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ORIGINAL ARTICLE

Physical rehabilitation interventions for adult patients during critical illness: an overview of systematic reviews

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ABSTRACT

Background Physical rehabilitation interventions aim to ameliorate the effects of critical illness-associated muscle dysfunction in survivors. We conducted an overview of systematic reviews (SR) evaluating the effect of these interventions across the continuum of recovery.

Methods Six electronic databases (Cochrane Library, CENTRAL, DARE, Medline, Embase, and Cinahl) were searched. Two review authors independently screened articles for eligibility and conducted data extraction and quality appraisal. Reporting quality was assessed and the Grading of Recommendations Assessment, Development and Evaluation approach applied to summarise overall quality of evidence.

Results Five eligible SR were included in this overview, of which three included meta-analyses. Reporting quality of the reviews was judged as medium to high. Two reviews reported moderate-to-high quality evidence of the beneficial effects of physical therapy commencing during intensive care unit (ICU) admission in improving critical illness polyneuropathy/myopathy, quality of life, mortality and healthcare utilisation. These interventions included early mobilisation, cycle ergometry and electrical muscle stimulation. Two reviews reported very low to low quality evidence of the beneficial effects of electrical muscle stimulation delivered in the ICU for improving muscle strength, muscle structure and critical illness polyneuropathy/myopathy. One review reported that due to a lack of good quality randomised controlled trials and inconsistency in measuring outcomes, there was insufficient evidence to support beneficial effects from physical rehabilitation delivered post-ICU discharge.

Conclusions Patients derive short-term benefits from physical rehabilitation delivered during ICU admission. Further robust trials of electrical muscle stimulation in the ICU and rehabilitation delivered following ICU discharge are needed to determine the long-term impact on patient care. This overview provides recommendations for design of future interventional trials and SR.

Trial registration number CRD42015001068.

INTRODUCTION

The profound physical impairments associated with critical illness are now increasingly recognised. Acute peripheral skeletal muscle wasting and dysfunction occur rapidly during the early stages of intensive care unit (ICU) admission^{1,2} and contribute to the development of ICU-acquired weakness (ICU-AW). In the long-term, deficits in physical

Key messages

What is the key question?

- What physical rehabilitation interventions are effective for patients during critical illness and when are they best delivered?

What is the bottom line?

- Evidence confirming physical rehabilitation delivered in the early stages of critical illness in the intensive care unit (ICU) produce improvements in a range of outcomes is of moderate-to-high quality, but there is insufficient evidence of effects from interventions delivered post-ICU discharge.

Why read on?

- This overview comprehensively examines the existing evidence for effectiveness of physical rehabilitation in patients with critical illness and provides informed recommendations for future trial design and systematic review conduct.

strength, functional performance and associated health-related quality of life are evident in survivors for many years following resolution of the original illness.^{3–5}

Rehabilitation is the cornerstone of management of critical illness-related morbidity.⁶ Physical-based rehabilitation interventions aim to ameliorate the effects of ICU-AW and its sequelae, and are advocated across the patient recovery continuum.⁷ Within the ICU, physical rehabilitation typically centres around early mobilisation encompassing a hierarchy of increasingly functional activities,^{8,9} with potential adjunctive technologies including electrical muscle stimulation¹⁰ and cycle ergometry.¹¹ Ward-based management emphasises progression towards levels of functional performance necessary to expedite hospital discharge, which can be enhanced by coordinated multidisciplinary therapy⁷ and input from generic rehabilitation assistants.¹² Following hospital discharge, physical rehabilitation has been characterised by delivery of either home-based or hospital-based exercise rehabilitation programmes including combined strength, cardiovascular and functional components.¹³

The growing interest in physical rehabilitation for critical illness patients has led to an exponential rise in the volume of published data investigating effectiveness of interventions in recent years, accompanied by multiple systematic reviews (SR) and meta-analyses aiming to integrate available evidence and generate conclusions on the most beneficial therapeutic options. These reviews include those focusing on delivery of physical rehabilitation during the peri-ICU phase and also the subsequent recovery stages post-ICU discharge. However while valuable, these individual SR are often restricted to a relatively narrow field of questioning regarding a defined ICU population, intervention, outcome and timepoint. This specificity of focus precludes a broader overview of the existing evidence base for physical rehabilitation during recovery from critical illness and limits translation of findings into clinical practice. Variability in review methodology and quality may further influence robustness of any conclusions.

The aim of this review was to conduct an overview of existing SR evaluating physical rehabilitation interventions for patients with critical illness across the continuum of recovery. The overview specifically aimed to address the following questions:

1. At which stage of the recovery continuum do physical rehabilitation interventions have the most effect?
2. Do particular patient populations gain more benefit from physical rehabilitation interventions than others?
3. Which type of physical rehabilitation interventions produce benefits (short-term and long-term) for post-critical illness patients?
4. What adverse events or harmful effects are experienced from receipt of any physical rehabilitation interventions?

METHODS

Protocol and registration

The protocol for this overview, modelled on the Cochrane Collaboration approach¹⁴ and written using the Preferred Reporting Items for Systematic review and Meta-Analysis Protocol (PRISMA-P) guidelines,¹⁵ has been registered (National Institute of Health Research International Prospective Register of Systematic Reviews (PROSPERO) CRD42015001068, available at <http://www.crd.york.ac.uk/PROSPERO/prosperto.asp>) and published previously.¹⁶

Eligibility

SR were eligible if they included and summarised the results of randomised controlled trials (RCTs) investigating the effect of any physical rehabilitation intervention following critical illness at any stage of the recovery continuum. Physical rehabilitation intervention reviews were included if they addressed: (1) exercise and/or mobility programmes for example, strengthening exercise to target specific muscles or functional activities such as lying to sitting over the edge of the bed, standing, stepping and walking; (2) use of cycle ergometers involving upper or lower limb pedalling at set levels of intensity or (3) the application of external adjuncts such as electrical muscle stimulation to enable activation of the muscle in patients unable to actively participate in rehabilitation. 'Critical illness' was defined as patients admitted to the ICU, irrespective of causal diagnosis but requiring invasive mechanical ventilation and multiorgan support. For reviews that included both RCTs and non-RCTs, we included the review only if we could extract the summary data from the RCTs. Further detail can be found in the online supplementary section E1.

Data sources and search strategy

Data sources were searched as described in the protocol.¹⁶ There were no temporal or linguistic limitations applied and

initial searches were conducted on 3 April 2015 and rerun on 29 October 2015. Full search strategies are included in the online supplementary section E2. There was no restriction on publication year for inclusion.

Overview procedure

Following removal of duplicate and non-relevant material (BC), two review authors (first search BC, LS; rerun BC, BO'N) independently screened search results based on abstract and title. Full-text systematic review selection, data extraction, synthesis and assessment of methodological quality within the overview were conducted as described in the protocol.¹⁶ Bespoke eligibility assessment and data extraction forms are presented in the online supplementary sections E3 and E4. Data extraction was conducted independently by two authors (BO'N and LS); information extracted included aims and rationale of the SR, stage of recovery continuum covered, types of studies included, population(s), intervention(s), comparator(s), primary and secondary outcomes (where specified), findings (effect size including 95% CI, results of pooling), date of last search and methods of quality assessment. Outcome measures were further categorised according to the WHO Classification of Functioning Disability and Health domains of 'Impairment', 'Activity limitation' and 'Participation restriction',¹⁷ with additional categories of 'Adverse events/harms' and 'Healthcare utilisation'.

Quality of reporting and methodological quality of included reviews were appraised independently by two authors (BC and BB) using the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA)¹⁸ checklist and the Assessment of Multiple Systematic Reviews (AMSTAR) tool¹⁹ (see online supplementary section E5). The PRISMA checklist details criteria for optimum reporting of SR across Title, Introduction, Methods, Results, Discussion and Funding sections. The AMSTAR tool assesses the appropriate conduct of SR, for example, performance of duplicate study selection and data extraction and provision of characteristics of included studies. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach²⁰ was used to assess overall quality of evidence for the interventions evaluated in included SR according to the outcomes identified. This approach assesses elements of risk of bias (methodological conduct), inconsistency (unexplained heterogeneity of results), indirectness (indirect population, intervention, control or outcomes) and imprecision (wide CIs) using the Cochrane Underlying Methodology.¹⁴ Where possible, we used information directly reported in the SR otherwise we graded the evidence.

RESULTS

Search results

There were 8835 potentially eligible studies, with a further 8 articles identified through the authors' personal libraries (figure 1). Following de-duplication and removal of non-relevant material, and abstract screening, a total of 30 articles underwent full-text screening for inclusion. Twenty-two SR were subsequently excluded (see online supplementary section E6). Complete agreement between the two independent reviewers was evident for eligibility of full-text articles (percentage agreement=100%, $\kappa=1.0$). Arbitration by a third reviewer was not required. Three SR were further excluded during the data extraction stage.²¹⁻²³ No meaningful data could be extracted from these reviews as they reported only a narrative summary and did not include or synthesise the results from included studies.

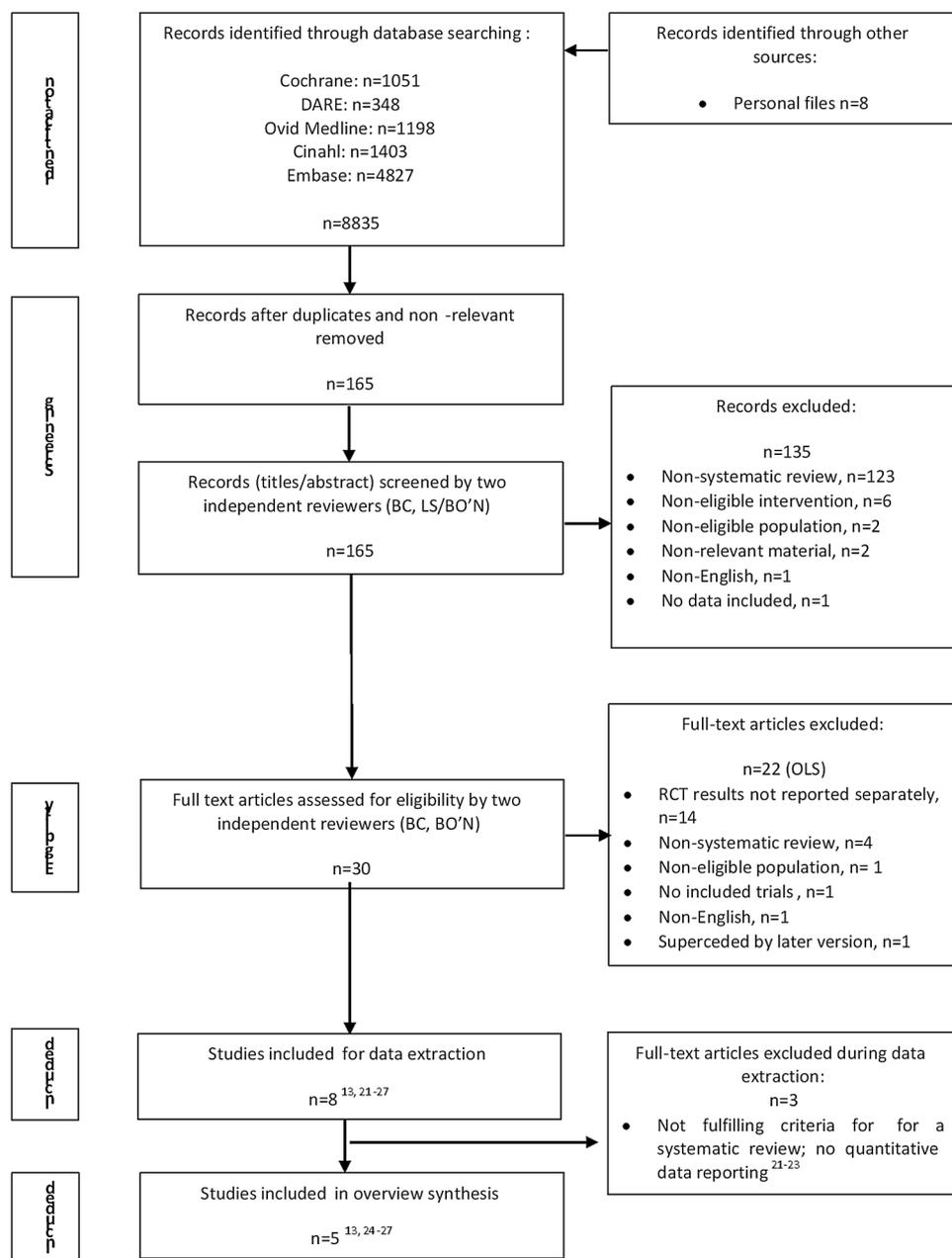


Figure 1 Flow diagram summarising systematic review selection. OLS, online supplementary material; RCT, randomised controlled trial.

Included systematic reviews and characteristics

Five SR were eligible for inclusion^{13 24-27} (table 1). Reviews were published between 2013 and 2015, with the most recent search date for included studies reported as 15 May 2014.¹³ A total of 24 relevant individual RCTs were included within the five SR, ranging between 2²⁵ and 10²⁶ overall (see online supplementary section E7). Six RCTs overlapped across two of the included SR, and two further additional RCTs overlapped across three of the included SR. Three SR included a meta-analysis: one review assessed the effect of early physical rehabilitation and electrical muscle stimulation on the primary outcome of incidence of critical illness polyneuropathy or myopathy,²⁵ one review assessed effect of physical therapy (multiple interventions) across a range of clinical outcomes²⁶ and one review did not specify their primary outcome, but assessed the effect of neuromuscular electrical stimulation (NMES) on

quadriceps muscle strength.²⁷ All reviews used an objective scale to assess methodological risk of bias in their included studies.

Three SR focused solely on physical rehabilitation interventions delivered within ICU.²⁵⁻²⁷ One review included all stages of the recovery continuum,²⁴ and another the post-ICU discharge stage only.¹³ There was overall consistency across all five SR with regard to target populations, which broadly centred on adult patients who had been admitted to the ICU with critical illness. However, individual SR reported varying levels of summary detail for characteristics of included patient populations (see online supplementary section E8). Interventions included physical or exercise-based therapy^{13 24-26} or NMES.²⁷ Further detail of the included interventions described in included SR is reported in the online supplementary section E9. Outcome measures used to determine effectiveness of interventions within RCTs of included SR varied considerably and only

Table 1 Characteristics of included systematic reviews

Author (year) Aim of SR	Stage of recovery continuum	Search dates* No. studies included Patients included (range; total)	Population†	Intervention	Comparator	Category of outcome Outcome measure/s (*denotes primary)	Quality appraisal method
Kayambu <i>et al</i> (2013) ²⁶ Review the evidence base for exercise in critically ill patients	In ICU	1980 to January 2012 10 24–140; 790	Patients receiving physical therapy in the ICU	Physical therapy	No or minimal physical therapy in contrast to the intervention group	<i>Impairment:</i> Peripheral muscle strength Respiratory muscle strength <i>Activity limitation:</i> PF <i>Participation restriction:</i> Quality of life <i>Healthcare utilisation:</i> Ventilator-free days ICU and hospital LOS Mortality	PEDro Revised-AMSTAR
Hermans <i>et al</i> (2014) ²⁵ ‡ Review the evidence for any intervention to reduce the incidence of CIP or CIM in critically ill individuals	In ICU	1966 to 4 October 2011 2 104–140; 244	Adult (≥18 years of age) admitted to a medical, surgical or mixed ICU	Physiotherapy EMS Rehabilitation programme	Placebo, no treatment or a different treatment	<i>Impairment:</i> Incidence of CIP/CIM in ICU* <i>Healthcare utilisation:</i> Duration of MV ICU LOS 30d and 180d mortality <i>Adverse events:</i> Serious adverse events	Cochrane Risk of Bias
Wageck <i>et al</i> (2014) ²⁷ Investigate the applications and effects of NMES in critically ill patients in the ICU	In ICU	Up until 26 November 2013 8 16–52; 274	Adult (≥18 years of age) critically ill patients in the ICU for ≥48 hours	NMES	Not specified	<i>Impairment:</i> Muscle strength Muscle structure <i>Healthcare utilisation:</i> ICU LOS Duration MV <i>Adverse events:</i> Complications from immobilisation and bed rest	PEDro
Calvo-Ayala <i>et al</i> (2013) ²⁴ § Identify effective interventions that improve long-term PF in ICU survivors	Across all stages	January 1990 to December 2012 7 16–195; 678	<i>Inclusion</i> Adult (≥18 years of age) patients admitted to an ICU <i>Exclusion</i> Acquired brain injury or underlying neuropathy/myopathy Long-term acute-care hospital patients	Exercise/physical therapy	Placebo, no treatment or a different treatment	<i>Activity limitation:</i> Long-term PF or its surrogates*	PEDro
Connolly <i>et al</i> (2015) ¹³ ¶ Assess effectiveness of exercise rehabilitation programmes initiated after ICU discharge in adult ICU survivors	Post-ICU discharge	1966 to 15 May 2014 6 16–195; 483	<i>Inclusion</i> Adult (≥18 years of age) patients admitted to an ICU or critical care unit; MV ≥24 hours Discharged from ICU at the time of receiving the intervention <i>Exclusion</i> Palliative care Patients with targeted rehabilitation pathways	Exercise rehabilitation or training	Any other intervention, control or 'usual care' programme	<i>Activity limitation:</i> Functional exercise capacity* <i>Participation restriction:</i> Health-related quality of life* <i>Healthcare utilisation:</i> Mortality <i>Adverse events:</i> Adverse events	Cochrane Risk of Bias

*Search dates reported as per individual systematic review and may/may not include specific detail.

†Population described as per individual systematic review and may/may not include specific 'Inclusion' and 'Exclusion' criteria.

‡SR includes any treatment related to decreasing risk of CIP/CIM; data reported relate to physical rehabilitation interventions included.

§SR includes any treatment where long-term PF was an outcome; data reported relate to physical rehabilitation interventions included.

¶NB include 'Other' outcomes related to trial intervention, for example, withdrawal rates, adherence and loss to follow-up.

AMSTAR, Assessment of Multiple Systematic Reviews; CIM, critical illness myopathy; CIP, critical illness polyneuropathy; EMS, electrical muscle stimulation; ICU, intensive care unit; LOS, length of stay; MV, mechanical ventilation; NMES, neuromuscular electrical stimulation; PEDro, Physiotherapy Evidence Database; PF, physical function.

three reviews specified their primary outcomes.^{13 24 25} Outcomes classified as reflecting ‘Impairment’¹⁷ tended to be adopted in reviews, where interventions were delivered in the ICU. Outcomes related to healthcare utilisation featured in four out of the five reviews.^{13 25–27} Three SR reported adverse events.^{13 25 27}

Assessment of methodological quality of included systematic reviews

Median (IQR) PRISMA and AMSTAR scores were 17.0 (16.5–25.0)/27 and 7.0 (6.3–9.0)/11, respectively. Percentage agreement between the two reviewers for scoring items on the PRISMA checklist was 70.4 (66.7–85.2)% and 72.7 (59.1–81.8)% for AMSTAR items. Any disagreements were resolved through consensus and no additional reviewer was required for arbitration. Two SR, scoring highest for PRISMA scores, also scored the greatest AMSTAR scores and were classified as high quality;^{13 25} these were both Cochrane reviews. Results are reported in [table 2](#) and online supplementary section E10.

When the individual sections of the PRISMA checklist were analysed (Title, Abstract, Introduction, Methods, Results, Discussion and Funding), the ‘Title’ section was most comprehensively completed across all included reviews (100%), and ‘Funding’ the least well completed (40%) ([figure 2](#)). [Figure 3](#) presents the frequency of each AMSTAR item that was addressed across the included SR. Items poorly completed were publication of a priori protocols, consideration of publication status as an inclusion criterion, assessment of publication bias and declaration of conflicts of interest.

Findings of included systematic reviews

The main findings and conclusions from each included SR are presented in the online supplementary section E11. Three SR reported benefits from delivery of early (during ICU) physical rehabilitation interventions comprising a variety of exercise, mobilisation, ergometry and muscle strengthening strategies^{24–26} (see online supplementary table E11). Outcomes were typically short-term, for example, peripheral muscle strength at ICU discharge, duration of mechanical ventilation, ICU length of stay (see online supplementary table E14). However, due to the heterogeneity of individual study designs and intervention protocols, it is not possible to specify a more precise therapeutic prescription. One SR reported favourable effects from electrical muscle stimulation.²⁷ The only SR that focused on post-ICU discharge rehabilitation was unable to conclude effectiveness of any intervention.¹³ Only two SR evaluated adverse events associated with physical rehabilitation interventions delivered in the ICU and post-ICU discharge, and no serious adverse events were reported.^{13 25} One review reported that delivery of electrical muscle stimulation had no effect on prevention of

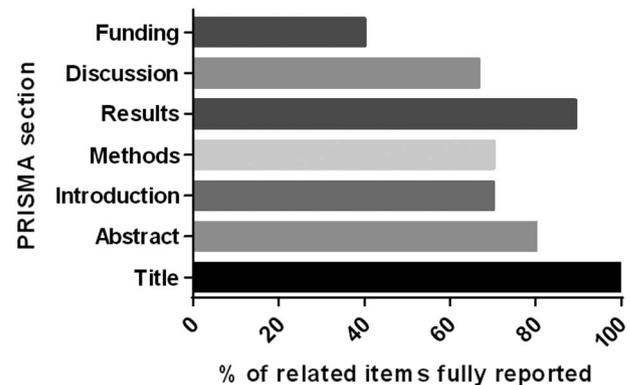


Figure 2 Summary of PRISMA checklist section items reported across all included reviews. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses.

complications, but no other specific adverse events related to the intervention itself were examined.²⁷

GRADE summary of evidence

The summary of evidence is presented in [table 3](#) for physical therapy interventions and [table 4](#) for NMES interventions conducted in the ICU. We report the pooled effect sizes or other data that were directly reported in the original SR. The GRADE data extraction tables are provided in the online supplementary section E12. For physical rehabilitation interventions delivered in the ICU, there was high-quality evidence of effect for critical illness polyneuropathy and myopathy (Impairment), quality of life (Participation restriction) and ICU length of stay, hospital length of stay and hospital mortality (Healthcare utilisation). The quality of evidence for peripheral and respiratory muscle strength and respiratory function was low. For NMES interventions conducted in ICU, the quality of evidence for critical illness polyneuropathy/myopathy and muscle structure was low and for muscle strength was very low. As only one SR evaluated physical therapy interventions in the post-ICU period, results are reported according to the original SR¹³ ([table 5](#)). Quality of evidence for outcomes was either low or very low.

DISCUSSION

The aim of this review was to conduct an overview of existing SR to synthesise the current state of the evidence for physical rehabilitation interventions for critically ill patients delivered across the recovery continuum. We identified five SR for inclusion of either high or moderate quality, three of which included meta-analyses. The majority of reviews focused on interventions delivered during the early stage of the recovery continuum during ICU admission, with favourable effects from physical exercise-based strategies and electrical muscle stimulation on

Table 2 Results for PRISMA and AMSTAR quality appraisal of included systematic reviews

Author	PRISMA score (/27)	PRISMA score (% of applicable)	AMSTAR score (/11)	AMSTAR score (% of applicable)	AMSTAR quality grade
Kayambu <i>et al</i> ²⁶	17	68.0	6	54.5	Medium
Hermans <i>et al</i> ²⁵	25	96.2	10	90.9	High
Wageck <i>et al</i> ²⁷	17	70.8	6.5	54.5	Medium
Calvo-Ayala <i>et al</i> ²⁴	16	69.6	7	70.0	Medium
Connolly <i>et al</i> ¹³	25	100	8	88.9	High
Summary	17.0 (16.5–25.0)	70.8 (68.8–98.1)	7.0 (6.3–9.0)	70.0 (54.5–89.9)	–

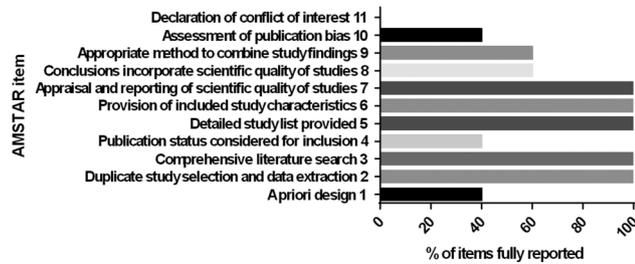


Figure 3 Summary of completion of AMSTAR items across all included reviews. For full AMSTAR item descriptors, see online supplementary section E5. AMSTAR, Assessment of Multiple Systematic Reviews.

short-term outcomes. Only one review solely examined the post-ICU discharge stage and was unable to demonstrate a benefit from interventions delivered at this time. While

overviews of SR have previously been conducted in other areas of clinical practice, the current overview is novel and timely in examining the evidence within the field of rehabilitation during critical illness, which has grown exponentially in recent years, and which has the advantage of allowing comparison and contrast of individual reviews to provide a précis of evidence at these different levels.²⁸ Furthermore, we have been able to establish recommendations for future interventional study design and SR conduct.

Findings related to overview questions

Stage of the recovery continuum where physical interventions have most effect

Our results support the findings for effectiveness of physical rehabilitation interventions delivered during the ICU stay for patients with critical illness. We would suggest that there is currently no requirement for further SR on physical interventions

Table 3 Summary of findings: intervention: physical rehabilitation; comparison: usual care

WHO domain outcome	Review author; N studies; N patients	Pooled effect (95% CI)	GRADE of evidence	Explanation
<i>Impairment</i>				
Peripheral muscle strength	Kayambu <i>et al</i> ²⁶ 2 244	Hedge's g=0.27 (0.02 to 0.52), p=0.03	⊖⊖ Low*	Downgraded –2 for serious risk of bias and imprecision
Respiratory muscle strength	Kayambu <i>et al</i> ²⁶ 2 105	Hedge's g=0.51 (0.12 to 0.89), p=0.01	⊖⊖ Low†	Downgraded –2 for serious risk of bias and imprecision
CIP/CIM	Hermans <i>et al</i> ²⁵ 1 104	RR 0.62 (0.39 to 0.96) p=0.03	⊕⊕⊕⊕ High	
<i>Activity limitation</i>				
Physical function‡	Kayambu <i>et al</i> ²⁶ 2 143	Hedge's g=0.46 (0.13 to 0.78), p=0.01	⊖⊖ Low§	Downgraded –2 for serious risk of bias and imprecision
<i>Participation restriction</i>				
Quality of Life	Kayambu <i>et al</i> ²⁶ 2 154	Hedge's g=0.40 (0.08 to 0.71), p=0.01	⊕⊕⊕⊕ High	
<i>Healthcare utilisation</i>				
VFD	Kayambu <i>et al</i> ²⁶ 3 334	Hedge's g=0.38 (0.16 to 0.59), p<0.001	⊖⊖⊖ Moderate¶	Downgraded –1 for imprecision
ICU LOS	Kayambu <i>et al</i> ²⁶ 6 597	Hedge's g=–0.34 (–0.51 to –0.18), p<0.001	⊕⊕⊕⊕ High	
Hospital LOS	Kayambu <i>et al</i> ²⁶ Hermans <i>et al</i> ^{25**} 5 441	Hedge's g=–0.34 (–0.53 to –0.15), p<0.001	⊕⊕⊕⊕ High	
Hospital mortality	Kayambu <i>et al</i> ²⁶ Hermans <i>et al</i> ^{25**} 3 274	OR 1.0. (0.54 to 1.85) p=1.0	⊕⊕⊕⊕ High	
Duration of MV	Hermans <i>et al</i> ²⁵ 1 Not reported	Median (IQR) 3.4 days (2.3 to 7.3) vs 6.1 days (4.0 to 9.6), p not reported	⊖⊖⊖ Moderate††	Downgraded –1 for inadequate reporting of effect

Stage of recovery: in the ICU.

*50% no random allocation; 50% no concealed allocation; 50% no blinded assessors; 50% not reported measures of key outcomes >85% patients and outcome was measured at different end points.

†50% no concealed allocation; 50% no blinded assessors; 50% not reported measures of key outcomes >85% patients; 100% no ITT and unclear end point in one study.

‡Data from Kayambu *et al*,²⁶ no pooled data reported in Calvo-Ayala *et al*.²⁴

§50% no allocation concealment; 50% not reported measures of key outcomes >85% patients; 50% no ITT and outcome was measured at different end points.

¶Measured at different end points.

**Outcome from same RCT reported in both reviews.

††Inadequate reporting of effect.

CIP/CIM, critical illness polyneuropathy/myopathy; ICU, intensive care unit; ITT, intention to treat; LOS, length of stay; MV, mechanical ventilation; RCT, randomised controlled trials; RR, risk ratio; VFD, ventilator-free days.

Table 4 Summary of findings; intervention: NMES

WHO domain outcome	Review author; N studies; N patients	Pooled effect (95% CI)	GRADE of evidence	Explanation
<i>Impairment</i>				
Muscle strength	Wageck <i>et al</i> ²⁷ 3 66	SMD 0.77, (0.13 to 1.40), p=0.02	⊖ Very low*	Downgraded –3 for serious risk of bias, inconsistency and imprecision
Muscle structure	Wageck <i>et al</i> ²⁷ 6	Not possible to pool	⊖⊖ Low†	Downgraded –2 for serious inconsistency and indirectness
CIP/CIM	Hermans <i>et al</i> ²⁵ 1 52	RR 0.32 (0.10 to 1.01), p=0.05	⊖⊖ Low‡	Downgraded –2 for serious risk of bias and indirectness

Comparison: usual care. Stage of recovery: in the ICU.

*50% no concealed allocation; 50% no blinded assessors; 50% not reported measures of key outcomes >85% patients; 50% no ITT and mean difference in one study does not fall within the 95% CI of the other.

†Three studies reported an effect and three did not; and different outcome measures were used at different timepoints.

‡High ROB reported by review for this study vis-à-vis randomisation, concealment, incomplete outcome data and selective reporting; and not all participants were evaluable. CIP/CIM, critical illness polyneuropathy/myopathy; ICU, intensive care unit; ITT, intention to treat; NMES, neuromuscular electrical stimulation; ROB, risk of bias; RR, risk ratio; SMD, standard mean difference.

delivered within the ICU, until the existing evidence base is supplemented by a volume of new trial data measuring functional outcomes, for example, Moss *et al*²⁹ or investigating electrical muscle stimulation, an ‘in-ICU’ intervention that still requires further evidence (table 6). Future studies would benefit by including long-term follow-up in addition to short-term assessment. Further studies are required to evaluate physical rehabilitation interventions delivered post-ICU discharge including the composition of such rehabilitation interventions. The review focusing on this stage of recovery highlighted a number of outstanding studies that were not included, but which would be evaluated when fully published and included in a future update of the review.¹³ The results of this may yet help to inform the direction of post-ICU discharge rehabilitation research.

Patient populations gaining greater benefit from physical rehabilitation interventions

Included reviews were broadly consistent with regard to eligible populations. However, the heterogeneity within the more detailed patient characteristic data that each review reported precluded us from identifying a specific population that gained greater benefit from physical rehabilitation interventions. Identifying target populations that respond to specific interventions may have positive impact on efficiency of rehabilitation resource utilisation. Epidemiological studies may be of benefit to characterise patient cohorts that respond to different therapies, for example, those with multiple comorbidities³⁰ or demonstrate particular features associated with ICU admission such as a defined duration of mechanical ventilation or degree of muscle wasting.

Physical rehabilitation interventions producing short-term and/or long-term benefit

Physical rehabilitation and NMES interventions delivered early during critical illness and ICU admission were found to be most effective at improving short-term outcomes. In these instances, initiation of intervention varied from within 72 hours of ICU admission to between 7 and up to 30 days of mechanical ventilation delivery. However, the GRADE quality of evidence for these outcomes was inconsistent and varied between very low and high. One SR reported a benefit on long-term physical function although interventions were commenced at varying stages across the recovery continuum and the duration and timepoints

of follow-up were inconsistent across included studies.²⁴ In the future, defining what constitutes *early* rehabilitation is vital to facilitate interpreting the effects of interventions at this stage of recovery.

Adverse events or harmful effects of physical rehabilitation interventions

Only two reviews, one examining physical rehabilitation interventions within the ICU and the other post-ICU discharge, reported adverse events. Based on findings from these reviews, there appear to be minimal risks associated with delivery of interventions. However, the majority of SR did not report this outcome, either due to choice of outcome measure selection or because none of the included studies within that review reported these data. We strongly recommend that all future RCTs report the frequency and nature of adverse events pertaining to the intervention under examination or explicitly indicate, if there were no adverse events. Furthermore, all future SR, regardless of stage of the recovery continuum under investigation, should include the incidence of adverse events as an outcome measure. Furthermore, we recommend that safety criteria for commencing or stopping rehabilitation should be reported to allow a more comprehensive review of methodology to facilitate comparison in future RCTs and SR.

Critique of the overview method

This overview of SR represents a novel approach to synthesising the existing evidence base of physical rehabilitation during critical illness. We adopted a number of strategies to strengthen our review methodology. We developed a robust protocol, modelled on the process outlined by the Cochrane Collaboration for undertaking an overview of this kind¹⁴ and reported in line with recent guidelines.¹⁵ This protocol was registered on an international database (PROSPERO), and fully published a priori.¹⁶ Our search strategies were comprehensive, and we undertook duplicate screening, data extraction and quality assessments. In addition to the validated AMSTAR instrument for rating methodological quality,¹⁹ we further examined the proportion of items reported by each systematic review from the recommended PRISMA checklist,¹⁸ and applied the GRADE approach²⁰ to summarising the quality of evidence.

There are several potential limitations to our review. We only included SR that included RCTs or where RCT findings were

Table 5 Summary of findings; intervention: physical rehabilitation

WHO domain outcome	Review author; N studies: N patients	Pooled effect (95% CI)	GRADE of evidence	Explanation
<i>Activity limitation</i>				
Functional exercise capacity	Connolly <i>et al</i> ¹³ 6 483*	Unable to pool data due to variability in use of outcome measures across individual studies	⊖ Very low	Downgraded –3 due to variability in multiple aspects of methodology across studies, risk of bias and differences in data reporting
<i>Participation restriction</i>				
Health-related quality of Life	Connolly <i>et al</i> ¹³ 2 254*	Unable to pool data due to variability in use of outcome measures across individual studies and small study number	⊖ Very low	Downgraded –3 due to variability in multiple aspects of methodology across studies, risk of bias and differences in data reporting
<i>Healthcare utilisation</i>				
Mortality	Connolly <i>et al</i> ¹³ 6 483	Unable to pool data due to variation in study design; no deaths reported in two studies; no difference in mortality rates between intervention and control groups in remaining four studies	⊖⊖ Low	Downgraded –2 due to serious inconsistency and imprecision
<i>Adverse events</i>				
Non-mortality adverse events	Connolly <i>et al</i> ¹³ 4 376	Three studies reported no adverse events; one study reported no significant difference between groups for adverse events (n=1 event only)	⊖⊖ Low	Downgraded –2 due to lack of reported data from two studies and serious imprecision

Comparison: usual care. Stage of recovery: post-ICU discharge.

*Data reported are overall number of participants enrolled in each study. Multiple outcome measures were observed across studies with variable numbers of patients for each measure according to each study. ICU, intensive care unit.

reported distinctly from non-RCT findings. This was the most common factor accounting for ineligibility and therefore contributed to the volume of evidence we were subsequently able to evaluate and base our conclusions on. To this end, we excluded a number of recent SR in the field, for example, studies by Parry *et al*³¹ and Li *et al*.³² We acknowledge a large volume of observational cohort data investigating physical rehabilitation in critical illness exists; many of these data that echo our findings have been reported in other SR that were also excluded.³³ However, RCT represent the most rigorous study design to evaluate the

effectiveness of an intervention and are the only data that can contribute to meta-analyses. In addition, we found considerable overlap between RCT evaluated in included and excluded SR in this overview, and where RCT did not overlap, their findings were in keeping with the results of the overview. By strictly adhering to our overview design, we have been able to focus on assimilating the findings from reviews where this was examined and reported. Clear delineation of reporting of findings from RCTs and observational study designs in a systematic review would facilitate interpretation of conclusions based on the

Table 6 Recommendations and rationale for future research

Recommendation	Rationale
<i>Future interventional trial</i>	
<i>Evidence</i> Focus on NMES interventions delivered in the ICU or physical rehabilitation interventions delivered after ICU discharge	The current evidence for these specific areas is currently low and/or insufficient. Focusing on these topics would address gaps in the existing evidence base
<i>Population</i> Define target population to benefit from interventions	Stratification of patient cohorts that would benefit from rehabilitation interventions would streamline the rehabilitation pathway, greater efficiency of resource utilisation and cost-effectiveness as well as delivering personalised care
<i>Intervention</i> Full and accurate reporting of intervention detail using Template for Intervention Description and Replication checklist and guide ⁴⁴	Increase transparency of intervention delivered within the trial, improve reporting of interventions in a systematic and structured manner, enhance interpretation of findings
<i>Comparison</i> Accurate and detailed description of usual care or the comparative intervention arm should be documented	Facilitate understanding of the clinical context in which the intervention was trialled, and assist in interpretation of findings and determining generalisability
<i>Outcomes</i> When available, use one or more relevant COS, for example, Connolly <i>et al</i> . ⁴⁵ In addition, ensure inclusion of a patient-reported outcome, long-term outcomes to fully evaluate effect of physical rehabilitation interventions and report adverse events or harms associated with the intervention	COS facilitate greater comparison across studies, pooling of datasets for meta-analyses and clinical applicability of results. Patient-reported outcomes were not evident from the current overview, and long-term follow-up was limited. Adverse event rates are valuable for considering clinical efficacy of an intervention even if statistically significant differences are observed
<i>Timepoint</i> Up-to-date literature search to underpin research question; further updated at the time of trial publication	Ensure trial findings are reported in context of most current existing data
Publication of a priori trial protocol developed in line with Standard Protocol Items: Recommendations for Interventional Trials guidance	Enhances credibility of final publication of trial findings by supplementing clinical trial registration; streamlines final publication text; comprehensive reporting of key trial components facilitates transparency
Include a process evaluation framework into trial design of complex interventions ⁴⁶	To distinguish true intervention effect from factors related to delivery of intervention and trial conduct; explain contextual influences and provide insight into wider implementation

COS, core outcome sets; ICU, intensive care unit; NMES, neuromuscular electrical stimulation.

relative weight of evidence from each category. Furthermore, we intended to appraise the quality of evidence at the level of each systematic review and for that reason we did not retrieve data from systematic review authors or primary RCTs included in reviews. This is in keeping with guidance for overview conduct,¹⁴ and as also evident in overviews from other clinical topics.³⁴

Our overview contains SR of varying methodological quality in terms of reporting and conduct. While use of the PRISMA checklist¹⁸ to quantify the quality of review reporting is not a validated method, collecting these data along with AMSTAR scores¹⁹ allowed us to identify the main areas of SR where reporting detail was lacking. A more recent revised version of the AMSTAR tool (AMSTAR-R) has been published that provides a greater level of criterion detail for each quality item,³⁵ this updated scoring system does not provide thresholds to classify overall quality.³⁶ Our adoption of the GRADE approach was novel and important when developing our conclusions and recommendations to address the relative quality of evidence.²⁰

We reran our searches such that this overview is current as of October 2015. However, due to the time-lag between the last date of a search conducted in a systematic review and its publication, there is the potential for more recent RCTs to have been published but not yet included in a systematic review. The authors are aware of a number of such RCTs.^{12 29 37–40} Individual review of these publications was beyond the scope and purpose of the current overview,¹⁴ and we have identified the last search date of included SR for readers' awareness of the currency of findings. We acknowledge that at present the volume of evidence for post-ICU discharge physical rehabilitation is lacking with only one published SR, which in itself is a limitation for this stage of recovery. That said, the aim of this overview was to include SR across the recovery continuum. Identifying that the post-ICU discharge phase requires greater focus of attention in the design and conduct of future trials is particularly important in the context of established critical care research priorities.⁴¹ We are the authors of one of the included SR.¹³ While our clearly defined eligibility criteria ensure transparent and justified inclusion of this review, and quality appraisal and data extraction were performed independently, in duplicate and using objective tools where applicable, it is possible that this introduces potential bias through insufficient independence when examining this review. That said, dual (co) authorship is increasingly typical in the conduct of overviews where expert authors may publish frequently in a particular field, and no standards have been agreed to comprehensively address this issue.⁴² Furthermore, as a Cochrane review, this review was subject to rigorous scrutiny during its conduct, reporting and editorial process, and data extraction pertained only to published data. Finally, due to the small number and variation in included reviews, we were unable to perform the intended subgroup and sensitivity analyses as planned in our original protocol.¹⁶

Recommendations for future research

The process of conducting this overview has informed a number of suggested recommendations for consideration with regard to the design and conduct of future trials of physical rehabilitation interventions, which are outlined in relation to the Evidence, Population, Intervention, Comparison, Outcome, Time stamp framework⁴³ (table 6). With regard future SR in this clinical area, to ensure transparency of conduct we recommend these should be prospectively registered on a relevant database in addition to a priori publication of the full protocol in line with

recognised guidelines.¹⁵ If applicable, outcome data and quality appraisal findings from RCT and non-RCT study designs should be reported separately to enhance clarity of interpretation; RCT data can contribute to meta-analyses and determine true effectiveness of an intervention. We recommend authors provide completed PRISMA¹⁸ and AMSTAR¹⁹ checklists as online supplementary material available for readers to encourage greater robustness in the reporting and methodological appraisal of reviews. In particular, based on the findings of this overview, PRISMA items related to the Introduction, Methods, Discussion and Funding sources, and AMSTAR items related to a priori Design, Eligibility, Conclusions, Methods of meta-analysis, Publication bias and Declaration of conflicts of interest should be more comprehensively addressed. This overview also identified Cochrane reviews as the highest quality. We would advise future authors to adopt Cochrane methodology where possible as a strategy to underpin review conduct and reporting.

CONCLUSION

This overview is the first to synthesise the systematic review evidence for physical rehabilitation interventions for patients with critical illness across the recovery continuum. Our findings confirm evidence of benefit in short-term outcomes from interventions delivered in the early stages of critical illness while in the ICU, but there is currently no evidence to conclude benefit from interventions delivered post-ICU discharge. Quality of evidence from these SR is inconsistent. We have made a number of research recommendations for design and conduct of further interventional trials and SR.

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REFERENCES

- 1 Puthuchery ZA, Rawal J, McPhail M, *et al*. Acute skeletal muscle wasting in critical illness. *JAMA* 2013;310:1591–600.
- 2 Puthuchery ZAP, Phadke RF, Rawal JM, *et al*. Qualitative ultrasound in acute critical illness muscle wasting. *Crit Care Med* 2015;43:1603–11.
- 3 Herridge MS, Tansey CM, Matté A, *et al*. Functional disability 5 years after acute respiratory distress syndrome. *N Engl J Med* 2011;364:1293–304.
- 4 Needham D, Dinglas V, Bienvu OJ, *et al*. One year outcomes in patients with acute lung injury randomised to initial trophic or full enteral feeding: prospective follow-up of EDEN randomised trial. *BMJ* 2013;346:f1532.
- 5 Fan E, Dowdy DW, Colantuoni E, *et al*. Physical complications in acute lung injury survivors: a two-year longitudinal prospective study. *Crit Care Med* 2014;42:849–59.

- 6 Connolly B. Describing and measuring recovery and rehabilitation after critical illness. *Curr Opin Crit Care* 2015;21:445–52.
- 7 NICE. *Rehabilitation after critical illness. NICE Clinical Guideline 83*. London, UK: National Institute for Health and Care Excellence, 2009; <http://www.nice.org.uk/guidance/cg83> (accessed 1 May 2015).
- 8 Hodgson C, Needham D, Haines K, et al. Feasibility and inter-rater reliability of the ICU Mobility Scale. *Heart Lung* 2014;43:19–24.
- 9 Needham DM, Korupolu R, Zanni JM, et al. Early physical medicine and rehabilitation for patients with acute respiratory failure: a quality improvement project. *Arch Phys Med Rehabil* 2010;91:536–42.
- 10 Gruther W, Kainberger F, Fialka-Moser V, et al. Effects of neuromuscular electrical stimulation on muscle layer thickness of knee extensor muscles in intensive care unit patients: a pilot study. *J Rehabil Med* 2010;42:593–7.
- 11 Burtin C, Clerckx B, Robbeets C, et al. Early exercise in critically ill patients enhances short-term functional recovery. *Crit Care Med* 2009;37:2499–505.
- 12 Walsh TS, Salisbury LG, Merriweather JL, et al. Increased hospital-based physical rehabilitation and information provision after intensive care unit discharge: the RECOVER randomized clinical trial. *JAMA Intern Med* 2015;175:901–10.
- 13 Connolly B, Salisbury L, O'Neill B, et al. Exercise rehabilitation for recovery from critical illness following intensive care unit discharge. *Cochrane Database Syst Rev* 2015;(5):CD008632.
- 14 Higgins J, Green SE. *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]*. The Cochrane Collaboration, 2011. <http://www.cochrane-handbook.org>
- 15 Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev* 2015;4:1.
- 16 Connolly B, O'Neill B, Salisbury L, et al. Physical rehabilitation interventions for adult patients with critical illness across the continuum of recovery: an overview of systematic reviews protocol. *Syst Rev* 2015;4:130.
- 17 World Health Organisation: International Classification of Functioning, Disability and Health (ICF). <http://www.who.int/classifications/icf/en/> (accessed 17 12 2014).
- 18 Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ* 2009;339:b2700.
- 19 Shea B, Grimshaw J, Wells G, et al. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. *BMC Med Res Methodol* 2007;7:10.
- 20 Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008;336:924–6.
- 21 Ferreira LL, Vanderlei LC, Valenti VE. Neuromuscular electrical stimulation in critically ill patients in the intensive care unit: a systematic review. *Einstein* 2014;12:361–5.
- 22 Maffioletti NA, Roig M, Karatzanos E, et al. Neuromuscular electrical stimulation for preventing skeletal-muscle weakness and wasting in critically ill patients: a systematic review. *BMC Medicine* 2013;11:137.
- 23 Pinheiro A, Christofolletti G. Motor physical therapy in hospitalized patients in an intensive care unit: a systematic review. *Rev Bras Ter Intensiva* 2012;24:188–96.
- 24 Calvo-Ayala E, Khan BA, Farber MO, et al. Interventions to improve the physical function of ICU survivors: a systematic review. *Chest* 2013;144:1469–80.
- 25 Hermans G, De Jonghe B, Bruyninckx F, et al. Interventions for preventing critical illness polyneuropathy and critical illness myopathy. *Cochrane Database Syst Rev* 2014;1:CD006832.
- 26 Kayambu G, Boots R, Paratz J. Physical therapy for the critically ill in the ICU: a systematic review and meta-analysis. *Crit Care Med* 2013;41:1543–54.
- 27 Wageck B, Nunes GS, Silva FL, et al. Application and effects of neuromuscular electrical stimulation in critically ill patients: systematic review. *Med* 2014;38:444–54.
- 28 Smith V, Devane D, Begley CM, et al. Methodology in conducting a systematic review of systematic reviews of healthcare interventions. *BMC Med Res Methodol* 2011;11:15.
- 29 Moss M, Nordon-Craft A, Malone D, et al. A Randomized trial of an intensive physical therapy program for acute respiratory failure patients. *Am J Respir Crit Care Med* 2015.
- 30 Puthucherry ZA, Denehy L. exercise interventions in critical illness survivors: understanding inclusion and stratification criteria. *Am J Respir Crit Care Med* 2015;191:1464–7.
- 31 Parry SM, Berney S, Granger CL, et al. Electrical muscle stimulation in the intensive care setting: a systematic review. *Crit Care Med* 2013;41:2406–18.
- 32 Li Z, Peng X, Zhu B, et al. Active mobilization for mechanically ventilated patients: a systematic review. *Arch Phys Med Rehabil* 2013;94:551–61.
- 33 Adler J, Malone D. Early mobilization in the intensive care unit: a systematic review. *Cardiopulm Phys Ther J* 2012;23:5–13.
- 34 Cheung A, Weir M, Mayhew A, et al. Overview of systematic reviews of the effectiveness of reminders in improving healthcare professional behavior. *Syst Rev* 2012;1:36.
- 35 Kung J, Chiappelli F, Cajulis OO, et al. From Systematic Reviews to Clinical Recommendations for Evidence-Based Health Care: Validation of Revised Assessment of Multiple Systematic Reviews (R-AMSTAR) for Grading of Clinical Relevance. *Open Dent J* 2010;4:84–91.
- 36 Sharif MO, Janjua-Sharif FN, Ali H, et al. Systematic reviews explained: AMSTAR—how to tell the good from the bad and the ugly. *Oral Health Dent Manag* 2013;12:9–16.
- 37 Connolly B, Thompson A, Douiri A, et al. Exercise-based rehabilitation after hospital discharge for survivors of critical illness with intensive care unit-acquired weakness: a pilot feasibility trial. *J Crit Care* 2015;30:589–98.
- 38 Jones C, Eddleston J, McCairn A, et al. Improving rehabilitation after critical illness through outpatient physiotherapy classes and essential amino acid supplement: a randomized controlled trial. *J Crit Care* 2015;30:901–7.
- 39 Kho ME, Truong AD, Zanni JM, et al. Neuromuscular electrical stimulation in mechanically ventilated patients: A randomized, sham-controlled pilot trial with blinded outcome assessment. *J Crit Care* 2015;30:32–9.
- 40 Kayambu G, Boots R, Paratz J. Early physical rehabilitation in intensive care patients with sepsis syndromes: a pilot randomised controlled trial. *Intensive Care Med* 2015;41:865–74.
- 41 Reay H, Arulkumaran N, Brett SJ. Priorities for future intensive care research in the UK: results of a James Lind alliance priority setting partnership. *J Intensive Care Soc* 2014;15:288–96.
- 42 Buchter RB, Pieper D. How do authors of Cochrane overviews deal with conflicts of interest relating to their own systematic reviews? In: *Filtering the information overload for better decisions. Abstracts of the 23rd Cochrane Colloquium*. Vienna, Austria: John Wiley & Sons, 2015.
- 43 Brown P, Brunnhuber K, Chalkidou K, et al. How to formulate research recommendations. *BMJ* 2006;333:804–6.
- 44 Hoffmann TC, Glasziou PP, Boutron I, et al. Better reporting of interventions: template for intervention description and replication (TIDieR) checklist and guide. *BMJ* 2014;348:g1687.
- 45 Connolly B, Blackwood B, Williamson P, et al. Development of a core outcomes set for trials of rehabilitation following critical illness Core Outcome Measures in Effectiveness Trials Initiative 2013. <http://www.comet-initiative.org/studies/details/288?result=true>
- 46 Developing and evaluating complex interventions: new guidance. Medical Research Council. 2008. <http://www.mrc.ac.uk/complexinterventionsguidance>