



# BMJ Open Response to physical rehabilitation and recovery trajectories following critical illness: individual participant data meta-analysis protocol

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## ABSTRACT

**Introduction** The number of inconclusive physical rehabilitation randomised controlled trials for patients with critical illness is increasing. Evidence suggests critical illness patient subgroups may exist that benefit from targeted physical rehabilitation interventions that could improve their recovery trajectory. We aim to identify critical illness patient subgroups that respond to physical rehabilitation and map recovery trajectories according to physical function and quality of life outcomes. Additionally, the utilisation of healthcare resources will be examined for subgroups identified.

**Methods and analysis** This is an individual participant data meta-analysis protocol. A systematic literature review was conducted for randomised controlled trials that delivered additional physical rehabilitation for patients with critical illness during their acute hospital stay, assessed chronic disease burden, with a minimum follow-up period of 3 months measuring performance-based physical function and health-related quality of life outcomes. From 2178 records retrieved in the systematic literature review, four eligible trials were identified by two independent reviewers. Principal investigators of eligible trials were invited to contribute their data to this individual participant data meta-analysis. Risk of bias will be assessed (Cochrane risk of bias tool for randomised trials). Participant and trial characteristics, interventions and outcomes data of included studies will be summarised. Meta-analyses will entail a one-stage model, which will account for the heterogeneity across and the clustering between studies. Multiple imputation using chained equations will be used to account for the missing data.

**Ethics and dissemination** This individual participant data meta-analysis does not require ethical review as anonymised participant data will be used and no new data collected. Additionally, eligible trials were granted approval by institutional review boards or research ethics committees and informed consent was provided for participants. Data sharing agreements are in place permitting contribution of data. The study findings will be disseminated at conferences and through peer-reviewed publications.

**PROSPERO registration number** CRD42019152526.

## Strengths and limitations of this study

- According to our literature searches, this will be the first individual participant data meta-analysis to examine the response to physical rehabilitation interventions and map recovery trajectories of patient subgroups with critical illness.
- Individual participant data meta-analyses provide greater statistical power than individual randomised controlled trials and more reliable subgroup analyses than systematic reviews that use aggregate data.
- The subgroup analyses outlined will provide valuable information on effect modifiers of physical rehabilitation interventions for patients with critical illness.
- This work will also assist with future trial design by informing eligibility and stratification criteria to maximise statistical power and potentially reduce sample size.
- Additionally, the planned subgroup analyses will inform clinical practice and future research on the delivery of targeted physical rehabilitation interventions for patients most likely to benefit, provided at the optimal time in their recovery.

## INTRODUCTION

The challenge facing many survivors of critical illness is disability, specifically, deficits in physical function that negatively impact quality of life and activities of daily living which can persist for several years.<sup>1–4</sup> There is level one evidence that physical rehabilitation provided in the intensive care unit (ICU) is safe<sup>5</sup> and reduces physical activity limitation at hospital discharge.<sup>6</sup> However, large randomised controlled trials measuring long-term outcomes do not uniformly report sustained improvements in physical function or health-related quality of life (HRQoL).<sup>7–11</sup> One of the factors potentially contributing to these inconclusive trial

results is the heterogeneity of the critical ill populations studied whereby patient subgroups with unique trajectories of recovery exist and may respond differently to physical rehabilitation interventions. Specifically, there is emerging evidence that patient characteristics, for example, chronic disease burden, are influential in recovery from critical illness<sup>3 12 13</sup> and may modify the effect of physical rehabilitation interventions delivered.<sup>14</sup>

Exploration of the physical function and HRQoL recovery trajectories of critically ill patients enrolled in physical rehabilitation trials is limited.<sup>12 14 15</sup> However, post hoc analyses of randomised controlled trials indicate that patient characteristics including chronic disease burden,<sup>14</sup> age and female sex<sup>15</sup> are associated with long-term physical performance outcomes. Post hoc analyses of published randomised controlled trials<sup>12 14–16</sup> also show that participant characteristics, specifically chronic disease burden,<sup>12 14</sup> can alter the recovery trajectory of critically ill patients. Acute illness severity has been shown to predict HRQoL in critically ill patients,<sup>17</sup> however, a recent post hoc analysis of a rehabilitation randomised controlled trial did not demonstrate an association between these variables.<sup>12</sup> Given a single randomised controlled trial has limited statistical power to detect significant subgroup treatment effects, further investigation of patient subgroups is warranted.<sup>18</sup>

Individual participant data meta-analyses are considered the gold standard of systematic reviews<sup>19 20</sup> enabling assessment of the interactions between interventions and patient characteristics with statistical power beyond a randomised controlled trial.<sup>21</sup> Additionally, use of individual participant data provides more reliable subgroup analysis results compared with systematic reviews that use aggregate level data, which rely on summary statistics.<sup>21</sup> Subgroup analyses will enable us to identify patient characteristics that modify the association between physical rehabilitation interventions and the outcomes of critically ill patients. This will allow us to identify patient subgroups that will most benefit from the intervention.<sup>22</sup> When identified, these patient characteristics could inform eligibility criteria of future randomised controlled trials and stratify participants enrolled, for example, according to chronic disease burden,<sup>14</sup> to maximise statistical power<sup>23</sup> and reduce sample size.<sup>24</sup> Clarity on patient characteristics that are important in response to physical rehabilitation interventions may also assist in uncovering the mechanism<sup>23</sup> behind the debilitating effects of critical illness. Additionally, identification of these patient characteristics could assist with unveiling differing phenotypes of critically ill patients and their rehabilitation needs. From this approach, the concept of personalised medicine could be applied to physical rehabilitation interventions for patients with critical illness.

Several systematic reviews and meta-analyses have been published that examine the effectiveness of physical rehabilitation for patients with critical illness<sup>6 25–27</sup> however, none use individual participant data. Therefore, the aim of this systematic review and individual participant data

meta-analysis is to identify subgroups of patients with critical illness that respond to physical rehabilitation and map their recovery trajectories according to physical function and HRQoL outcomes. The objectives are:

1. For each outcome of interest (physical function measured at hospital discharge, 3 and 6 months, and HRQoL measured at 3, 6 and 12 months), we will assess whether there is an interaction between the treatment group (intervention vs control) and each of the, a priori identified, participant characteristics (ie, chronic disease burden, sex, age group and acute illness severity) and the outcome.
2. For the following outcomes relating to utilisation of healthcare resources: mechanical ventilation duration (days), ICU length of stay (days), hospital length of stay (days) and discharge location (home, rehabilitation facility, another hospital, skilled nursing or aged care facility, other), we will assess whether there is an interaction between the treatment group and each of the, a priori identified, participant characteristics (ie, chronic disease burden, sex, age group and acute illness severity).

## METHODS AND ANALYSIS

This systematic review and individual participant data meta-analysis was registered a priori with the International Prospective Register of Systematic Reviews. Our PROSPERO registration (CRD42019152526) was lodged on 27 September 2019 (start date) and the anticipated study completion date is 31 December 2020. This study is also registered with research registry (reviewregistry759). Important protocol amendments will be documented with an accompanying explanation and be made publicly available on the registration record. Prior to registration, PROSPERO and the Cochrane Database of Systematic Reviews were searched to check no other similar systematic review and individual participant data meta-analysis was registered or undertaken. The individual participant data meta-analysis will be conducted according to the Cochrane Individual Participant Data Meta-analysis Methods Group recommendations<sup>19 28</sup> and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses of Individual Participant Data.<sup>20</sup>

### Part I: systematic review to identify eligible trials

#### Information sources

Four electronic bibliographic databases: Medical Literature Analysis and Retrieval System Online (MEDLINE) via Ovid, Excerpta Medica Database (Embase) via Ovid, Cumulative Index to Nursing and Allied Health Literature (CINAHL) Complete via EBSCOhost and Cochrane Central Register of Controlled Trials (CENTRAL) via the Cochrane Library were searched from inception to 28 September 2019. Reference lists of eligible studies and relevant systematic reviews were cross-checked and eligible trial principal investigators consulted regarding

**Table 1** Medical Literature Analysis and Retrieval System Online (MEDLINE) search strategy via Ovid platform

Search line	Search terms	Search term type
Tier 1: Population		
1	critical illness/ or critical care/ or intensive care unit/	Subject headings
2	((intensive adj care) or (critical adj care) or (intensive adj care adj unit*) or (critically adj ill) or (critical adj illness) or ICU).mp.(mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word)	Keywords
3	1 or 2	
Tier 2: Intervention		
4	Rehabilitation/ or Exercise/ or Resistance Training/ or "PHYSICAL AND REHABILITATION MEDICINE"/ OR EXERCISE THERAPY/ or Physical Therapy Modalities/ or Early Ambulation/	Subject headings
5	(mobilisation or mobilization or physiotherapy or (physical adj therapy) or exercise or (exercise adj training) or (strength adj training) or (resistance adj training) or (exercise adj therapy) or rehabilitation or (physical adj rehabilitation) or (exercise adj therapy) or (rehabilitation adj medicine)).mp.(mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word)	Keywords
6	4 or 5	
Tier 3: Study Design		
7	Randomized Controlled Trial/	Subject headings
8	((randomised adj controlled adj trial) or (randomized adj controlled adj trial) or (randomised adj clinical adj trial) or (randomized adj clinical adj trial) or RCT).mp.(mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word)	Keywords
9	7 or 8	
10	3 and 6 and 9	

additional potentially relevant studies. No date or language restrictions were applied to the search.

### Search strategy

A three-tier search strategy was performed using both subject headings and keywords according to: (1) population, (2) intervention and (3) study design. Population: intensive care OR critical care OR critical care outcomes OR critical illness OR ICU OR critically ill. Intervention: physical rehabilitation OR strength training OR exercise therapy OR physical therapy. Study design: randomised controlled trial OR randomised clinical trial. The search strategy for MEDLINE is shown in [table 1](#).

### Selection process

The study selection process is summarised in [figure 1](#). One reviewer (JRAJ) designed the search, screened titles of retrieved articles and removed duplicate and non-relevant references. The remaining titles and abstracts were screened independently and in duplicate by two reviewers (JRAJ and LAM) according to the eligibility criteria (see below). When there was insufficient information to determine whether a study was eligible, the full text was obtained and reviewed. Full texts were reviewed independently and in duplicate by two reviewers (JRAJ

and LAM) to assess for eligibility. Disagreements between the two independent reviewers (JRAJ and LAM) were resolved through discussion and did not require consultation with a third independent reviewer. Records were managed in EndNote X9. From 2178 records, four randomised controlled trials<sup>7–10</sup> were deemed eligible for the individual participant data meta-analysis.

### Eligibility criteria

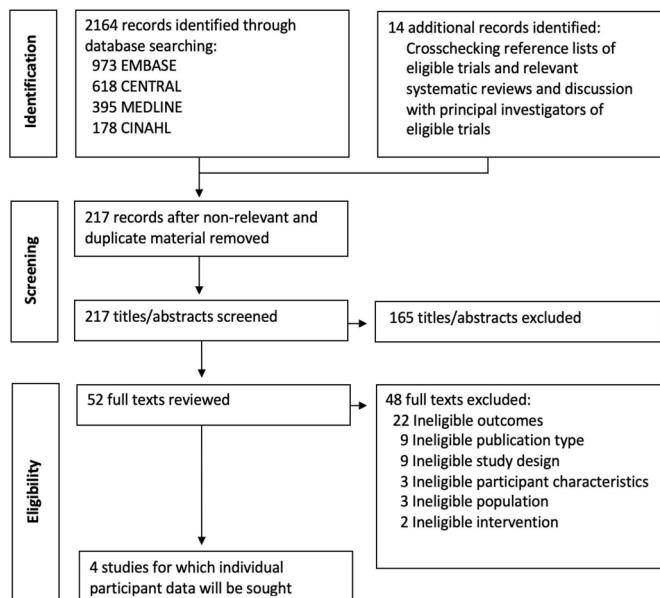
Eligibility criteria were applied at trial level and are listed below according to population, study design, intervention, comparator, outcomes, participant characteristics and publication type.

#### Population

Adults aged 18 years and older admitted to ICU.

#### Study design

Randomised controlled trials with more than 50 participants were included. The sample size criterion was incorporated as a pragmatic approach to study selection, whereby larger randomised controlled trials were prioritised to improve feasibility of individual participant data acquisition.



**Figure 1** Trial selection process. CENTRAL, Cochrane Central Register of Controlled Trials; CINAHL, Cumulative Index to Nursing and Allied Health Literature; EMBASE, Excerpta Medica Database; MEDLINE, Medical Literature Analysis and Retrieval System Online.

### Intervention

The intervention group received additional physical rehabilitation that included exercise training (strength or endurance) or functional retraining during the acute hospital stay (ICU and/or acute hospital ward). Trials that examined the effectiveness of neuromuscular electrical stimulation, respiratory management or inspiratory muscle training alone were excluded.

### Comparator

Comparison with a control group that received standard physiotherapy or physical therapy care.

### Outcomes

Minimum follow-up period of 3 months measuring both performance-based physical function and HRQoL outcomes.

### Participant characteristics

Recorded participant chronic disease burden in sufficient detail to permit scoring with the Functional Comorbidity Index.<sup>29</sup>

### Publication type

Randomised controlled trials published in full in a peer-reviewed journal were eligible. Research letters, trial protocols and conference abstracts were excluded. While no language restrictions were applied to the electronic bibliographic searches, records retrieved that were not published in English were excluded during the study selection process.

### Risk of bias assessment

The revised Cochrane risk-of-bias tool for randomised trials<sup>30</sup> will be used. Two reviewers (JRAJ and LAM) will

conduct the risk of bias assessment independently. If discrepancies in the risk of bias assessment by the two reviewers (JRAJ and LAM) cannot be resolved by discussion, verification will be sought from the relevant trial principal investigators, and a third independent reviewer (LD) will make the final decision. Published data will be used to inform the risk of bias assessment; however, individual participant data will be checked for key potential biases, including balance of baseline participant characteristics by treatment group.

## Part II: collection, checking and harmonisation of individual participant data

### Data collection

Principal investigators of identified eligible trials<sup>7–10</sup> have been invited to contribute individual participant data to the study and join the CRITICALConnect collaboration. Data sharing agreements are in place. Anonymised data sets will be accepted in any form, provided variables and categories are clearly labelled. Individual participant data that will be obtained are listed below according to participant characteristics, intervention and outcomes.

### Participant characteristics

Chronic disease burden assessed with the Functional Comorbidity Index,<sup>29</sup> age, sex and acute illness severity measured with the Acute Physiology, Age, Chronic Health Evaluation II score.<sup>31</sup>

### Intervention

Number of physical rehabilitation intervention sessions.

### Outcomes

A core outcome measurement set has been developed for research with acute respiratory failure survivors, where the 36-Item Short Form Health Survey version 2 is recommended to comprehensively assess satisfaction with life and personal enjoyment.<sup>32</sup> For assessment of HRQoL, we will accept version 1 and 2 of the 36-Item and 12-Item Short Form Health Surveys to ensure maximum inclusivity of trials. Consensus could not be reached on which physical function measures to include in the core outcome set,<sup>32</sup> we will collect information on all performance-based measures of physical function, but we will only analyse the measure that is most prevalent across the individual studies. Utilisation of healthcare resources measured according to mechanical ventilation duration (days), ICU length of stay (days), hospital length of stay (days) and discharge location (home, rehabilitation facility, another hospital, skilled nursing or aged care facility, other) will also be requested.

There are no published recommendations on standard time points for performance-based measures of physical function and HRQoL outcomes for rehabilitation trials with critically ill patients. Therefore, performance-based physical function at hospital discharge, 3 and 6 months, and HRQoL at 3, 6 and 12 months were considered to be of greatest importance to clinicians, researchers, patients and their families. Participant-reported outcomes of

HRQoL can involve retrospective consideration, specifically, the Short Form Health Surveys include questions pertaining to work, social and regular daily activities in the past 4 weeks making application in hospitalised critically ill patients difficult, therefore, the hospital discharge time point was considered not appropriate.

#### Data checking

We will use standard checks to identify missing or duplicate data. Where data are missing, we will verify with the trial investigators that the data are in fact missing. Data validity and consistency will be assessed with range checks on variables supplied and checking the distribution of relevant baseline participant characteristics and number of participants against published records. To assess randomisation integrity, we will check for balance of key baseline participant characteristics by treatment group. Any data queries will be verified by the trial investigators or appropriate research personnel.

#### Data harmonisation

To ensure accurate pooling of data, data sets will be converted to a common format and variables renamed for consistency. The individual trial data sets will then be combined to form the master data set with a variable to indicate the data corresponding to the original trial.

### Part III: statistical analyses

We will describe trial-level and participant-level characteristics of included studies. For all meta-analytic models, we will use a one-stage approach (ie, a generalised multi-level model) to synthesise the data from multiple trials, which fully accounts for the heterogeneity across the studies.<sup>33 34</sup> The multi-level models will allow for clustering between studies.<sup>35</sup> We will present the proportions of missing data for the variables of interest by study. Next, we will use multiple imputation with 20 imputed data sets obtained using chained equations to account for the missing data.<sup>36</sup> Mortality will occur throughout each of the trials. However, based on the previous research,<sup>6</sup> we will assume that the interventions are not associated with mortality and that a 'survivors only' analysis is valid.<sup>37</sup> Additionally, it is widely accepted and concordant with common sense that it is not appropriate to impute for death when participant-reported outcomes, for example HRQoL, are used.<sup>38</sup> Analyses will therefore be conducted with subjects retained in their original assigned groups, which means that the analyses will be modified intention to treat; no missing values due to mortality will be imputed, and deaths prior to an analysis time point will be omitted from analysis at that time point.

#### Objective 1

We will use longitudinal models to assess the effect of physical rehabilitation according to performance-based physical function outcomes at hospital discharge, 3 and 6 months, and HRQoL outcomes at 3, 6 and 12 months. We will fit models with separate interaction terms to assess

whether the effects are modified by the following patient characteristics that were selected a priori:

1. Participants with low chronic disease burden (Functional Comorbidity Index score  $\leq 1$ ) versus those who are multimorbid (Functional Comorbidity Index score  $\geq 2$ ).
2. Age ranges of published disability risk groups for survivors of critical illness: young ( $\leq 45$  years), older ( $>45$  and  $<66$  years) and oldest ( $\geq 66$  years).<sup>39</sup>
3. Male versus female sex.
4. Acute illness severity according to Acute Physiology, Age, Chronic Health Evaluation II score based on tertiles of the sample distribution.

#### Objective 2

The individual participant data will also be analysed to compare between group differences (intervention and control) for the utilisation of healthcare resources for the subgroups of objective one. A priori healthcare utilisation variables include mechanical ventilation duration (days), ICU length of stay (days), hospital length of stay (days) and discharge location (home, rehabilitation facility, another hospital, skilled nursing or aged care facility, other). Models will be fitted as described by Debray *et al.*<sup>33</sup>

#### Sensitivity analyses

We will undertake the following sensitivity analyses in order to assess the robustness of our results. We will use a two-stage approach to synthesise the complete data from multiple trials. In this approach, the data are first analysed separately for each trial (ie, the first stage) and then combined using a random effects model to obtain a pooled estimate (ie, the second stage). This will allow us to generate forest plots, investigate heterogeneity, visualise differences across the above-mentioned subgroups. As only four trials will be included in this individual participant data meta-analysis, we will not be able to examine small study effects.<sup>40 41</sup> We will also repeat the one-stage analysis using complete case analysis to assess the robustness of the assumptions made using multiple imputation to handle the missing data. Finally, we will include only studies with a low risk of bias to assess the impact of studies of lower methodological quality on the findings. All statistical analyses will be undertaken using Stata version 15.1.<sup>42</sup>

#### Patient and public involvement

Patient and public involvement will not be sought for the design or conduct of the study or dissemination of the results.

### ETHICS AND DISSEMINATION

This study does not require ethical review as only anonymised data will be used and no new data will be collected.<sup>43</sup> Each of the eligible randomised controlled trial identified from the systematic literature review were granted approval from their respective institutional review boards

or research ethics committees, and informed consent was provided for all participants enrolled.<sup>7–10</sup> Additionally, data sharing agreements are in place permitting contribution of individual participant data by each of the identified eligible trials. The study findings will be submitted for presentation at national (Australia) and international conferences. Through the combined efforts of our international collaborative group, CRITICALConnect, the study findings will be presented to the wider critical care community. Additionally, the results of this study will be submitted for publication in a leading peer-reviewed journal for the field.

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**Contributors** JRAJ, LD, SB and ZP contributed to the initial conception of the study. MJB, DCF, DMG, PEM, MM, AN-C and TW made significant subsequent contributions to the study design. JRAJ and LAM made significant contributions to the systematic literature review. IG and AK made significant contributions to the statistical analysis section. JRAJ, SB, IG, AK and LD drafted the manuscript. All authors revised the manuscript and approved the final version. The guarantor of the review is LD.

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