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Response to Physical Rehabilitation and Recovery Trajectories Following Critical Illness: Individual Participant Data Meta-Analysis Protocol

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Author Contributions JRAJ, LD, SB and ZP contributed to the initial conception of the study. MB, DCF, DMG, PEM, MM, ANC 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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ABSTRACT

Introduction The number of inconclusive physical rehabilitation randomised controlled trials for patients with critical illness are 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. Addtionally, 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 three 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 provided for participants. Data sharing agreements are in place permitting contribution of data. Study findings will be presented at conferences and published in peer reviewed journal.

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Keywords Critical Illness, Rehabilitation, Recovery of Function, Quality of Life.

ARTICLE SUMMARY

Strengths and Limitations of this Study

- According to our literature searches, no published systematic reviews have used individual participant data to examine the response to physical rehabilitation interventions and map recovery trajectories of patient subgroups with critical illness.
- Individual participant data meta-analyses are considered the gold standard of systematic reviews and provide more reliable subgroup analyses than

systematic reviews that use aggregate data. However, due to the processes involved in data acquisition, checking and harmonisation these analyses are more time and resource intensive.

- This research will therefore provide valuable information on the moderators of treatment effect for physical rehabilitation interventions for patients with critical illness and assist with future trial design by informing eligibility and stratification criteria to maximise statistical power and potentially reduce sample size.
- Additionally, this study will help inform clinical practice and future research on the delivery of targeted physical rehabilitation interventions for patients most likely to benefit and 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[1-4]. There is level one evidence that physical rehabilitation provided in the intensive care unit (ICU) is safe[5] and reduces physical activity limitation at hospital discharge[6]. 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)[7-11]. 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, e.g. chronic disease burden, are influential in recovery from critical illness[3, 12, 13] and may moderate the effect of physical rehabilitation interventions delivered[14].

Exploration of the physical function and HRQoL recovery trajectories of critically ill patients enrolled in physical rehabilitation trials is limited [12, 14, 15]. However, post-hoc analyses of randomised controlled trials indicate that patient characteristics including chronic disease burden[14], age and female sex[15] and ICU exposures (ICU length of stay and continuous intravenous sedation days)[15] are associated with long term physical performance outcomes. Post-hoc analyses of published randomised controlled tirials[12, 14-16] also show that participant characteristics, specifically chronic disease burden[12, 14], can alter the recovery trajectory of critically ill patients. However such analyses should be interpreted with caution as a single randomised controlled trial has limited statistical power to detect significant subgroup treatment effects[17].

Individual participant data meta-analyses are considered the gold standard of systematic reviews[18, 19] enabling assessment of the interactions between interventions and patient characteristics with statistical power beyond a randomised controlled trial[20]. Additionally, use of individual participant data provides more reliable subgroup analysis results compared to systematic reviews that use aggregate level data, which rely on summary statistics[20]. Such subgroup analyses will assist with identification of moderators of physical rehabilitation interventions and in turn inform eligibility criteria of future randomised controlled trials[21]. When identified, moderators could also be used to stratify participants enrolled in randomised controlled trials, e.g. according to chronic disease burden[14], to maximise statistical power[21] and reduce sample size[22]. Clarity on moderators of rehabilitation outcomes may also assist in uncovering the mechanism[21] behind the debilitating effects of critical illness. Additionally, identification of moderators 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[6, 23-25] 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, three and six months and HRQoL measured at three, six and 12 months), we will assess whether there is an interaction between the treatment group (intervention versus control) and each of the, *a priori* identified, participant characteristics (i.e. 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 (i.e. chronic disease burden, sex, age group and acute illness severity).

METHODS AND ANALYSIS

This systematic review and individual participant data meta-analysis is registered with the International Prospective Register of Systematic Reviews (PROSPERO

CRD42019152526 available at https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=152526) and Research Registry (unique identifying number: reviewregistry759 available at https://www.researchregistry.com/browse-the-registry#registryofsystematicreviewsmeta-analyses/registryofsystematicreviewsmeta-analysesdetails/5dc33f4cb4aab200154af661/). Important protocol amendments will be documented with an accompanying explanation and made publically 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[18, 26] and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses of Individual Participant Data (PRISMA-IPD)[19].

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 September 28, 2019. Reference lists of eligible studies and relevant systematic reviews were cross-checked and eligible trial principal investigators consulted regarding 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 post intensive care syndrome OR ICU OR critically ill. Intervention: physical rehabilitation OR endurance training OR strength training OR exercise therapy OR physical therapy. Study design: randomised controlled trial OR 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 LM) according to the eligibility criteria (see below). When there was insufficient information to determine if 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. Disagreement between the two independent reviewers (JRAJ and LAM) was 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[7-10] 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.

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 three 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[27].

Publication Type: Randomised controlled trials published in full in a peer reviewed journal were eligible. Research letters, trial protocols and conference abstracts were excluded. Whilst no language restrictions were applied to the electronic biographic searches, records retrieved that werenot published in English were excluded during the study selection process.

Risk of Bias Assessment

The revised Cochrane risk-of-bias tool for randomised trials (RoB 2)[28] 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, then verification will be sought from the relevant trial principal investigators. 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[7-10] have been invited to contribute individual participant data to the study and join the CRITICALConnect Collaboration. Data sharing agreements are in place. Anonymised datasets 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[27], age, sex and acute illness severity measured with the Acute Physiology, Age, Chronic Health Evaluation II score[29].

Intervention: Number of physical rehabilitation intervention sessions.

Outcomes: Performance-based physical function at hospital discharge, three and six months. Health-related quality of life at three, six and 12 months. 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[30]. For assessment of HRQoL, we will accept version one and two of the 36- 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[30], therefore all performance-based measures of physical function will be accepted. Utilisation of health care 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.

Data Checking

We will use standard checks to identify missing or duplicate data. Where data are missing, we will verify with the trial inverstigators 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, datasets will be converted to a common format and variables renamed for consistency. The individual trial datasets will then be combined to form the master dataset 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 (i.e. a generalised multi-level model) to synthesise the data from

multiple trials, which fully accounts for the heterogeneity across the studies[31, 32]. The multilevel models will allow for clustering between studies[33]. We will present the proportions of missing data for the variables of interest by study. Next, we will use multiple imputation with 20 imputed datasets obtained using chained equations to account for the missing data[34]. Mortality will occur throughout each of the trials. However, based on previous research[6] we will assume that the interventions are not associated with mortality and that a "survivors only" analysis is valid[35]. Additionally, it is widely accepted and concordant with common sense that it is not appropriate to impute for death when participant-reported outcomes, e.g.HRQoL, are used[36]. 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 One

We will use longitudinal models to assess the effect of physical rehabilitation according performance-based physical function at hospital discharge, three and six months and HRQoL at three, six and 12 months. *A priori* subgroup analyses will be investigated using interaction tests between treatment group and the following subgroup variables:

1) Participants with low chronic disease burden (Functional Comorbidity Index score≤1) versus those who are multimorbid (Functional Comorbidity Index score ≥2).
2) Age ranges of published disability risk groups for survivors of critical illness: young (<44 years), older (45 to 66 years) and oldest (≥ 66 years)[37].
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 Two

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[31].

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 (i.e. the first-stage) and then combined using a random-effects model to obtain a pooled estimate (i.e. 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[38, 39]. 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[40].

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[41]. Each of the eligible randomised controlled trials 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[7-10]. 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.

TABLE 1

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	Keywords

	(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]	
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	

TABLE LEGEND

Table 1: Medical Literature Analysis and Retrieval System Online (MEDLINE) search strategy via OVID platform.

FIGURE LEGNED

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

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Data Availability Statement No data are or will be made available as we will add to these data over the next several years as a combined dataset and continue to interrogate it.

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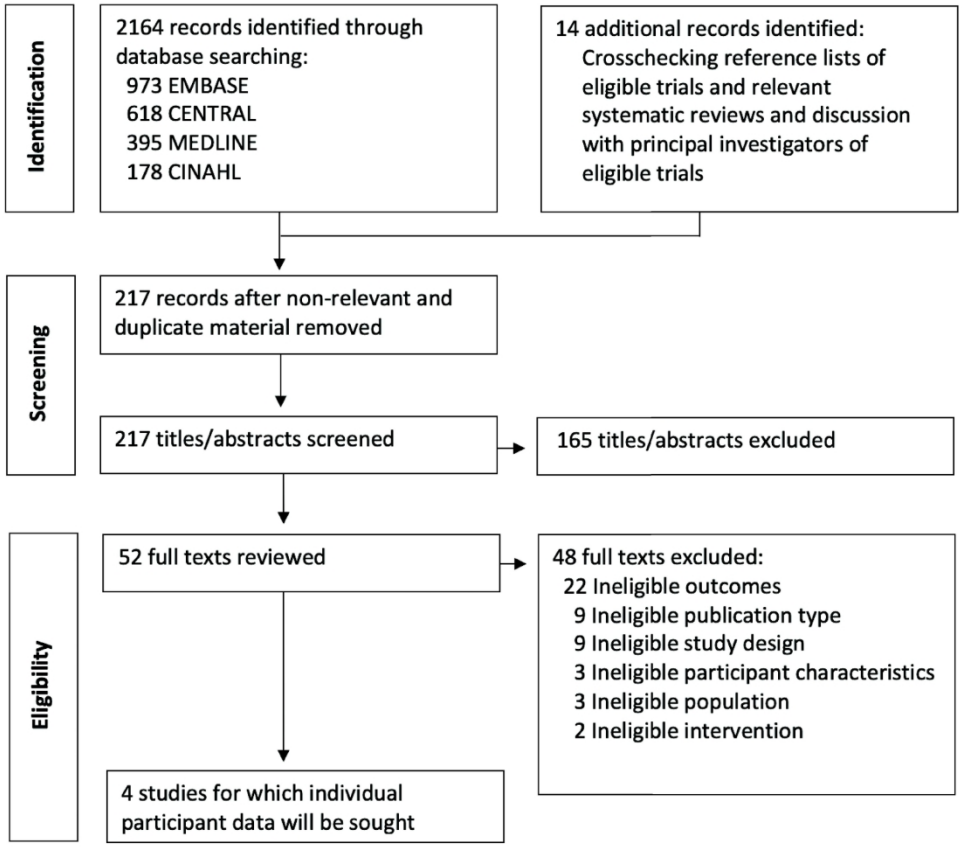

Figure 1: Trial selection process, MEDLINE Medical Literature Analysis and Retrieval System Online, EMBASE Excerpta Medica Database, CINAHL Cumulative Index to Nursing and Allied Health Literature, CENTRAL Cochrane Central Register of Controlled Trials.

180x160mm (300 x 300 DPI)

PRISMA-P 2015 Checklist

This checklist has been adapted for use with protocol submissions to *Systematic Reviews* from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 **4**:1

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	☒	☐	1-2
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	☐	☒	Not Applicable
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	☒	☐	90-91
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	☒	☐	3-34
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	☒	☐	35-41
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	☒	☐	182-184
Support					
Sources	5a	Indicate sources of financial or other support for the review	☒	☐	42-56
Sponsor	5b	Provide name for the review funder and/or sponsor	☒	☐	42-43
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	☒	☐	56-57
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	☒	☐	113-158
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	☒	☐	159-172
METHODS					

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	☒	☐	224-248
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	☒	☐	193-202
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	☒	☐	Table 1
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	☒	☐	221, 347-348
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	☒	☐	211-223
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	☒	☐	259-263, 283-291
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	☒	☐	266-282
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	☒	☐	266-282
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	☒	☐	249-257
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	☒	☐	297-348
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2, Kendall's tau)	☒	☐	297-348
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	☒	☐	297-348
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	☐	☒	Not Applicable
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	☒	☐	254-257, 335-348
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	☒	☐	335-348

BMJ Open

Response to Physical Rehabilitation and Recovery Trajectories Following Critical Illness: Individual Participant Data Meta-Analysis Protocol

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Primary Subject Heading:	Intensive care
Secondary Subject Heading:	Rehabilitation medicine
Keywords:	Adult intensive & critical care < INTENSIVE & CRITICAL CARE, REHABILITATION MEDICINE, INTENSIVE & CRITICAL CARE

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Response to Physical Rehabilitation and Recovery Trajectories Following Critical Illness: Individual Participant Data Meta-Analysis Protocol

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Author Contributions JRAJ, LD, SB and ZP contributed to the initial conception of the study. MB, DCF, DMG, PEM, MM, ANC 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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Competing Interests None declared.

Word count 2832.

ABSTRACT

Introduction The number of inconclusive physical rehabilitation randomised controlled trials for patients with critical illness are 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, 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 three 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 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 CRD42019152526

Research Registry reviewregistry759

Keywords Critical Illness, Rehabilitation, Recovery of Function, Quality of Life.

ARTICLE SUMMARY

Strengths and Limitations of this Study

- According to our literature searches, this will be the first individual participant data meta-analysis to examine 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[1-4]. There is level one evidence that physical rehabilitation provided in the intensive care unit (ICU) is safe[5] and reduces physical activity limitation at hospital discharge[6]. 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)[7-11]. 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, e.g. chronic disease burden, are influential in recovery from critical illness[3, 12, 13] and may modify the effect of physical rehabilitation interventions delivered[14].

Exploration of the physical function and HRQoL recovery trajectories of critically ill patients enrolled in physical rehabilitation trials is limited [12, 14, 15]. However, post-hoc analyses of randomised controlled trials indicate that patient characteristics

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

Individual participant data meta-analyses are considered the gold standard of systematic reviews[19, 20] enabling assessment of the interactions between interventions and patient characteristics with statistical power beyond a randomised controlled trial[21]. Additionally, use of individual participant data provides more reliable subgroup analysis results compared to systematic reviews that use aggregate level data, which rely on summary statistics[21]. 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[22]. When identified, these patient characteristics could inform eligibility criteria of future randomised controlled trials and stratify participants enrolled, e.g. according to chronic disease burden[14], to maximise statistical power[23] and reduce sample size[24]. Clarity on patient characteristics that are important in response to physical rehabilitation interventions may also assist in uncovering the mechanism[23] 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[6, 25-27] 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, three and six months and HRQoL measured at three, six and 12 months), we will assess whether there is an interaction between the treatment group (intervention versus control) and each of the, *a priori* identified, participant characteristics (i.e. 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 (i.e. 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 (PROSPERO CRD42019152526 available athttps://www.crd.york.ac.uk/prospero/display_record.php?RecordID=152526). Our PROSPERO registration was lodged on September 27, 2019 (start date) and the anticipated study completion date is December 31, 2020. This study is also registered with Research Registry (unique identifying number: reviewregistry759 available at https://www.researchregistry.com/browse-the-registry#registryofsystematicreviewsmeta-analyses/registryofsystematicreviewsmeta-analysesdetails/5dc33f4cb4aab200154af661/). Important protocol amendments will be documented with an accompanying explanation and 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[19, 28] and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses of Individual Participant Data (PRISMA-IPD)[20].

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 September 28, 2019. Reference lists of eligible studies and relevant systematic reviews were cross-checked and eligible trial principal investigators consulted regarding 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 post intensive care syndrome OR ICU OR critically ill. Intervention: physical rehabilitation OR endurance training OR strength training OR exercise therapy OR physical therapy. Study design: randomised controlled trial OR 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 if 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. Disagreement between the two independent reviewers (JRAJ and LAM) was 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[7-10] 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.

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 three 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[29].

Publication Type: Randomised controlled trials published in full in a peer reviewed journal were eligible. Research letters, trial protocols and conference abstracts were excluded. Whilst 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 (RoB 2)[30] 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[7-10] have been invited to contribute individual participant data to the study and join the CRITICALConnect collaboration. Data sharing agreements are in place. Anonymised datasets 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[29], age, sex and acute illness severity measured with the Acute Physiology, Age, Chronic Health Evaluation II score[31].

Intervention: Number of physical rehabilitation intervention sessions.

Outcomes: Performance-based physical function at hospital discharge, three and six months. Health-related quality of life at three, six and 12 months. 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, three and six months and HRQoL at three, six and 12 months were considered to be of greatest importance to clinicians, researchers, patients and their families. Participant-reported outcomes of HRQoL involve retrospective consideration (e.g. in the last four weeks) and are not valid in hospitalised patients, therefore the hospital discharge time point was considered not appropriate.

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[32]. For assessment of HRQoL, we will accept version one and two of the 36- 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[32], 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 health care 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.

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, datasets will be converted to a common format and variables renamed for consistency. The individual trial datasets will then be combined to form the master dataset 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 (i.e. a generalised multi-level model) to synthesise the data from multiple trials, which fully accounts for the heterogeneity across the studies[33, 34]. The multilevel models will allow for clustering between studies[35]. We will present the proportions of missing data for the variables of interest by study. Next, we will use multiple imputation with 20 imputed datasets obtained using chained equations to account for the missing data[36]. Mortality will occur throughout each of the trials. However, based on previous research[6] we will assume that the interventions are not associated with mortality and that a "survivors only" analysis is valid[37]. Additionally, it is widely accepted and concordant with common sense that it is not appropriate to impute for death when participant-reported outcomes, e.g. HRQoL, are used[38]. 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 One

We will use longitudinal models to assess the effect of physical rehabilitation according to performance-based physical function outcomes at hospital discharge, three and six months and HRQoL outcomes at three, six 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≤1) versus those who are multimorbid (Functional Comorbidity Index score ≥2).
2) Age ranges of published disability risk groups for survivors of critical illness: young (≤45 years), older (>45 and <66 years) and oldest (≥66 years)[39].
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 Two

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[33].

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 (i.e.

the first-stage) and then combined using a random-effects model to obtain a pooled estimate (i.e. 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[40, 41]. 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[42].

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[43]. Each of the eligible randomised controlled trials 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[7-10]. 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.

TABLE 1

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	

TABLE LEGEND

Table 1: Medical Literature Analysis and Retrieval System Online (MEDLINE) search strategy via OVID platform.

FIGURE LEGNED

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

Acknowledgements None.

Data Availability Statement No data are or will be made available as we will add to these data over the next several years as a combined dataset and continue to interrogate it.

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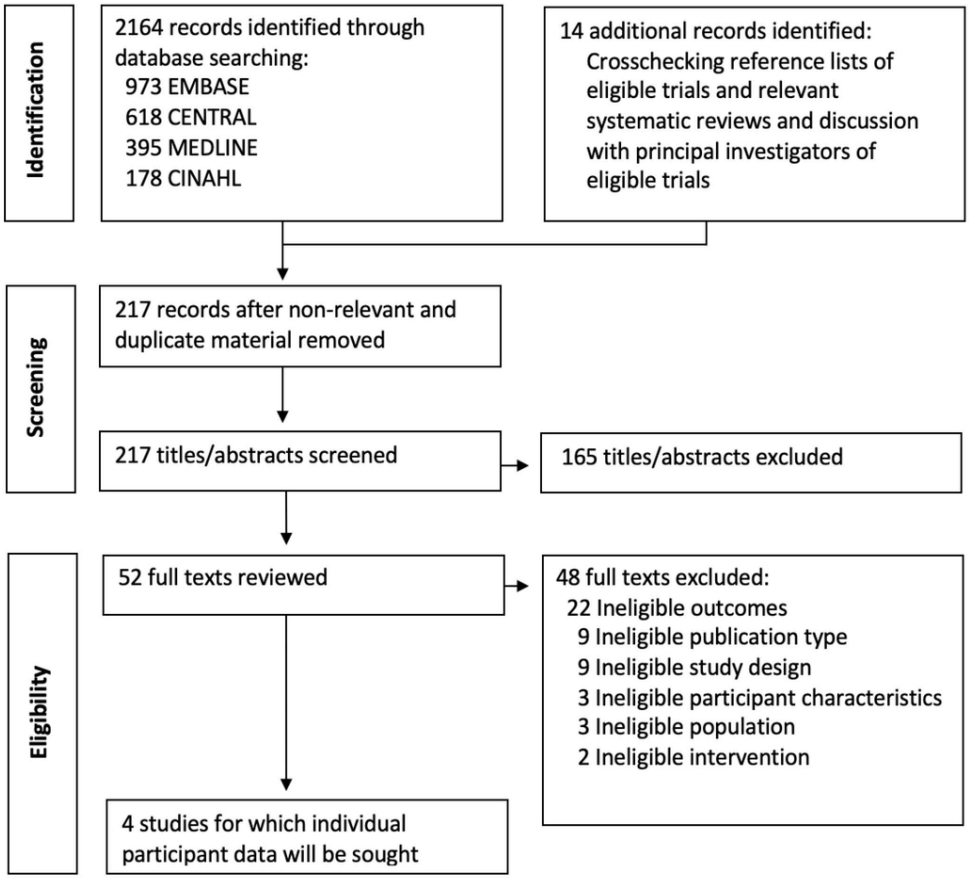

Figure 1: Trial selection process, MEDLINE Medical Literature Analysis and Retrieval System Online, EMBASE Excerpta Medica Database, CINAHL Cumulative Index to Nursing and Allied Health Literature, CENTRAL Cochrane Central Register of Controlled Trials.

90x90mm (300 x 300 DPI)

PRISMA-P 2015 Checklist

This checklist has been adapted for use with protocol submissions to *Systematic Reviews* from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 **4**:1

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	☒	☐	1-2
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	☐	☒	Not Applicable
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	☒	☐	88-89
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	☒	☐	3-34
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	☒	☐	35-40
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	☒	☐	183-185
Support					
Sources	5a	Indicate sources of financial or other support for the review	☒	☐	41-55
Sponsor	5b	Provide name for the review funder and/or sponsor	☒	☐	41-42
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	☒	☐	55-56
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	☒	☐	107-157
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	☒	☐	158-171
METHODS					

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	☒	☐	223-247
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	☒	☐	193-201
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	☒	☐	Table 1
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	☒	☐	220, 355-356
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	☒	☐	210-222
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	☒	☐	258-264, 291-299
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	☒	☐	265-290
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	☒	☐	269-290
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	☒	☐	248-256
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	☒	☐	305-356
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2, Kendall's tau)	☒	☐	305-356
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	☒	☐	305-356
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	☐	☒	Not Applicable
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	☒	☐	254-256, 353-355
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	☒	☐	343-355

BMJ Open

Response to Physical Rehabilitation and Recovery Trajectories Following Critical Illness: Individual Participant Data Meta-Analysis Protocol

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-035613.R2
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Primary Subject Heading:	Intensive care
Secondary Subject Heading:	Rehabilitation medicine
Keywords:	Adult intensive & critical care < INTENSIVE & CRITICAL CARE, REHABILITATION MEDICINE, INTENSIVE & CRITICAL CARE

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Response to Physical Rehabilitation and Recovery Trajectories Following Critical Illness: Individual Participant Data Meta-Analysis Protocol

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Author Contributions JRAJ, LD, SB and ZP contributed to the initial conception of the study. MB, DCF, DMG, PEM, MM, ANC 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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Competing Interests None declared.

Word count 2832.

ABSTRACT

Introduction The number of inconclusive physical rehabilitation randomised controlled trials for patients with critical illness are 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, 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 three 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 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 CRD42019152526

Research Registry reviewregistry759

Keywords Critical Illness, Rehabilitation, Recovery of Function, Quality of Life.

ARTICLE SUMMARY

Strengths and Limitations of this Study

- According to our literature searches, this will be the first individual participant data meta-analysis to examine 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[1-4]. There is level one evidence that physical rehabilitation provided in the intensive care unit (ICU) is safe[5] and reduces physical activity limitation at hospital discharge[6]. 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)[7-11]. 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, e.g. chronic disease burden, are influential in recovery from critical illness[3, 12, 13] and may modify the effect of physical rehabilitation interventions delivered[14].

Exploration of the physical function and HRQoL recovery trajectories of critically ill patients enrolled in physical rehabilitation trials is limited [12, 14, 15]. However, post-hoc analyses of randomised controlled trials indicate that patient characteristics

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

Individual participant data meta-analyses are considered the gold standard of systematic reviews[19, 20] enabling assessment of the interactions between interventions and patient characteristics with statistical power beyond a randomised controlled trial[21]. Additionally, use of individual participant data provides more reliable subgroup analysis results compared to systematic reviews that use aggregate level data, which rely on summary statistics[21]. 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[22]. When identified, these patient characteristics could inform eligibility criteria of future randomised controlled trials and stratify participants enrolled, e.g. according to chronic disease burden[14], to maximise statistical power[23] and reduce sample size[24]. Clarity on patient characteristics that are important in response to physical rehabilitation interventions may also assist in uncovering the mechanism[23] 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[6, 25-27] 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, three and six months and HRQoL measured at three, six and 12 months), we will assess whether there is an interaction between the treatment group (intervention versus control) and each of the, *a priori* identified, participant characteristics (i.e. 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 (i.e. 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 (PROSPERO CRD42019152526 available athttps://www.crd.york.ac.uk/prospero/display_record.php?RecordID=152526). Our PROSPERO registration was lodged on September 27, 2019 (start date) and the anticipated study completion date is December 31, 2020. This study is also registered with Research Registry (unique identifying number: reviewregistry759 available at https://www.researchregistry.com/browse-the-registry#registryofsystematicreviewsmeta-analyses/registryofsystematicreviewsmeta-analysesdetails/5dc33f4cb4aab200154af661/). Important protocol amendments will be documented with an accompanying explanation and 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[19, 28] and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses of Individual Participant Data (PRISMA-IPD)[20].

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 September 28, 2019. Reference lists of eligible studies and relevant systematic reviews were cross-checked and eligible trial principal investigators consulted regarding 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 post intensive care syndrome OR ICU OR critically ill. Intervention: physical rehabilitation OR endurance training OR strength training OR exercise therapy OR physical therapy. Study design: randomised controlled trial OR 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 if 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. Disagreement between the two independent reviewers (JRAJ and LAM) was 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[7-10] 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.

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 three 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[29].

Publication Type: Randomised controlled trials published in full in a peer reviewed journal were eligible. Research letters, trial protocols and conference abstracts were excluded. Whilst 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 (RoB 2)[30] 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[7-10] have been invited to contribute individual participant data to the study and join the CRITICALConnect collaboration. Data sharing agreements are in place. Anonymised datasets 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[29], age, sex and acute illness severity measured with the Acute Physiology, Age, Chronic Health Evaluation II score[31].

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[32]. For assessment of HRQoL, we will accept version one and

two of the 36- 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[32], 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 health care 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, three and six months and HRQoL at three, six 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 four 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, datasets will be converted to a common format and variables renamed for consistency. The individual trial datasets will then be combined to form the master dataset 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 (i.e. a generalised multi-level model) to synthesise the data from multiple trials, which fully accounts for the heterogeneity across the studies[33, 34]. The multilevel models will allow for clustering between studies[35]. We will present the proportions of missing data for the variables of interest by study. Next, we will use multiple imputation with 20 imputed datasets obtained using chained equations to account for the missing data[36]. Mortality will occur throughout each of the trials. However, based on previous research[6] we will assume that the interventions are not associated with mortality and that a "survivors only" analysis is valid[37]. Additionally, it is widely accepted and concordant with common sense that it is not appropriate to impute for death when participant-reported outcomes, e.g. HRQoL, are used[38]. 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 One

We will use longitudinal models to assess the effect of physical rehabilitation according to performance-based physical function outcomes at hospital discharge, three and six months and HRQoL outcomes at three, six 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≤1) versus those who are multimorbid (Functional Comorbidity Index score ≥2).
2) Age ranges of published disability risk groups for survivors of critical illness: young (≤45 years), older (>45 and <66 years) and oldest (≥66 years)[39].
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 Two

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[33].

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 (i.e.

the first-stage) and then combined using a random-effects model to obtain a pooled estimate (i.e. 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[40, 41]. 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[42].

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[43]. Each of the eligible randomised controlled trials 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[7-10]. 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.

TABLE 1

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	

TABLE LEGEND

Table 1: Medical Literature Analysis and Retrieval System Online (MEDLINE) search strategy via OVID platform.

FIGURE LEGNED

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

Acknowledgements None.

Data Availability Statement No data are or will be made available as we will add to these data over the next several years as a combined dataset and continue to interrogate it.

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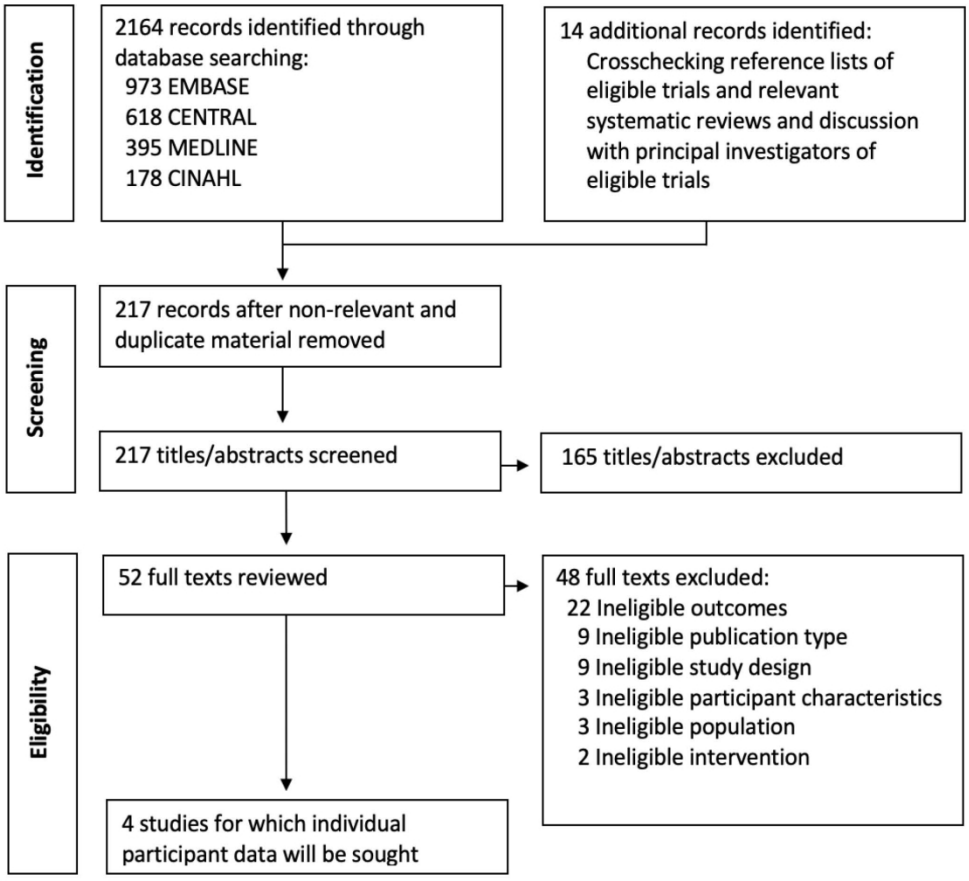

Figure 1: Trial selection process, MEDLINE Medical Literature Analysis and Retrieval System Online, EMBASE Excerpta Medica Database, CINAHL Cumulative Index to Nursing and Allied Health Literature, CENTRAL Cochrane Central Register of Controlled Trials.

90x90mm (600 x 600 DPI)

PRISMA-P 2015 Checklist

This checklist has been adapted for use with protocol submissions to *Systematic Reviews* from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 **4**:1

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	☒	☐	1-2
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	☐	☒	Not Applicable
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	☒	☐	88-89
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	☒	☐	3-34
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	☒	☐	35-40
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	☒	☐	183-185
Support					
Sources	5a	Indicate sources of financial or other support for the review	☒	☐	41-55
Sponsor	5b	Provide name for the review funder and/or sponsor	☒	☐	41-42
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	☒	☐	55-56
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	☒	☐	107-157
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	☒	☐	158-171
METHODS					

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	☒	☐	223-247
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	☒	☐	193-201
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	☒	☐	Table 1
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	☒	☐	220, 355-356
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	☒	☐	210-222
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	☒	☐	258-264, 291-299
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	☒	☐	265-290
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	☒	☐	269-290
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	☒	☐	248-256
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	☒	☐	305-356
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2, Kendall's tau)	☒	☐	305-356
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	☒	☐	305-356
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	☐	☒	Not Applicable
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	☒	☐	254-256, 353-355
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	☒	☐	343-355