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## Improving physical function of patients following Intensive Care Unit admission (EMPRESS): Protocol of a randomised controlled feasibility trial

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# Improving physical function of patients following Intensive Care Unit admission (EMPRESS): Protocol of a randomised controlled feasibility trial

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4 **Improving physical function of patients following Intensive Care Unit admission (EMPRESS):**  
5 **protocol of a randomised controlled feasibility trial**  
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8 **Introduction:** Physical rehabilitation delivered early following admission to the Intensive Care Unit  
9 (ICU) has the potential to improve short and long-term outcomes. The use of supine cycling together  
10 with other rehabilitation techniques has potential as a method of introducing rehabilitation earlier in  
11 the patient journey. The objective of the study is to determine the feasibility of recruitment and  
12 delivery of a randomised clinical trial comparing an early mobilisation programme including cycling  
13 with usual care to inform a larger multicentred study.  
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17 **Methods and Analysis:** 90 acute medical patients from 2 mixed medical-surgical ICUs will be  
18 recruited. We will include within 72 hours of initiation of mechanical ventilation and expected to be  
19 ventilated a further 48 hours or more. Patients will receive usual care or usual care plus two 30-  
20 minute rehabilitation sessions 5 days per week.  
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23  
24 Feasibility outcomes are: i) recruitment 1-2 patients per month per site, ii) protocol fidelity with >  
25 75% of patients commencing interventions within 72 hours of mechanical ventilation, > 70%  
26 interventions delivered and iii) blinded outcome measures recorded at 3 time points in > 80%  
27 of patients. Secondary outcomes are: i) strength and function; the Physical Function ICU Test-scored  
28 (PFITs) measured on ICU discharge, ii) hospital length of stay and iii) mental health and physical  
29 ability at 3 months using the WHODAS 2. An economic analysis using hospital health services data  
30 reported with an embedded health economic study will collect and assess economic and QoL data.  
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37 **Ethics and Dissemination:** The study has ethical approval from South Central Hampshire A  
38 Research Ethics Committee (19/SC/0016). An independent trial monitoring committee is overseeing  
39 the study. Results will be made available to critical care survivors, their caregivers, the critical care  
40 societies and other researchers.  
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44 **Trial registration number:** NCT03771014

45 **Sponsor:** University Hospital Southampton NHS Foundation Trust.  
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50 **Strengths and limitations of study**  
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- 52 • Will investigate the implementation of an early mobilisation intervention, which is usual care  
53 in one NHS/University Teaching institution, in other NHS institutions with different  
54 structures  
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- 56 • The defined cohort has been demonstrated to benefit from this type of rehabilitation in  
57 alternative health care systems  
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- Results will inform the design of a multi-centred RCT
- This study is not designed to assess effectiveness of the intervention
- Inability to blind the intervention to patients, physiotherapist and clinicians involved in the study.

## Introduction

In 2018/19 there were over 290,000 admissions to adult intensive care units (ICU) in the United Kingdom<sup>1</sup>. Treatment advances have reduced mortality associated with critical illness<sup>2,3</sup>, however, survival does not represent the end of the story<sup>4</sup>. A complex interplay between baseline health status, acute disease and the traumatic effects of intensive care treatment is associated with long-term physical, psychological and social hardship with cognitive impairment and substantially reduced quality of life<sup>5-10</sup>. Within the UK, patients discharged from ICU have a higher mortality, higher health service costs and a 50% reduction in employment in the 5-years following discharge, compared to hospitalised patients not requiring ICU<sup>8,11</sup>.

ICU acquired weakness (ICU-AW) is characterised by rapid muscle wasting, polyneuropathy and bone demineralisation, causing pain, weakness and impaired physical function<sup>12-14</sup>. Risk factors are multifactorial although immobility principally due to the sedation required for tolerance of ventilation plays an important role<sup>15,16</sup>. Efforts to mitigate these consequences have included a move towards earlier mobilisation of critical care patients<sup>17,18</sup>, defined as commencing within 5 days of admission to the ICU<sup>19</sup>. A seminal RCT of early mobilisation intensive care patients in 2009 found patients who received early physical therapy (within 1.5 days of mechanical ventilation) had greater functional independence at hospital discharge than the patients who received usual care physical therapy commencing 7.4 days mechanical ventilation (59% vs 35% p=0.02)<sup>20</sup>. While meta-analyses and systematic reviews report that early rehabilitation and mobilisation of ICU patients improves short term physical outcomes<sup>21-23</sup> a number of studies with a delayed start of rehabilitation have not had similar outcomes<sup>24-30</sup>. Physical rehabilitation is difficult to implement early during a patient's stay in the ICU, and often delayed beyond a week after ICU admission<sup>31-33</sup>. Contributory barriers can be attributed to patient factors such as safety concerns, heavy sedation or agitation and organisational factors such as resources and culture within an individual unit<sup>34</sup>. A number of studies report the feasibility and safety of using cycle ergometry in critically ill patients<sup>35-37</sup>. In-bed cycle ergometry can facilitate passive activity in the acute phase of illness in patients who are heavily sedated and receiving vasopressors<sup>38,39</sup> with minimal physiological demand<sup>39,40</sup> and transition to active cycling as the patient's condition improves. Early cycle ergometry has been shown to preserve muscle cross sectional area in patients presenting with septic shock<sup>41</sup>, and greater increase in muscle strength in patients receiving passive cycling<sup>42</sup> However recent systematic reviews do not conclusively report

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2  
3 find any differences in physical function, duration of mechanical ventilation, ICU and hospital length  
4 of stay in patients who received cycle ergometry in ICU <sup>43,44</sup>.

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8 As a Quality Improvement process, we introduced cycle ergometry as part of an early mobility  
9 programme which included employing physiotherapy technician to support the additional workload  
10 involved <sup>45</sup>. Like other investigators our intervention reduced both number of ventilator days and ICU  
11 length of stay indicating potential of cost effectiveness <sup>46-49</sup>. The benefits of such early mobility  
12 programmes are supported by a recent RCT on the impact of a progressive ICU mobility programme  
13 which found that patients who had a progressive mobility programme in addition to usual care had  
14 better functional status at discharge from the ICU <sup>50</sup>

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20 The primary aim of this study is to establish feasibility and trends in efficacy to support a prospective,  
21 randomised, multi-centre study in the UK is needed to determine if early mobilisation including if  
22 cycling in ICU confers patient benefit. This protocol is reported according to SPIRIT <sup>51</sup> and TIDieR<sup>52</sup>  
23 guidelines.  
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### 26 27 28 **Aim and Hypotheses**

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EMPRESS is a randomised feasibility study which aims to assess if an early mobilisation programme  
that includes cycling can be delivered, with follow-up assessments, in two NHS Intensive Care Units  
in the UK. We hypothesise that early rehabilitation with cycling will be successfully carried out in  
critically ill patients in ICU with acceptable intervention fidelity.

## 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60 **METHODS AND ANALYSIS**

### **Study design:**

This is a two-centre feasibility study using a two-arm RCT, randomised 1:1, with blinded outcome  
assessments at ICU discharge, hospital discharge and 3-month follow-up. Participants will be  
recruited from two general intensive care units, located in the south of the UK. Each site will have a  
principal investigator from the NIHR Clinical Research Network, experienced in delivering clinical  
trials.

### **Participants:**

Ninety participants meeting eligibility criteria will be recruited. Eligible patients will be over 42 years  
old and have an acute/unplanned medical admission to the ICU. They will be functionally  
independent prior to ICU admission (Barthel Index >80), in hospital for <5 days prior to intubation  
and ventilation, intubated and ventilated for <72 hrs and expected to remain ventilated for a further  
48 hours. Patients will be excluded if in hospital for 5 days or more prior to ICU admission, have  
acute brain or spinal cord injury, known or suspected neurological / muscular impairment, condition

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3 limiting use of cycle ergometry (e.g. lower limb fracture / amputation), not expected to survive >48hrs  
4 decided by consulting Intensivist, persistent therapy exemptions in first 3 days of mechanical  
5 ventilation. (Figure 1) presents the planned flow of patients through the study.  
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### 8 9 **Recruitment, consent and randomisation:**

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11 ICU researches will screen all patients for trial eligibility. Recruitment began in June 2019 (and was  
12 temporarily suspended in March 2020 due to the COVID 19 pandemic). It is anticipated recruitment  
13 will continue until early 2022. The majority of participants will have diminished capacity, therefore,  
14 the consent process is multi-layered and designed in accordance with the Mental Capacity Act (MCA)  
15 2005<sup>53</sup> (Figure 2). *Patient Informed Consent*: Wherever possible, informed consent will be directly  
16 sought from the patient. *Personal Consultee Informed Assent*: If the participant is unable to provide  
17 consent, informed assent will be sought from the patient's personal consultee, within 6 hours of  
18 confirmation of eligibility. If the personal consultee is not available in person, attempts will be made  
19 to contact them by telephone. They will be asked to provide written assent, at the earliest possible  
20 convenience. *Professional Consultee Informed Assent*: Where both patient and personal consultee  
21 are not available to approve enrolment within 6 hours of confirmation of eligibility, assent will be  
22 sought from a professional consultee in accordance with the MCA. The professional consultee will  
23 be a consultant medical practitioner, independent from the study. The patient's personal consultee  
24 will be consulted at the earliest possible opportunity and assent requested to continue in the study.  
25 In all cases, once the participant has regained capacity they will be informed of the study and consent  
26 continuation sought. Following consent or assent, patients will be registered on a bespoke electronic  
27 data collection tool (ALEA™) and randomly assigned to early mobilisation or usual care.  
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### 39 **Staff Training/ site set-up:**

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41 Participating sites will employ the equivalent of a full-time therapy technician to deliver the study  
42 intervention, under the supervision of a senior critical care therapist. Both senior critical care  
43 therapists and therapy technicians will complete a training package delivered by the primary  
44 institution (University Hospital Southampton), where early rehabilitation with cycling is well  
45 established and embedded in usual care. This includes seminars on the delivery of early mobilisation,  
46 use of the bespoke electronic database and 5-days of clinical shadowing. An electronic copy of the  
47 full training program used at the primary institution has been given to the study sites for reference.  
48 The manufacturer supplied additional training on use of the cycle ergometer.  
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### 55 **Interventions:**

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57 All participants will receive usual medical, nursing and physiotherapy care while in intensive care.  
58 Each bedside nurse will be asked at the start of the shift if they have been involved caring for a patient  
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3 in the intervention arm of the study. The ICU physiotherapy team, who are not involved in delivery  
4 of the study intervention, will deliver all usual physiotherapy interventions in both groups. The  
5 physiotherapist delivering usual care will be asked to verify if they have delivered any of the study  
6 interventions. At the start of each physiotherapy intervention the participants level of sedation will  
7 be assessed using the Richmond Agitation-Sedation Scale (RASS)<sup>54,55</sup> and the Confusion Assessment  
8 Method for ICU (CAM-ICU)<sup>56</sup>. Sedation will be targeted to a RASS between -1 and +1 by the  
9 bedside nurse. After 28 days of ICU admission, all participants will receive usual care physiotherapy  
10 interventions.  
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16 Group 1: Usual care control group

17 Participants will receive physiotherapy interventions guided by individual assessment prior to each  
18 intervention. This includes, where appropriate, passive or active range of movement (PROMs),  
19 positioning and respiratory physiotherapy, and when able, sitting on the edge of the bed, standing  
20 (assisted or unassisted), standing to transfer to chair, marching on the spot and walking . (Figure 3).  
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23 Group 2: Early mobilisation pathway

24 Participants will receive usual care physiotherapy, in addition to commencing the early mobilisation  
25 pathway within 72 hours of ICU admission. Participants will be screened for criteria to withhold the  
26 intervention prior to each planned intervention session(Table 1).  
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**Table 1 Safety criteria for delivery of physical therapy interventions**

|                    | <b>Criteria to commence physiotherapy</b>   | <b>Criteria to stop / withhold physiotherapy intervention</b>  |
|--------------------|---|--|
| Blood pressure     | MAP 60 – 100 mmHg, no change in vasopressor dose requirement for preceding 2 hours                          | Catecholamine resistant hypotension with MAP < 60 mmHg   |
| Heart rate         | Between 40-140 bpm  | <50 or >140 bpm  |
| Respiratory rate   | Sustained < 40 breaths/min  | Sustained >40 breaths/min  |
| Temperature        |   | >40 °C   |
| Oxygen requirement | If FiO <sub>2</sub> >0.8 for passive exercise only<br>FiO <sub>2</sub> <0.8 and PEEP <15 cmH <sub>2</sub> O |  |
| Desaturation       |   | Sats fall <85% for > 1 minute  |
| Other              |   | <ul style="list-style-type: none"> <li>· Fall</li> <li>· Unplanned extubation</li> <li>· Acute bleeding</li> <li>· New onset arrhythmia</li> <li>· Signs/symptoms of acute myocardial ischaemia</li> <li>· Patient pain/distress</li> <li>· Clinical team decide therapy intervention not appropriate</li> <li>· Refusal by patient or representative</li> </ul> |

Those meeting criteria to withhold intervention will have issues addressed and will be reassessed for intervention 2 hours later. Usual physiotherapy will be delivered by the ward physiotherapists. Additional mobilisation sessions will be delivered by the research physiotherapy staff. This will initially comprise one additional mobility session, chosen at the discretion of the physiotherapist, plus one 30-minute session of supine cycling.

The first mobilisation intervention each day will include activities such as PROMS, passive cycling, active cycling, in bed exercises, sitting, mobilisation out of bed and walking. Daily assessment of the patient will be made to ensure the highest level of activity is provided for each individual patient.

The second session will be cycling based. We will use an in-bed supine cycle ergometer (MotoMed

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3 Letto 2™) to engage in passive, assisted or active cycling, or a combination, depending on the degree  
4 of patient co-operation (Figure3). The aim is for the patient to have 30 minutes of cycling per day,  
5 following a standardised cycling programme. If cycling is in passive mode, they commence cycling  
6 at 5 revolutions per minute (RPM), building up to 20 RPM over a 5-minute period and continue this  
7 for 20 minutes before 5-minute 5RPM cool down. In the assisted or active mode, after the 5-minute  
8 warm up, cycling will continue for 20 minutes at patient selected RPM followed by a 5-minute cool  
9 down at 5 RPM. In-bed cycling sessions will stop when the patient is deemed to be able to stand and  
10 transfer from bed to chair for both mobility sessions for two consecutive days. If participants are  
11 considered unable to have concurrent mobility therapy and respiratory weaning, mobility therapy will  
12 take priority, in agreement with the senior clinical team. Individual participants will receive the trial  
13 intervention on five days per week (Monday to Friday) for the duration of their ICU stay or maximum  
14 of 28 days whichever comes first. Participants will be monitored for cardiovascular and respiratory  
15 stability and safety of indwelling lines, tubes and catheters with pre-determined criteria for  
16 termination of any session (Table 1). Deviations from the planned protocol will be reported to  
17 determine potential barriers to implementation. Participants will be able to decline any intervention  
18 or outcome assessment at any time without compromise to their care.  
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### 30 **Feasibility outcomes: Primary Outcomes**

31 Feasibility will be determined by measures of the recruitment process, intervention fidelity and  
32 outcome measurement completeness, specifically:  
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- 34 1. Study accrual rates: a minimum of 30% of eligible patients or 1-2 patients per site per month  
35 are enrolled
- 36 2. Protocol adherence: 75% of patients commencing intervention within 72 hours of ICU  
37 admission; minimum of 70% of planned interventions delivered
- 38 3. Blinded outcome assessment: functional assessment performed at 3 time-points in 80% of  
39 survivors.  
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### 46 **Secondary Outcomes:**

47 The schedule of outcome assessments is detailed in Table 2  
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### **Strength and Function**

We will measure the Physical Function ICU Test-scored (PFITs) measured at awakening as described by deJonghe<sup>57</sup> then weekly within ICU and on ICU discharge<sup>58</sup>. PFITs is a reliable and valid 4 item scale (arm strength, leg strength, ability to stand and step cadence), with a score range of 0-10 and is responsive to change and predictive of key outcomes<sup>59</sup>. Medical Research Council Manual Muscle Test Sum Score (MRC-ss)<sup>60 61</sup> and Hand Held Dynamometry (HHD)<sup>62</sup> will be measured on awakening, weekly, on ICU discharge and hospital discharge. Chelsea Critical Care Physical Assessment tool (CPAX)<sup>63</sup> and ICU Mobility Scale<sup>64</sup> will be assessed three times during the first week within ICU, on awakening, weekly thereafter within the ICU and at ICU discharge. Timed Up and Go (TUG)<sup>65 66</sup>, Clinical Frailty Score (CFS)<sup>67-69</sup> and Barthel Index will be assessed at ICU discharge, hospital discharge and 3-months post-hospital discharge. Pre-admission Barthel Index and CFS will be assessed by proxy on admission from family member or next of kin. Six-minute walk test (6MWT)<sup>70</sup> will be performed, in accordance with American Thoracic Society guidelines, at hospital discharge and 3-months post-hospital discharge.

### **Health related quality of life Outcomes**

The following will be measured at 3-months post-hospital discharge : WHODAS-2.0<sup>71</sup>, Hospital Anxiety and Depression Score (HADS)<sup>72 73</sup>, Euroqol-5 Dimension-5Level (EQ-5D-5L)<sup>74</sup>, Impact of Event Score (IES)<sup>75</sup> and Client Service Receipt Inventory questionnaire (CSRI), designed for this study to evaluate costs that fall on patients and their carers. Resource use and costs including direct intervention costs of therapists and equipment and General Hospital costs (per bed day) will be recorded for each patient

### **Health economic sub-study**

Alongside the feasibility RCT we will conduct an embedded health economic study with the aim to identify and define data collection for the future RCT where a full cost effectiveness analysis (CEA) will be conducted. Within the feasibility study we aim to address the following research questions: what is the quality of the data and potential problems reporting QoL (EQ-5D-5L), resource use and costs; what are the cost implications of the proposed intervention in terms of impact for the NHS (inpatient stay bed days) and identifying the main cost drivers; is the EQ-5D-5L appropriate for use in the future RCT. The economic outcomes will include: secondary care resource use from hospitals during inpatient stay, primary care resource use following discharge up to 3m and resource use providing the intervention. The results will be reported in the form of descriptive statistics and will be used to inform a future CEA within a definitive RCT.

### **Additional data collection**

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3 We will collect baseline data including demographic information, Functional Comorbidity Index,  
4 ICU diagnosis, APACHE II score, ventilation duration, ventilator free days, ICU and hospital  
5 length of Stay, within ICU drug history and duration and type of usual care physiotherapy.  
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### 9 **Implementation Evaluation**

10 We aim to investigate whether the early mobilisation programme used in one NHS institution is  
11 transferable, as an RCT, into other similar NHS health institutions. The design of a future multi-  
12 centre study will be informed by identified facilitators and barriers to implementation.  
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14 Implementation assessment will be based on the measures described by Proctor <sup>76</sup>. A cross section  
15 of ICU staff and patients will complete questionnaires at trial completion by direct questioning and  
16 use of questionnaires. Understanding of the integration and sustainability of the intervention are  
17 necessary to inform the design of a powered RCT. Acceptability will be measured at the beginning  
18 and end of the study from investigators and clinical staff by direct discussions and questionnaire.  
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20 Our experience informs us that the introduction of this intervention is dependent on a cultural  
21 change within any unit for a pro-active focus on early mobilisation. We aim to explore measures to  
22 help optimise implementation. Adoption, feasibility and fidelity measures will be monitored during  
23 the study by regular meetings with the investigators. Patient screening logs will identify the number  
24 of patients eligible for the study and barriers to enrolment. We will assess the degree to which it is  
25 possible to separate the staff caring for the intervention group from those caring for the patients in  
26 the control group.  
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39 We will report whether trial participation has influenced usual care within the participating units by  
40 pre- and post-study audits. Participating sites will collect data regarding number and seniority of  
41 therapy staff with dedicated time to work within the ICU; delirium and sedation protocols used;  
42 time, type and frequency of rehab interventions delivered, who delivers the interventions and  
43 reasons why usual care may not be delivered.  
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45 The feasibility outcomes are described above and will be used to power a full randomised control  
46 trial.  
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### 51 **Data entry and checks**

52 Data will be entered into the electronic case report form (ALEA™) and data validation will take  
53 place according to the procedures set out in the data management plan and data validation plan,  
54 both developed apriori. Missing data will be assessed to identify any specific challenges with any  
55 items of data collected. Missing data level expected to be less the 20%. Data loss and mortality will  
56 inform number of participants needed to design a larger randomised trial. As this is a feasibility  
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3 study data imputation will not be undertaken. Prior to statistical analysis, variables will be checked  
4 for missing and impossible and improbable values as defined by clinical opinion. Questions  
5 regarding the data will go to the data manager.  
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### 10 **Sample size calculation**

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12 This is a feasibility study the results of which will be used to power a definitive study if  
13 appropriate, as such no formal sample size calculation has been undertaken. A total of 90  
14 participants will be recruited to this study aiming for 30-45 participants at each site. We anticipate  
15 a 30% in hospital mortality /loss to follow-up with an estimated total of 60 patients completing the  
16 study. This sample size will provide enough data to be representative of the population of ICU  
17 patients requiring rehabilitation.  
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### 23 **Statistical analysis**

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25 The analysis will be reported in line with the feasibility studies extension to the CONSORT  
26 statement<sup>77</sup>. The main aims of the study are to estimate the recruitment, compliance and retention  
27 rates to inform the design of a future study and is not powered for hypothesis testing regarding the  
28 effectiveness of the intervention. Baseline and demographic characteristics of randomised  
29 participants will be summarised and the two groups compared to ensure balanced recruitment.  
30 Mortality and participant drop out will be examined. Primary and secondary outcome measures will  
31 be presented using summary statistics using means and standard deviations or medians and  
32 ranges/interquartile ranges, as applicable.  
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### 39 **Trial management**

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41 The Chief Investigator will ensure all study personnel are appropriately orientated and trained,  
42 oversee recruitment and report to the trial safety monitoring committee. Training will occur across  
43 sites using competency based training developed at the primary site (University Hospital  
44 Southampton). A study steering group, consisting of an independent chair, expert members and 2  
45 lay advisors will meet every 3-months. Fortnightly teleconferences with trial sites will be held to  
46 monitor conduct and progress. Timing and intervals of visits and teleconferences will be reviewed  
47 at 3 months to ensure optimal time use.  
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52 The CI and PIs will facilitate local monitoring by the R&D quality manager, REC review and  
53 provide access to source data as required. A monitoring report will be produced, summarising the  
54 visit, documents and findings. The CI will ensure that all findings are addressed appropriately. The  
55 steering group will review all events in a timely manner. Additional monitoring will be scheduled  
56 where there is evidence or suspicion of non-compliance with the Study protocol.  
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3 A Data Management and Safety Committee will be chaired by an independent expert. Quarterly  
4 reports will be given to the committee once recruitment has commenced.  
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### 7 **Patient and Public Involvement**

8 The study has been supported by patient advisory representatives. These representatives are  
9 members of the trial steering committee. Patient advisors partnered with us for the design of the  
10 study, the informational material to support the intervention, the burden of the intervention from the  
11 patient's perspective and contributed to the dissemination plan  
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### 15 **Ethics and dissemination**

16 Ethical approval has been granted by South Central - Hampshire A Research Ethics Committee  
17 (REC reference 19/SC/0016). EMPRESS was registered with clinicaltrials.gov NCT03771014 on  
18 December 10<sup>th</sup> 2018.  
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23 Results of this proposed feasibility study will be disseminated for four key audiences: i) patients  
24 and public; ii) Intensive care staff, healthcare workers and potential future research delivery  
25 partners; iii) service delivery organisations and iv) academic and potential future research  
26 collaborators. Dissemination activities will include: Feedback to PPI study focus group, feedback to  
27 study participants, presentations to local clinical teams and managers and commissioners and  
28 presentation at conferences attended by appropriate healthcare professionals. Where appropriate,  
29 results will be published in peer reviewed journals.  
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### 36 **Safety and adverse events**

37 Early mobility within ICUs is safe. In a review of physiotherapy in a critical care rehabilitation  
38 programme of 2.5years, 1110 patients received 5267 rehabilitation sessions physiological  
39 abnormalities or potential adverse events occurred in only 6 per 1000 interventions<sup>78</sup>. Of these  
40 patients 628 intervention sessions included in-bed cycling with 1 safety event. Mobilisation  
41 interventions will only be delivered if patients fit the safety criteria defined in table 1. Similar safety  
42 criteria have been used in other ICU rehabilitation studies<sup>79 80</sup> .  
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45 All interventions will be documented. Any intervention will cease according to stopping criteria  
46 detailed in table 1. Any such event will be recorded as an adverse event. The Chief Investigator will  
47 provide a monthly update to the safety monitoring committee. Serious adverse events are events that  
48 result in death, are life threatening or require prolonged hospitalisation. Any such event will be  
49 reported in accordance with the NHS Health Research Authority guidance.  
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### 59 **Discussion:**

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3 Empress is a feasibility study to determine if an early mobilisation programme, that includes cycling  
4 can be delivered in ventilated patients, with blinded follow-up assessments. It is not powered to  
5 determine any potential effectiveness or cost-effectiveness of the early mobility programme described  
6 however the results of this study will inform the design of a future multi-centre RCT. In-bed cycle  
7 ergometry circumvents the need for volitional engagement from the patient enabling our  
8 physiotherapy interventions to commence very soon after the patient's admission to intensive care.  
9 The protocol facilitates early initiation of the intervention, commencing when the patient is  
10 physiologically stable but may still be heavily sedated and receiving vasopressors, with progression  
11 from passive to active in-bed cycling and then to out of bed mobility activities as the patient becomes  
12 more engaged. Due to the increased workload of delivering the additional physiotherapy sessions,  
13 the physiotherapy team will be supported by a full-time therapy technician to the therapy team.  
14 Economic and implementation evaluations will determine cost effectiveness and identify challenges  
15 that will need to be considered in the design of a future larger study.  
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31 the original idea for the study, RJC, LD, IR, NH, AD, GS, ID, MPWG developed the trial protocol,  
32 IR devised the statistical analysis plan, MC developed the economic analysis. AB, GS, ID and RJC  
33 prepared and submitted documents for Research and Development and ethical approval. RJC, KM  
34 and AB wrote the manuscript. All authors reviewed the final version.  
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43  
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46 **Competing Interests:** None Declared  
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49 **Ethics Approval:** The study has ethical approval from South Central Hampshire A Research Ethics  
50 Committee (19/SC/0016).  
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54 application  
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58 **Disclaimer:** The views expressed are those of the author(s) and not necessarily those of the NIHR,  
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Table 2 Schedule of assessments

|                                      | Randomisation | Day 1 | Day 3 | Day 7 | Awakening | Weekly | ICU Discharge | Hospital Discharge | 3 months post hospital discharge |
|--------------------------------------|---------------|-------|-------|-------|-----------|--------|---------------|--------------------|----------------------------------|
| <b>Demographic Data</b>              | X             |       |       |       |           |        |               |                    |                                  |
| <b>Muscle assessment:</b>            |               |       |       |       |           |        |               |                    |                                  |
| MRCss <sup>60,61</sup>               |               |       |       |       | X         | X      | X             | X                  |                                  |
| Grip strength <sup>62</sup>          |               |       |       |       | X         | X      | X             | X                  |                                  |
| <b>Physical function:</b>            |               |       |       |       |           |        |               |                    |                                  |
| CPAX <sup>63</sup>                   |               | X     | X     | X     | X         | X      | X             |                    |                                  |
| ICU mobility <sup>64</sup>           |               | X     | X     | X     | X         | X      | X             |                    |                                  |
| PFITs <sup>59</sup>                  |               |       |       |       | X         | X      | X             |                    |                                  |
| Timed-Up and Go (TUG)                |               |       |       |       |           |        | X             | X                  | X                                |
| Clinical Frailty Score <sup>69</sup> |               | (X)   |       |       |           |        | X             | X                  | X                                |
| Barthel Index                        |               | (X)   |       |       |           |        | X             | X                  | X                                |
| 6-minute walk test <sup>70</sup>     |               |       |       |       |           |        |               | X                  | X                                |

| HRQL:                               |   |
|-------------------------------------|---|
| WHODAS 2 <sup>71</sup>              | X |
| HADS <sup>72,73</sup>               | X |
| EQ5D-5L <sup>74</sup>               | X |
| Impact of Event Scale <sup>75</sup> | X |
| Health Economic Evaluation (CSRI)*  | X |

Physical Function ICU Test-scored (PFITs); Medical Research Council Manual Muscle Test Sum Score (MRC-ss); Chelsea Critical Care Assessment Tool (CPAX); World Health Organisation Disability Assessment; Euroqol 5 dimension 5 level health related quality of life questionnaire; Hospital anxiety and depression scale (HADs); Client service receipt inventory(CSRI)

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Table 2 Schedule of assessments

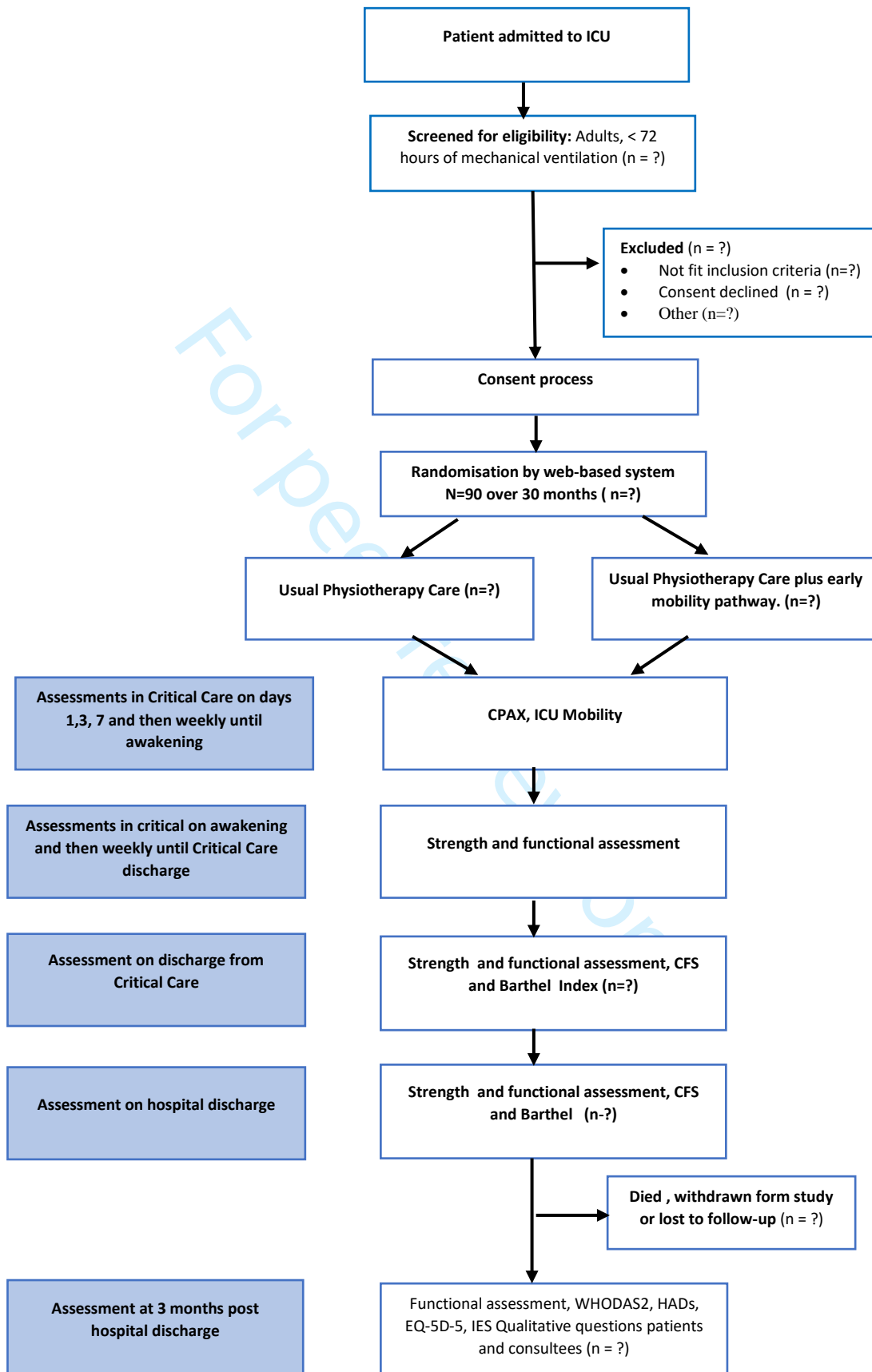
|                                      | Randomisation | Day 1 | Day 3 | Day 7 | Awakening | Weekly | ICU Discharge | Hospital Discharge | 3 months post hospital discharge |
|--------------------------------------|---------------|-------|-------|-------|-----------|--------|---------------|--------------------|----------------------------------|
| <b>Demographic Data</b>              | X             |       |       |       |           |        |               |                    |                                  |
| <b>Muscle assessment:</b>            |               |       |       |       |           |        |               |                    |                                  |
| MRCss <sup>60,61</sup>               |               |       |       |       | X         | X      | X             | X                  |                                  |
| Grip strength <sup>62</sup>          |               |       |       |       | X         | X      | X             | X                  |                                  |
| <b>Physical function:</b>            |               |       |       |       |           |        |               |                    |                                  |
| CPAX <sup>63</sup>                   |               | X     | X     | X     | X         | X      | X             |                    |                                  |
| ICU mobility <sup>64</sup>           |               | X     | X     | X     | X         | X      | X             |                    |                                  |
| PFITs <sup>59</sup>                  |               |       |       |       | X         | X      | X             |                    |                                  |
| Timed-Up and Go (TUG)                |               |       |       |       |           |        | X             | X                  | X                                |
| Clinical Frailty Score <sup>69</sup> |               | (X)   |       |       |           |        | X             | X                  | X                                |
| Barthel Index                        |               | (X)   |       |       |           |        | X             | X                  | X                                |
| 6-minute walk test <sup>70</sup>     |               |       |       |       |           |        |               | X                  | X                                |
| <b>HRQL:</b>                         |               |       |       |       |           |        |               |                    |                                  |
| WHODAS 2 <sup>71</sup>               |               |       |       |       |           |        |               |                    | X                                |
| HADS <sup>72,73</sup>                |               |       |       |       |           |        |               |                    | X                                |
| EQ5D-5L <sup>74</sup>                |               |       |       |       |           |        |               |                    | X                                |
| Impact of Event Scale <sup>75</sup>  |               |       |       |       |           |        |               |                    | X                                |
| Health Economic Evaluation (CSRI)*   |               |       |       |       |           |        |               |                    | X                                |

Physical Function ICU Test-scored (PFITs); Medical Research Council Manual Muscle Test Sum Score (MRC-ss); Chelsea Critical Care Assessment Tool (CPAX); World Health Organisation Disability Assessment; Euroqol 5 dimension 5 level health related quality of life questionnaire; Hospital anxiety and depression scale (HADS); Client service receipt inventory(CSRI)

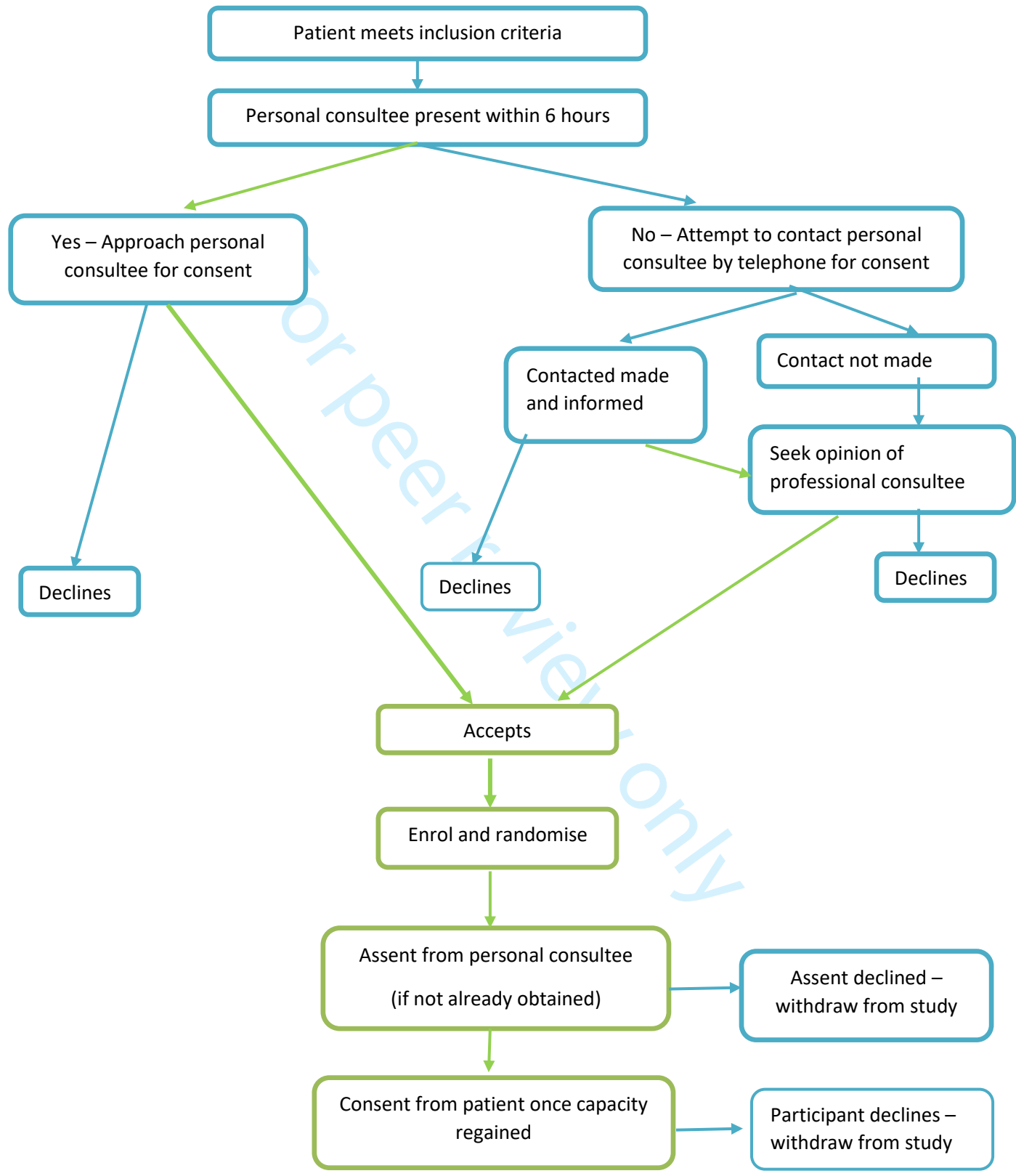


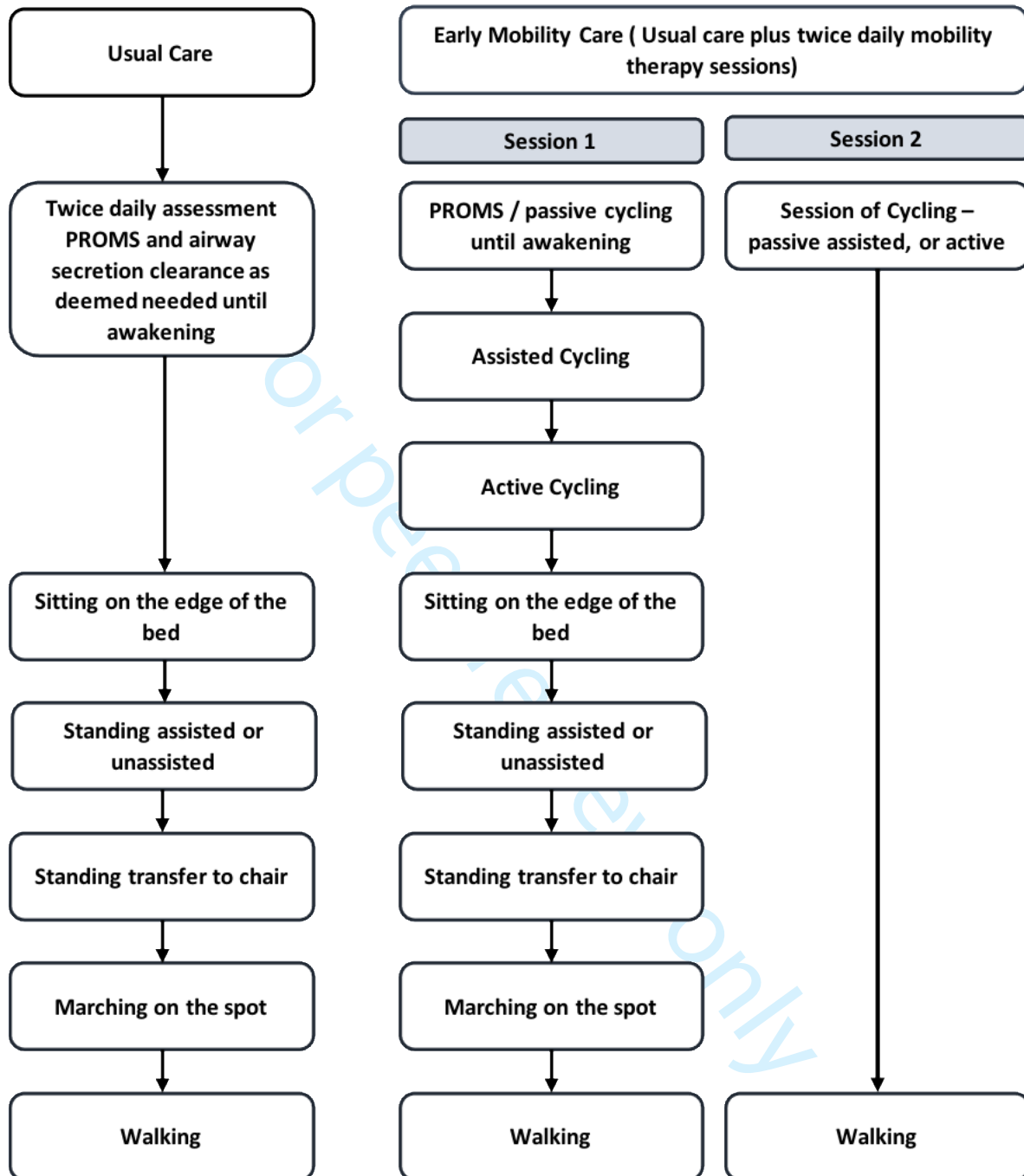
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# BMJ Open

## Improving physical function of patients following Intensive Care Unit admission (EMPRESS): Protocol of a randomised controlled feasibility trial

|                                 |   |
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| Keywords:                       | Adult intensive & critical care < INTENSIVE & CRITICAL CARE, Quality in health care < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, REHABILITATION MEDICINE  |
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# Improving physical function of patients following Intensive Care Unit admission (EMPRESS): Protocol of a randomised controlled feasibility trial

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Keywords: Critical care, physical therapy, rehabilitation, cycling

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3 **1 Improving physical function of patients following Intensive Care Unit admission (EMPRESS):**  
4 **2 protocol of a randomised controlled feasibility trial**  
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8 **4 Introduction:** Physical rehabilitation delivered early following admission to the Intensive Care Unit  
9 (ICU) has the potential to improve short and long-term outcomes. The use of supine cycling together  
10 with other rehabilitation techniques has potential as a method of introducing rehabilitation earlier in the  
11 patient journey. The aim of the study is to determine the feasibility of delivering the designed protocol  
12 of a randomised clinical trial, comparing an protocolised early rehabilitation programme including  
13 cycling with usual care. This feasibility study will inform a larger multicentre study.

14 **10 Methods and Analysis:** 90 acute medical patients from 2 mixed medical-surgical ICUs will be  
15 recruited. We will include ventilated patients within 72 hours of initiation of mechanical ventilation  
16 and expected to be ventilated a further 48 hours or more. Patients will receive usual care or usual care  
17 plus two 30-minute rehabilitation sessions 5 days per week.

18 Feasibility outcomes are: i) recruitment 1-2 patients per month per site, ii) protocol fidelity with > 75%  
19 of patients commencing interventions within 72 hours of mechanical ventilation, > 70% interventions  
20 delivered and iii) blinded outcome measures recorded at 3 time points in > 80% of patients. Secondary  
21 outcomes are: i) strength and function; the Physical Function ICU Test-scored (PFITs) measured on  
22 ICU discharge, ii) hospital length of stay and iii) mental health and physical ability at 3 months using  
23 the WHODAS 2. An economic analysis using hospital health services data reported with an embedded  
24 health economic study will collect and assess economic and QoL data including Hospital Anxiety and  
25 Depression score (HADS), Euroqol-5 Dimension-5Level (EQ-5D-5L) and the Impact of Event Score  
26 (IES). .  
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41 **24 Ethics and Dissemination:** The study has ethical approval from South Central Hampshire A Research  
42 Ethics Committee (19/SC/0016). All amendments will be approved by this committee. An independent  
43 trial monitoring committee is overseeing the study. Results will be made available to critical care  
44 survivors, their caregivers, the critical care societies and other researchers.  
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47 **28 Trial registration number:** NCT03771014

48 **29 Sponsor:** University Hospital Southampton NHS Foundation Trust.  
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54 **32 Strengths and limitations of study**

- 55 33
- 56 34 • Will investigate the implementation of an protocolised early rehabilitation intervention, that is  
57 35 usual care in one NHS/University Teaching institution, in other NHS institutions with different  
58 organisational structures  
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- The defined cohort has been demonstrated to benefit from this type of rehabilitation in alternative health care systems
- Results will inform the design of a multi-centre randomised controlled trial (RCT)
- This study is not designed to assess effectiveness of the intervention
- Inability to blind the intervention to patients, physiotherapist and clinicians involved in the delivery of the intervention.

## Introduction

In 2018/19 there were over 290,000 admissions to adult ICUs in the United Kingdom (UK)<sup>1</sup>. Treatment advances have reduced mortality associated with critical illness<sup>2,3</sup>, however, survival does not represent the end of the story<sup>4</sup>. A complex interplay between baseline health status, acute disease and the traumatic effects of intensive care treatment are associated with long-term physical, psychological and social hardship<sup>5-10</sup>. Patients discharged from ICU have higher mortality, higher health service costs and a reduction in employment status compared to hospitalised patients not requiring ICU<sup>8,11</sup>.

ICU acquired weakness (ICU-AW) is characterised by rapid muscle wasting, polyneuropathy and bone demineralisation, causing pain, weakness and impaired physical function<sup>12-14</sup>. Contributing factors are multifactorial although immobility due to the sedation required for tolerance of ventilation plays an important role<sup>15, 16</sup>. Early mobilisation may mitigate these effects<sup>17-19</sup>. In 2009 Schweickert et al. reported that patients who received early physical therapy (within 1.5 days of mechanical ventilation) had greater functional independence at hospital discharge than patients that received usual care physical therapy<sup>20</sup>. A recent RCT on the impact of a progressive ICU mobility programme reported improved functional status at ICU discharge<sup>21</sup>. Meta-analyses and systematic reviews report that early mobilisation of ICU patients may reduce duration of mechanical ventilation and improve short term physical outcomes<sup>22-24</sup>, however mobilisation can be difficult to implement during a patient's stay in the ICU. Moreover studies which utilised delayed rehabilitation, often more than a week after ICU admission<sup>25-27</sup>, have not replicated these outcomes<sup>28-34</sup>. Barriers to early mobilisation include heavy sedation, patient's illness, lack of resources and/or clinician buy-in<sup>35-38</sup>. In-bed cycle ergometry can provide passive activity in heavily sedated patients who are receiving vasopressors<sup>39, 40</sup> with minimal physiological demand<sup>40, 41</sup> and can be transitioned to active cycling as the patient's condition improves<sup>23, 42-44</sup>.

We implemented cycle ergometry as part of an early protocolised rehabilitation quality improvement programme with physiotherapy technicians supporting the additional workload<sup>45</sup>. Like other investigators, we reported reduced number of ventilator days and ICU length of stay<sup>21, 46-49</sup>.

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3 72 The primary aim of this study is to evaluate the feasibility of a (RCT) investigating the effect of  
4 73 early protocolised rehabilitation versus usual physiotherapy care in ICU patients. Results will inform a  
5 74 prospective fully powered multi-centre RCT. This protocol is reported according to SPIRIT<sup>50</sup> and  
6 75 TIDieR<sup>51</sup> guidelines.  
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## 11 77 **Aim**

12 78 The aim of this study is to determine the feasibility to deliver study procedures comparing an early  
13 79 protocolised mobilisation programme that includes cycling with usual care.  
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## 17 81 **Objectives**

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19 82 Feasibility will be determined by measures of the recruitment process, intervention fidelity and outcome  
20 83 measurement completeness, specifically: i) Study accrual rates: a minimum of 30% of eligible patients  
21 84 or 1-2 patients per site per month are enrolled; ii) Protocol adherence: 75% of patients commencing  
22 85 intervention within 72 hours of ICU admission; minimum of 70% of planned interventions delivered  
23 86 and iii) Blinded outcome assessment: functional assessment performed at 3 time-points in 80% of  
24 87 survivors. The results will inform a larger fully powered RCT.  
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## 29 30 89 **METHODS AND ANALYSIS**

### 31 90 **Study design:**

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33 91 This is a two-centre feasibility study using a two-arm RCT, randomised 1:1, with blinded outcome  
34 92 assessments at ICU discharge, hospital discharge and 3-month follow-up. Patients will be recruited from  
35 93 two general ICUs, located in the south of the UK. They will not be recruited from our ICU on account  
36 94 that the intervention is now standard practice at this site. Prior to each site opening to recruitment an  
37 95 audit of current physiotherapy practice will be undertaken over a four-week period to evaluate what  
38 96 constitutes 'usual care' in each institution  
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### 44 98 **Participants:**

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46 99 Ninety patients will be recruited. Eligible patients will be over 42 years old and have an acute/unplanned  
47 100 medical admission to the ICU. They will be functionally independent prior to ICU admission (Barthel  
48 101 Index >80), in hospital for <5 days prior to intubation and ventilation, intubated and ventilated for <72  
49 102 hrs and expected to remain ventilated for a further 48 hours. Patients will be excluded if in hospital for  
50 103 5 days or more prior to ICU admission, have acute brain or spinal cord injury, known or suspected  
51 104 neurological / muscular impairment, condition limiting use of cycle ergometry (e.g. lower limb fracture  
52 105 / amputation), not expected to survive >48hrs decided by consulting Intensivist, persistent therapy  
53 106 exemptions in first 3 days of mechanical ventilation. (Figure 1) presents the planned flow of patients  
54 107 through the study.  
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3 109 **Recruitment, consent and randomisation:**

4 110 The study team will screen all patients for eligibility. Recruitment began in June 2019 (and was  
5 111 temporarily suspended in March 2020 due to the COVID 19 pandemic). It is anticipated recruitment  
6 112 will continue until early 2022. The majority of patients will have diminished capacity when first eligible,  
7 113 therefore, the consent process is multi-layered and designed in accordance with the Mental Capacity  
8 114 Act (MCA) 2005<sup>52</sup> (Figure 2). *Patient Informed Consent*: Wherever possible, informed consent will be  
9 115 directly sought from the patient. *Personal Consultee Informed Assent*: If the patient is unable to provide  
10 116 consent, informed assent will be sought from the patient's personal consultee, within 6 hours of  
11 117 confirmation of eligibility. If the personal consultee is not available in person, attempts will be made to  
12 118 contact them by telephone. They will be asked to provide written assent, at the earliest possible  
13 119 convenience. *Professional Consultee Informed Assent*: Where both patient and personal consultee are  
14 120 not available to approve enrolment within 6 hours of confirmation of eligibility, assent will be sought  
15 121 from a professional consultee in accordance with the MCA. The professional consultee will be a  
16 122 consultant medical practitioner, independent from the study. The patient's personal consultee will be  
17 123 consulted at the earliest possible opportunity and assent requested to continue in the study.

18 124 In all cases, once the patient has regained capacity they will be informed of the study and consent  
19 125 continuation sought. Following consent or assent, patients will be registered on a bespoke electronic  
20 126 data collection tool (ALEA™) and randomly assigned to the protocolised early rehabilitation or usual  
21 127 care.

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27 129 **Staff training/ site set-up:**

28 130 Participating sites will employ the equivalent of a full-time therapy technician to deliver the study  
29 131 intervention, under the supervision of a senior critical care therapist. Both senior critical care therapists  
30 132 and therapy technicians will complete a training package delivered by the primary institution  
31 133 (University Hospital Southampton NHS Foundation Trust), where early rehabilitation with cycling is  
32 134 well established and embedded in usual care. This package includes seminars on the delivery of the  
33 135 protocolised early rehabilitation , use of the bespoke electronic database and 5-days of clinical  
34 136 shadowing.

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38 138 **Interventions:**

39 139 All patients will receive usual medical, nursing and physiotherapy care while in intensive care. Each  
40 140 bedside nurse will be asked at the start of the shift if they have been involved caring for a patient in the  
41 141 intervention arm of the study. The ICU physiotherapy team, who are not involved the study delivery  
42 142 of, will deliver all usual physiotherapy interventions in both groups. The physiotherapist delivering  
43 143 usual care will be asked to verify if they have delivered any of the study interventions. In the  
44 144 intervention arm the protocolised physiotherapy programme will commence within 72 hours of ICU  
45 145 admission or as soon as possible thereafter and continue for 28 days or until ICU discharge, whichever

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3 146 occurs first. Patients respiratory support can range from full mandatory ventilation through to oxygen  
4 147 supplementation with no mechanical support following extubation. Sedation is targeted throughout the  
5 148 time that the patient is intubated and ventilation mode adjusted to patients' needs, compliance and  
6 149 comfort at discretion. At the start of each physiotherapy intervention the participants level of sedation  
7 150 will be assessed using the Richmond Agitation-Sedation Scale (RASS)<sup>53 54</sup> and the Confusion  
8 151 Assessment Method for ICU (CAM-ICU)<sup>55</sup>.will be undertaken. RASS will be targeted to a RASS  
9 152 between -1 and +1 by the bedside nurse. After 28 days of ICU admission, all patients will receive usual  
10 153 care physiotherapy interventions.  
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### 155 **Group 1: Usual care control group**

156 In this pragmatic study physiotherapy interventions will be guided by individual assessment and start  
157 in accordance with the usual care pathway within each institution. The focus of each session may be  
158 respiratory support, mobilisation or a combination of both. Interventions delivered will be determined  
159 by the physiotherapist in conjunction with the attending physician. Interventions include, where  
160 appropriate, passive or active range of movement, positioning and respiratory physiotherapy, and when  
161 able, sitting on the edge of the bed, standing (assisted or unassisted), standing to transfer to chair,  
162 marching on the spot and walking. (Figure 3). Usual interventions may occur at any time of day.  
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### 164 **Group 2: Protocolised rehabilitation pathway**

165 Patients will receive usual care physiotherapy, in addition to the two protocolised intervention within  
166 72 hours of ICU admission or as soon as possible thereafter. Patients will be screened for safety criteria  
167 to withhold the intervention prior to each planned intervention session (Table 1).  
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168

169 **Table 1**

|                    | <b>Criteria to commence physiotherapy</b>  | <b>Criteria to stop / withhold physiotherapy intervention</b>  |
|--------------------|--|--|
| Blood pressure     | MAP 60 – 100 mmHg, no change in vasopressor dose requirement for preceding 2 hours                         | Catecholamine resistant hypotension with MAP < 60 mmHg   |
| Heart rate         | Between 40-140 bpm   | <50 or >140 bpm  |
| Respiratory rate   | Sustained < 40 breaths/min   | Sustained >40 breaths/min  |
| Temperature        |  | >40 °C   |
| Oxygen requirement | If FiO <sub>2</sub> >0.8 for passive exercise only<br>FiO <sub>2</sub> <0.8 and PEEP<15 cmH <sub>2</sub> O |  |
| Desaturation       |  | Sats fall <85% for > 1 minute  |
| Other              |  | <ul style="list-style-type: none"> <li>· Fall</li> <li>· Unplanned extubation</li> <li>· Acute bleeding</li> <li>· New onset arrhythmia</li> <li>· Signs/symptoms of acute myocardial ischaemia</li> <li>· Patient pain/distress</li> <li>· Clinical team decide therapy intervention not appropriate</li> <li>· Refusal by patient or representative</li> </ul> |

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173 Those meeting criteria to withhold interventions will have issues addressed and reassessed for  
 174 interventions 2 hours later. The two additional rehabilitation sessions will be delivered by the research  
 175 physiotherapy staff including a therapy technician. This will comprise of two mobility sessions the  
 176 modality of the first, chosen at the discretion of the physiotherapist. The second session will be 30-  
 177 minutes of supine cycling, delivered in the afternoon.

178 The first rehabilitation intervention each day will be delivered in the morning. Planned interventions  
 179 include passive or active range of movements, passive cycling, active cycling, in bed exercises, sitting,  
 180 mobilisation out of bed and walking. Daily assessment of the patient will be made to ensure the highest

181 level of activity possible is provided for each individual patient given safety considerations and  
182 capability of the patient.

183 The second session will be cycling based. An in-bed supine cycle ergometer (MotoMed Letto 2™) will  
184 be used to engage the participant in passive, assisted or active cycling, or a combination, depending on  
185 the degree of patient co-operation (Figure3). The aim is for the patient to have 30 minutes of cycling  
186 per day, following a standardised cycling programme. If cycling is in passive mode, patients will  
187 commence cycling at 5 revolutions per minute (RPM), building up to 20 RPM over a 5minutes and  
188 continue this for 20 minutes before 5-minute 5RPM cool down. In the assisted or active mode, after the  
189 5-minute warm up, cycling will continue for 20 minutes at patient selected RPM followed by a 5-minute  
190 cool down at 5 RPM. In-bed cycling sessions will stop when the patient is deemed to be able to stand  
191 and transfer from bed to chair for both mobility sessions for two consecutive days. If patients are  
192 considered unable to have concurrent mobility therapy and respiratory weaning, mobility therapy will  
193 take priority, in agreement with the senior clinical team. Individual participants will receive the trial  
194 intervention on five days per week (Monday to Friday) for the duration of their ICU stay or maximum  
195 of 28 days whichever comes first. Patients will be monitored for cardiovascular and respiratory stability  
196 and safety of indwelling lines, tubes and catheters with pre-determined criteria for termination of any  
197 session (Table 1). Deviations from the planned protocol will be reported to determine potential barriers  
198 to implementation. Patients will be able to decline any intervention or outcome assessment at any time  
199 without compromise to their care.

200

#### 201 **Primary Outcome: Feasibility to deliver the protocol as designed**

202 Feasibility will be determined by measures of the recruitment process, intervention fidelity and outcome  
203 measurement completeness, specifically:

- 204 1. Study accrual rates: a minimum of 30% of eligible patients or 1-2 patients per site per month  
205 are enrolled
- 206 2. Protocol adherence: 75% of patients commencing intervention within 72 hours of ICU  
207 admission; minimum of 70% of planned interventions delivered
- 208 3. Blinded outcome assessment: functional assessment performed at 3 time-points in 80% of  
209 survivors by physiotherapists working within the hospital but not within the ICU

210

#### 211 **Secondary Outcomes:**

212 The schedule of outcome assessments is detailed in Table 2

#### 213 **Strength and Function**

214 We will measure the Physical Function ICU Test-scored (PFITs) at awakening as described by  
215 deJonghe<sup>56</sup> then weekly within ICU and on ICU discharge<sup>57</sup>. PFITs is a reliable and valid 4 item scale  
216 (arm strength, leg strength, ability to stand and step cadence), with a score range of 0-10 and is  
217 responsive to change and predictive of key outcomes<sup>58</sup>. Medical Research Council Manual Muscle Test

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3 218 Sum Score (MRC-ss)<sup>59, 60</sup> and Handheld Dynamometry (HHD)<sup>61</sup> will be measured on awakening,  
4 219 weekly, on ICU discharge and hospital discharge. Chelsea Critical Care Physical Assessment tool  
5 220 (CPAX)<sup>62</sup> and ICU Mobility Scale<sup>63</sup> will be assessed three times during the first week within ICU, on  
6 221 awakening, weekly thereafter within the ICU and at ICU discharge. Timed Up and Go (TUG)<sup>64, 65</sup>,  
7 222 Clinical Frailty Score (CFS)<sup>66-68</sup> and Barthel Index will be assessed at ICU discharge, hospital discharge  
8 223 and 3-months post-hospital discharge. Pre-admission Barthel Index and CFS will be assessed by proxy  
9 224 on admission from family member or next of kin. Six-minute walk test (6MWT)<sup>69</sup> will be performed,  
10 225 in accordance with American Thoracic Society guidelines, at hospital discharge and 3-months post-  
11 226 hospital discharge.

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### 18 228 **Health related quality of life Outcomes**

19 229 The following will be measured at 3-months post-hospital discharge : WHODAS-2.0<sup>70</sup> , Hospital  
20 230 Anxiety and Depression Score (HADS)<sup>71, 72</sup> , Euroqol-5 Dimension-5Level (EQ-5D-5L)<sup>73</sup>, Impact of  
21 231 Event Score (IES)<sup>74</sup> and Client Service Receipt Inventory questionnaire (CSRI), designed for this  
22 232 study to evaluate costs that fall on patients and their carers. Resource use and costs including direct  
23 233 intervention costs of therapists and equipment and general hospital costs (per bed day) will be  
24 234 recorded for each patient

### 25 235 **Health economic sub-study**

26 236 We will also conduct an embedded health economic study to identify and define data collection for a  
27 237 future RCT where a full cost effectiveness analysis (CEA) can be conducted. Within the feasibility  
28 238 study we aim to address the following:

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32 239
- 33 240 • what the quality of the data and what potential problems are there for reporting QoL (EQ-5D-5L), resource use and costs;
  - 34 241 • the cost implications of the proposed intervention in terms of impact for the NHS (inpatient stay bed days) and identifying the main cost drivers;
  - 35 242 • is the EQ-5D-5L appropriate for use in the future RCT.
- 36 243

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43 244 The economic outcomes will include: secondary care resource use within hospitals during inpatient  
44 245 stay, primary care resource use following discharge up to 3months and resource use related to  
45 246 providing the intervention. The results will be reported in the form of descriptive statistics and will be  
46 247 used to inform a future CEA within a definitive RCT.

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### 53 249 **Additional data collection**

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3 250 We will collect baseline data including demographic information, Functional Comorbidity Index, ICU  
4 diagnosis, APACHE II score, ventilation duration, ventilator free days, ICU and hospital length of  
5 251 stay, within ICU drug history and duration and type of usual care physiotherapy.  
6 252  
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8 253

### 9 254 **Implementation Evaluation**

11 255 We aim to investigate whether the protocolised early rehabilitation programme used in one NHS  
12 256 institution is transferable, as an RCT, into other similar NHS institutions. The design of a future multi-  
13 257 centre study will be informed by identified facilitators and barriers to implementation. Implementation  
14 258 assessment will be based on the measures described by Proctor<sup>75</sup>. A cross section of ICU staff and  
15 259 patients will be interviewed and complete questionnaires at trial completion to identify barriers  
16 260 impacting delivery of the study . Understanding of the integration and sustainability of the  
17 261 intervention are necessary to inform the design of a powered RCT. Acceptability will be measured at  
18 262 the beginning and end of the study from investigators and clinical staff by direct discussions and  
19 263 questionnaire. Our experience informs us that the introduction of this intervention is dependent on a  
20 264 cultural change within any unit for a pro-active focus on early mobilisation. We aim to explore  
21 265 measures to help optimise implementation. Adoption, feasibility, and fidelity measures will be  
22 266 monitored during the study by regular meetings with the investigators. Patient screening logs will  
23 267 identify the number of patients eligible for the study and barriers to enrolment. We will assess the  
24 268 degree to which it is possible to separate the staff caring for the intervention group from those caring  
25 269 for the patients in the control group.  
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37 270  
38 271 We will report whether trial participation has influenced usual care within the participating units by  
39 272 pre- and post-study audits. Participating sites will collect data regarding number and seniority of  
40 273 therapy staff with dedicated time to work within the ICU; delirium and sedation protocols used; time,  
41 274 type and frequency of rehabilitation interventions delivered, who delivers the interventions and  
42 275 reasons why usual care may not be delivered.  
43  
44

45 276 The feasibility outcomes described above will be used to power a larger RCT.  
46  
47

### 48 278 **Data entry and checks**

49 279 Data will be entered into the secure electronic case report form (ALEA™) and data validation will  
50 280 take place according to the procedures set out in the data management plan and data validation plan,  
51 281 both developed a priori. Missing data will be assessed to identify any specific challenges with any  
52 282 items of data collected. Missing data level is expected to be less than 20%. Data loss and mortality  
53 283 will inform number of participants needed to design a larger RCT. As this is a feasibility study data  
54 284 imputation will not be undertaken. Prior to statistical analysis, variables will be checked for missing  
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3 285 and impossible and improbable values as defined by clinical opinion. Questions regarding the data  
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5 286 will be directed to the data manager.

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9 288 **Sample size calculation**

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11 289 .

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13 290 This is a feasibility study the results of which will be used to power a definitive study if  
14  
15 291 appropriate, as such no formal sample size calculation for effectiveness of the intervention  
16  
17 292 has been undertaken. 90 patients will be recruited aiming for 30-45 participants at each site.  
18  
19 293 We anticipate a 30% in hospital mortality /loss to follow-up with an estimate of 60 patients  
20  
21 294 completing the study. This sample size of 90 will allow the estimate of recruitment rate to be  
22  
23 295 made with a 95% confidence interval of  $\pm 5.2\%$  if the rate is observed to be around 30%, and  
24  
25 296 with a confidence interval of  $\pm 7.3\%$  if the recruitment rate is observed to be around 50%. In  
26  
27 297 addition, the sample of 90 recruited patients will allow the estimate of the mortality rate to be  
28  
29 298 made with a 95% confidence interval of  $\pm 9.5\%$  assuming the mortality rate was around 30%.  
30  
31 299 Finally, assuming the recruitment rate was around 30%, a sample of 300 patients approached  
32  
33 300 to take part in the study leading to 90 enrolled patients would allow for the recruitment rate to  
34  
35 301 be estimated with a 95% confidence interval of  $\pm 5.2\%$ . If the recruitment rate was nearer  
36  
37 302 50%, with 180 patients approached to recruit the 90 enrolled patients, the recruitment rate  
38  
39 303 would be estimated with a 95% confidence interval of  $\pm 7.3\%$ .

40  
41 304 **Statistical analysis**

42  
43 305 The analysis will be reported in line with the feasibility studies extension to the CONSORT statement  
44  
45 306 <sup>76</sup>. The aims of the study are to estimate the recruitment, compliance and retention rates to inform the  
46  
47 307 design of a future study and is not powered for hypothesis testing regarding the effectiveness of the  
48  
49 308 intervention. Feasibility outcomes (recruitment, compliance, and retention rates) will be  
50  
51 309 presented with 95% confidence intervals across the whole study population. Compliance and  
52  
53 310 retention rates will also be presented by treatment arm to ensure balanced recruitment, but no  
54  
55 311 formal statistical comparison tests will be made. Mortality and participant dropout rates will  
56  
57 312 be presented with 95% confidence intervals across the whole study population and within  
58  
59 313 treatment arm. Clinical outcome data (secondary outcomes) will be presented as summary  
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314 statistics using means and standard deviations or medians and ranges/interquartile ranges, as  
315 applicable, across the whole study population and by treatment arm. These data will be used

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3 316 to inform the future trial but will not be used to draw conclusions about the effectiveness of  
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5 317 the protocolised early rehabilitation intervention within this study  
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8 **318 Trial management**  
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10 319 The Chief Investigator (CI) will ensure all study personnel are appropriately orientated and trained,  
11 320 oversee recruitment and report to the trial safety monitoring committee. Training will occur across  
12 321 sites using competency-based training developed at the primary site (University Hospital  
13 322 Southampton NHS Foundation Trust). A study steering group, consisting of an independent chair,  
14 323 expert members and 2 lay advisors will meet every 3-months. Fortnightly teleconferences with trial  
15 324 sites will be held to monitor conduct and progress. Timing and intervals of visits and teleconferences  
16 325 will be reviewed at 3 months to ensure optimal time use.

17 326 The CI and Principal Investigators will facilitate local monitoring by the Research and Development  
18 327 quality manager, Research Ethics committee (REC) review and provide access to source data as  
19 328 required. A monitoring report will be produced, summarising the visit, documents and findings. The  
20 329 CI will ensure that all findings are addressed appropriately. The steering group will review all events  
21 330 in a timely manner. Additional monitoring will be scheduled where there is evidence or suspicion of  
22 331 non-compliance with the study protocol.

23 332 A Data Management and Safety Committee will be chaired by an independent expert. Quarterly  
24 333 reports will be given to the committee once recruitment has commenced.  
25

26 334 **Patient and Public Involvement**  
27

28 335 The study has been supported by patient advisory representatives. These representatives are  
29 336 members of the trial steering committee. Patient advisors partnered with us for the design of the study,  
30 337 the informational material to support the intervention, the burden of the intervention from the patient's  
31 338 perspective and contributed to the dissemination plan  
32

33 339 **Ethics and dissemination**  
34

35 340 Ethical approval has been granted by South Central - Hampshire A Research Ethics Committee (REC  
36 341 reference 19/SC/0016). EMPRESS was registered with Clinical Trials.gov (ref:NCT03771014) on  
37 342 10th December, 2018.  
38

39 343 Results of this proposed feasibility study will be disseminated for four key audiences: i) patients and  
40 344 public; ii) Intensive care staff, healthcare workers and potential future research delivery partners; iii)  
41 345 service delivery organisations and iv) academic and potential future research collaborators.  
42

43 346 Dissemination activities will include: feedback to Patients and Public Involvement study focus group,  
44 347 feedback to study participants, presentations to local clinical teams and managers and commissioners  
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3 348 and presentation at conferences attended by appropriate healthcare professionals. Where appropriate,  
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5 349 results will be published in peer reviewed journals.

6 350

### 8 351 **Safety and adverse events**

9 352 Early mobility within ICUs is safe. In a review of physiotherapy in a critical care rehabilitation  
10  
11 353 programme, 1110 patients received 5267 rehabilitation sessions physiological abnormalities or  
12  
13 354 potential adverse events occurred in only 6 per 1000 interventions<sup>77</sup>. Mobilisation interventions will  
14  
15 355 only be delivered if patients fit the safety criteria defined in table 1. Similar safety criteria have been  
16  
17 356 used in other ICU rehabilitation studies<sup>78, 79</sup>.

17 357 All adverse events will be documented. Any intervention will cease according to stopping criteria  
18  
19 358 detailed in Table 1. Any such event will be recorded as an adverse event. The CI will provide a monthly  
20  
21 359 update to the safety monitoring committee. Serious adverse events are events that result in death, are  
22  
23 360 life threatening or require prolonged hospitalisation. Any such event will be reported in accordance with  
24  
25 361 the NHS Health Research Authority guidance.

26 362

### 28 363 **Discussion:**

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31 364 EMPRESS is a feasibility study to assess if a randomised controlled trial of protocolised rehabilitation  
32  
33 365 with supine cycling can be delivered in ventilated patients in ICUs with differing organisational  
34  
35 366 structures with blinded follow-up assessments. A recent meta-analysis indicated that protocolised  
36  
37 367 rehabilitation significantly reduces duration of mechanical ventilation and ICU length of stay<sup>23</sup>. This is  
38  
39 368 consistent with our findings when we introduced the early rehabilitation programme outlined here in  
40  
41 369 our intensive care unit<sup>45</sup>. Passive cycling commenced on ventilated patients may assist the recovery  
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43 370 muscle strength in ICU patients<sup>43</sup> although the overall benefits of leg cycle ergometry in the critically  
44  
45 371 ill is inconclusive<sup>44</sup>. We describe a protocolised rehabilitation programme with supine cycling delivered  
46  
47 372 as close to intubation as possible, at an intensity according to the patients' highest performance  
48  
49 373 capability.

47 374 Both patient and organisational issues are recognised to the delivery of early rehabilitation of the  
48  
49 375 critically ill patients<sup>35</sup>. A frequently reported challenge is the lack of appropriately qualified staff<sup>80</sup>.  
50  
51 376 This study evaluates the safety, feasibility, effectiveness of delivery and cost efficiency of using therapy  
52  
53 377 technicians to deliver protocolised rehabilitation interventions. In addition to the clinical benefits, early  
54  
55 378 physical rehabilitation can also be cost saving<sup>49</sup>. Even with the employment of additional therapy  
56  
57 379 technicians specifically to assist in the delivery of we have found this early rehabilitation programme  
58  
59 380 cost effective<sup>81</sup>.

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3 381 This study will collect data on the dose of intervention delivered to all patients, reasons for non-delivery  
4 382 of protocol interventions, and the level of experience of therapists delivering the interventions. A  
5 383 qualitative process evaluation is designed to identify both patient and organisational challenges that  
6 384 have potential to be addressed in a potential future study. Findings will inform refinement of trial design  
7 385 and evaluation of the intervention, clarifying causal mechanisms behind study outcomes and providing  
8 386 additional context not adequately captured by the quantitative data. The process evaluation will be  
9 387 consistent with Medical Research Council guidance for conducting process evaluations of complex  
10 388 healthcare interventions<sup>82</sup>.

11 389 Targeted sedation is embedded within this protocol as oversedation is one of the more commonly cited  
12 390 barriers to mobilisation of the ventilated patient<sup>35</sup>. This study opened to recruitment prior to the  
13 391 publication of the recommended core outcome set for critical care ventilation trials<sup>83</sup> however three of  
14 392 the six outcomes listed (duration of mechanical ventilation, duration of stay and health related quality  
15 393 of life) are secondary outcomes in this study and the other 3 outcomes are included in the data collected  
16 394 This will be addressed should we proceed to a full RCT. Due to the nature of the intervention, it is not  
17 395 possible for this to be blinded however the follow-up assessments will be carried out by a blinded.

18 396 Results from EMPRESS will inform the design of a multi-centred RCT, both identifying barriers to the  
19 397 implementation of the designed protocol and exploring how these may be addressed from feedback  
20 398 from the therapy and nursing teams in addition to the feedback from patients and their next of kin.

21 399

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34 412

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36 414

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3 415 **Ethics Approval:** The study has ethical approval from South Central Hampshire A Research Ethics  
4 Committee (19/SC/0016). Protocol Version 1.3 7<sup>th</sup> Feb 2019  
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8 418 **Provenance and Peer review:** Not commissioned. Protocol peer-reviewed for ethical and funding  
9 application  
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11 420

12 421 **Disclaimer:** The views expressed are those of the author(s) and not necessarily those of the NIHR, NHS  
14 or the Department of Health and Social Care.  
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For peer review only

426 **Table 2**

|                                      | Randomisation | Day 1 | Day 3 | Day 7 | Awakening | Weekly | ICU Discharge | Hospital Discharge | 3 months post hospital discharge |
|--------------------------------------|---------------|-------|-------|-------|-----------|--------|---------------|--------------------|----------------------------------|
| <b>Demographic Data</b>              | X             |       |       |       |           |        |               |                    |                                  |
| <b>Muscle assessment:</b>            |               |       |       |       |           |        |               |                    |                                  |
| MRCss <sup>60,61</sup>               |               |       |       |       | X         | X      | X             | X                  |                                  |
| Grip strength <sup>62</sup>          |               |       |       |       | X         | X      | X             | X                  |                                  |
| <b>Physical function:</b>            |               |       |       |       |           |        |               |                    |                                  |
| CPAX <sup>63</sup>                   |               | X     | X     | X     | X         | X      | X             |                    |                                  |
| ICU mobility <sup>64</sup>           |               | X     | X     | X     | X         | X      | X             |                    |                                  |
| PFITs <sup>59</sup>                  |               |       |       |       | X         | X      | X             |                    |                                  |
| Timed-Up and Go (TUG)                |               |       |       |       |           |        | X             | X                  | X                                |
| Clinical Frailty Score <sup>69</sup> |               | (X)   |       |       |           |        | X             | X                  | X                                |
| Barthel Index                        |               | (X)   |       |       |           |        | X             | X                  | X                                |
| 6-minute walk test <sup>70</sup>     |               |       |       |       |           |        |               | X                  | X                                |
| <b>HRQL:</b>                         |               |       |       |       |           |        |               |                    |                                  |
| WHODAS 2 <sup>71</sup>               |               |       |       |       |           |        |               |                    | X                                |
| HADS <sup>72,73</sup>                |               |       |       |       |           |        |               |                    | X                                |
| EQ5D-5L <sup>74</sup>                |               |       |       |       |           |        |               |                    | X                                |
| Impact of Event Scale <sup>75</sup>  |               |       |       |       |           |        |               |                    | X                                |
| Health Economic Evaluation (CSRI)*   |               |       |       |       |           |        |               |                    | X                                |

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428 Physical Function ICU Test-scored (PFITs); Medical Research Council Manual Muscle Test Sum Score (MRC-ss); Chelsea Critical Care Assessment Tool  
 429 (CPAX); World Health Organisation Disability Assessment; Euroqol 5 dimension 5 level health related quality of life questionnaire; Hospital anxiety and  
 430 depression scale (HADS); Client service receipt inventory(CSRI)

## Legends

**Table 1 Safety criteria for delivery of physical therapy interventions**

**Table 2 Schedule of assessments and collection of outcome data**

**Figure 1 Planned participants' flow**

**Figure 2 Study consent process**

**Figure 3 EMPRESS study participant rehabilitation pathway**

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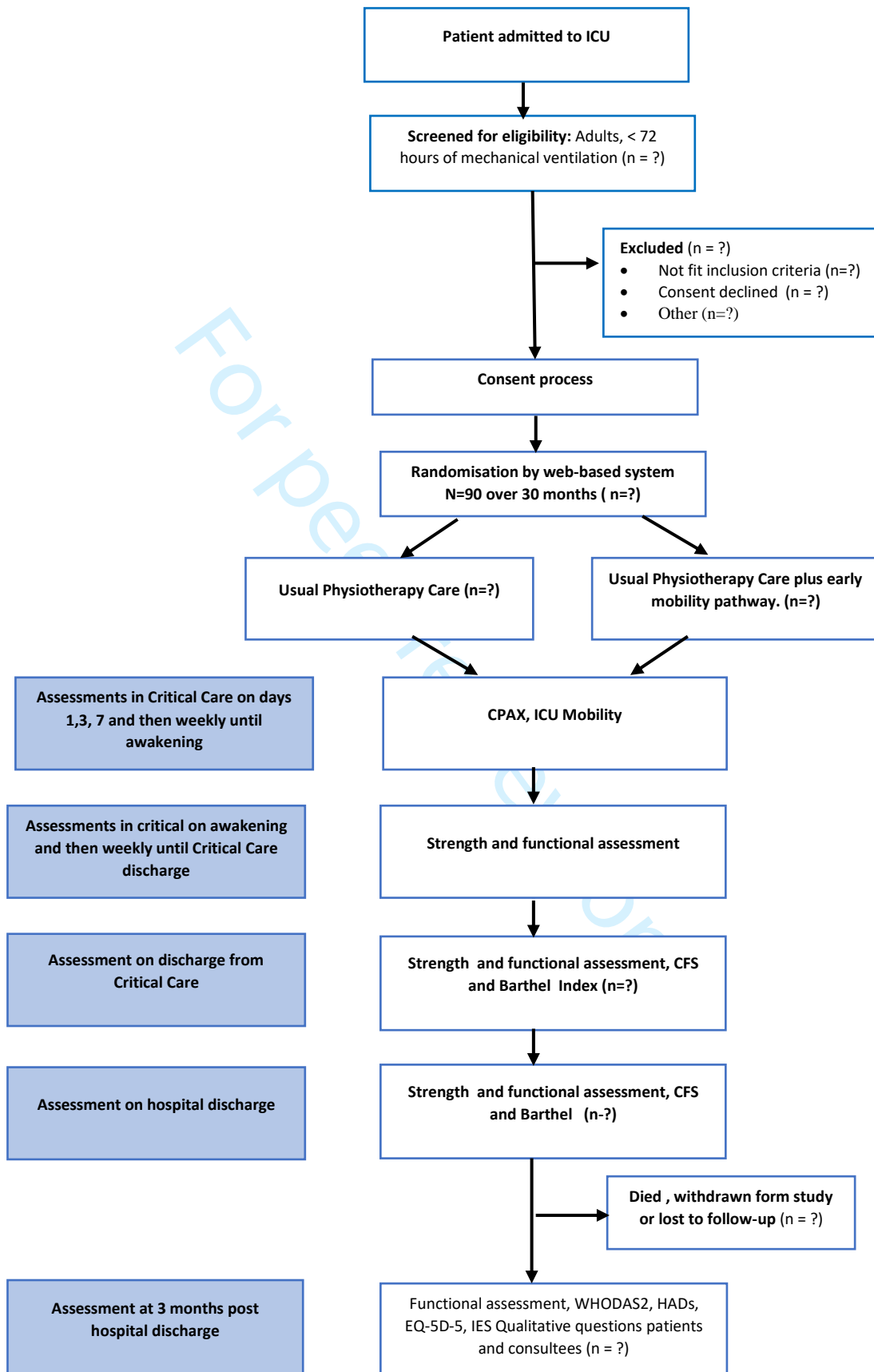


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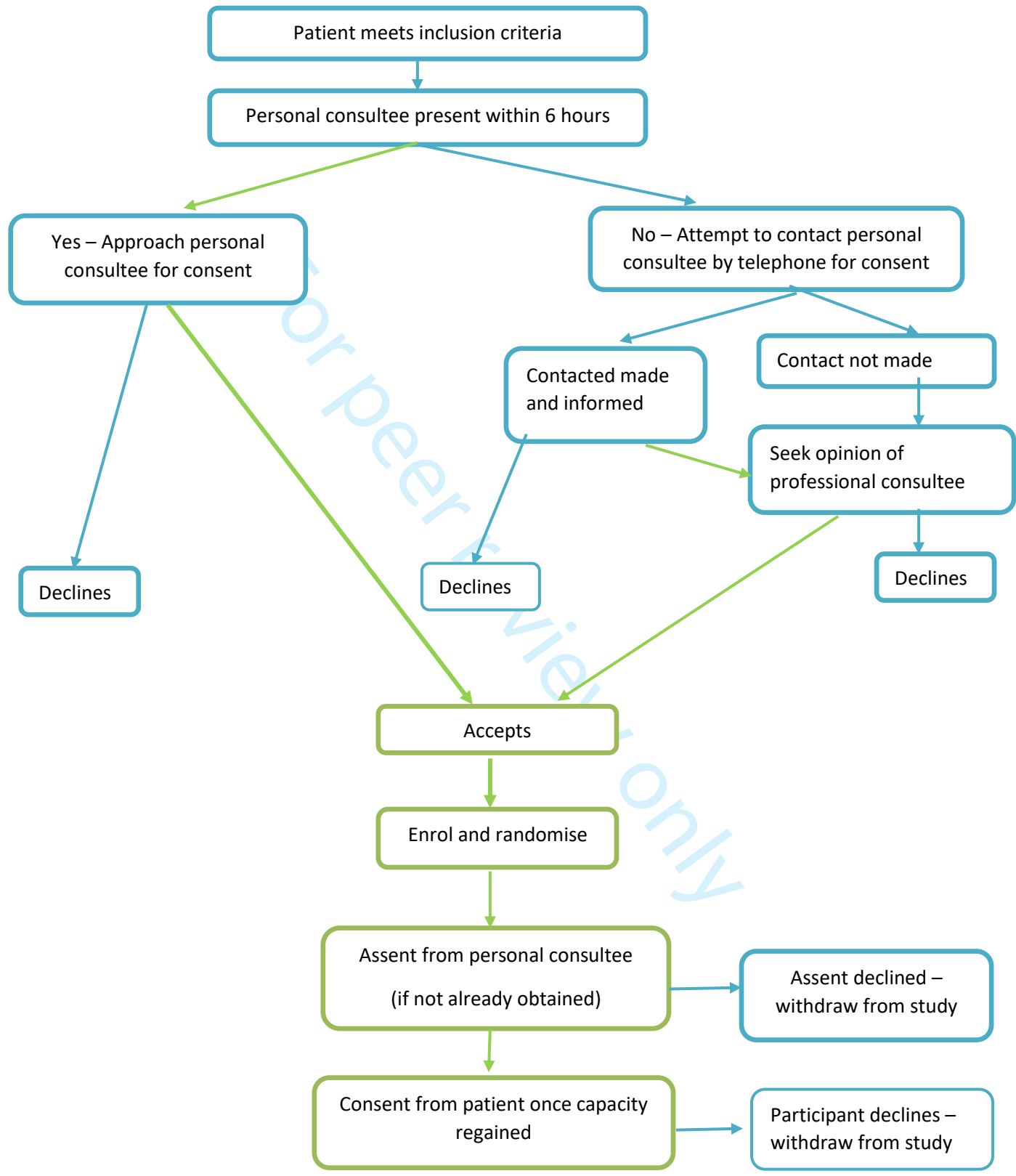
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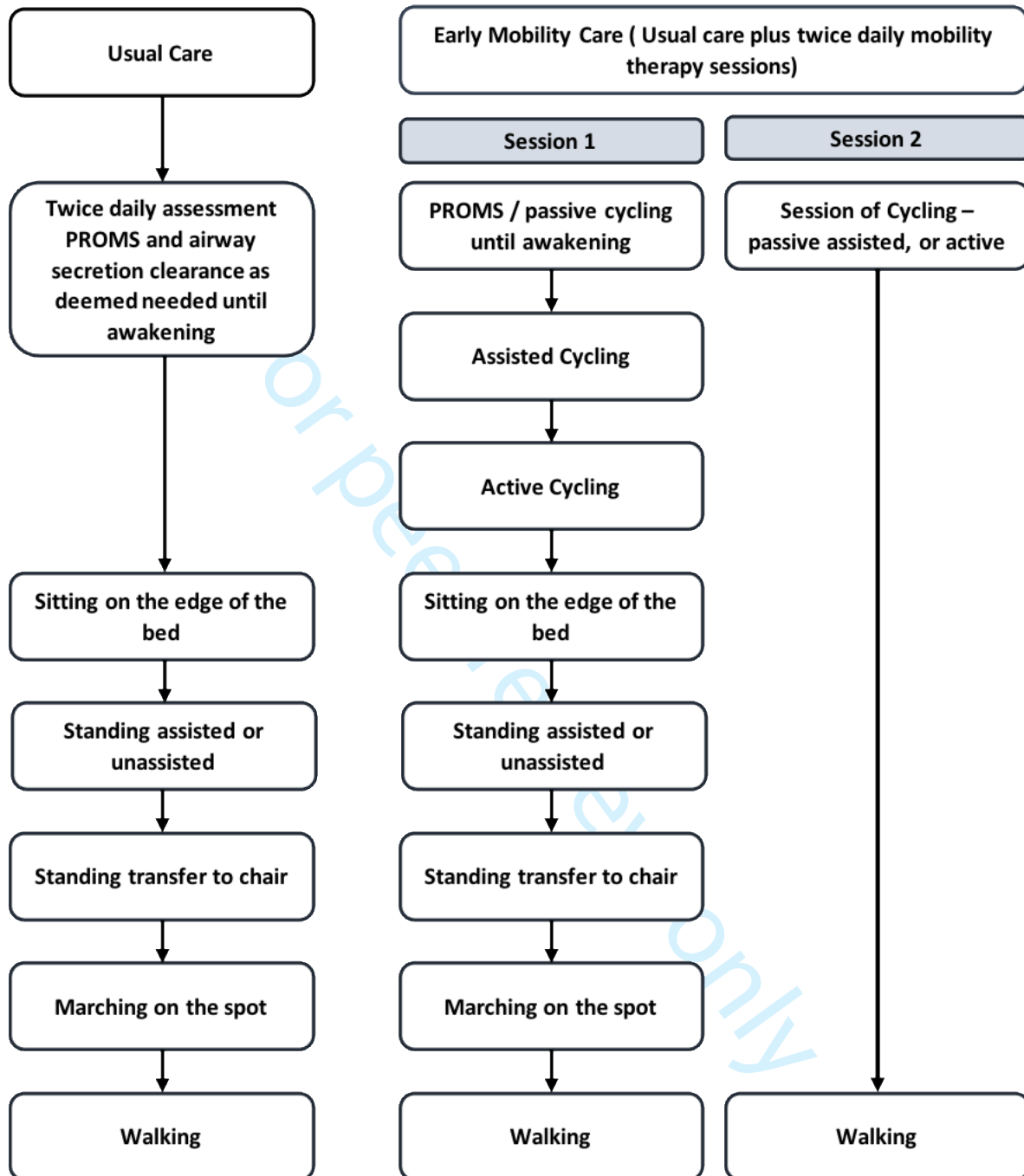
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STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents\*

| Section/item                      | Item No | Description   |
|-----------------------------------|---------|---|
| <b>Administrative information</b> |         |   |
| Title                             | 1       | Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym <b>Pg1 lines 1-2</b>   |
| Trial registration                | 2       | Trial identifier and registry name. If not yet registered, name of intended registry <b>Pg2 line 28</b>   |
| Protocol version                  | 3       | Date and version identifier <b>Pg 14 line 410</b>   |
| Funding                           | 4       | Sources and types of financial, material, and other support <b>Pg 14 lines 403-4</b>  |
| Roles and responsibilities        | 5a      | Names, affiliations, and roles of protocol contributors <b>Title page</b>   |
|                                   | 5b      | Name and contact information for the trial sponsor <b>Pg2 line 29</b>   |
|                                   | 5c      | Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities <b>N/A</b>   |
|                                   | 5d      | Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) <b>Trial management group/ Data safety group/PPI group -- Pg12 Lines 315 to Pg 13 line 334</b> |
| <b>Introduction</b>               |         |   |
| Background and rationale          | 6a      | Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention <b>See introduction Pg3 line 44-Pg line 80</b>   |
|                                   | 6b      | Explanation for choice of comparators <b>See introduction Pg3 line 44-Pg line 80</b>  |
| Objectives                        | 7       | Specific objectives or hypotheses <b>Pg 3 lines 82-88</b>   |



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|--------------|---|--|
| Trial design | 8 | Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) <b>Study design Pg 4 lines 91-97</b> |
|--------------|---|--|

### **Methods: Participants, interventions, and outcomes**

|                      |     |  |
|----------------------|-----|--|
| Study setting        | 9   | Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained <b>Pg 4 Lines 93-95</b>   |
| Eligibility criteria | 10  | Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) <b>Pg4 Lines 99 -108</b>  |
| Interventions        | 11a | Interventions for each group with sufficient detail to allow replication, including how and when they will be administered <b>Pg 5- 8 lines 137 - 198</b>  |
|                      | 11b | Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) <b>Table 1</b>  |
|                      | 11c | Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) <b>N/A</b>   |
|                      | 11d | Relevant concomitant care and interventions that are permitted or prohibited during the trial <b>N/A</b>   |
| Outcomes             | 12  | Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended <b>Primary outcomes Pg8 lines 200-208; Secondary outcomes lines 210-244</b> |
| Participant timeline | 13  | Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) <b>Table 2</b>  |
| Sample size          | 14  | Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations <b>Pg 10 line 284-300</b>  |
| Recruitment          | 15  | Strategies for achieving adequate participant enrolment to reach target sample size <b>Pg5 Lines 110-127</b>   |

### **Methods: Assignment of interventions (for controlled trials)**

## Allocation:

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4      Sequence      16a      Method of generating the allocation sequence (eg, computer-  
5      generation                generated random numbers), and list of any factors for stratification.  
6                          To reduce predictability of a random sequence, details of any planned  
7                          restriction (eg, blocking) should be provided in a separate document  
8                          that is unavailable to those who enrol participants or assign  
9                          interventions **Pg10 Line 126-7**  
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12      Allocation      16b      Mechanism of implementing the allocation sequence (eg, central  
13      concealment                telephone; sequentially numbered, opaque, sealed envelopes),  
14      mechanism                describing any steps to conceal the sequence until interventions are  
15                          assigned **Pg10 line 126-7**  
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17      Implementation 16c      Who will generate the allocation sequence, who will enrol participants,  
18                          and who will assign participants to interventions **Pg10 line 126-7**  
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21      Blinding      17a      Who will be blinded after assignment to interventions (eg, trial  
22      (masking)                participants, care providers, outcome assessors, data analysts), and  
23                          how **Pg14 line 390**  
24  
25                17b      If blinded, circumstances under which unblinding is permissible, and  
26                          procedure for revealing a participant's allocated intervention during  
27                          the trial **N/A**  
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**Methods: Data collection, management, and analysis**

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32      Data collection      18a      Plans for assessment and collection of outcome, baseline, and other  
33      methods                trial data, including any related processes to promote data quality (eg,  
34                          duplicate measurements, training of assessors) and a description of  
35                          study instruments (eg, questionnaires, laboratory tests) along with  
36                          their reliability and validity, if known. Reference to where data  
37                          collection forms can be found, if not in the protocol **Lines 278 - 286**  
38  
39                18b      Plans to promote participant retention and complete follow-up,  
40                          including list of any outcome data to be collected for participants who  
41                          discontinue or deviate from intervention protocols **Lines 306-7**  
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44      Data      19      Plans for data entry, coding, security, and storage, including any  
45      management                related processes to promote data quality (eg, double data entry;  
46                          range checks for data values). Reference to where details of data  
47                          management procedures can be found, if not in the protocol **Lines**  
48                          **279-86**  
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51      Statistical      20a      Statistical methods for analysing primary and secondary outcomes.  
52      methods                Reference to where other details of the statistical analysis plan can be  
53                          found, if not in the protocol **Lines 305- 317**  
54  
55                20b      Methods for any additional analyses (eg, subgroup and adjusted  
56                          analyses) **N/A**  
57  
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59  
60

1  
2 20c Definition of analysis population relating to protocol non-adherence  
3 (eg, as randomised analysis), and any statistical methods to handle  
4 missing data (eg, multiple imputation) [Line 84](#)  
5

## 6 **Methods: Monitoring**

7  
8 Data monitoring 21a Composition of data monitoring committee (DMC); summary of its role  
9 and reporting structure; statement of whether it is independent from  
10 the sponsor and competing interests; and reference to where further  
11 details about its charter can be found, if not in the protocol.  
12 Alternatively, an explanation of why a DMC is not needed [Lines 332-](#)  
13 [333](#)  
14

15  
16 21b Description of any interim analyses and stopping guidelines, including  
17 who will have access to these interim results and make the final  
18 decision to terminate the trial [N/A](#)  
19

20  
21 Harms 22 Plans for collecting, assessing, reporting, and managing solicited and  
22 spontaneously reported adverse events and other unintended effects  
23 of trial interventions or trial conduct [Lines 351-361](#)  
24

25 Auditing 23 Frequency and procedures for auditing trial conduct, if any, and  
26 whether the process will be independent from investigators and the  
27 sponsor [N/A](#)  
28  
29

## 30 **Ethics and dissemination**

31  
32 Research ethics 24 Plans for seeking research ethics committee/institutional review board  
33 approval [Line 24-27](#)  
34

35 Protocol 25 Plans for communicating important protocol modifications (eg,  
36 amendments changes to eligibility criteria, outcomes, analyses) to relevant parties  
37 (eg, investigators, REC/IRBs, trial participants, trial registries, journals,  
38 regulators) [.Line 25](#)  
39

40  
41 Consent or assent 26a Who will obtain informed consent or assent from potential trial  
42 participants or authorised surrogates, and how (see Item 32) [Lines](#)  
43 [109-122](#)  
44

45 26b Additional consent provisions for collection and use of participant data  
46 and biological specimens in ancillary studies, if applicable [N/A](#)  
47

48 Confidentiality 27 How personal information about potential and enrolled participants will  
49 be collected, shared, and maintained in order to protect confidentiality  
50 before, during, and after the trial [Line 279](#)  
51

52  
53 Declaration of 28 Financial and other competing interests for principal investigators for  
54 interests the overall trial and each study site [Line 413](#)  
55

56 Access to data 29 Statement of who will have access to the final trial dataset, and  
57 disclosure of contractual agreements that limit such access for  
58 investigators [Line 326-7 and 332-333](#)  
59  
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|----|-------------------|-----|--|
| 1  |                   |     |  |
| 2  | Ancillary and     | 30  | Provisions, if any, for ancillary and post-trial care, and for               |
| 3  | post-trial care   |     | compensation to those who suffer harm from trial participation <b>Lines</b>  |
| 4  |                   |     | <b>360-361</b>   |
| 5  |                   |     |  |
| 6  | Dissemination     | 31a | Plans for investigators and sponsor to communicate trial results to          |
| 7  | policy            |     | participants, healthcare professionals, the public, and other relevant       |
| 8  |                   |     | groups (eg, via publication, reporting in results databases, or other        |
| 9  |                   |     | data sharing arrangements), including any publication restrictions           |
| 10 |                   |     | <b>Lines 343-345</b>   |
| 11 |                   |     |  |
| 12 |                   |     |  |
| 13 |                   | 31b | Authorship eligibility guidelines and any intended use of professional       |
| 14 |                   |     | writers <b>Lines 402-406</b>   |
| 15 |                   |     |  |
| 16 |                   | 31c | Plans, if any, for granting public access to the full protocol, participant- |
| 17 |                   |     | level dataset, and statistical code <b>Lines 348-</b>                        |
| 18 |                   |     |  |
| 19 |                   |     |  |
| 20 | <b>Appendices</b> |     |  |
| 21 |                   |     |  |
| 22 | Informed consent  | 32  | Model consent form and other related documentation given to                  |
| 23 | materials         |     | participants and authorised surrogates <b>Can be supplied if required</b>    |
| 24 |                   |     |  |
| 25 | Biological        | 33  | Plans for collection, laboratory evaluation, and storage of biological       |
| 26 | specimens         |     | specimens for genetic or molecular analysis in the current trial and for     |
| 27 |                   |     | future use in ancillary studies, if applicable <b>N/A</b>                    |
| 28 |                   |     |  |

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\*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "[Attribution-NonCommercial-NoDerivs 3.0 Unported](https://creativecommons.org/licenses/by-nc-nd/3.0/)" license.

# BMJ Open

## Improving physical function of patients following Intensive Care Unit admission (EMPRESS): Protocol of a randomised controlled feasibility trial

|                                 |   |
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3 **Improving physical function of patients following Intensive Care Unit**  
4 **admission (EMPRESS): Protocol of a randomised controlled feasibility**  
5 **trial**  
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49 Word Count: 4237

50 Keywords: Critical care, physical therapy, rehabilitation, cycling  
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3 **1 Improving physical function of patients following Intensive Care Unit admission (EMPRESS):**  
4 **2 protocol of a randomised controlled feasibility trial**  
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8 **4 Introduction:** Physical rehabilitation delivered early following admission to the Intensive Care Unit  
9 (ICU) has the potential to improve short and long-term outcomes. The use of supine cycling together  
10 with other rehabilitation techniques has potential as a method of introducing rehabilitation earlier in the  
11 patient journey. The aim of the study is to determine the feasibility of delivering the designed protocol  
12 of a randomised clinical trial, comparing a protocolised early rehabilitation programme including  
13 cycling with usual care. This feasibility study will inform a larger multicentre study.

14 **10 Methods and Analysis:** 90 acute medical patients from 2 mixed medical-surgical ICUs will be  
15 recruited. We will include ventilated patients within 72 hours of initiation of mechanical ventilation  
16 and expected to be ventilated a further 48 hours or more. Patients will receive usual care or usual care  
17 plus two 30-minute rehabilitation sessions 5 days per week.

18 Feasibility outcomes are: i) recruitment 1-2 patients per month per site, ii) protocol fidelity with > 75%  
19 of patients commencing interventions within 72 hours of mechanical ventilation, > 70% interventions  
20 delivered and iii) blinded outcome measures recorded at 3 time points in > 80% of patients. Secondary  
21 outcomes are: i) strength and function; the Physical Function ICU Test-scored (PFITs) measured on  
22 ICU discharge, ii) hospital length of stay and iii) mental health and physical ability at 3 months using  
23 the WHODAS 2. An economic analysis using hospital health services data reported with an embedded  
24 health economic study will collect and assess economic and QoL data including Hospital Anxiety and  
25 Depression score (HADS), Euroqol-5 Dimension-5 Level (EQ-5D-5L) and the Impact of Event Score  
26 (IES).

27 **24 Ethics and Dissemination:** The study has ethical approval from South Central Hampshire A Research  
28 Ethics Committee (19/SC/0016). All amendments will be approved by this committee. An independent  
29 trial monitoring committee is overseeing the study. Results will be made available to critical care  
30 survivors, their caregivers, the critical care societies and other researchers.

31 **28 Trial registration number:** NCT03771014

32 **29 Sponsor:** University Hospital Southampton NHS Foundation Trust.

33 **32 Strengths and limitations of study**

- 34 • Will investigate the implementation of a protocolised early rehabilitation intervention, that is  
35 usual care in one NHS/University Teaching institution, in other NHS institutions with different  
36 organisational structures



- The defined cohort has been demonstrated to benefit from this type of rehabilitation in alternative health care systems
- Results will inform the design of a multi-centre randomised controlled trial (RCT)
- This study is not designed to assess effectiveness of the intervention
- Inability to blind the intervention to patients, physiotherapist and clinicians involved in the delivery of the intervention.

## Introduction

In 2018/19 there were over 290,000 admissions to adult ICUs in the United Kingdom (UK)<sup>1</sup>. Treatment advances have reduced mortality associated with critical illness<sup>2,3</sup>, however, survival does not represent the end of the story<sup>4</sup>. A complex interplay between baseline health status, acute disease and the traumatic effects of intensive care treatment are associated with long-term physical, psychological and social hardship<sup>5-10</sup>. Patients discharged from ICU have higher mortality, higher health service costs and a reduction in employment status compared to hospitalised patients not requiring ICU<sup>8,11</sup>.

ICU acquired weakness (ICU-AW) is characterised by rapid muscle wasting, polyneuropathy and bone demineralisation, causing pain, weakness and impaired physical function<sup>12-14</sup>. Contributing factors are multifactorial although immobility due to the sedation required for tolerance of ventilation plays an important role<sup>15,16</sup>. Early mobilisation may mitigate these effects<sup>17-19</sup>. In 2009 Schweickert et al. reported that patients who received early physical therapy (within 1.5 days of mechanical ventilation) had greater functional independence at hospital discharge than patients that received usual care physical therapy<sup>20</sup>. A recent RCT on the impact of a progressive ICU mobility programme reported improved functional status at ICU discharge<sup>21</sup>. Meta-analyses and systematic reviews report that early mobilisation of ICU patients may reduce duration of mechanical ventilation and improve short term physical outcomes<sup>22-24</sup>, however mobilisation can be difficult to implement during a patient's stay in the ICU. Moreover studies which utilised delayed rehabilitation, often more than a week after ICU admission<sup>25-27</sup>, have not replicated these outcomes<sup>28-34</sup>. Barriers to early mobilisation include heavy sedation, patient's illness, lack of resources and/or clinician buy-in<sup>35-38</sup>. In-bed cycle ergometry can provide passive activity in heavily sedated patients who are receiving vasopressors<sup>39, 40</sup> with minimal physiological demand<sup>40,41</sup> and can be transitioned to active cycling as the patient's condition improves<sup>23, 42-44</sup>.

We implemented cycle ergometry as part of an early protocolised rehabilitation quality improvement programme with physiotherapy technicians supporting the additional workload<sup>45</sup>. Like other investigators, we reported reduced number of ventilator days and ICU length of stay<sup>21, 46-49</sup>.

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3 72 The primary aim of this study is to evaluate the feasibility of a (RCT) investigating the effect of early  
4 73 protocolised rehabilitation versus usual physiotherapy care in ICU patients. Results will inform a  
5 74 prospective fully powered multi-centre RCT. This protocol is reported according to SPIRIT<sup>50</sup> and  
6 75 TIDieR<sup>51</sup> guidelines.  
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## 11 77 **Aim**

12 78 The aim of this study is to determine the feasibility to deliver study procedures comparing an early  
13 79 protocolised mobilisation programme that includes cycling with usual care.  
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## 17 81 **Objectives**

18  
19 82 Feasibility will be determined by measures of the recruitment process, intervention fidelity and outcome  
20 83 measurement completeness, specifically: i) Study accrual rates: a minimum of 30% of eligible patients  
21 84 or 1-2 patients per site per month are enrolled; ii) Protocol adherence: 75% of patients commencing  
22 85 intervention within 72 hours of ICU admission; minimum of 70% of planned interventions delivered  
23 86 and iii) Blinded outcome assessment: functional assessment performed at 3 time-points in 80% of  
24 87 survivors. The results will inform a larger fully powered RCT.  
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## 29 30 89 **METHODS AND ANALYSIS**

### 31 90 **Study design:**

32  
33 91 This is a two-centre feasibility study using a two-arm RCT, randomised 1:1, with blinded outcome  
34 92 assessments at ICU discharge, hospital discharge and 3-month follow-up. Patients will be recruited from  
35 93 two general ICUs, located in the south of the UK. They will not be recruited from our ICU on account  
36 94 that the intervention is now standard practice at this site. Prior to each site opening to recruitment an  
37 95 audit of current physiotherapy practice will be undertaken over a four-week period to evaluate what  
38 96 constitutes 'usual care' in each institution.  
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### 44 98 **Participants:**

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46 99 Ninety patients will be recruited. Eligible patients will be over 42 years old and have an acute/unplanned  
47 100 medical admission to the ICU. They will be functionally independent prior to ICU admission (Barthel  
48 101 Index >80), in hospital for <5 days prior to intubation and ventilation, intubated and ventilated for <72  
49 102 hrs and expected to remain ventilated for a further 48 hours. Patients will be excluded if in hospital for  
50 103 5 days or more prior to ICU admission, have acute brain or spinal cord injury, known or suspected  
51 104 neurological / muscular impairment, condition limiting use of cycle ergometry (e.g. lower limb fracture  
52 105 /amputation), not expected to survive >48hrs decided by consulting Intensivist, persistent therapy  
53 106 exemptions in first 3 days of mechanical ventilation. (Figure 1) presents the planned flow of patients  
54 107 through the study.  
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### 109 **Recruitment, consent and randomisation:**

110 The study team will screen all patients for eligibility. Recruitment began in June 2019 (and was  
111 temporarily suspended in March 2020 due to the COVID 19 pandemic). It is anticipated recruitment  
112 will continue until early 2022. The majority of patients will have diminished capacity when first eligible,  
113 therefore, the consent process is multi-layered and designed in accordance with the Mental Capacity  
114 Act (MCA) 2005<sup>52</sup> (Figure 2). *Patient Informed Consent*: Wherever possible, informed consent will be  
115 directly sought from the patient (see supplementary files 1 and 2). *Personal Consultee Informed Assent*:  
116 If the patient is unable to provide consent, informed assent will be sought from the patient's personal  
117 consultee, within 6 hours of confirmation of eligibility. If the personal consultee is not available in  
118 person, attempts will be made to contact them by telephone. They will be asked to provide written  
119 assent, at the earliest possible convenience (see supplementary files 3 and 4). *Professional Consultee*  
120 *Informed Assent*: Where both patient and personal consultee are not available to approve enrolment  
121 within 6 hours of confirmation of eligibility, assent will be sought from a professional consultee in  
122 accordance with the MCA. The professional consultee will be a consultant medical practitioner,  
123 independent from the study. The patient's personal consultee will be consulted at the earliest possible  
124 opportunity and assent requested to continue in the study.  
125 In all cases, once the patient has regained capacity they will be informed of the study and consent  
126 continuation sought. Following consent or assent, patients will be registered on a bespoke electronic  
127 data collection tool (ALEA™) and randomly assigned to the protocolised early rehabilitation or usual  
128 care.

### 130 **Staff training/ site set-up:**

131 Participating sites will employ the equivalent of a full-time therapy technician to deliver the study  
132 intervention, under the supervision of a senior critical care therapist. Both senior critical care therapists  
133 and therapy technicians will complete a training package delivered by the primary institution  
134 (University Hospital Southampton NHS Foundation Trust), where early rehabilitation with cycling is  
135 well established and embedded in usual care. This package includes seminars on the delivery of the  
136 protocolised early rehabilitation, use of the bespoke electronic database and 5-days of clinical  
137 shadowing.

### 139 **Interventions:**

140 All patients will receive usual medical, nursing and physiotherapy care while in intensive care. Each  
141 bedside nurse will be asked at the start of the shift if they have been involved caring for a patient in the  
142 intervention arm of the study. The ICU physiotherapy team, who are not involved the study delivery  
143 of, will deliver all usual physiotherapy interventions in both groups. The physiotherapist delivering  
144 usual care will be asked to verify if they have delivered any of the study interventions. In the  
145 intervention arm the protocolised physiotherapy programme will commence within 72 hours of ICU

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3 146 admission or as soon as possible thereafter and continue for 28 days or until ICU discharge, whichever  
4 147 occurs first. Patients respiratory support can range from full mandatory ventilation through to oxygen  
5 148 supplementation with no mechanical support following extubation. Sedation is targeted throughout the  
6 149 time that the patient is intubated and ventilation mode adjusted to patients' needs, compliance and  
7 150 comfort at discretion. At the start of each physiotherapy intervention the participants level of sedation  
8 151 will be assessed using the Richmond Agitation-Sedation Scale (RASS)<sup>53,54</sup> and the Confusion  
9 152 Assessment Method for ICU (CAM-ICU)<sup>55</sup>.will be undertaken. RASS will be targeted to a RASS  
10 153 between -1 and +1 by the bedside nurse. After 28 days of ICU admission, all patients will receive usual  
11 154 care physiotherapy interventions.  
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### 19 156 **Group 1: Usual care control group**

20 157 In this pragmatic study physiotherapy interventions will be guided by individual assessment and start  
21 158 in accordance with the usual care pathway within each institution. The focus of each session may be  
22 159 respiratory support, mobilisation or a combination of both. Interventions delivered will be determined  
23 160 by the physiotherapist in conjunction with the attending physician. Interventions include, where  
24 161 appropriate, passive or active range of movement, positioning and respiratory physiotherapy, and when  
25 162 able, sitting on the edge of the bed, standing (assisted or unassisted), standing to transfer to chair,  
26 163 marching on the spot and walking. (Figure 3). Usual interventions may occur at any time of day.  
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### 33 165 **Group 2: Protocolised rehabilitation pathway**

34 166 Patients will receive usual care physiotherapy, in addition to the two protocolised intervention within  
35 167 72 hours of ICU admission or as soon as possible thereafter. Patients will be screened for safety criteria  
36 168 to withhold the intervention prior to each planned intervention session (Table 1).  
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170 **Table 1 Safety criteria for delivery of physical therapy interventions**

|                    | <b>Criteria to commence physiotherapy</b>  | <b>Criteria to stop / withhold physiotherapy intervention</b>  |
|--------------------|--|--|
| Blood pressure     | MAP 60 – 100 mmHg, no change in vasopressor dose requirement for preceding 2 hours                         | Catecholamine resistant hypotension with MAP < 60 mmHg   |
| Heart rate         | Between 40-140 bpm   | <50 or >140 bpm  |
| Respiratory rate   | Sustained < 40 breaths/min   | Sustained >40 breaths/min  |
| Temperature        |  | >40 °C   |
| Oxygen requirement | If FiO <sub>2</sub> >0.8 for passive exercise only<br>FiO <sub>2</sub> <0.8 and PEEP<15 cmH <sub>2</sub> O |  |
| Desaturation       |  | Sats fall <85% for > 1 minute  |
| Other              |  | <ul style="list-style-type: none"> <li>· Fall</li> <li>· Unplanned extubation</li> <li>· Acute bleeding</li> <li>· New onset arrhythmia</li> <li>· Signs/symptoms of acute myocardial ischaemia</li> <li>· Patient pain/distress</li> <li>· Clinical team decide therapy intervention not appropriate</li> <li>· Refusal by patient or representative</li> </ul> |

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174 Those meeting criteria to withhold interventions will have issues addressed and reassessed for  
 175 interventions 2 hours later. The two additional rehabilitation sessions will be delivered by the research  
 176 physiotherapy staff including a therapy technician. This will comprise of two mobility sessions the  
 177 modality of the first, chosen at the discretion of the physiotherapist. The second session will be 30-  
 178 minutes of supine cycling. delivered in the afternoon.

179 The first rehabilitation intervention each day will be delivered in the morning. Planned interventions  
 180 include passive or active range of movements, passive cycling, active cycling, in bed exercises, sitting,  
 181 mobilisation out of bed and walking. Daily assessment of the patient will be made to ensure the highest

182 level of activity possible is provided for each individual patient given safety considerations and  
183 capability of the patient.

184 The second session will be cycling based. An in-bed supine cycle ergometer (MotoMed Letto 2™) will  
185 be used to engage the participant in passive, assisted or active cycling, or a combination, depending on  
186 the degree of patient co-operation (Figure3). The aim is for the patient to have 30 minutes of cycling  
187 per day, following a standardised cycling programme. If cycling is in passive mode, patients will  
188 commence cycling at 5 revolutions per minute (RPM), building up to 20 RPM over 5 minutes and  
189 continue this for 20 minutes before 5-minute 5 RPM cool down. In the assisted or active mode, after  
190 the 5-minute warm up, cycling will continue for 20 minutes at patient selected RPM followed by a 5-  
191 minute cool down at 5 RPM. In-bed cycling sessions will stop when the patient is deemed to be able to  
192 stand and transfer from bed to chair for both mobility sessions for two consecutive days. If patients are  
193 considered unable to have concurrent mobility therapy and respiratory weaning, mobility therapy will  
194 take priority, in agreement with the senior clinical team. Individual participants will receive the trial  
195 intervention on five days per week (Monday to Friday) for the duration of their ICU stay or maximum  
196 of 28 days whichever comes first. Patients will be monitored for cardiovascular and respiratory stability  
197 and safety of indwelling lines, tubes and catheters with pre-determined criteria for termination of any  
198 session (Table 1). Deviations from the planned protocol will be reported to determine potential barriers  
199 to implementation. Patients will be able to decline any intervention or outcome assessment at any time  
200 without compromise to their care.

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### 202 **Primary Outcome: Feasibility to deliver the protocol as designed**

203 Feasibility will be determined by measures of the recruitment process, intervention fidelity and outcome  
204 measurement completeness, specifically:

- 205 1. Study accrual rates: a minimum of 30% of eligible patients or 1-2 patients per site per month  
206 are enrolled
- 207 2. Protocol adherence: 75% of patients commencing intervention within 72 hours of ICU  
208 admission; minimum of 70% of planned interventions delivered
- 209 3. Blinded outcome assessment: functional assessment performed at 3 time-points in 80% of  
210 survivors by physiotherapists working within the hospital but not within the ICU

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### 212 **Secondary Outcomes:**

213 The schedule of outcome assessments is detailed in Table 2

### 214 **Strength and Function**

215 We will measure the Physical Function ICU Test-scored (PFITs) at awakening as described by  
216 deJonghe<sup>56</sup> then weekly within ICU and on ICU discharge<sup>57</sup>. PFITs is a reliable and valid 4 item scale  
217 (arm strength, leg strength, ability to stand and step cadence), with a score range of 0-10 and is  
218 responsive to change and predictive of key outcomes<sup>58</sup>. Medical Research Council Manual Muscle Test

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3 219 Sum Score (MRC-ss)<sup>59, 60</sup> and Handheld Dynamometry (HHD)<sup>61</sup> will be measured on awakening,  
4 220 weekly, on ICU discharge and hospital discharge. Chelsea Critical Care Physical Assessment tool  
5 221 (CPAX)<sup>62</sup> and ICU Mobility Scale<sup>63</sup> will be assessed three times during the first week within ICU, on  
6 222 awakening, weekly thereafter within the ICU and at ICU discharge. Timed Up and Go (TUG)<sup>64, 65</sup>,  
7 223 Clinical Frailty Score (CFS)<sup>66-68</sup> and Barthel Index will be assessed at ICU discharge, hospital discharge  
8 224 and 3-months post-hospital discharge. Pre-admission Barthel Index and CFS will be assessed by proxy  
9 225 on admission from family member or next of kin. Six-minute walk test (6MWT)<sup>69</sup> will be performed,  
10 226 in accordance with American Thoracic Society guidelines, at hospital discharge and 3-months post-  
11 227 hospital discharge.  
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### 19 229 **Health related quality of life Outcomes**

20 230 The following will be measured at 3-months post-hospital discharge : WHODAS-2.0<sup>70</sup> , Hospital  
21 231 Anxiety and Depression Score (HADS)<sup>71, 72</sup>, Euroqol-5 Dimension-5Level (EQ-5D-5L)<sup>73</sup>, Impact of  
22 232 Event Score (IES)<sup>74</sup> and Client Service Receipt Inventory questionnaire (CSRI), designed for this  
23 233 study to evaluate costs that fall on patients and their carers. Resource use and costs including direct  
24 234 intervention costs of therapists and equipment and general hospital costs (per bed day) will be  
25 235 recorded for each patient  
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### 31 236 **Health economic sub-study**

32 237 We will also conduct an embedded health economic study to identify and define data collection for a  
33 238 future RCT where a full cost effectiveness analysis (CEA) can be conducted. Within the feasibility  
34 239 study we aim to address the following:

- 38 240 • what the quality of the data and what potential problems are there for reporting QoL (EQ-5D-  
39 241 5L), resource use and costs.
- 41 242 • the cost implications of the proposed intervention in terms of impact for the NHS (inpatient  
42 243 stay bed days) and identifying the main cost drivers.
- 44 244 • is the EQ-5D-5L appropriate for use in the future RCT.

46 245 The economic outcomes will include: secondary care resource use within hospitals during inpatient  
47 246 stay, primary care resource use following discharge up to 3months and resource use related to  
48 247 providing the intervention. The results will be reported in the form of descriptive statistics and will be  
49 248 used to inform a future CEA within a definitive RCT.  
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### 54 249 55 56 250 **Additional data collection**

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3 251 We will collect baseline data including demographic information, Functional Comorbidity Index, ICU  
4 252 diagnosis, APACHE II score, ventilation duration, ventilator free days, ICU and hospital length of  
5 253 stay, within ICU drug history and duration and type of usual care physiotherapy.  
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### 9 255 **Implementation Evaluation**

10 256 We aim to investigate whether the protocolised early rehabilitation programme used in one NHS  
11 257 institution is transferable, as an RCT, into other similar NHS institutions. The design of a future multi-  
12 258 centre study will be informed by identified facilitators and barriers to implementation. Implementation  
13 259 assessment will be based on the measures described by Proctor<sup>75</sup>. A cross section of ICU staff and  
14 260 patients will be interviewed and complete questionnaires at trial completion to identify barriers  
15 261 impacting delivery of the study. Understanding of the integration and sustainability of the intervention  
16 262 are necessary to inform the design of a powered RCT. Acceptability will be measured at the  
17 263 beginning and end of the study from investigators and clinical staff by direct discussions and  
18 264 questionnaire. Our experience informs us that the introduction of this intervention is dependent on a  
19 265 cultural change within any unit for a pro-active focus on early mobilisation. We aim to explore  
20 266 measures to help optimise implementation. Adoption, feasibility, and fidelity measures will be  
21 267 monitored during the study by regular meetings with the investigators. Patient screening logs will  
22 268 identify the number of patients eligible for the study and barriers to enrolment. We will assess the  
23 269 degree to which it is possible to separate the staff caring for the intervention group from those caring  
24 270 for the patients in the control group.  
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36 271  
37 272 We will report whether trial participation has influenced usual care within the participating units by  
38 273 pre- and post-study audits. Participating sites will collect data regarding number and seniority of  
39 274 therapy staff with dedicated time to work within the ICU; delirium and sedation protocols used; time,  
40 275 type and frequency of rehabilitation interventions delivered, who delivers the interventions and  
41 276 reasons why usual care may not be delivered.  
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45 277 The feasibility outcomes described above will be used to power a larger RCT.  
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### 48 279 **Data entry and checks**

49 280 Data will be entered into the secure electronic case report form (ALEA™) and data validation will  
50 281 take place according to the procedures set out in the data management plan and data validation plan,  
51 282 both developed a priori. Missing data will be assessed to identify any specific challenges with any  
52 283 items of data collected. Missing data level is expected to be less than 20%. Data loss and mortality  
53 284 will inform number of participants needed to design a larger RCT. As this is a feasibility study data  
54 285 imputation will not be undertaken. Prior to statistical analysis, variables will be checked for missing  
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3 286 and impossible and improbable values as defined by clinical opinion. Questions regarding the data  
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5 287 will be directed to the data manager.

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9 **289 Sample size calculation**

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11 290 .

12  
13 291 This is a feasibility study the results of which will be used to power a definitive study if  
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15 292 appropriate, as such no formal sample size calculation for effectiveness of the intervention  
16  
17 293 has been undertaken. 90 patients will be recruited aiming for 30-45 participants at each site.  
18  
19 294 We anticipate a 30% in hospital mortality /loss to follow-up with an estimate of 60 patients  
20  
21 295 completing the study. This sample size of 90 will allow the estimate of recruitment rate to be  
22  
23 296 made with a 95% confidence interval of  $\pm 5.2\%$  if the rate is observed to be around 30%, and  
24  
25 297 with a confidence interval of  $\pm 7.3\%$  if the recruitment rate is observed to be around 50%. In  
26  
27 298 addition, the sample of 90 recruited patients will allow the estimate of the mortality rate to be  
28  
29 299 made with a 95% confidence interval of  $\pm 9.5\%$  assuming the mortality rate was around 30%.  
30  
31 300 Finally, assuming the recruitment rate was around 30%, a sample of 300 patients approached  
32  
33 301 to take part in the study leading to 90 enrolled patients would allow for the recruitment rate to  
34  
35 302 be estimated with a 95% confidence interval of  $\pm 5.2\%$ . If the recruitment rate was nearer  
36  
37 303 50%, with 180 patients approached to recruit the 90 enrolled patients, the recruitment rate  
38  
39 304 would be estimated with a 95% confidence interval of  $\pm 7.3\%$ .

40  
41 305 **Statistical analysis**

42  
43 306 The analysis will be reported in line with the feasibility studies extension to the CONSORT statement  
44  
45 307 <sup>76</sup>. The aims of the study are to estimate the recruitment, compliance and retention rates to inform the  
46  
47 308 design of a future study and is not powered for hypothesis testing regarding the effectiveness of the  
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49 309 intervention. Feasibility outcomes (recruitment, compliance, and retention rates) will be  
50  
51 310 presented with 95% confidence intervals across the whole study population. Compliance and  
52  
53 311 retention rates will also be presented by treatment arm to ensure balanced recruitment, but no  
54  
55 312 formal statistical comparison tests will be made. Mortality and participant dropout rates will  
56  
57 313 be presented with 95% confidence intervals across the whole study population and within  
58  
59 314 treatment arm. Clinical outcome data (secondary outcomes) will be presented as summary  
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315 statistics using means and standard deviations or medians and ranges/interquartile ranges, as  
316 applicable, across the whole study population and by treatment arm. These data will be used

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3 317 to inform the future trial but will not be used to draw conclusions about the effectiveness of  
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5 318 the protocolised early rehabilitation intervention within this study  
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8 319 **Trial management**  
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10 320 The Chief Investigator (CI) will ensure all study personnel are appropriately orientated and trained,  
11 321 oversee recruitment and report to the trial safety monitoring committee. Training will occur across  
12 322 sites using competency-based training developed at the primary site (University Hospital  
13 323 Southampton NHS Foundation Trust). A study steering group, consisting of an independent chair,  
14 324 expert members and 2 lay advisors will meet every 3-months. Fortnightly teleconferences with trial  
15 325 sites will be held to monitor conduct and progress. Timing and intervals of visits and teleconferences  
16 326 will be reviewed at 3 months to ensure optimal time use.

17 327 The CI and Principal Investigators will facilitate local monitoring by the Research and Development  
18 328 quality manager, Research Ethics committee (REC) review and provide access to source data as  
19 329 required. A monitoring report will be produced, summarising the visit, documents and findings. The  
20 330 CI will ensure that all findings are addressed appropriately. The steering group will review all events  
21 331 in a timely manner. Additional monitoring will be scheduled where there is evidence or suspicion of  
22 332 non-compliance with the study protocol.

23 333 A Data Management and Safety Committee will be chaired by an independent expert. Quarterly  
24 334 reports will be given to the committee once recruitment has commenced.  
25

26 335 **Patient and Public Involvement**  
27

28 336 The study has been supported by patient advisory representatives. These representatives are  
29 337 members of the trial steering committee. Patient advisors partnered with us for the design of the study,  
30 338 the informational material to support the intervention, the burden of the intervention from the patient's  
31 339 perspective and contributed to the dissemination plan  
32

33 340 **Ethics and dissemination**  
34

35 341 Ethical approval has been granted by South Central - Hampshire A Research Ethics Committee (REC  
36 342 reference 19/SC/0016). EMPRESS was registered with Clinical Trials.gov (ref: NCT03771014) on  
37 343 10th December, 2018.  
38

39 344 Results of this proposed feasibility study will be disseminated for four key audiences: i) patients and  
40 345 public; ii) Intensive care staff, healthcare workers and potential future research delivery partners; iii)  
41 346 service delivery organisations and iv) academic and potential future research collaborators.  
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43 347 Dissemination activities will include feedback to Patients and Public Involvement study focus group,  
44 348 feedback to study participants, presentations to local clinical teams and managers and commissioners  
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3 349 and presentation at conferences attended by appropriate healthcare professionals. Where appropriate,  
4 results will be published in peer reviewed journals.  
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### 8 352 **Safety and adverse events**

9 353 Early mobility within ICUs is safe. In a review of physiotherapy in a critical care rehabilitation  
10 programme, 1110 patients received 5267 rehabilitation sessions physiological abnormalities or  
11 potential adverse events occurred in only 6 per 1000 interventions<sup>77</sup>. Mobilisation interventions will  
12 only be delivered if patients fit the safety criteria defined in table 1. Similar safety criteria have been  
13 used in other ICU rehabilitation studies<sup>78, 79</sup>.  
14

15 356 All adverse events will be documented. Any intervention will cease according to stopping criteria  
16 detailed in Table 1. Any such event will be recorded as an adverse event. The CI will provide a monthly  
17 update to the safety monitoring committee. Serious adverse events are events that result in death, are  
18 life threatening or require prolonged hospitalisation. Any such event will be reported in accordance with  
19 the NHS Health Research Authority guidance.  
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### 22 361 **Discussion:**

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28 365 EMPRESS is a feasibility study to assess if a randomised controlled trial of protocolised rehabilitation  
29 with supine cycling can be delivered in ventilated patients in ICUs with differing organisational  
30 structures with blinded follow-up assessments. A recent meta-analysis indicated that protocolised  
31 rehabilitation significantly reduces duration of mechanical ventilation and ICU length of stay<sup>23</sup>. This is  
32 consistent with our findings when we introduced the early rehabilitation programme outlined here in  
33 our intensive care unit<sup>45</sup>. Passive cycling commenced on ventilated patients may assist the recovery  
34 muscle strength in ICU patients<sup>43</sup> although the overall benefits of leg cycle ergometry in the critically  
35 ill is inconclusive<sup>44</sup>. We describe a protocolised rehabilitation programme with supine cycling delivered  
36 as close to intubation as possible, at an intensity according to the patients' highest performance  
37 capability.  
38

39 370 Both patient and organisational issues are recognised to the delivery of early rehabilitation of the  
40 critically ill patients<sup>35</sup>. A frequently reported challenge is the lack of appropriately qualified staff<sup>80</sup>.  
41 This study evaluates the safety, feasibility, effectiveness of delivery and cost efficiency of using therapy  
42 technicians to deliver protocolised rehabilitation interventions. In addition to the clinical benefits, early  
43 physical rehabilitation can also be cost saving<sup>49</sup>. Even with the employment of additional therapy  
44 technicians specifically to assist in the delivery of we have found this early rehabilitation programme  
45 cost effective<sup>81</sup>.  
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3 382 This study will collect data on the dose of intervention delivered to all patients, reasons for non-delivery  
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5 383 of protocol interventions, and the level of experience of therapists delivering the interventions. A  
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7 384 qualitative process evaluation is designed to identify both patient and organisational challenges that  
8  
9 385 have potential to be addressed in a potential future study. Findings will inform refinement of trial design  
10  
11 386 and evaluation of the intervention, clarifying causal mechanisms behind study outcomes and providing  
12  
13 387 additional context not adequately captured by the quantitative data. The process evaluation will be  
14  
15 388 consistent with Medical Research Council guidance for conducting process evaluations of complex  
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17 389 healthcare interventions<sup>82</sup>.

18  
19 390 Targeted sedation is embedded within this protocol as oversedation is one of the more commonly cited  
20  
21 391 barriers to mobilisation of the ventilated patient<sup>35</sup>. This study opened to recruitment prior to the  
22  
23 392 publication of the recommended core outcome set for critical care ventilation trials<sup>83</sup> however three of  
24  
25 393 the six outcomes listed (duration of mechanical ventilation, duration of stay and health related quality  
26  
27 394 of life) are secondary outcomes in this study and the other 3 outcomes are included in the data collected  
28  
29 395 This will be addressed should we proceed to a full RCT. Due to the nature of the intervention, it is not  
30  
31 396 possible for this to be blinded however the follow-up assessments will be carried out by a blinded.

32  
33 397 Results from EMPRESS will inform the design of a multi-centred RCT, both identifying barriers to the  
34  
35 398 implementation of the designed protocol and exploring how these may be addressed from feedback  
36  
37 399 from the therapy and nursing teams in addition to the feedback from patients and their next of kin.

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39 400

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402

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404  
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406  
407 devised the statistical analysis plan, MC developed the economic analysis. AB, GS, ID and RJC  
408  
409 prepared and submitted documents for Research and Development and ethical approval. RJC, KM and  
410  
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416  
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418  
419 author(s) and not necessarily those of the NIHR, or the Department of Health and Social Care

420  
421 **Competing Interests:** None declared

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423 415

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3 416 **Ethics Approval:** The study has ethical approval from South Central Hampshire A Research Ethics  
4 Committee (19/SC/0016). Protocol Version 1.3 7<sup>th</sup> Feb 2019  
5

6 418

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8 419 **Provenance and Peer review:** Not commissioned. Protocol peer-reviewed for ethical and funding  
9 application  
10

11 421

12 422 **Disclaimer:** The views expressed are those of the author(s) and not necessarily those of the NIHR, NHS  
13 or the Department of Health and Social Care.  
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For peer review only

427 **Table 2 Schedule of assessments**

|                                      | Randomisation | Day 1 | Day 3 | Day 7 | Awakening | Weekly | ICU Discharge | Hospital Discharge | 3 months post hospital discharge |
|--------------------------------------|---------------|-------|-------|-------|-----------|--------|---------------|--------------------|----------------------------------|
| <b>Demographic Data</b>              | X             |       |       |       |           |        |               |                    |                                  |
| <b>Muscle assessment:</b>            |               |       |       |       |           |        |               |                    |                                  |
| MRCss <sup>60,61</sup>               |               |       |       |       | X         | X      | X             | X                  |                                  |
| Grip strength <sup>62</sup>          |               |       |       |       | X         | X      | X             | X                  |                                  |
| <b>Physical function:</b>            |               |       |       |       |           |        |               |                    |                                  |
| CPAX <sup>63</sup>                   |               | X     | X     | X     | X         | X      | X             |                    |                                  |
| ICU mobility <sup>64</sup>           |               | X     | X     | X     | X         | X      | X             |                    |                                  |
| PFITs <sup>59</sup>                  |               |       |       |       | X         | X      | X             |                    |                                  |
| Timed-Up and Go (TUG)                |               |       |       |       |           |        | X             | X                  | X                                |
| Clinical Frailty Score <sup>69</sup> |               | (X)   |       |       |           |        | X             | X                  | X                                |
| Barthel Index                        |               | (X)   |       |       |           |        | X             | X                  | X                                |
| 6-minute walk test <sup>70</sup>     |               |       |       |       |           |        |               | X                  | X                                |
| <b>HRQL:</b>                         |               |       |       |       |           |        |               |                    |                                  |
| WHODAS 2 <sup>71</sup>               |               |       |       |       |           |        |               |                    | X                                |
| HADS <sup>72,73</sup>                |               |       |       |       |           |        |               |                    | X                                |
| EQ5D-5L <sup>74</sup>                |               |       |       |       |           |        |               |                    | X                                |
| Impact of Event Scale <sup>75</sup>  |               |       |       |       |           |        |               |                    | X                                |
| Health Economic Evaluation (CSRI)*   |               |       |       |       |           |        |               |                    | X                                |

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429 Physical Function ICU Test-scored (PFITs); Medical Research Council Manual Muscle Test Sum Score (MRC-ss); Chelsea Critical Care Assessment Tool  
 430 (CPAX); World Health Organisation Disability Assessment; Euroqol 5-dimension 5 level health related quality of life questionnaire(EQ5D-5L); Hospital anxiety  
 431 and depression scale (HADs); Client service receipt inventory (CSRI)

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5 **Figure 1: Study design**  
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7 **Figure 2: Consent pathway**  
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9 **Figure 3: Study intervention pathway**  
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11 **References**  
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Figure 1 Study design

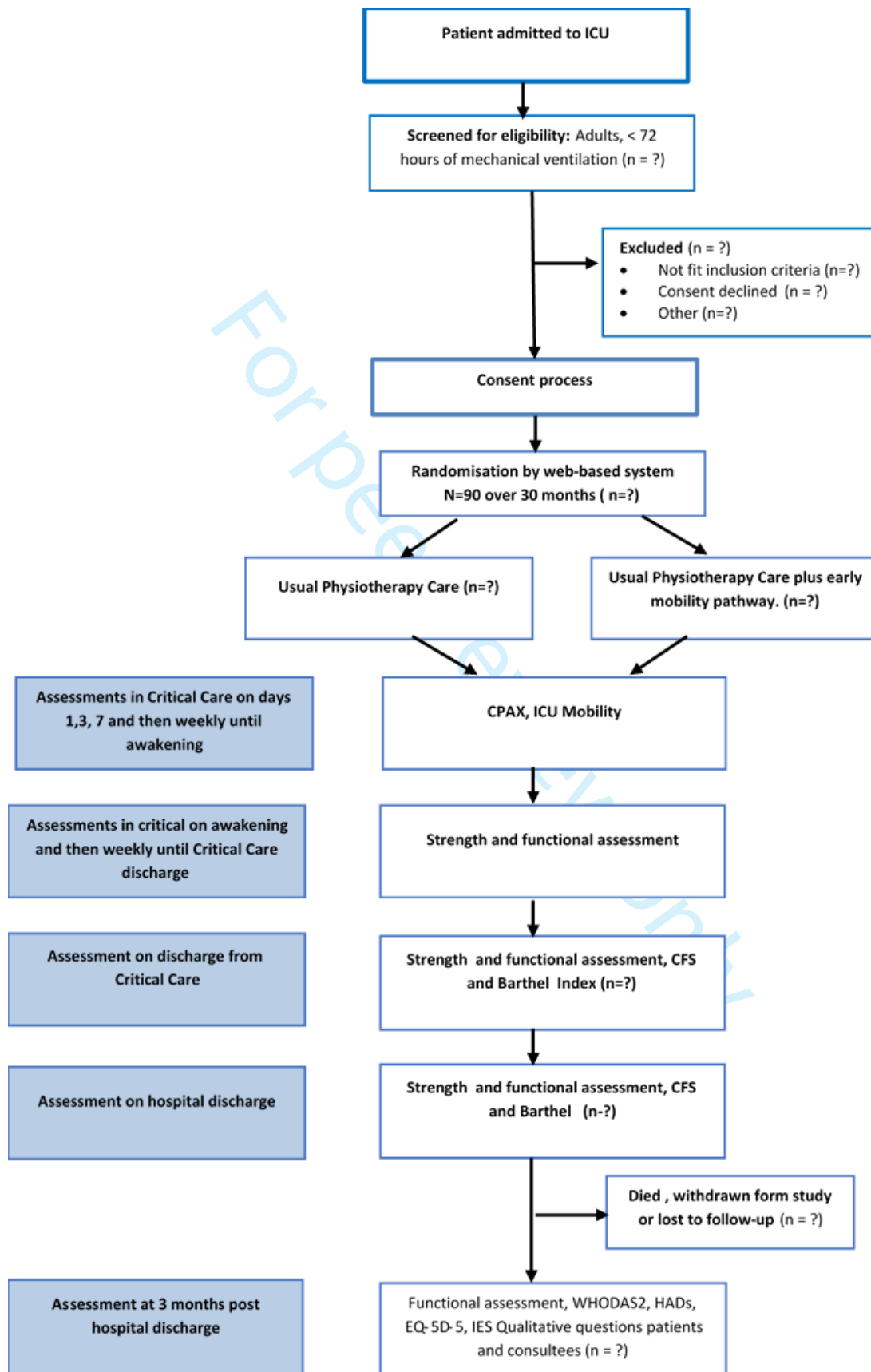


Figure 2 Consent pathway

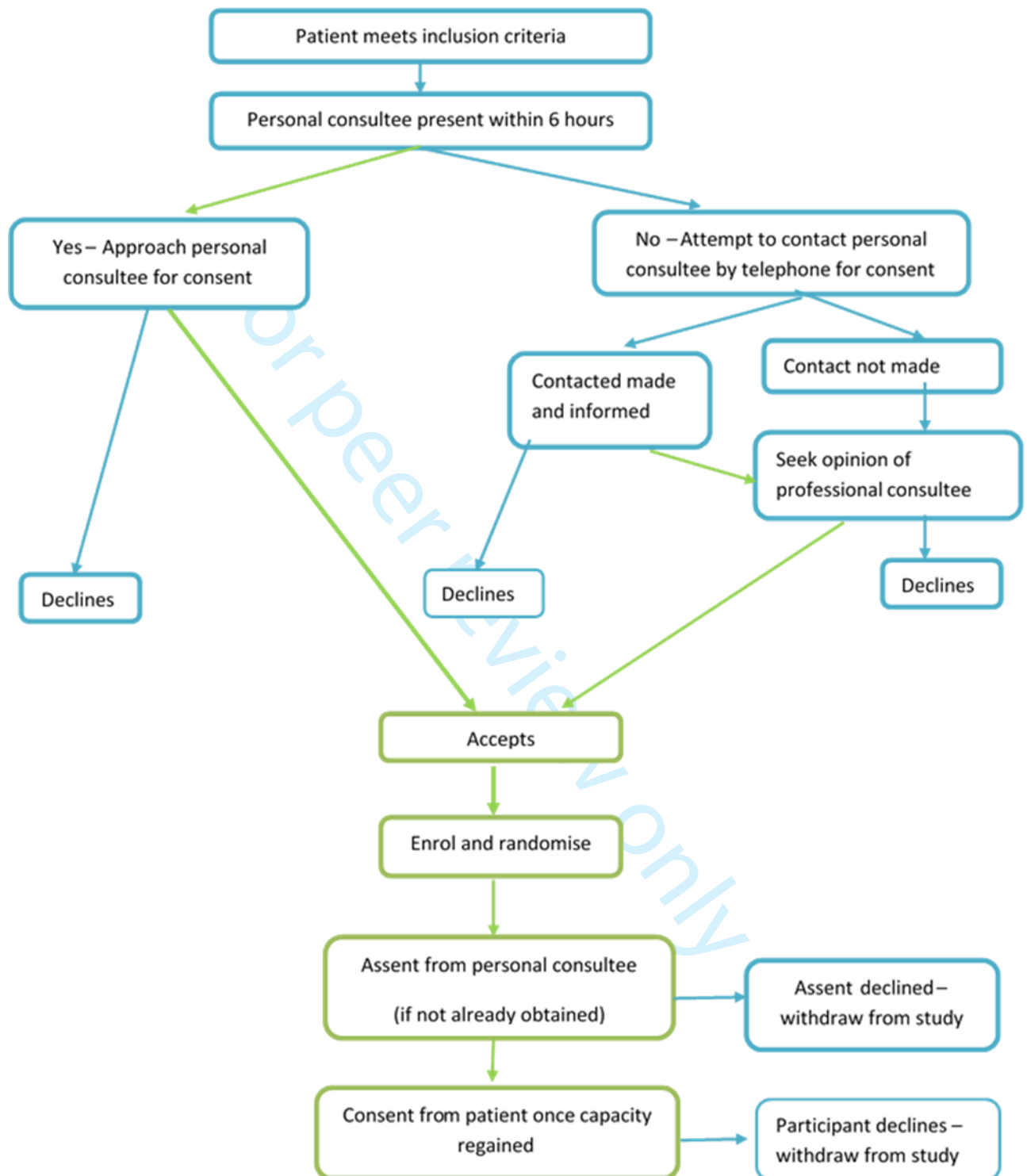
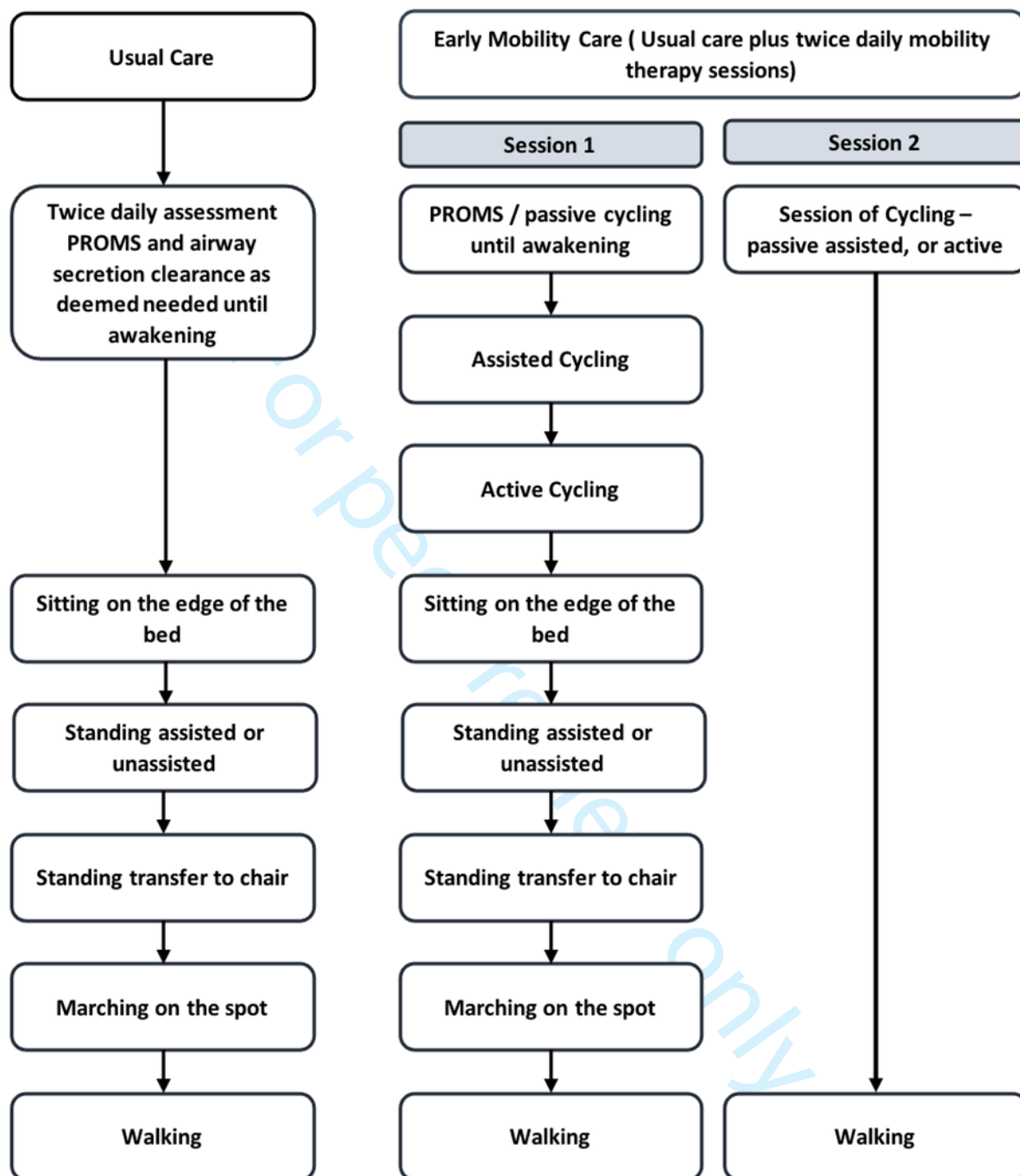


Figure 3 Study Intervention Pathway



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## **EMPRESS.**

### **A feasibility study of early mobilisation in Critical Care.**

#### **Patient Information Sheet**

Version 2: 29<sup>th</sup> January 2019

### **Introduction**

**Study Title:** EMPRESS: A study of very early mobilisation in Critical Care.

#### **Invitation:**

Your consultee has agreed on your behalf, to your participation on a research study. We would like to invite you to confirm whether you wish to continue or withdraw your participation from this research study.

This hospital is taking part in a national research study to investigate whether starting rehabilitation in the Intensive Care Unit, as soon as possible, will improve patient's long-term physical ability and quality of life.

When patients are sedated in Intensive Care, muscle wasting and weakness can occur very quickly and this can take a long time to recover from. Because we feel that it may be important to deliver rehabilitation physiotherapy as early as possible, it was agreed by your doctor and / or your relative/ friend that you could be involved in this study. This research has been approved by Hampshire Research Ethics Committee (IRAS number: 250165).

This patient information sheet provides information about the study to help you decide if you would like to continue to participate in it. It is important that you understand why the research is being done and what it involves.

Knowing what is involved will help you decide if you want to continue to take part in the research, so this Information Sheet explains the tests and treatments involved.

- Part 1 tells you about why we are doing this study and what will happen to you if you continue to take part.
- Part 2 gives you more detailed information about how we will run the study.

If you have no objection to continue taking part, we will ask you to read and sign a form that records your permission, called the consent declaration. We'll then give you a copy to keep. We will keep you fully informed during the study so you can let us know if you have any concerns or if you would prefer to be withdrawn. Taking part in this research is entirely voluntary. If you decide not to continue, you will still be offered the best possible standard of care.

Please ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

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## **PART ONE: Why are we doing this study and what will happen to you?**

### **What is the purpose of this study?**

We know that when patients are very unwell and need sedation in the Intensive Care Unit, they can lose muscle strength and size very quickly. It is normal to offer rehabilitation, but this often starts after the patient has woken up. By this time the muscles have already been affected. Previous studies have shown that this can take many months to recover from and may affect a patient's quality of life after leaving hospital.

In Southampton Hospital, researchers and physiotherapists started performing rehabilitation exercises much earlier than usual, even while the patient was sedated. They showed that this method reduced the patient's time on the ventilator and reduced the amount of time that they needed to be in Intensive Care.

We are now trying to discover whether this method will work in a number of different hospitals in the UK. We will also do some tests to see whether the patients who have this type of rehabilitation are stronger and able to engage in physical activity more easily, when they leave hospital and 3 months later.

### **Why have you been chosen?**

You were enrolled in this study because during your admission to the Intensive Care you needed a ventilator (a machine to help you breathe) and sedation was needed to help keep you calm and comfortable. The treating doctor and physiotherapist thought that either very early rehabilitation or standard rehabilitation would be equally suitable. We may have given you very early physiotherapy already in the intensive care unit, because we are testing such early rehabilitation, but we would like to ask for your permission to continue.

### **Do I have to take part?**

No. It is up to you to decide whether or not you would like to continue to take part. If you do, you will be given this information sheet to keep and be asked to sign the consent form. You are still free to withdraw at any time without giving a reason. The decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive.

### **What will happen to me if I take part?**

Participation in the study began in the Intensive Care Unit. The final tests will take place 3 months after you leave hospital.

**In the Intensive Care Unit:** Your treating doctor has assessed you to be eligible to take part in this study: EMPRESS. You were randomly allocated (like the flip of a coin) to receive either of the following:

- **Standard physiotherapy:** All patients on the trial will receive their normal physiotherapy. This will normally include activities to assist in keeping your airway

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clear and activities to maintain limb flexibility. These will not be affected by being on the trial.

## OR

- **Standard physiotherapy, as above, plus an extra 2 sessions of 30 minutes of rehabilitation from Monday to Friday.** For patients receiving extra, early rehabilitation, in addition to your normal physiotherapy, you have been using a cycle machine that is designed to work, in the bed, even with sedated patients. As you wake up you have started to pedal for yourself, do some more bed-based exercises and finally get out of bed and start moving. All of these sessions have been and will continue to be run by a well-trained physiotherapist and the bedside nurses. We have already tested this method in University Hospital Southampton and it has reduced the length of time on the ventilator and ICU stay. During these sessions, you have been and will continue to be very carefully monitored for your own safety and the safety of lines, tubes and catheters.

These exercises will continue for a maximum of 28 days or less if you leave the Intensive care unit before then.

## BOTH GROUPS

- **Additional assessments:** So that we can test whether our new method works, patients on the trial will undertake some extra assessments. These include a simple test of grip strength by using a hand held pressure monitor; a test of arm and leg strength, ability to stand and step and mobility and walking tests. There will also be quality of life and health questionnaires.

There was a 50/50 chance of being allocated to either group. Neither you nor your doctor can decide which. No samples of blood are required for this research study.

**In the hospital ward:** When you have been discharged to a normal hospital ward, you won't receive any extra physiotherapy. Just before you go home, you will be tested again for muscle strength and mobility, including how far you can walk in 6 minutes. These tests will be supervised by a trained and experienced physiotherapist

**Following discharge from hospital:** Regardless of which group you were allocated to, after going home, you should follow the advice given to you by your doctors and physiotherapists. We have designed our study so that this will not affect our results.

You will be contacted by one of the critical care research team 3 months after you have been discharged home. We will arrange to see you for approximately one hour. During this visit we will test your walking speed, strength and agility. We will also ask for some questionnaires to be completed, which will assess how you feel about your quality of life and recovery.

The researchers would also like to have access to your medical record to obtain information relevant to the study. This information would be anonymised and kept confidential.

If you have any questions regarding the trial procedures, please don't hesitate to ask the intensive care or research doctors, physiotherapists and nurses.

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### **What do I have to do?**

It is important to tell the doctor and the research staff about any treatments or medications you may have been taking, including over-the-counter medications, vitamins or herbal remedies, acupuncture or other alternative treatments. We would also like to know about any medical conditions which may affect the exercise.

Please let us know if you are involved in any other studies at this time.

### **What are the alternatives to participation?**

Participation in this research is not the only option. You may decide to receive only standard or usual care. This is absolutely fine. Please feel free to discuss these options with your doctor before deciding whether or not to continue to take part in this research project.

### **What are the possible disadvantages of taking part?**

Early mobility within ICU is safe. Potential risks may include, but not be limited to blood pressure or heart rate problems, breathing problems, problems with the tubes, lines and catheters.

In a review of physiotherapy within Intensive Care Units, involving over 1100 patients and 5267 episodes of physiotherapy in similar patients, there were 34 potential safety events (equivalent to 6 events in 1000 episodes of physiotherapy), Most of these were potentially related to changes in heart rate or blood pressure which settle quickly in stopping the physiotherapy.

In Southampton, over a four year period, we have treated over 500 patients in this way and had 2 non-serious adverse events.

The doctors, physiotherapists and nurses who will be caring for you while in the ICU, are trained to recognise the effects on the body associated with physical rehabilitation and will treat you accordingly. You will be continue to be monitored and assessed. Your safety is always our number one priority.

There may be side effects that the researchers do not expect or do not know about and that may be serious. Please tell the doctor immediately about any new or unusual symptoms that you get.

### **What are the possible benefits of taking part?**

We cannot guarantee or promise that you will receive any benefits from this research. This study aims to further medical knowledge and may improve future treatment of patients who need to be on a ventilator, however it may not directly benefit you.

### **For how long will I be in the research study?**

The final research assessment will take place 3 months after discharge from hospital. Once that is done, your participation in the study will end.

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### What happens if there is a problem?

We will keep you fully informed of any problems which may be related to the study.

### Will taking part in the study be kept confidential?

Yes. All of the information about participation and the data collected will be kept confidential.

Information held by the NHS and records maintained by the NHS Information Centre and the NHS Central Register may be used to help contact you and provide information about your health status. This information may be obtained and stored by the study research team to enable long term follow-up.

University Hospital Southampton is the sponsor for this study based in the United Kingdom. We will be using information from you and/or your medical records in order to undertake this study and will act as the data controller for this study. This means that we are responsible for looking after your information and using it properly. University Hospital Southampton will keep information about you for 10 years after the study has finished.

Your rights to access, change or move your information are limited, as we need to manage your information in specific ways in order for the research to be reliable and accurate. If you withdraw from the study, we will keep the information about you that we have already obtained. To safeguard your rights, we will use the minimum personally-identifiable information possible.

You can find out more about how we use your information at <https://www.hra.nhs.uk/information-about-patients/>.

[Local NHS site name] will collect information from you and/or your medical records for this research study in accordance with our instructions.

(Local NHS site name) will keep your name, NHS number and contact details confidential and will not pass this information to University Hospital Southampton. [Local NHS site name] will use this information as needed, to contact you about the research study, and make sure that relevant information about the study is recorded for your care, and to oversee the quality of the study. Certain individuals from University Hospital Southampton and regulatory organisations may look at your medical and research records to check the accuracy of the research study. University Hospital Southampton will only receive information without any identifying information. The people who analyse the information will not be able to identify you and will not be able to find out your name, NHS number or contact details.

[Local NHS site name] will keep identifiable information about you, including the consent form from this study for 10 years after the study has finished.

## Contact Details:

### Local PI

Consultant Critical Care,  
Hospital address

Dr XXXX: 02381 XXXXXX

Research Nurse: 02381 XXXXXX

ICU: 02381 XXXXXX

## PART 2: How we will run this study.

### What if relevant new information becomes available?

During the research project, new information about the risks and benefits of the study may become known to the researchers. If this occurs, you will be told about this new information and the doctor will discuss whether this new information affects you.

If any information becomes available which could affect your participation in the study the research doctor will tell you about it and discuss whether you want to continue in the study. If you decide to not continue in the study, the research doctor will make arrangements for your care to continue as normal. If you decide to continue in the study you will be asked to sign an updated consent form.

Also, on receiving new information the research doctor might consider it to be in your best interests to withdraw you from the study. He/she will explain the reasons and arrange for your care to continue.

If the study is stopped for any other reason, you will be told why and your continuing care will be arranged.

### What will happen if I don't want to carry on with the study?

You can withdraw from the study at any time without giving an explanation and be assured that it will not impact on any part of your further treatment.

If you decide to withdraw from the study, the researchers would like to keep your health information that has already been collected. This is to help them make sure that the results of the research can be measured properly. If you do not want them to do this, you can tell them when you withdraw from the research project.

### What if there is a problem?

If you have any concerns regarding the study, please ask to speak to the ICU doctor in charge of your care or ask to speak to **name of local PI**, the consultant who is in charge of the study.

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### **Complaints:**

If you have a concern about any aspect of this study, you should ask to speak with the researchers or the Intensive Care doctors and nurses, who will do their best to answer your questions. If you remain unhappy and wish to complain formally, you can do this through the NHS Complaints Procedure. **Please localise with your hospital PALS contact details.**

### **Harm:**

In the event that something does go wrong and you are harmed during the research study there are no special compensation arrangements. If you are harmed and this is due to someone's negligence then you may have grounds for a legal action for compensation against University Hospital Southampton, but you may have to pay the legal costs. The normal National Health Service complaints mechanisms will still be available to you.

### **Involvement of the General Practitioner/Family doctor (GP)**

If you are agreeable we would like to inform your GP of your participation in the study. If you do not wish for your GP to be informed, please let us know and indicate on the consent form that you do not wish your GP to be informed.

### **Will taking part in this study be kept confidential?**

If you continue with the study, some parts of your medical records and the data collected for the study will be looked at by authorised researchers from University Hospital Southampton and University of Southampton who are sponsoring and organising the research. They may also be looked at by authorised people to check that the study is being carried out correctly. All will have a strict duty of confidentiality to you, as a research participant and we will do our best to meet this duty.

All information that is collected about you during the course of the research will be kept strictly confidential. Any information about you that leaves the hospital will have your name and address removed so that you cannot be recognised from it.

Anonymised data collected during the study may be sent to associated researchers in other countries, where the laws don't protect your privacy to the same extent as the law in the UK but the study team will take all reasonable steps to protect your privacy.

You have the right to check the accuracy of data held about you and correct any errors.

### **What will happen to the results of the research study?**

They will be published in a medical journal, presented at conferences and lay press where possible.

### **Who is organising and funding the research?**

Dr Rebecca Cusack from University Hospital Southampton is the lead researcher, who is organising the research.

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Version 2: 29<sup>th</sup> January 2019

IRAS ID:250165

1  
2  
3 The research is funded by the NHS through the National Institute for Health Research,  
4 Research for Patient Benefit scheme.  
5

6 **Who has reviewed the study?**

7 Hampshire Research Ethics Committee (IRAS number: 250165) have reviewed this study  
8 and given their approval.  
9  
10

11  
12 Thank you very much for taking the time to read this information sheet at this very stressful  
13 time.  
14

15 If you have any further questions please ask the doctors in Intensive Care, Dr (local PI) or  
16 one of the research team.  
17

18 If you agree to continuing participation in this study, please keep this information sheet and  
19 you will be given a copy of the agreement form that you will be asked to sign.  
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FORM TO BE ON SITE SPECIFIC HEADED PAPER

University Hospital Southampton   
NHS Foundation Trust

Critical Care, Anaesthesia & Peri-operative Medicine Dept,  
Research office CE 93. MP 24,  
University Hospital Southampton,  
Tremona Road,  
Southampton  
SO16 6YD

Tel: 023 8120 5308

Fax: 023 8120 5378

**Consent form for patients participating in EMPRESS.**  
**A feasibility study of early  
mobilisation programmes in Critical Care.**

Name of Researcher: \_\_\_\_\_

Please initial box

1. I confirm that I have read and understood the Patient Information Sheet (version \_\_\_\_ Dated \_\_\_\_\_) for the EMPRESS study. I have had the opportunity to ask questions about the study and understand what is involved.

2. I have no objection to taking part in the above study.

3. I understand that my participation is voluntary and that I am free to withdraw from the study at any time, without giving any reason and without my care or legal rights being affected.

4. I understand that relevant sections of my medical notes and data collected during the study, may be looked at by individuals from the research team, from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.

5. I understand that information held by the NHS and records maintained by the NHS Information Centre and the NHS Central Register may be used to help contact me and provide information about my health status. I give permission for this information to be obtained and stored by the study research team to enable long term follow-up.

6. I agree to my GP being informed of my participation in the study.

7. I agree to take part in the above study



---

Version 2: 29<sup>th</sup> January 2019 IRAS ID:250165



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7 **Name of Participant:**

**Signature:**

**Date:**

8  
9  
10 \_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

11  
12  
13 **Person undertaking consultation (researcher):** **Signature:**

**Date:**

14  
15  
16 \_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

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23 **Original Informed Consent form to be filed in the Investigator Site File.**

24  
25  
26 *1 copy to be given to the patient*

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28  
29  
30 *1 copy to be filed in the patients' hospital notes.*

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4 **Site specific header to be inserted here**  
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8 **EMPRESS.**  
9

10 **A feasibility study of early mobilisation in Critical Care.**

11 **Information for Consultee**

12 Version 2: 29th January 2019  
13  
14  
15

16 **Introduction**  
17  
18

19 **Study Title:** EMPRESS: A study of very early mobilisation in Critical Care.  
20  
21

22 **Invitation:** This hospital is taking part in a national research study to investigate whether  
23 starting rehabilitation in the Intensive Care Unit, as soon as possible, will improve patients'  
24 long-term physical ability and quality of life.  
25

26 When patients are sedated in the Intensive Care unit, muscle wasting and weakness can  
27 occur very quickly and this can take a long time to recover from. Because we feel that it may  
28 be important to deliver rehabilitation physiotherapy as early as possible, we wish for your  
29 relative/friend to participate in the trial.  
30

31 Because your relative/friend is unable to decide for himself/herself whether to participate in  
32 this research, we'd like to ask your opinion as to whether or not they would want to be  
33 involved. Please consider what you know about their wishes and feelings and what you think  
34 may be best for them.  
35

36 If we have been unable to contact you, your relative/friend may have been enrolled as a  
37 participant in this research project with the approval of their treating doctor and the  
38 Hampshire Research Ethics Committee (IRAS number: 250165). If this is the case, then we  
39 seek to confirm that you are in agreement.  
40

41 Knowing what is involved will help you decide if you want your relative/friend to continue to  
42 take part in the research, so this information sheet explains the tests and treatments  
43 involved.  
44

- 45 • Part 1 tells you about why we are doing this study and what will happen to your relative if  
46 they take part.
- 47 • Part 2 gives you more detailed information about how we will run the study.  
48

49 If you decide your relative/friend would have no objection to taking part, we will ask you to  
50 read and sign a form that records your permission, called the consultee declaration. We'll  
51 then give you a copy to keep. We will keep you fully informed during the study so you can  
52 let us know if you have any concerns or you think your relative/friend should be withdrawn.  
53 Taking part in this research is entirely voluntary. If you decide not to continue, they will still  
54 be offered the best possible standard of care.  
55

56 Please ask us if there is anything that is not clear or if you would like more information. Take  
57 time to decide whether or not you wish your relative/friend to take part.  
58

59 **EMPRESS: A feasibility study of early mobilisation programmes in Critical Care.**

60 **Consultee Information Sheet Version 2: 29th January 2019**

**IRAS Project ID:250165**

## **PART ONE: Why are we doing this study and what will happen to my friend / relative?**

### **What is the purpose of this study?**

We know that when patients are very unwell and need sedation in the Intensive Care Unit, they can lose muscle strength and size very quickly. It is normal to offer rehabilitation, but this often starts after the patient has woken up. By this time the muscles have already been affected. Previous studies have shown that this muscle weakness may take many months to recover from and may affect a patient's quality of life after leaving hospital.

In Southampton Hospital, researchers and physiotherapists started performing rehabilitation exercises much earlier than usual, even while the patient was sedated. They showed that this method reduced the patient's time on the ventilator and reduced the amount of time that they needed to be in Intensive Care.

We are now trying to discover whether this method will work in a number of different hospitals in the UK. We will also do some tests to see whether the patients who have this type of rehabilitation are stronger and able to engage in physical activity more easily, when they leave hospital and 3 months later.

### **Why has my relative been chosen?**

Your relative has been enrolled in this study because during their admission to the Intensive Care Unit he/she needed a ventilator (a machine to help them breathe) and sedation to help keep them calm and comfortable. The treating doctor and physiotherapist thought that either very early rehabilitation or standard rehabilitation would be equally suitable. We may have made a start already, because we are testing such very early rehabilitation, but we would like to ask for your permission to continue.

### **Does my relative/ friend have to take part?**

No. It is up to you to decide whether or not you would like him/her to continue to take part. If you decide they can, you will be given this information sheet to keep and be asked to sign a permission form. You are still free to withdraw your relative at any time without giving a reason. The decision to withdraw at any time, or a decision not to take part, will not affect the standard of care your relative receives.

At an appropriate time, when we hope your relative has recovered sufficiently, we will ask their permission to use the data we have collected. If they do not agree we will not collect any new data and ask if we may use the data already collected.

### **What will happen to my relative if they take part?**

Participation in the study will begin in the Intensive Care Unit. The final tests will take place 3 months after they leave hospital.

**In the Intensive Care Unit:** Your friend/ relative's treating doctor has assessed them to be eligible to take part in this study: EMPRESS. They were randomly allocated (like the flip of a coin) to receive either of the following:

**EMPRESS: A feasibility study of early mobilisation programmes in Critical Care.**

Consultee Information Sheet Version 2: 29th January 2019

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- **Standard physiotherapy:** All patients on the trial will receive their normal physiotherapy. This will normally include activities to assist in keeping their airway clear and activities to maintain limb flexibility. These will not be affected by being on the trial.

## OR

- **Standard physiotherapy, as above, plus an extra 2 sessions of 30 minutes of rehabilitation from Monday to Friday.** For patients receiving extra, early rehabilitation, in addition to their normal physiotherapy, they will start using a cycle machine that is designed to work, in the bed, even with sedated patients. As your friend/ relative wakes up they will start to pedal for themselves, do some more bed-based exercises and finally get out of bed and start moving. All of these sessions will be run by a well-trained physiotherapist and the bedside nurses. We have already tested this method in University Hospital Southampton and it has reduced the length of time on the ventilator and ICU stay. During these sessions, they will be very carefully monitored for their own safety and the safety of their lines, tubes and catheters.

These exercises will continue for a maximum of 28 days or less if they leave the Intensive care unit before then.

## BOTH GROUPS

- **Additional assessments:** So that we can test whether our new method works, patients on the trial will undertake some extra assessments. These include a simple test of grip strength by using a hand held pressure monitor; a test of arm and leg strength, ability to stand and step and mobility and walking tests. There will also be quality of life and health questionnaires.

There was a 50/50 chance of being allocated to either group. Neither you nor their doctor can decide which. No samples of blood are required for this research study.

**In the hospital ward:** When your friend/ relative has been discharged to a normal hospital ward, they won't receive any extra physiotherapy. Just before they go home, they will be tested again for muscle strength and mobility, including how far they can walk in 6 minutes. These tests will be supervised by a trained and experienced physiotherapist

**Following discharge from hospital:** Regardless of which group your friend/ relative was allocated to, after going home, they should follow the advice given to them by their doctors and physiotherapists. We have designed our study so that this will not affect our results.

They will be contacted by one of the critical care research team 3 months after they have been discharged home. We will arrange to see them for approximately one hour. During this visit we will test their walking speed, strength and agility. We will also ask for some questionnaires to be completed, which will assess how they feel about their quality of life and recovery.

The researchers would also like to have access to your relative or friend's medical record to obtain information relevant to the study. This information would be anonymised and kept confidential.

EMPRESS: A feasibility study of early mobilisation programmes in Critical Care.

Consultee Information Sheet Version 2: 29th January 2019

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1  
2  
3 If you have any questions regarding the trial procedures, please don't hesitate to ask the  
4 intensive care or research doctors, physiotherapists and nurses.  
5  
6

### 7 **What do I have to do?**

9 It is important to tell the doctor and the research staff about any treatments or medications  
10 you know your relative/friend may have been taking, including over-the-counter medications,  
11 vitamins or herbal remedies, acupuncture or other alternative treatments. We would also like  
12 to know about any medical conditions which may affect the exercise.  
13

14 Please just let us know if your relative/friend is involved in any other studies at this time.  
15  
16

### 17 **What are the alternatives to participation?**

19 Participation in this research is not the only option. You may decide for your relative to  
20 receive only standard care physiotherapy. That is absolutely fine. Please feel free to discuss  
21 these options with your relative's doctor before deciding whether or not to continue to take  
22 part in this research project.  
23  
24

### 25 **What are the possible disadvantages of taking part?**

27 Early mobility within ICU is safe. Potential risks may include, but not be limited to blood  
28 pressure or heart rate problems, breathing problems, problems with the tubes, lines and  
29 catheters.  
30

31 In a review of physiotherapy within Intensive Care Units, involving over 1100 patients and  
32 5267 episodes of physiotherapy in similar patients, there were 34 potential safety events  
33 (equal to 6 events in 1000 episodes of physiotherapy). Most of these were related to changes  
34 in heart rate or blood pressure and settles quickly on stopping the physiotherapy.  
35  
36

37 In Southampton, over a 4 year period, we have treated over 500 patients in this way and had 2  
38 events needing attention but neither resulted in harm to the patient..  
39

40 The doctors, physiotherapists and nurses who will be caring for your relative or friend while  
41 in the ICU, are trained to recognise the effects on the body associated with physical  
42 rehabilitation and will treat accordingly. Your friend/ relative will be continually monitored  
43 and assessed. Their safety will always be our number one priority.  
44

45 There may be side effects that the researchers do not expect or do not know about and that  
46 may be serious. Please tell the doctor immediately if you are worried about any new or  
47 unusual symptoms that your relative/friend gets.  
48  
49

### 50 **What are the possible benefits of taking part?**

51 We cannot guarantee or promise that your relative will receive any benefits from this  
52 research. This study aims to further medical knowledge and may improve future treatment of  
53 patients who need to be on a ventilator, however it may not directly benefit your  
54 relative/friend.  
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59 **EMPRESS: A feasibility study of early mobilisation programmes in Critical Care.**

60 **Consultee Information Sheet Version 2: 29th January 2019**

**IRAS Project ID:250165**

1  
2  
3 **For how long will my relative/ friend be in the research study?**  
4

5 The final research assessment will take place 3 months after discharge from hospital. Once  
6 that is done, your friend/ relative's participation in the study will end.  
7  
8

9 **What happens if there is a problem?**  
10

11 We will keep you and your friend/ relative, fully informed of any problems which may be  
12 related to the study.  
13  
14

15 **Will taking part in the study be kept confidential?**  
16

17 Yes. All of the information about participation and the data collected will be kept  
18 confidential.  
19

20 Information held by the NHS and records maintained by the NHS Information Centre and the  
21 NHS Central Register may be used to help contact your friend/ relative and provide  
22 information about their health status. This information may be obtained and stored by the  
23 study research team to enable long term follow-up.  
24

25 University Hospital Southampton is the sponsor for this study based in the United Kingdom.  
26 We will be using information from their medical records in order to undertake this study and  
27 will act as the data controller for this study. This means that we are responsible for looking  
28 after their information and using it properly. University Hospital Southampton will keep  
29 information about them for 10 years after the study has finished.  
30

31 Your friend/ relative's rights to access, change or move your information are limited, as we  
32 need to manage the information in specific ways in order for the research to be reliable and  
33 accurate. If they withdraw from the study, we will keep the information that we have already  
34 obtained. To safeguard their rights, we will use the minimum personally-identifiable  
35 information possible.  
36

37 You can find out more about how we use information at [https://www.hra.nhs.uk/information-  
38 about-patients/](https://www.hra.nhs.uk/information-about-patients/)  
39

40 [Local NHS site name] will collect information from their medical records for this research  
41 study in accordance with our instructions.  
42

43 (Local NHS site name) will keep name, NHS number and contact details confidential and  
44 will not pass this information to University Hospital Southampton. [Local NHS site name]  
45 will use this information as needed, to contact your relative/ friend about the research study,  
46 and make sure that relevant information about the study is recorded for their care, and to  
47 oversee the quality of the study. Certain individuals from University Hospital Southampton  
48 and regulatory organisations may look at medical and research records to check the accuracy  
49 of the research study. University Hospital Southampton will only receive information without  
50 any identifying information. The people who analyse the information will not be able to  
51 identify patients and will not be able to find out their name, NHS number or contact details.  
52  
53  
54

55 [Local NHS site name] will keep identifiable information, including the consent form from  
56 this study, for 10 years after the study has finished.  
57  
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60 **EMPRESS: A feasibility study of early mobilisation programmes in Critical Care.**

Consultee Information Sheet Version 2: 29th January 2019

IRAS Project ID:250165

## Contact Details:

### Local PI details

#### Address

Dr local PI: 02381 XXXXXXX

Research Nurse: 02381 XXXXXXX

ICU: 02381 XXXXXXX

## PART 2: How we will run this study.

### What if relevant new information becomes available?

During the research project, new information about the risks and benefits of the study may become known to the researchers. If this occurs, you will be told about this new information and the doctor will discuss whether this new information affects your relative.

If any information becomes available which could affect participation in the study the research doctor will tell you about it and discuss whether you want your relative to continue in the study. If you decide your relative should not continue in the study, the research doctor will make arrangements for your relative's care to continue as normal. If you decide to allow your relative to continue in the study you will be asked to sign an updated agreement form.

Also, on receiving new information the research doctor might consider it to be in your relative's best interests to withdraw them from the study. He/she will explain the reasons and arrange for their care to continue.

If the study is stopped for any other reason, you will be told why and your relative's continuing care will be arranged.

### What will happen if I don't want my relative to carry on with the study?

You can withdraw your relative from the study at any time without giving an explanation and be assured that it will not impact on any part of your relative's further treatment.

If you decide to withdraw your relative from the study, the researchers would like to keep your relative's health information that has been collected. This is to help them make sure that the results of the research can be measured properly. If you do not want them to do this, you can tell them when you withdraw your relative from the research project.

### What if there is a problem?

If you have any concerns regarding the study, please ask to speak to the ICU doctor in charge of your friend/ relative's care or ask to speak to (name of local PI), the consultant who is in charge of the study.

EMPRESS: A feasibility study of early mobilisation programmes in Critical Care.

Consultee Information Sheet Version 2: 29th January 2019

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### Complaints:

If you have a concern about any aspect of this study, you should ask to speak with the researchers or the Intensive Care doctors and nurses, who will do their best to answer your questions. If you remain unhappy and wish to complain formally, you can do this through the NHS Complaints Procedure. (Please localise with your hospital PALS contact details)

### Harm:

In the event that something does go wrong and your relative is harmed during the research study there are no special compensation arrangements. If your relative is harmed and this is due to someone's negligence then your relative may have grounds for a legal action for compensation against University Hospital Southampton, but they may have to pay the legal costs. The normal National Health Service complaints mechanisms will still be available to them.

### Involvement of the General Practitioner/Family doctor (GP)

If you are agreeable we would like to inform your friend/ relative's GP of their participation in the study. If you do not wish for their GP to be informed, please let us know and indicate on the consent form that you do not wish for their GP to be informed.

### Will allowing my relative to take part in this study be kept confidential?

If your relative joins the study, some parts of their medical records and the data collected for the study will be looked at by authorised persons from University Hospital Southampton and University of Southampton who are sponsoring and organising the research. They may also be looked at by authorised people to check that the study is being carried out correctly. All will have a strict duty of confidentiality to your relative as a research participant and we will do our best to meet this duty.

All information that is collected about your relative during the course of the research will be kept strictly confidential. Any information about your relative that leaves the hospital will have their name and address removed so that they cannot be recognised from it.

Anonymised data collected during the study may be sent to associated researchers in other countries, where the laws don't protect your privacy to the same extent as the law in the UK but the study team will take all reasonable steps to protect your privacy.

Your relative has the right to check the accuracy of data held about them and correct any errors.

### What will happen to the results of the research study?

They will be published in a medical journal, presented at conferences and lay press where possible.

EMPRESS: A feasibility study of early mobilisation programmes in Critical Care.

Consultee Information Sheet Version 2: 29th January 2019

IRAS Project ID:250165



1  
2  
3 **Who is organising and funding the research?**  
4

5 Dr Rebecca Cusack from University Hospital Southampton is the lead researcher, who is  
6 organising the research.

7  
8 The research is funded by the NHS through the National Institute for Health Research,  
9 Research for Patient Benefit scheme.  
10

11  
12  
13 **Who has reviewed the study?**  
14

15 Hampshire Research Ethics Committee (IRAS number: 250165) have reviewed this study  
16 and given their approval.  
17

18  
19  
20 Thank you very much for taking the time to read this information sheet at this very stressful  
21 time.  
22

23 If you have any further questions please ask the doctors in Intensive Care, Dr (local PI) or  
24 one of the research team.

25 If you agree to your relative participating in this study please keep this information sheet and  
26 you will be given a copy of the agreement form that you will be asked to sign.  
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EMPRESS: A feasibility study of early mobilisation programmes in Critical Care.

Consultee Information Sheet Version 2: 29th January 2019

IRAS Project ID:250165

## FORM TO BE ON SITE SPECIFIC HEADED PAPER

University Hospital Southampton   
NHS Foundation Trust

Critical Care, Anaesthesia & Peri-operative Medicine Dept,  
Research office CE 93. MP 24,  
University Hospital Southampton,  
Tremona Road,  
Southampton  
SO16 6YD

Tel: 023 8120 5308

Fax: 023 8120 5378

Consultee declaration form for patients participating in EMPRESS.  
A feasibility study of early  
mobilisation programmes in Critical Care.

Name of Researcher: \_\_\_\_\_

Please initial box

1. I \_\_\_\_\_ [name of consultee] have been consulted about \_\_\_\_\_ [name of potential participant]'s participation in this research project. I have read and understood the Consultee Information Sheet (version \_\_; Dated \_\_\_\_\_). I have had the opportunity to ask questions about the study and understand what is involved.

2. In my opinion he/she would have no objection to taking part in the above study.

3. I understand that I can request he/she is withdrawn from the study at any time, without giving any reason and without his/her care or legal rights being affected.

4. I understand that relevant sections of his/her medical notes and data collected during the study, may be looked at by individuals from the research team, from regulatory authorities or from the NHS Trust, where it is relevant to their taking part in this research. I give permission for these individuals to have access to their records.

5. I understand that information held by the NHS and records maintained by the NHS Information Centre and the NHS Central Register may be used to help contact me or my friend / relative and provide information about their health status. I give permission for this information to be obtained and stored by the study research team to enable long term follow-up.

6. I agree to their GP being informed of their participation in the study.

Please confirm either:

I confirm that I will act as the personal consultee for: \_\_\_\_\_

Relationship to participant: \_\_\_\_\_

|                    |            |       |
|--------------------|------------|-------|
| Name of consultee: | Signature: | Date: |
| _____              | _____      | _____ |

|   |            |       |
|---|------------|-------|
| Person undertaking consultation (researcher): | Signature: | Date: |
| _____   | _____      | _____ |

**Original** Informed Consent form to be filed in the Investigator Site File.

*1 copy to be given to the patient*

*1 copy to be filed in the patients' hospital notes.*

For peer review only



SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents\*

| Section/item                      | Item No | Description   |
|-----------------------------------|---------|---|
| <b>Administrative information</b> |         |   |
| Title                             | 1       | Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym <b>Pg1 lines 1-2</b>   |
| Trial registration                | 2       | Trial identifier and registry name. If not yet registered, name of intended registry <b>Pg2 line 28</b>   |
| Protocol version                  | 3       | Date and version identifier <b>Pg 14 line 410</b>   |
| Funding                           | 4       | Sources and types of financial, material, and other support <b>Pg 14 lines 403-4</b>  |
| Roles and responsibilities        | 5a      | Names, affiliations, and roles of protocol contributors <b>Title page</b>   |
|                                   | 5b      | Name and contact information for the trial sponsor <b>Pg2 line 29</b>   |
|                                   | 5c      | Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities <b>N/A</b>   |
|                                   | 5d      | Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) <b>Trial management group/ Data safety group/PPI group -- Pg12 Lines 315 to Pg 13 line 334</b> |
| <b>Introduction</b>               |         |   |
| Background and rationale          | 6a      | Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention <b>See introduction Pg3 line 44-Pg line 80</b>   |
|                                   | 6b      | Explanation for choice of comparators <b>See introduction Pg3 line 44-Pg line 80</b>  |
| Objectives                        | 7       | Specific objectives or hypotheses <b>Pg 3 lines 82-88</b>   |

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Trial design 8 Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) **Study design Pg 4 lines 91-97**

### Methods: Participants, interventions, and outcomes

Study setting 9 Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained **Pg 4 Lines 93-95**

Eligibility criteria 10 Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) **Pg4 Lines 99 -108**

Interventions 11a Interventions for each group with sufficient detail to allow replication, including how and when they will be administered **Pg 5- 8 lines 137 - 198**

11b Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) **Table 1**

11c Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) **N/A**

11d Relevant concomitant care and interventions that are permitted or prohibited during the trial **N/A**

Outcomes 12 Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended **Primary outcomes Pg8 lines 200-208; Secondary outcomes lines 210-244**

Participant timeline 13 Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) **Table 2**

Sample size 14 Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations **Pg 10 line 284-300**

Recruitment 15 Strategies for achieving adequate participant enrolment to reach target sample size **Pg5 Lines 110-127**

### Methods: Assignment of interventions (for controlled trials)

## Allocation:

- 1  
2  
3  
4      Sequence      16a      Method of generating the allocation sequence (eg, computer-  
5      generation                generated random numbers), and list of any factors for stratification.  
6                          To reduce predictability of a random sequence, details of any planned  
7                          restriction (eg, blocking) should be provided in a separate document  
8                          that is unavailable to those who enrol participants or assign  
9                          interventions **Pg10 Line 126-7**  
10  
11  
12      Allocation      16b      Mechanism of implementing the allocation sequence (eg, central  
13      concealment                telephone; sequentially numbered, opaque, sealed envelopes),  
14      mechanism                describing any steps to conceal the sequence until interventions are  
15                          assigned **Pg10 line 126-7**  
16  
17      Implementation      16c      Who will generate the allocation sequence, who will enrol participants,  
18                          and who will assign participants to interventions **Pg10 line 126-7**  
19  
20  
21      Blinding      17a      Who will be blinded after assignment to interventions (eg, trial  
22      (masking)                participants, care providers, outcome assessors, data analysts), and  
23                          how **Pg14 line 390**  
24  
25                17b      If blinded, circumstances under which unblinding is permissible, and  
26                          procedure for revealing a participant's allocated intervention during  
27                          the trial **N/A**  
28  
29

**Methods: Data collection, management, and analysis**

- 30  
31  
32      Data collection      18a      Plans for assessment and collection of outcome, baseline, and other  
33      methods                trial data, including any related processes to promote data quality (eg,  
34                          duplicate measurements, training of assessors) and a description of  
35                          study instruments (eg, questionnaires, laboratory tests) along with  
36                          their reliability and validity, if known. Reference to where data  
37                          collection forms can be found, if not in the protocol **Lines 278 - 286**  
38  
39                18b      Plans to promote participant retention and complete follow-up,  
40                          including list of any outcome data to be collected for participants who  
41                          discontinue or deviate from intervention protocols **Lines 306-7**  
42  
43  
44      Data      19      Plans for data entry, coding, security, and storage, including any  
45      management                related processes to promote data quality (eg, double data entry;  
46                          range checks for data values). Reference to where details of data  
47                          management procedures can be found, if not in the protocol **Lines**  
48                          **279-86**  
49  
50  
51      Statistical      20a      Statistical methods for analysing primary and secondary outcomes.  
52      methods                Reference to where other details of the statistical analysis plan can be  
53                          found, if not in the protocol **Lines 305- 317**  
54  
55                20b      Methods for any additional analyses (eg, subgroup and adjusted  
56                          analyses) **N/A**  
57  
58  
59  
60

1  
2 20c Definition of analysis population relating to protocol non-adherence  
3 (eg, as randomised analysis), and any statistical methods to handle  
4 missing data (eg, multiple imputation) [Line 84](#)  
5

## 6 **Methods: Monitoring**

7  
8 Data monitoring 21a Composition of data monitoring committee (DMC); summary of its role  
9 and reporting structure; statement of whether it is independent from  
10 the sponsor and competing interests; and reference to where further  
11 details about its charter can be found, if not in the protocol.  
12 Alternatively, an explanation of why a DMC is not needed [Lines 332-](#)  
13 [333](#)  
14

15  
16 21b Description of any interim analyses and stopping guidelines, including  
17 who will have access to these interim results and make the final  
18 decision to terminate the trial [N/A](#)  
19

20  
21 Harms 22 Plans for collecting, assessing, reporting, and managing solicited and  
22 spontaneously reported adverse events and other unintended effects  
23 of trial interventions or trial conduct [Lines 351-361](#)  
24

25 Auditing 23 Frequency and procedures for auditing trial conduct, if any, and  
26 whether the process will be independent from investigators and the  
27 sponsor [N/A](#)  
28  
29

## 30 **Ethics and dissemination**

31  
32 Research ethics 24 Plans for seeking research ethics committee/institutional review board  
33 approval [Line 24-27](#)  
34

35 Protocol 25 Plans for communicating important protocol modifications (eg,  
36 amendments changes to eligibility criteria, outcomes, analyses) to relevant parties  
37 (eg, investigators, REC/IRBs, trial participants, trial registries, journals,  
38 regulators) [.Line 25](#)  
39

40  
41 Consent or assent 26a Who will obtain informed consent or assent from potential trial  
42 participants or authorised surrogates, and how (see Item 32) [Lines](#)  
43 [109-122](#)  
44

45 26b Additional consent provisions for collection and use of participant data  
46 and biological specimens in ancillary studies, if applicable [N/A](#)  
47

48 Confidentiality 27 How personal information about potential and enrolled participants will  
49 be collected, shared, and maintained in order to protect confidentiality  
50 before, during, and after the trial [Line 279](#)  
51

52  
53 Declaration of 28 Financial and other competing interests for principal investigators for  
54 interests the overall trial and each study site [Line 413](#)  
55

56 Access to data 29 Statement of who will have access to the final trial dataset, and  
57 disclosure of contractual agreements that limit such access for  
58 investigators [Line 326-7 and 332-333](#)  
59  
60

|    |                   |     |  |
|----|-------------------|-----|--|
| 1  |                   |     |  |
| 2  | Ancillary and     | 30  | Provisions, if any, for ancillary and post-trial care, and for               |
| 3  | post-trial care   |     | compensation to those who suffer harm from trial participation <b>Lines</b>  |
| 4  |                   |     | <b>360-361</b>   |
| 5  |                   |     |  |
| 6  | Dissemination     | 31a | Plans for investigators and sponsor to communicate trial results to          |
| 7  | policy            |     | participants, healthcare professionals, the public, and other relevant       |
| 8  |                   |     | groups (eg, via publication, reporting in results databases, or other        |
| 9  |                   |     | data sharing arrangements), including any publication restrictions           |
| 10 |                   |     | <b>Lines 343-345</b>   |
| 11 |                   |     |  |
| 12 |                   |     |  |
| 13 |                   | 31b | Authorship eligibility guidelines and any intended use of professional       |
| 14 |                   |     | writers <b>Lines 402-406</b>   |
| 15 |                   |     |  |
| 16 |                   | 31c | Plans, if any, for granting public access to the full protocol, participant- |
| 17 |                   |     | level dataset, and statistical code <b>Lines 348-</b>                        |
| 18 |                   |     |  |
| 19 |                   |     |  |
| 20 | <b>Appendices</b> |     |  |
| 21 |                   |     |  |
| 22 | Informed consent  | 32  | Model consent form and other related documentation given to                  |
| 23 | materials         |     | participants and authorised surrogates <b>Supplied</b>                       |
| 24 |                   |     |  |
| 25 | Biological        | 33  | Plans for collection, laboratory evaluation, and storage of biological       |
| 26 | specimens         |     | specimens for genetic or molecular analysis in the current trial and for     |
| 27 |                   |     | future use in ancillary studies, if applicable <b>N/A</b>                    |
| 28 |                   |     |  |

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\*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "[Attribution-NonCommercial-NoDerivs 3.0 Unported](https://creativecommons.org/licenses/by-nc-nd/3.0/)" license.