

Investigating the safety of mobilising intensive care unit patients receiving vasoactive drugs: An exploratory observational study

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This protocol describes this study and provides information about procedures for entering participants. Every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the study. Problems relating to this study should be referred, in the first instance, to the Chief Investigator.

This study will adhere to the principles outlined in the NHS Research Governance Framework for Health and Social Care (2nd edition). It will be conducted in compliance with the protocol, the Data Protection Act and other regulatory requirements as appropriate.

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GLOSSARY OF ABBREVIATIONS

6MWT	6-Minute Walk Test
AE	Adverse event
APACHE II	Acute physiology and chronic health evaluation II
ICU	Intensive care unit
IMS	ICU Mobility Scale
RASS	Richmond Agitation-Sedation Scale

RCT	Randomised controlled trial
SAE	Serious adverse event
SF-36 v2	36-item Short Form Health Survey Version 2
SOFA	Sequential Organ Failure Assessment
RAND SF-36 v1	RAND 36-Item Health Survey 1.0 Questionnaire
WHODAS 2.0	World Health Organisation's Disability Assessment Schedule 2.0

KEYWORDS

Early Ambulation; Critical Care
Intensive Care; Patient Safety
Vasoactive drugs

STUDY SUMMARY

TITLE Investigating the safety of mobilising intensive care unit patients receiving vasoactive drugs: An exploratory observational study

DESIGN Exploratory observational study

AIMS 1. To describe current practice in one healthcare organisation of mobilising ICU patients receiving vasoactive drugs.
2. To describe the preliminary feasibility of measuring the safety of mobilising ICU patients receiving vasoactive drugs.

OUTCOME MEASURES Key outcomes include: Hypothetical recruitment rate for a future randomised controlled trial; follow-up rate of participants for day-60 outcomes.

POPULATION Adult patients admitted to the intensive care units.

ELIGIBILITY For patient participants:
Inclusion criteria: Patients admitted to the ICU who are receiving vasoactive drugs; age greater than or equal to 18 years old; expected to remain admitted to the ICU for at least 24 hours post-enrolment.
Exclusion criteria: Patient expected to die imminently; mobilisation is contraindicated by the nature of patients existing injuries; where it is clear from the medical records that participants are prisoners or offenders on probation; patient and/or their consultee is unable to speak English; patients with neuromuscular disease or acute brain injury or spinal cord injury.

DURATION 01/11/2018 – 09/08/2019

1. INTRODUCTION

1.1 BACKGROUND

Muscle wasting in an intensive care unit (ICU) population is a considerable concern as it has been found to be fast-developing during an ICU admission (Puthuchearry et al., 2013). Muscle weakness extends substantially beyond an ICU stay and is associated with deficits in physical functioning and quality of life (Fan et al., 2014). These deficits are known to be long term (Dowdy et al., 2006) having been demonstrated five years after an ICU stay (Herridge et al., 2011). These long-term complications have also been associated with increased healthcare costs (Lone et al., 2016).

Early mobilisation as part of physical rehabilitation has been recommended as a strategy to help address these poor physical outcomes and is advocated in several practice guidelines for ICUs (NICE, 2009, Girard et al., 2017). Early mobilisation is mobilisation occurring whilst the patient is still on the ICU (Bailey et al., 2007). Examples of mobilisation can include:

‘turning and moving in bed, active-assisted and active exercise, use of cycling pedals in bed, sitting over the edge of the bed, standing, stepping in place, transferring from the bed or chair, chair exercises and walking’ (Gosselink et al., 2008, p. 1190).

The evidence base for early mobilisation has developed substantially (Connolly et al., 2016), with a recent increase in the number of randomised clinical trials (Wright et al., 2018, Morris et al., 2016, Schaller et al., 2016, Moss et al., 2015, Denehy et al., 2013, Schweickert et al., 2009). These have demonstrated beneficial effects for ICU patients such as improved ability to mobilise (Schaller et al., 2016), less delirium (Schweickert et al., 2009) and a decreased length of stay (Schaller et al., 2016). Furthermore, these benefits of improved mobility and function have continued to be measured at discharge from hospital (Schaller et al., 2016, Schweickert et al., 2009). Indeed, six months after critical illness, meta-analysis has demonstrated an increased amount of days out of hospital (Tipping et al., 2017). Early mobilisation is also regularly reported as being safe with low rates of adverse events recorded (Nydahl et al., 2017, Sricharoenchai et al., 2014, Bailey et al., 2007, Stiller et al., 2004).

1.2 RATIONALE FOR CURRENT STUDY

Trials of early ICU mobilisation have shown mixed results to date, with some studies concluding no evidence of beneficial effect of mobilisation on short term outcomes (Denehy et al., 2013, Morris et al., 2016, Moss et al., 2015) and limited long-term beneficial effects (Wright et al., 2018, Morris et

al., 2016, Denehy et al., 2013, Moss et al., 2015). Further, concern remains over potential adverse outcomes resulting from physical rehabilitation interventions on intensive care. Firstly this has arisen from a non-statistically significant increase in mortality demonstrated in a recent meta-analysis (Tipping et al., 2017) requiring further investigation (Cuthbertson and Goddard, 2017). Secondly there are methodological limitations in previous studies, which include a wide variety of defining adverse event criteria (Nydahl et al., 2017), a lack of recording of adverse events (Connolly et al., 2016) and concerns around the heterogeneous population in an ICU and whether safety differs for each individual (Tipping et al., 2017). Therefore measuring the relative benefits and harms of early mobilisation in different subgroups of the ICU population is a current research priority (Connolly et al., 2016, Cuthbertson and Goddard, 2017, Parry et al., 2018)

One subgroup of interest are those patients receiving vasoactive drugs, such as inotropes (drugs aiding contraction of the myocardium) and vasopressors (drugs that constrict the blood vessels to help maintain blood pressure) (Bangash et al., 2012). If a patient requires vasoactive drugs to maintain cardiovascular stability, there may be more risk of adverse events occurring during mobilisation because there is less cardiovascular reserve to cope with the demands of exercise (Stiller and Phillips, 2003). The evidence for the safety of early ICU mobilisation with patients who are receiving vasoactive drugs consists of limited observational data (Rebel et al., 2018, Boyd et al., 2018, Hickmann et al., 2016, Nievera et al., 2016). The current evidence is insufficient to accurately guide clinicians to know when it is safe to start mobilising this patient group.

Greater understanding is required, therefore there is a need for a future randomised controlled trial (RCT) answering the question 'Is it safe to mobilise ICU patients receiving vasoactive drugs? However, before a robust trial can be designed, a study is required to address several uncertainties. To address these uncertainties, it is proposed to carry out an exploratory observational study to prepare to investigate the safety of mobilising ICU patients receiving vasoactive drugs.

This protocol presents phase two of this study, which aims to clarify uncertainties such as potential recruitment and follow-up rate. Additionally, clarification is required as to when clinicians are uncertain about mobilising ICU patients receiving vasoactive drugs. Further, although there is a substantial argument for the existence of equipoise in the literature, it is not known whether clinicians and patients are personally convinced of this equipoise to the extent that randomisation of patients in a clinical trial would be acceptable. Finally, information is required to inform the choice of a suitable primary outcome measure that adequately measures the effects of mobilisation in this group.

2. STUDY OBJECTIVES

Primary objective 1

To describe current practice in one healthcare organisation of mobilising ICU patients receiving vasoactive drugs.

Secondary objectives

1. To measure the mobilisation that occurs while patients receive vasoactive drugs in terms of the type of mobilisation and type and dosage of vasoactive drugs.
2. To describe which patients receiving vasoactive drugs are not mobilised and the reasons why.
3. To measure the adverse event rate occurring in patients mobilised on vasoactive drugs.
4. To describe how clinicians judged the risk of mobilising patients receiving vasoactive drugs.
5. To measure what standard care is in relation to mobilisation treatment milestones.
6. To measure cost of care related to ICU and hospital length of stay and mobilisation received.

Primary objective 2

To describe the preliminary feasibility of measuring the safety of mobilising ICU patients receiving vasoactive drugs.

Secondary objectives

2 a) Recruitment

1. To measure the number of patients who would consent in principle to be recruited into an RCT on the safety of mobilising patients receiving vasoactive drugs and to describe the reasons why patients would not consent.
2. To understand the acceptability to patients and clinicians, of randomising patients receiving vasoactive drugs to an intervention or control arm in a future RCT on the safety of mobilising patients receiving vasoactive drugs.
3. To test the feasibility of clinicians and clinician researchers taking informed consent from patients or their consultees on ICU.

2 b) Sample size

1. To measure mortality, disability, physical functioning and health related quality of life outcome measures of ICU patients to inform a future sample size calculation.

2 c) Outcomes

1. To describe the feasibility of measuring mortality, physical functioning, disability and health related quality of life outcomes to inform a future primary outcome choice.
2. To measure whether an adverse event tool captures all unsafe events that occur during or immediately after early mobilisation of adult intensive care patients receiving vasoactive drugs.
3. To describe the feasibility of an adverse event tool, during clinical practice by ICU clinicians and retrospectively by researchers.

3. STUDY DESIGN

This study is phase two of a two phase feasibility, where phase one (IRAS 251108) is a review of current practice (figure 1).

This study (phase two) will recruit ICU patients to measure preliminary feasibility outcomes using a survey, analysis of mobilisation treatments and assessment outcomes at day 60 post-enrolment.

- a) Firstly clinicians and patients or their consultees will be surveyed about the acceptability of recruitment and randomisation into an RCT. In addition we will measure the feasibility of collecting baseline data on pre-admission function, frailty and comorbidities.
- b) Secondly, we will analyse routine mobilisation treatments of patients receiving vasoactive drugs to describe clinician's reasons for judging whether it was safe to mobilise and the feasibility of a new adverse event tool.
- c) Finally, we will describe the feasibility of measuring outcomes at day 60 to inform the selection of a primary outcome measure.

The duration of this study will be from 01/11/2018 – 09/08/2019.

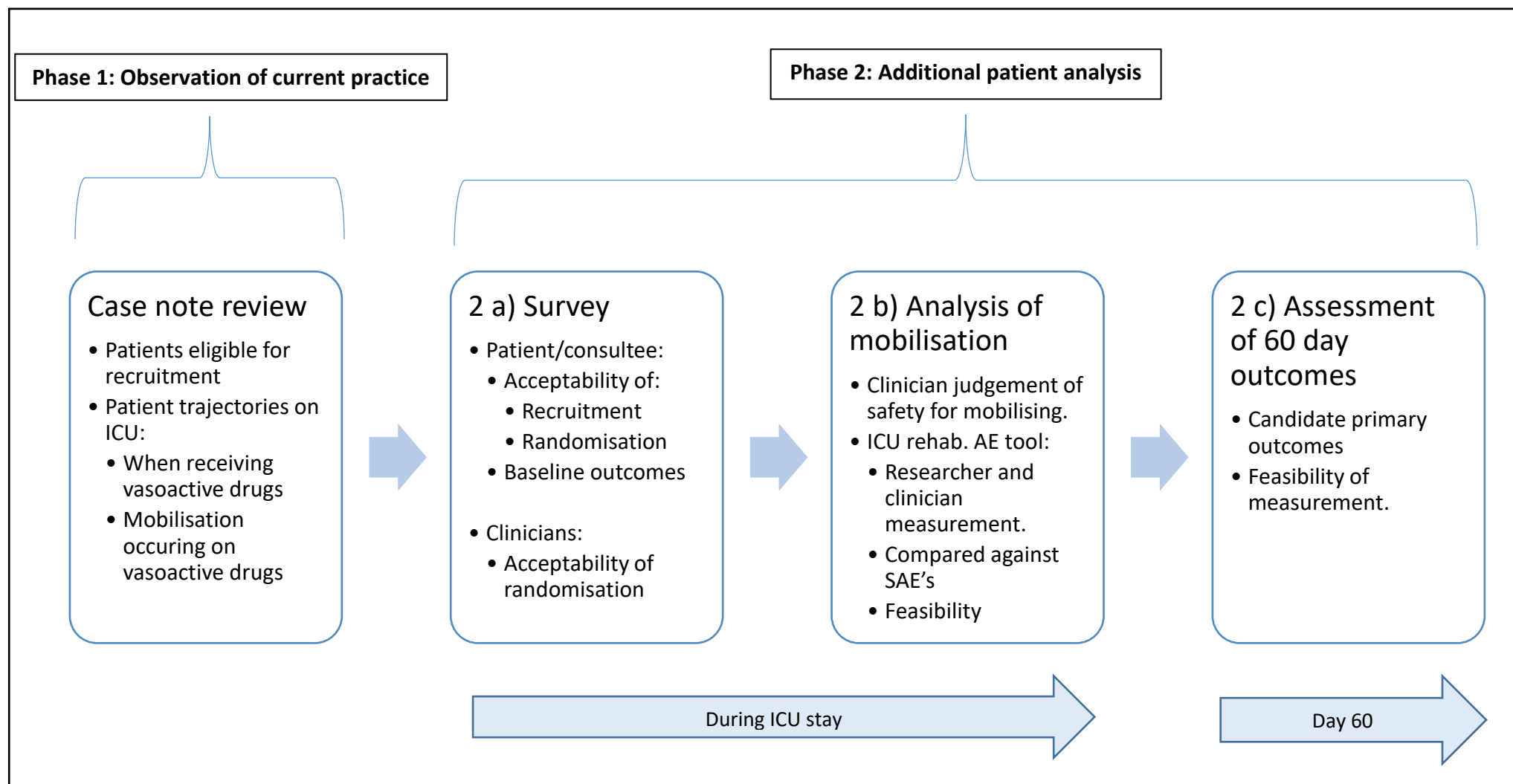


Figure 1: Outline of feasibility study.

ICU: Intensive Care Unit; rehab: rehabilitation; AE: adverse event; SAE: serious adverse event.

3.1 STUDY SETTING

This study will be based at the intensive care units at Imperial College Healthcare NHS Trust. Follow up at day 60 will be coordinated through Imperial College Healthcare NHS Trust (e.g. for telephone questionnaires), with assessment of performance-based outcomes occurring at Imperial College Healthcare NHS Trust.

4. PARTICIPANT ENTRY

Current ICU clinical records will be screened for inclusion and exclusion criteria as set out below. Any uncertainties will be clarified in discussion with other members of the clinical team.

4.1 PRE-REGISTRATION EVALUATIONS

No additional screening procedures will need to be carried out before participants enter the study.

4.2 INCLUSION CRITERIA

4.2.1 Patient participants

- Patients admitted to the ICU who are receiving vasoactive drugs: Patients receiving vasoactive drugs are the group of interest for the potential future RCT.
- Age greater than or equal to 18 years old.
- Expected to remain admitted to the ICU for at least 24 hours post-enrolment to allow potential for mobilisation to occur.

4.2.2 Clinician participants in the survey on acceptability of randomisation

- Clinicians who work in the intensive care unit where a patient participant has been admitted. These clinicians will be answering a survey about a recently recruited patient participant.

4.2.3 Clinician participants in the survey on feasibility of adverse event tool

- An ICU clinician at the research site.
- Has used the ICU physical rehabilitation adverse event tool as part of this research study.

4.3 EXCLUSION CRITERIA

4.3.1 Patient participants

- We will exclude any patient who is expected to die imminently, as per clinical opinion.
- We will exclude any patient where mobilisation is contraindicated by the nature of their existing injuries.
- Where it is clear from the medical records that participants are prisoners or offenders on probation. This is because of the additional ethical implications of including these patients.
- Patients with neuromuscular disease or acute brain injury or spinal cord injury. Exclusion of this group is firstly because early rehabilitation of stroke patients is associated with worse outcomes (Avert Group, 2015, Cuthbertson and Goddard, 2017) and secondly because mobilisation of these patients is much more complex.
- If the patient and/or their consultee is unable to speak English. Spoken English is required for consent and outcome measurement and there is not provision for an interpreter.

4.3.2 Clinician participants in either the survey on acceptability of randomisation or the survey on feasibility of adverse event tool

No exclusion criteria.

4.4 WITHDRAWAL CRITERIA

If participants withdraw their consent, we will not collect further data about them. We will ask the participant's permission for data already collected to be kept and used in the analysis.

5. STUDY PROCEDURES

The main data sources will include the routinely collected clinical data contained within the NHS Trust systems, data provided by the participant/their consultee/proxy and data provided by clinicians. Further details and other data sources are outlined below.

5.1 PARTICIPANT RECRUITMENT DATA

ICU patients will be recruited as set out elsewhere in this protocol and data about recruitment will be collected:

- Standard recruitment data that records the numbers of individuals at the different stages of the study (for example numbers eligible, numbers excluded) and any reason for not taking part at each stage. This will also include details about any consultee advice given.
- Data to inform which research staff will be required for future recruitment of patients in the RCT will be collected by measuring the number of participants recruited by the clinicians (physiotherapists, doctors or nurses), research nurses or clinician researchers.
- Whether the participant was enrolled before the first mobilisation session has occurred to measure whether this is feasible and the day of ICU stay that consent was obtained.

For each participant enrolled, the following procedures will be carried out (figure 1). In addition, for important feasibility outcomes, we have specified feasibility ‘success’ criteria which are an indication to consider future investigation of the mobilisation of patients receiving vasoactive drugs. If these criteria are not met, then further consideration is required before deciding whether future investigation of mobilisation of this patient group is needed.

5.2 DEMOGRAPHIC DATA

Baseline data will be collected for all participants included in the study in order to provide information on the characteristics of patients potentially eligible for a future RCT. This data will be used to describe baseline characteristics (for example age, gender), characteristics of ICU admission (for example reason for admission, APACHE (Acute physiology and chronic health evaluation) II score (Knaus et al., 1985), SOFA (Sequential Organ Failure Assessment) score (Vincent et al., 1998), and the length of time receiving mechanical ventilation and/or non-invasive ventilation. Contact details of the patient and next of kin will be recorded to facilitate day 60 follow-up.

5.3 KEY OUTCOMES

Key outcomes for this exploratory study are:

- Hypothetical recruitment rate for the future RCT.
- Follow-up rate of participants for day-60 outcomes.

More details about these outcomes, plus the secondary outcomes for this study are detailed below.

5.4 SURVEY

5.4.1 Patient/consultee survey

Once a patient has been recruited into the feasibility study, a short survey will be carried out with the patient, or consultee if they were the one to give 'consent' on behalf of the patient. For a full list of the questions / the form where the information will be logged, please see the 'Patient participant initial survey Case Report Form'. Firstly they will be presented with a summary of the future RCT plus three randomisation scenarios for patients receiving vasoactive drugs: (1) early physical rehabilitation or no rehabilitation; (2) early physical rehabilitation or standard care; or (3) 'protocolised care' (where the decision to mobilise is based on a pre-defined risk stratification protocol – based on the results of the results of a previous Delphi study (IRAS project ID: 212066; REC reference: 17/LO/0830)) or standard care. The following outcomes will then be assessed:

- Acceptability of hypothetical recruitment into the future RCT. This will be measured by a hypothetical recruited rate for the future RCT. Reasons why patients would not consent will also be collected. Feasibility 'success' is defined as two patients per ICU per month (Hodgson et al., 2016)
- Acceptability of hypothetical randomisation into the RCT. This will be measured by the number of feasibility participants who would accept the randomisation scenarios described above and the reasons for their decisions.

Recent evidence has shown how comorbidities (Puthuchearry and Denehy, 2015), pre-morbid frailty (Muscedere et al., 2017, Ferrante et al., 2018) and physical function/disability (Ferrante et al., 2015, Biehl et al., 2015) influence long-term physical outcomes and mortality after an ICU admission. As a result, the importance of recording this data for trial participants has been emphasised to ensure that groups are comparable (Azoulay et al., 2017, Connolly and Denehy, 2018). Therefore as part of the above survey, patient co-morbidities (for example using the Functional Comorbidity Index (Groll et al., 2005) and the Charlson Comorbidity Index (Charlson et al., 1987)), pre-morbid frailty (for instance using the Clinical Frailty Scale (Pugh et al., 2018, Rockwood et al., 2005)) and physical functioning (for example using the World Health Organization Disability Assessment Schedule 2.0 (WHODAS 2.0) 36-item or 12-item version (Ustun et al., 2010)) will be measured. The feasibility of measuring baseline comorbidities, frailty and physical functioning through patient or consultee (proxy) reporting or through information contained in the case notes will then be measured by the number of completed outcomes for each patient recruited into the feasibility study. Feasibility 'success' is defined as completing the above

outcomes for 98% of participants. The time point that the above information is collected will also be recorded.

5.4.2 Clinician survey

For each patient recruited into the feasibility study, ICU clinicians (consultant doctor in charge, nurse in charge and the senior physiotherapist following recruitment) will be presented with a brief outline of the future RCT as well as the randomisation scenarios outlined above. This will occur ad hoc on the ICU following recruitment. For a full list of the questions / the form where the information will be logged, please see the 'Clinician survey on acceptability of randomisation Case Report Form'. The following outcome will be measured:

- Acceptability of hypothetical randomisation into a future RCT. This will be measured by the number of clinicians who would accept the randomisation scenarios described above for each patient recruited into the feasibility study, and the reasons for their decisions. Feasibility success is if 80% of participants are acceptable to be randomised (in whichever scenario). The time point that the clinicians are asked will also be recorded.

5.5 ANALYSIS OF MOBILISATION

Whenever a physiotherapist reviews a patient recruited into the feasibility study for potential physical rehabilitation whilst they are receiving vasoactive drugs, they will complete an extra proforma in the case notes. This will record the following data to provide information on the decision-making process on the readiness of a patient to mobilise and the feasibility of using an adverse event tool:

- Who made the final decision whether to mobilise the patient and the reasons for the decision.
- Was the presence of vasoactive drugs a factor in the decision of whether to mobilise, either from the perspective of clinicians or in discussion with the patient/family/carers themselves?
- If a mobilisation treatment is carried out the following will also be completed:
 - The reasons why the mobilisation treatment was stopped. This is measured to capture clinicians perceived risk thresholds for discontinuing mobilisation. This informs the measurement of the usability of the adverse event tool.

- An ICU physical rehabilitation adverse event tool used to measure adverse events that occur during or immediately after the mobilisation treatment. This is a new adverse event tool developed by the authors using an international, expert consensus Delphi process (IRAS project ID: 212066; REC reference: 17/LO/0830). The tool outlines specific adverse events including cardiovascular, respiratory, neurological, airway, attachments, falls and injury related events agreed as important to record when measuring the safety of ICU mobilisation.
- The approximate time taken to complete the adverse event tool to inform the assessment of its feasibility. Feasibility success is defined as less than 5 minutes

Alongside this, a case note review will be completed by the research team for each mobilisation treatment of patients receiving vasoactive drugs enrolled into the feasibility study. The researcher will record ICU physical rehabilitation adverse events and serious adverse events that occur during or immediately after mobilisation treatment. The following outcomes will then be measured:

- ICU rehabilitation adverse event rate and SAE rate. SAEs will be measured during the note review and as reported by clinicians and researchers during the study as part of the mandated safety reporting. This will highlight the most efficient way to collect SAEs and both measures will inform a description of the safety of usual care.
- Description of the number and type of rehabilitation adverse events and serious adverse events. Recorded to measure whether the rehabilitation AE tool is fit for purpose and able to capture all unsafe events that occur in this population of patients mobilising on vasoactive drugs.
- Description of number and type of rehabilitation adverse events recorded prospectively by the treating clinician and retrospectively by researcher case note review. This data will provide information on the usability of the tool and the most feasible way to record AE's in future research.
- Loss of information that occurs when the ICU rehabilitation AE tool is completed by clinicians and researchers will also be recorded to provide feasibility data. For clinicians this will be assessed by the number of mobilisation treatments on vasoactive drugs occurring in patients recruited into the feasibility study where the rehabilitation adverse event tool is not completed or incomplete. For researchers, this will be assessed by the number of mobilisation treatments on vasoactive drugs where the researcher was unable to complete tool using the information available in the case notes. Feasibility success is less than or equal to 10% loss of information.

Towards the end of the data collection period for patients on ICU, a short survey will be carried out of clinicians who completed the ICU rehabilitation adverse event tool. This survey will ask about the usability and feasibility of completing the AE tool in the context of clinical practice.

In addition to the above, the following data will be recorded for participants to further quantify standard care:

- Amount of time the patient received vasoactive drugs during the admission.
- Mobilisation occurring whilst patients are receiving vasoactive drugs, for example, by:
 - Number of patients who are mobilised whilst receiving vasoactive drugs.
 - Number of mobilisation treatment sessions on vasoactive drugs.
 - Number of days on vasoactive drugs where mobilisation treatment occurred.
 - Highest level of mobilisation achieved in each treatment session using the ICU Mobility Scale (IMS) (Hodgson et al., 2014a, Tipping et al., 2016).
 - Type and dose of vasoactive drugs patient received during mobilisation treatment.
- Patients receiving vasoactive drugs who are not mobilising, for example, by:
 - Number of days receiving vasoactive drugs where mobilisation is not occurring.
 - On these days, any documented reasons for not mobilising.

The following outcomes will be used to describe standard care, for potential use as surrogate outcomes in a future pilot trial or feasibility study:

- Time to first mobilisation treatment and whether this first mobilisation treatment occurred whilst the patient was still receiving vasoactive drugs.
- Time to first being able to sit out of bed, stand and walk (regardless of the assistance required) (Nickels et al., 2017, TEAM Study Investigators et al., 2015).
- ICU Mobility Scale (IMS) level at ICU discharge.
- ICU and hospital length of stay.

5.6 ASSESSMENT OF DAY 60 OUTCOMES

To inform the future choice of suitable primary outcome measure for the future RCT, we will describe the feasibility of measuring candidate primary outcome measures at day 60 post-enrolment in the study. Data from outcome measurement will also inform a future sample size

calculation. The following outcomes will be recorded as soon as possible after day 60 post-enrolment.

- Mortality:

Alive/deceased status will be recorded including date of death. This will be confirmed using clinical data contained within the NHS Trust systems, from NHS Spine (a national database held by NHS Digital, but accessible within the research sites to research nurses), or contacting the participant's GP to clarify any uncertainty. The GP will be informed that the participant has been enrolled in the study after consent is taken and will be sent a copy of the participant information sheet. If no date of death is recorded, the participant will be contacted to measure the other outcome measures below. If at this point it is discovered that the participant is no longer alive, then date of death will be recorded as informed by relatives/carers.

- Health-related quality of life:

Measured using the EQ - 5D (5 Level) questionnaire (EQ-5D-5L) (EuroQol, 1990, Herdman et al., 2011, Janssen et al., 2013).

- Disability:

Measured using the World Health Organisation's Disability Assessment Schedule 2.0 (WHODAS 2.0) 36-item or 12-item version (Hodgson et al., 2017, Ustun et al., 2010).

- Physical functioning:

Because they have been shown to measure different components of physical functioning (Denehy et al., 2014), this domain will be measured using a patient-reported outcome measure (for example the physical function domain of the 36-item Short Form Health Survey Version 2 (SF-36 v2) (Ware, 2000, McDowell et al., 2017) or the physical function domain of the RAND 36-Item Health Survey 1.0 Questionnaire (RAND SF-36 v1) (Ware and Sherbourne, 1992, Needham et al., 2017)) and a performance-based outcome (6-Minute Walk Test (6MWT) (Laboratories, 2002, Needham et al., 2017)).

Firstly, the above procedures will be carried out to ascertain the participant's alive/deceased status as close to day 60 post-enrolment as possible. If no evidence of date of death is found, then the participant will be contacted to arrange a suitable time to carry out the rest of the outcomes. Patient-reported outcome measures (questionnaires) will either be carried out over the phone, by post, or in person (e.g. if the participant is still an in-patient at the hospital site). The performance-based outcome will be carried out at the site and reasonable travel expenses reimbursed for participants as appropriate. Outcomes will be recorded as soon after day 60 as possible, with exact time to follow-up being recorded to inform the feasibility of doing so.

Feasibility of outcome measurement will be primarily assessed by the follow-up rate. Other measures of feasibility will include: number of patients where all outcomes are completed plus any reasons why outcomes were not completed, for instance drop out/withdrawal rate, loss to follow up or death. If a participant is deceased at the time of follow-up, then they will still be counted as having completed the other candidate primary outcome measures. The number of patients who completed each individual outcome will also be measured. Measures of central tendency and variability of data for each outcome will inform suitability for future primary outcome measurement and a future sample size calculation for the RCT. Feasibility success for follow-up rate will be 80% minimum (Hodgson et al., 2016). After the 31st May 2019, we will not contact patient participants directly at day 60 follow-up, for example to confirm survival status or to carry out the follow-up questionnaires or walking test. However, in order to maximise participant follow up, we will still confirm survival status by the means set out above that do not involve direct contact with the participant. We will send a letter to patients that we will not follow up in person at day 60, to inform them of the change in study procedures. If retrospective consent has not yet been gained, the letter will be sent to the consultee.

5.7 END OF STUDY

The end of the study will be the completion of 60-day follow up for all recruited participants, or when the end date of the study is reached, whichever occurs first.

6. SAMPLE SIZE

6.1 PATIENT PARTICIPANTS

As outlined above, key outcomes for this study are hypothetical recruitment rate for the future RCT and follow-up rate of participants for day-60 outcomes.

As this is an exploratory observational study with preliminary feasibility objectives, we will aim to recruit as many as possible to estimate these key outcomes before 31st May 2019, with a maximum of **40** participants. This maximum sample size number is based on local experience of what is feasible for recruitment to critical care studies at the host NHS Trust. A similar sample size justification (recruiting as many participants as possible within a pragmatic timeframe) has been used in a similar feasibility study for rehabilitation of patients from critical illness (Salisbury et al., 2010), and is appropriate for the exploratory/preliminary feasibility nature of our study.

6.2 CLINICIAN PARTICIPANTS IN THE SURVEY ON ACCEPTABILITY OF RANDOMISATION

As a maximum, we will aim to survey a nurse, doctor and physiotherapist for each patient participant recruited. Therefore, a maximum sample size of up to **120** clinicians will be recruited for this survey (three clinicians for each of the 40 patient participants). However, it is likely that the final number of clinicians recruited for this survey will be less than 120, for example because it may be appropriate to survey the same clinician for several patient participants.

6.3 CLINICIAN PARTICIPANTS IN THE SURVEY ON FEASIBILITY OF THE ADVERSE EVENT TOOL

We would like to recruit every clinician who has used the ICU physical rehabilitation adverse event tool as part of this research study. We are unable to accurately predict how many will use the tool because we are uncertain how often patient participants will be mobilised. However, a pragmatic estimate is that no more than 50 clinicians will use the adverse event tool. Therefore the sample size for this survey will be a maximum of up to **50** clinicians. If less clinicians use the tool, less clinicians will be recruited.

7. ADVERSE EVENTS

7.1 DEFINITIONS

Adverse Event (AE): any untoward medical occurrence in a patient or clinical study subject.

Serious Adverse Event (SAE): any untoward and unexpected medical occurrence or effect that:

- **Results in death**
- **Is life-threatening** – *refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe*
- **Requires hospitalisation, or prolongation of existing inpatients' hospitalisation**
- **Results in persistent or significant disability or incapacity**
- **Is a congenital anomaly or birth defect**

Medical judgement should be exercised in deciding whether an AE is serious in other situations. Important AEs that are not immediately life-threatening or do not result in death or hospitalisation

but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

7.2 REPORTING PROCEDURES

All adverse events should be reported. Depending on the nature of the event the reporting procedures below should be followed. Any questions concerning adverse event reporting should be directed to the Chief Investigator in the first instance. This study is observational (not involving changes to standard care) therefore we will only monitor for and report AEs and SAEs that are related to study procedures which involve contact with the participant.

7.2.1 Non serious AEs

All such events, whether expected or not, should be recorded.

7.2.2 Serious AEs

An SAE form should be completed and emailed to the Chief Investigator within 24 hours. However, relapse and death due to pre-existing conditions, and hospitalisations for elective treatment of a pre-existing condition do not need reporting as SAEs.

All SAEs should be reported to the Wales Research Ethics Committee 6 where in the opinion of the Chief Investigator, the event was:

- 'related', ie resulted from the administration of any of the research procedures; and
- 'unexpected', ie an event that is not listed in the protocol as an expected occurrence

Reports of related and unexpected SAEs should be submitted within 15 days of the Chief Investigator becoming aware of the event, using the NRES SAE form for non-IMP studies. The Chief Investigator must also notify the Sponsor of all SAEs.

Local investigators should report any SAEs as required by their Local Research Ethics Committee, Sponsor and/or Research & Development Office.

Contact details for reporting SAEs
jrc@imperial.ac.uk
CI email (and contact details below)
Please send SAE forms to: [REDACTED]
Tel: [REDACTED] **(Mon to Fri 09.00 – 17.00)**

8. STATISTICS AND DATA ANALYSIS

For the quantitative data, descriptive statistics will be used to describe and summarise the outcomes set out above. For example the mean and standard deviation or median and interquartile range for continuous variables and numbers and percentages for categorical variables. All qualitative data will be analysed using qualitative content analysis (Elo and Kyngas, 2008).

Where relevant, secondary analysis may be carried out, using descriptive statistics to describe relevant outcomes in different patient subgroups, for example those subgroups defined in a recent Delphi process carried out by the authors (IRAS project ID: 212066; REC reference: 17/LO/0830).

9. REGULATORY ISSUES

9.1 ETHICS APPROVAL

The Study Coordination Centre has obtained approval from the Wales Research Ethics Committee (REC) 6 and Health Regulator Authority (HRA). The study will also receive confirmation of capacity and capability from each participating NHS Trust before accepting participants into the study or any research activity is carried out. The study will be conducted in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions.

Because this study is observational and does not change standard care, we are not aware of any overt risks to participants. The data collected for the study may have several implications. Firstly an extra burden of time on the patient/consultee when carrying out the initial survey after enrolment. In addition there is the burden of time in carrying out the outcome measures at day 60. This data collection will be carried out at a time convenient to the patient/consultee. The most amount of time is required for the patient coming back to the NHS site for the 6 minute walk test. This test would take about 45 minutes and participants will be reimbursed reasonable travel expenses for attending as appropriate. This test would be carried out in a hospital department where other people are close by and can be stopped early if required. Indeed, the purposes of this study is to test whether it is feasible to collect the above outcomes (i.e. is it an acceptable burden to patients) before they are considered in a future trial.

If answering surveys/questionnaires either at the beginning of the study or at day 60 are upsetting to participants, if it is felt appropriate, this will either be escalated to the ICU/hospital team (if an in-patient) or the researcher will signpost the participant to their GP or to the Improving Access to Psychological Therapies service to provide support if needed. If there are concerns about the patients' health at day-60 follow up, the participant's healthcare provider would be informed. One potential risk of collecting additional data for research is that to confidentiality and steps to minimise this are outlined below. Because this study is an observational design, we are not aware of any additional benefits to the patient of taking part.

As this study is an observational design with no changes made to current practice, no conflict of interest between the interests of the researcher and their duty as a health care professional are anticipated. If unsafe practice is identified during the research, this will be escalated to the relevant senior member of the clinical care team, and correct policies of the host NHS Trust followed. If concerns such as unsafe practice were highlighted by patient representatives, the researcher would signpost the patient representative to the relevant Patient Advice and Liaison Service (PALS). Participants will be informed that if they would like to know the study results that they can contact the researchers for a summary. As all data collection will be carried out at the hospital site where other people are present, there are no risks identified for the researchers.

9.2 CONSENT

9.2.1 Identification of potential participants

Potential participants will be identified through screening of routinely collected clinical data contained within the NHS Trust systems by members of the clinical care team.

9.2.2 Approaching potential participants

If inclusion criteria are met and no exclusion criteria are present, potential participants will be directly approached by a member of the clinical research team on the ICU.

Informed consent will be sought from the patient, however because of the nature of their illnesses and treatments on intensive care, there is a potential for a significant proportion not to have capacity to consent. For example, this could be because they have reduced consciousness due to their critical illness or sedation required for mechanical ventilation. In these instances their consultee will be approached instead, then retrospective consent sought from the patient once

they have capacity. This approach will be taken because this is an exploratory study trying to clarify standard care, it is important to gain consent early in an ICU stay so that a full picture of standard care can be gained. Further, our exploratory study is in preparation for a future RCT of ICU mobilisation. Previous trials of ICU mobilisation have tried to start the mobilisation intervention early in an ICU stay. Therefore, for our observational study, when assessing hypothetical acceptability of recruitment for patients, it is important to ask them at an equivalent time in their ICU stay.

9.2.3 Informed consent from the patient

Patients will be provided with a participant information sheet and given a full explanation of the study. Adequate time will be allowed for consideration and written informed consent will be sought if interest is expressed. Potential participants will be given as much time as they want for consideration, although as this study is observational and does not involve a change to clinical practice (and therefore is low risk) consent may be taken less than 24 hours after provision of the participant information sheet if participants are happy to do so. The right of the participant to refuse to participate without giving reasons will be respected. All participants are free to withdraw at any time from the study without giving reasons and without prejudicing further treatment. Signed participant or consultee consent will be obtained by a member of the clinical research team who has completed GCP training and who has received study-specific training. This may include doctors, physiotherapists and research nurses.

Because of the nature of ICU illness and treatment, participant's capacity may fluctuate. If a participant has given informed consent, then loses capacity, we will continue to respect that informed consent decision and continue to include them in the study. However, if the participant has not regained capacity at day 60 follow up, we will not carry out the patient-reported questionnaires or the performance-based outcome measure, recording loss of capacity as the reason. Indeed, measuring that outcomes cannot be completed for this reason is important for answering the study objective on feasibility of outcome measurement, therefore it is important not to completely exclude these patients from the study as it would bias these results.

We will not continue recruitment of patient participants after 31st May 2019 because it is anticipated that adequate recruitment will occur before this date to answer the main research objectives. In addition, as set out above, day 60 follow up involving direct contact with the patient participant will not occur after 31st May 2019.

9.2.4 Consultee advice

If the patient lacks capacity to give informed consent, then the advice of a consultee will be sought on whether the patient would want to participate in the study. In the first instance, the research team will try to contact a personal consultee who is able to advise on the views and feelings of the patient. If their advice cannot be sought within a reasonable timeframe, then the advice of a nominated consultee (i.e. an intensive care consultant at the site – who may or may not be directly responsible for the patient, but not part of the study team) will be sought.

The consultee will initially be approached with a consultee information sheet, the principles of consent will as outlined above and consultee advice will be recorded on a consultee declaration form. If the personal consultee is found after a nominated consultee has signed a consultee declaration form, then the personal consultee's advice will be sought. If the participant is conscious, but does not have capacity, efforts will be made to provide verbal information to them about the research study. If participants appear to object to any study procedures, then their consultee's advice will be sought over whether to continue their participation in the study. If it is clear from the consultee or from the ICU case notes that there is an advanced decision or statement by the participants that makes it clear they would oppose taking part in the research, then their participation will not be sought.

9.2.5 Retrospective consent from the patient

If consultee advice has been gained for a participant, but then the participant regains capacity, then they will be informed of their current participation in the study, then retrospective consent will be sought from them, following the principles outlined above. If the participant wishes to withdraw from the study, we will not collect further data about them. We will ask the participant's permission for data already collected to be kept and used in the analysis. There may be cases where retrospective consent is sought at day-60 follow up. If the participant is physically present at the research site for follow up (for example they are returning to the site to complete the follow up walking test), then written consent will be sought as described above. If the participant is not present at the research site at follow up (for example they are unable to complete the walking test but wish to complete the follow up questionnaires over the phone) then verbal retrospective consent will be sought (and we will offer to post a copy of the retrospective participant information sheet). As outlined above, after 31st May 2019, day 60 follow up involving direct contact with the participant will not be carried out. Therefore, for participants where day 60 occurs after this date, we will continue to seek retrospective consent whilst they remain an in-patient at the research site.

If the participant/consultee is unable to read the information sheet in English, they will not be recruited as there is no financial provision for translators.

9.2.6 Clinician recruitment for survey on acceptability of randomisation

When patient participants are recruited, clinicians will be asked about the hypothetical acceptability of patient participant's randomisation in a future RCT and consent will be sought from clinicians to carry out this survey. Initial approach will be in person or via an information sheet emailed to potential clinical participants. This email will be sent from the clinical research team to the potential clinicians, i.e. sent from members of the clinical team who have routine access to clinician's contact details.

When a clinician is approached to take part in the survey, they will be offered the information sheet again, given a full explanation of the study and adequate time allowed for consideration. Then informed written consent will be sought if interest is expressed. The clinician will be given as much time as they want for consideration, although as completing the survey is low risk, consent may be taken less than 24 hours after provision of the participant information sheet if clinicians are happy to do so. The right of the clinician to refuse to participate without giving reasons will be respected.

Signed consent will be obtained by a member of the clinical research team who has completed GCP training and who has received study-specific training as above. This consent will be for the duration of the study so they can then be asked about acceptability of randomisation for any future patient participants. All clinician participants are free to withdraw at any time from the study without giving reasons.

9.2.7 Clinician recruitment for survey on feasibility of adverse event tool

Towards the end of data collection, clinicians who have used the adverse event tool will be sent a brief survey about the feasibility of its use. Clinicians will be emailed the survey, which will also contain an information sheet about the study. Consent for taking part in this survey will be implied by clinicians returning it to the clinical research team.

Initial approach will be in person, or via email with the survey will be sent from the clinical research team to the potential clinicians, i.e. from members of the clinical team who have routine access to clinician's contact details. Clinicians will be given adequate time for consideration and the right of

the clinician to refuse to participate without giving reasons will be respected. All clinician participants are free to withdraw at any time from the study without giving reasons.

9.3 CONFIDENTIALITY

The Chief Investigator will preserve the confidentiality of participants taking part in the study and is registered under the Data Protection Act. We will maintain confidentiality of personal data in the following ways:

9.3.1 Initial data collection

- Identifiable data will be accessed for this research study by members of the clinical care team. This includes the critical care clinical research nurse team employed by the NHS Trust.
- Participant recruitment into the study will be recorded in the case notes and clinicians will be informed so that they can complete the adverse event tool.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

- All data collected for enrolled participants will be anonymised as soon as feasibly possible.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

9.3.2 Analysis of data

- [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED] This data may include direct quotes from patient

participants and clinicians as recorded in the surveys. These anonymous direct quotes may

also be published and this will be noted on participant information sheets.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

9.3.3 Long-term storage of data

- Data and all appropriate documentation will be stored for a minimum of 10 years after the completion of the study, including the follow-up period, as per Imperial College London Joint Research Compliance Office standard operating procedures.
- Data held at the NHS Trust will be stored and archived for 10 years.
- All anonymised research data transferred to Imperial College London will be archived at Imperial College London for 10 years after the end of the study
- Anonymised data may be shared with other researchers to support other research projects in the future.

9.4 INDEMNITY

Imperial College London holds negligent harm and non-negligent harm insurance policies which apply to this study.

9.5 SPONSOR

Imperial College London will act as the main Sponsor for this study. Delegated responsibilities will be assigned to the NHS trusts taking part in this study.

9.6 FUNDING

This protocol details independent research arising from a Clinical Doctoral Research Fellowship, awarded to Huw Woodbridge, (ICA-CDRF-2015-01-026) supported by the National Institute for Health Research and Health Education England. The views expressed in this protocol are those of the author(s) and not necessarily those of the NHS, the National Institute for Health Research, Health Education England or the Department of Health.

9.7 AUDITS

The study may be subject to inspection and audit by Imperial College London under their remit as sponsor and other regulatory bodies to ensure adherence to GCP and the NHS Research Governance Framework for Health and Social Care (2nd edition).

10. STUDY MANAGEMENT

The day-to-day management of the study will be co-ordinated through Huw Woodbridge. Research management will be provided by Huw Woodbridge, Prof Anthony Gordon, Prof Stephen Brett, Dr Caroline Alexander, and the Imperial College Joint Research Office. A steering group which includes a patient representative will meet regularly to discuss any issues.

11. PUBLICATION POLICY

It is anticipated that this proposal will produce findings that can be disseminated to open access peer-reviewed journals and presented at relevant conferences. Dissemination at a local level will occur by presentations to ICU clinicians at Imperial College Healthcare NHS Trust.

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