mobilisation (MMS) Sleep score (RCSQ) Barthel index Semi-structured interviews Mortality
Hospital discharge	Post-ICU length of stay Mortality

CAM-ICU, Confusion Assessment Method for the Intensive Care Unit; MMS, Manchester Mobility Score; RASS, Richmond Agitation and Sedation Score; RCSQ, Richards-Campbell Sleep Questionnaire; SOFA, Sequential Organ Failure Assessment.

- Mobilisation-related complications (eg, altered vital signs, line dislodgement, fall).
- Mobility level at ICU discharge (using the MMS).

Sample size

Since this is a feasibility study, the sample size is not determined by a power calculation but rather aims to estimate the rate of recruitment and retention to inform the future trial. Local data suggest approximately 500 eligible patients annually at each site. To test a recruitment rate of 25%, we would expect to enrol 125 participants per year (approximately 2–3 participants per week) at each site. We would therefore expect to recruit in the region of 60 patients (2–3 patients from each site per week) during the recruitment period. To test recruitment rates across two sites we will aim for an equal proportion across each and recruit up to a maximum of 30 participants from each site. This sample size will ensure sufficient numbers to test the individual components of the intervention and provide a suitable sample for the qualitative interviewing. We estimate we will have sufficient data to identify key issues and themes after having interviewed approximately five members of staff and eight patients from each site unless saturation is deemed to be achieved before this point.

Assignment of interventions

Randomisation

Eligible participants are randomised on a 1:1 ratio to receive either the intervention or usual care using a concealed envelope system with randomly sized block design and stratified by study site.

Blinding

Given the nature of the intervention it is not possible to fully blind physiotherapists or participants to group allocation. However, all assessments will be completed by a team member blinded to randomisation and group allocation.

Data collection, management and analysis

Data collection

Clinical data are collected at baseline (pre-randomisation), daily for up to 7 days post-randomisation, at ICU discharge and hospital discharge. Data collected are outlined in the study schematic in figure 2 and detailed in table 1.

Data related to mobilisation and sleep quality will be collected throughout the study intervention period in both the control and intervention groups.

The MMS is a simple 7-point mobility scale used and validated for assessing mobility levels within critical care.[29] The RCSQ is a six-item self-report questionnaire that is used to assess perceived sleep depth, time to fall asleep, number of awakenings, sleep efficiency and quality, and perceived night time noise.[28] Each item is scored on a visual analogue scale with higher scores representing better sleep. The mean score of the six items is calculated and represents the overall perception of sleep.

Data management

All data for an individual participant will be extracted from patient charts by the Principal Investigator or their delegated nominees and recorded on paper case report forms (CRFs). This is then entered into a password protected database and stored on a secure server within the NHS Trust. Audio transcripts from the participant and staff interviews will be recorded on an encrypted device, and stored along with the word transcription on the same secure server. All paper documentation (such as CRFs and consent forms) are stored in the Investigator Site File under secure conditions.

Data analysis

Results will be reported in accordance with the Consolidated Standards of Reporting Trials extension to

Table 2 'Traffic light' system to determine progression to a definitive trial

	Recruitment of rate proposed (%)	Total number of participants recruited	Intervention fidelity (%)
Green (go)	>75	45–60	>70 (equivalent to completion of at least 5/7 sessions)
Amber (amend)	40–75	24–45	40–70 (equivalent to completion of at least 3/7 sessions)
Red (stop)	<40	<24	<40 (equivalent to completing less than 3/7 sessions)

randomised pilot and feasibility trials[30] and the Consolidated criteria for Reporting Qualitative research.[31]

The feasibility design was chosen to assess recruitment, retention and intervention adherence rates on the basis that unless reasonable rates can be achieved a formal trial will not be possible. Rates will be estimated based on data collected and a 95% CI determined for these measures. Statistical power calculations for the definitive trial will be reviewed based on data collected in this feasibility trial. A traffic light system shown in table 2 that is recommended for best practice will be used as a guide for progression to a definitive trial.[32]

Descriptive statistics will be used to explore the demographic, clinical and outcome data between the two groups depending on the type of data (eg, mean/median; SD/IQR; frequency, proportion and 95% CI; range). Intervention fidelity will be explored using descriptive statistics for each component, and also broken down to examine variation between provider staff. During fidelity evaluation, examples of good practice will be identified for use during training for a future definitive trial.

Verbatim anonymised transcripts of semi-structured interviews will be thematically analysed by two members of the study team independently.[33] Codes and themes will be identified from the data, and refined using an iterative process. Analysis of interview transcripts will be supported by NVivo 12 (NVivo qualitative analysis software; QSR International Pty Ltd. V.12).

Patient and public involvement

We have planned full involvement across the research cycle. We have collaborated with patient partners to ensure the study addresses key needs that are currently missing from routine care in the ICU and that the design is appropriate for potentially anxious and functionally impaired patients. We have identified PPI coapplicants through ICU Steps (national patient support group) and the UHCW PPI group. Both groups expressed strong support for the proposal. Our PPI coapplicants have helped develop the plain English summary, inclusion criteria, personalised intervention and proposed outcomes. They will be full members of the trial team and will assist with analysis and interpretation of the acceptability data (research methods training will be offered), as well as advise on trial delivery and dissemination.

Ethics and dissemination

The study has received a favourable ethical approval from the Wales Research and Ethics Committee 6 (22/WA/0106). Health Research Authority approval was obtained on 10 May 2022. Participants are required to provide written informed consent. This paper reports protocol version 1.1 (April 2022) and has been written with reference to the Standard Protocol Items: Recommendations for Interventional Trials checklist.[34]

Results from this study will be disseminated at regional and international conferences and in peer-reviewed journals, as well as via social media. Authorship of any papers related to this study will follow the ICMJE recommendations (http://www.icmje.org/recommendations/).

Author affiliations
[1]Centre for Care Excellence, University Hospitals Coventry and Warwickshire NHS Trust, Coventry, UK
[2]Centre for Care Excellence, Coventry University, Coventry, UK
[3]Adult Intensive Care Unit, Oxford University Hospitals NHS Foundation Trust, Oxford, UK
[4]Nursing Research, Universitatsklinikum Schleswig-Holstein, Kiel, Germany
[5]Nuffield Department of Clinical Neurosciences, Oxford University, Oxford, UK
[6]Patient Representative, Plymouth, UK
[7]Critical Care, University Hospitals Coventry and Warwickshire NHS Trust, Coventry, UK
[8]Oxford Allied Health Professions Research & Innovation Unit, Oxford University Hospitals NHS Foundation Trust, Oxford, UK

Twitter David McWilliams @Davido744, Peter Nydahl @NydahlPeter and Owen Gustafson @OxfordICUPhysio

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Contributors DM and PN conceived the study. DM, EK, PN, JLD, LG, CB and OG contributed to the study design. DM, PN, OG, EK and DB developed the intervention. JLD and LG led the patients and public involvement for the development of the protocol. All authors contributed to the development of the study protocol. OG and DM led the development of the manuscript. All authors read the manuscript, provided critical input and approved the final manuscript.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

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ORCID iDs
David McWilliams http://orcid.org/0000-0002-9086-2557
Peter Nydahl http://orcid.org/0000-0002-5178-0364
Owen Gustafson http://orcid.org/0000-0002-5450-3696

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