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

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ONLINE SUPPLEMENT

E1. Systematic review eligibility

Further detail of systematic review eligibility is presented in Table E1.

Table E1. Systematic review characteristics for overview eligibility

Characteristic	Inclusion	Exclusion
Review design	Systematic reviews of RCTs and/or quasi-RCTs investigating the effect of any physical rehabilitation intervention following critical illness at any stage of the recovery continuum. Where non-RCTs are included, the review will be eligible only if RCT findings are reported separately	Systematic reviews including only non-RCTs
Participants	Adult patients (≥18years) admitted to the ICU with critical illness irrespective of causal diagnosis	Studies of short-stay ICU management e.g. post-operative
Intervention	All types of physical rehabilitation interventions including exercise-based treatments and adjunctive strategies e.g. electrical muscle stimulation or cycling	Studies of composite interventions e.g. combined physical and cognitive rehabilitation
Control/comparator	Standard or usual care, or an alternative physical rehabilitation	Studies involving a comparator of the same intervention delivered at a different intensity level
Outcome measures	*Primary* Any measure reflecting recovery of any aspect physical function, long-term measures of physical function or its surrogates *Secondary* Structure, content and format of rehabilitation interventions; Specific patient populations examined; Reported rates of adverse events or harmful effects; Effect on any other domains of outcomes where examined and reported e.g. health-related quality of	n/a

	life	
Publication	No publication date or language restriction will be applied during the initial search	Non-English language studies will be excluded from further review after the initial search

Abbreviations: RCT = randomised controlled trial

E2. Data sources and search strategies

Electronic databases (n=6) were searched by one reviewer (BC). Databases were accessed via King's College London, United Kingdom and included the Cochrane Systematic Review Database (October 2015), Database of Abstracts of Reviews of Effectiveness (October 2015), Cochrane Central Register of Controlled Trials (CENTRAL, Issue 10, 2015), Ovid SP Medline (1966 to October 2015), Ovid SP Excerpta Medica Database (EMBASE, 1988 to October 2015), and Cumulative Index to Nursing and Allied Health Literature via EBSCO host (CINAHL, 1982 to October 2015). Additional references were identified by cross-checking reference lists of included articles and searching the personal libraries of the authors.

Search strategies for electronic databases are presented below. Searches were not storable in the DARE database however the search involved terms used the summaries below.

Cochrane search strategy (Cochrane)

#1 intensive care unit
#2 intensive care
#3 ICU
#4 critical care unit
#5 critical care
#6 critically ill
#7 critical illness
#8 mechanical ventilation
#9 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8
#10 exercise
#11 exercise rehabilitation
#12 physical rehabilitation
#13 physical therapy
#14 physiotherapy
#15 early mobilisation
#16 physical ftiness

#17 muscle strength

#18 cycling

#19 cycle ergometry

#20 electrical muscle stimulation

#21 neuromuscular stimulation

#22 NMES

#23 #10 0R #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22

#24 randomized controlled trial.pt

#25 controlled clinical trial.pt

#26 randomized.ab

#27 randomly.ab

#28 placebo.ab

#29 trial.ab

#30 groups.ab

#31 #24 or #25 or #26 or #27 or #28 or #29 or #30

#32 systematic review.pt

#33 meta-analysis.pt

#34 #32 or #33

#35 #9 and #23 and #31 Online Publication Date from Oct 2014 to Mar 2015

#36 #9 and #23 and #34 Online Publication Date from Oct 2014 to Mar 2015

MEDLINE search strategy (Ovid SP)

1. ((intensive or critical) adj1 care unit).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
2. ((intensive or critical) adj1 care).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
3. exp Intensive Care Units/ or exp Intensive Care/ or ICU.mp. or exp Critical Care/
4. critical illness.mp. or exp Critical Illness/
5. mechanical ventilation.mp. or exp Respiration, Artificial/
6. 1 or 2 or 3 or 4 or 5
7. exp Exercise Therapy/ or exercise.mp. or exp Exercise/
8. ((exercise or physical) adj2 rehabilitation).mp. [mp=title, abstract, original title, name of substance

word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

9. physiotherapy.mp.
10. physical therapy.mp.
11. exp Early Ambulation/ or early mobilisation.mp.
12. early mobilization.mp.
13. physical fitness.mp. or exp Physical Fitness/
14. muscle strength.mp. or exp Muscle Strength/
15. cycling.mp.
16. cycle ergometry.mp.
17. exp Electric Stimulation Therapy/ or electrical muscle stimulation.mp.
18. neuromuscular stimulation.mp.
19. NMES.mp.
20. 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19
21. randomized controlled trial.pt.
22. controlled clinical trial.pt.
23. randomized.ab.
24. placebo.ab.
25. randomly.ab.
26. trial.ab.
27. groups.ab.
28. 21 or 22 or 23 or 24 or 25 or 26 or 27
29. exp animals/ not humans.sh.
30. 28 not 29
31. Meta-Analysis as Topic/
32. meta analy$.tw.
33. metaanaly$.tw.
34. Meta-Analysis/
35. (systematic adj (review$1 or overview$1)).tw.
36. exp Review Literature as Topic/
37. or/31-36
38. cochrane.ab.
39. embase.ab.
40. (cinahl or cinhal).ab.

41. science citation index.ab.
42. or/38-41
43. reference list$.ab.
44. bibliograph$.ab.
45. hand-search$.ab.
46. relevant journals.ab.
47. manual search$.ab.
48. or/43-47
49. selection criteria.ab.
50. data extraction.ab.
51. 49 or 50
52. Review/
53. 51 and 52
54. Comment/
55. Letter/
56. Editorial/
57. animal/
58. human/
59. 57 not (57 and 58)
60. or/54-56,59
61. 37 or 42 or 48 or 53
62. 61 not 60
63. 6 and 20 and 30
64. 6 and 20 and 62

CINAHL search strategy (EbscoHost)

S52 S10 AND S28 AND S38
S51 S10 AND S28 AND S38
S50 S10 AND S28 AND S49
S49 S43 not S48
S48 Or/S44-S47
S47 Animals/
S46 PT Editorial
S45 PT Letter

S44 PT Commentary

S43 S40 OR S41 OR S42

S42 systematic review/

S41 Literature review/

S40 Meta analysis/

S39 S38 not AB animal*

S38 S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37

S37 ("Clinical trials") OR ("Randomized controlled trials") OR ("Clinical trial registry") OR ("multicentre studies") OR ("Cochrane library")

S36 "("Clinical trials") OR ("Randomized controlled trials") OR ("Clinical trial registry") OR ("multicentre studies") OR ("Cochrane library")"

S35 AB groups

S34 AB trial

S33 AB randomly

S32 AB placebo

S31 AB randomized

S30 TX controlled clinical trial

S29 TX randomized controlled trial

S28 S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27

S27 (MH "exercise") OR (MH "exercise rehabilitation") OR (MH "physical rehabilitation") OR (MH "physical therapy") OR (MH "physiotherapy") OR (MH "mobilisation") OR (MH "early mobilisation") OR (MH "mobilization") OR (MH "early mobilization") OR (MH "physical fitness") OR (MH "muscle strength") OR (MH "cycling") OR (MH "cycle ergometry") OR (MH "electrical muscle stimulation") OR (MH "neuromuscular stimulation") OR (MH "NMES")

S26 TX NMES

S25 TX neuromuscular stimulation

S24 TX electrical muscle stimulation

S23 TX cycle ergometry

S22 TX cycling

S21 TX muscle strength

S20 TX physical fitness

S19 TX early mobilization

S18 TX mobilization

S17 TX early mobilization

S16 TX mobilization

S15 TX physiotherapy

S14 TX physical therapy

S13 TX physical rehabilitation

S12 TX exercise rehabilitation

S11 TX exercise

S10 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9

S9 (MH "intensive care unit") OR (MH "intensive care") OR (MH "ICU") OR (MH "critical care unit") OR (MH "critical care") OR (MH "critically ill") OR (MH "critical illness") OR (MH "mechanical ventilation")

S8 TX mechanical ventilation

S7 TX critical illness

S6 TX critically ill

S5 TX critical care

S4 TX critical care unit

S3 TX ICU

S2 TX intensive care

S1 TX intensive care unit

EMBASE search strategy (Ovid SP)

1. ((intensive or critical) adj1 care unit).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
2. ((intensive or critical) adj1 care).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
3. exp intensive care/ or exp intensive care unit/ or ICU.mp.
4. critical illness.mp. or exp critical illness/
5. mechanical ventilation.mp. or exp artificial ventilation/
6. 1 or 2 or 3 or 4 or 5
7. exp exercise/ or exercise.mp.
8. ((exercise or physical) adj2 rehabilitation).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
9. physiotherapy.mp. or exp physiotherapy/
10. physical therapy.mp.

11. exp mobilization/ or early mobilisation.mp.
12. early mobilization.mp.
13. physical fitness.mp. or exp fitness/
14. muscle strength.mp. or exp muscle strength/
15. cycling.mp. or exp cycling/
16. cycle ergometry.mp.
17. electrical muscle stimulation.mp.
18. exp neuromuscular electrical stimulation/ or neuromuscular stimulation.mp.
19. NMES.mp.
20. 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19
21. randomized controlled trial/
22. controlled clinical trial/
23. randomized.ab.
24. placebo.ab.
25. randomly.ab.
26. trial.ab.
27. groups.ab.
28. 21 or 22 or 23 or 24 or 25 or 26 or 27
29. animals/
30. humans/
31. 29 not (29 and 30)
32. 28 not 31
33. exp Meta Analysis/
34. ((meta adj analy$) or metaanalys$).tw.
35. (systematic adj (review$1 or overview$1)).tw.
36. or/33-35
37. cochrane.ab.
38. embase.ab.
39. (cinahl or cinhal).ab.
40. science citation index.ab.
41. or/37-40
42. reference lists.ab.
43. bibliograph$.ab.
44. hand-search$.ab.

45. manual search$.ab.
46. relevant journals.ab.
47. or/42-46
48. data extraction.ab.
49. selection criteria.ab.
50. 48 or 49
51. review.pt.
52. 50 and 51
53. letter.pt.
54. editorial.pt.
55. animal/
56. human/
57. 55 not (55 and 56)
58. or/53-54,57
59. 36 or 41 or 47 or 52
60. 59 not 58
61. 6 and 20 and 32
62. 6 and 20 and 60

E3. Assessment of systematic review eligibility

A bespoke assessment form of systematic review eligibility for inclusion into the overview was used for documentation of full-text screening and summarised in Table E2.

E4. Data extraction of included systematic reviews

A bespoke data extraction form was developed for independent detailed data extraction from included systematic reviews and summarised in Table E3.

Table E2. Systematic review eligibility form

First author Year	Systematic review design (Yes / No / Unclear)	Location of patients included in review (ICU/HDU/ward/ post discharge) (Yes / No / Unclear and state which)	Relevant physical interventions (Yes / No / Unclear)	RCTs/Quasi RCTs only or with a distinct report of synthesis of findings and quality (Yes / No / Unclear)	Comparator placebo/usual care/alternative (i.e. not different dose) (Yes / No / Unclear)	Additional comments	Include (Yes / No / Unclear)

Table E3. Data extraction form

Review ID number Title of SR Author (year)	Focus/Stage of rehab delivery Category of Interventions that the SR included Population included and number	Number of included studies Search dates including date assessed as up to date List references included	Quality tool used; is yes indicate which Meta analysis included (y/N)	Population Intervention Comparator Outcomes Adverse events	Main/key results (list for each outcome; intervention and comparator groups; numbers of participants in each group; effect size (95%CI); risk	Review authors' conclusions

E5. Assessment of methodological quality of included systematic reviews

Two review authors (BC and BB) independently assessed the quality of reporting and the methodological quality of included systematic reviews using the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) checklist[1] and the Assessment of Multiple Systematic Reviews (AMSTAR) tool[2] (Tables E4 and E5 respectively).

Table E4. The PRISMA checklist for systematic review and meta-analysis reporting

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	

Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	

Taken from Liberati *et al* [1].

Table E5. The AMSTAR tool

	YES	NO	?	N/A
1. Was an 'a priori' design provided? The research question and inclusion criteria should be established before the conduct of the review.				
2. Was there duplicate study selection and data extraction? Should be at least two independent data extractors and a consensus procedure				
3. Was a comprehensive literature search performed? At least two electronic sources; must include years and databases used. Key words and/or MESH terms; search strategy should be provided. Supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts & references				
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion? State whether or not they excluded any reports (from the systematic review), based on their publication status, language etc.				
5. Was a list of studies (included and excluded) provided?				
6. Were the characteristics of the included studies provided? Table, data from the original studies on the participants, interventions and outcomes. Characteristics analyzed e.g. age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases.				
7. Was the scientific quality of the included studies assessed and documented? 'A priori' methods of assessment				
8. Was the scientific quality of the included studies used appropriately in formulating conclusions? The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and stated in formulating recommendations				
9. Were the methods used to combine the findings of studies appropriate? For pooled results, assess their homogeneity (i.e. Chi squared test for homogeneity, I2). If heterogeneity exists a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration				
10. Was the likelihood of publication bias assessed? (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test).				
11. Was the conflict of interest stated? Potential sources of support should be clearly acknowledged in both the systematic review and the included studies.				

Taken from Shea *et al* [2]

E6. Excluded systematic reviews

Twenty-two systematic reviews were excluded following full text assessment for eligibility (n=14, both RCT and non-RCT study designs included, but a synthesis of the findings and quality of the RCTs was not reported separately[3-16]; n=4, design of non-systematic review methodology[17-20]; n=1, non-eligible patient population[21]; n=1, no eligible studies were included and therefore no data were reported[22]; n=1 full-text not available in English[23]; n=1 where the review was superceded by a later version[24]). All but one of these SR pertained to the 'during ICU' phase of the recovery pathway, with one examining rehabilitation interventions post ICU discharge [7].

The 14 SR excluded for not reporting RCT and non-RCT study designs separately [3-16], were further examined to determine potential RCTs missing from the overview synthesis as a result of these exclusions. Table E7 presents the individual studies for each of these SR. Twenty-four RCTs were evaluated across these SR, of which 15 (62.5%) overlapped with the current overview (Table E7, highlighted in red). In total, data from 9 RCTs were not encompassed by SR in the current overview, of which 3 would have been ineligible (respiratory therapy rehabilitation intervention [25], other non-physical rehabilitation intervention examined – ICU follow-up clinic [26] and intensive care diary [27]). To establish whether these non-overlapping RCTs may have influenced the findings from the overview, we reviewed the abstracts for their conclusions (Table E8); the findings from these RCTs were in keeping with those from the main overview.

Table E8. Main findings from RCT that did not overlap between included and excluded SR

RCT	Main finding
Brummel et al [28]	Pilot feasibility study of early physical and cognitive therapy. Cognitive therapy was feasible to deliver as part of early rehabilitation (during ICU admission). Cognitive, functional and health-related quality of life outcomes did not differ between groups at 3m follow-up.
Chang et al [29]	Standing for 5mins with the assistance of a tilt table significantly increased ventilation in critical care patients during and immediately after the intervention
Chen et al [30]	Six weeks physical therapy training plus 6 weeks unsupervised maintenance exercise enhanced functional levels and increased survival for patients with prolonged mechanical ventilation compared with those with no such intervention
Chen et al [31]	Subjects with prolonged mechanical ventilation demonstrated significant improvement in pulmonary mechanics and functional status after exercise training
Denehy et al [32]	No difference in exercise capacity as 12months post ICU discharge from an exercise programme delivered during the ICU, post ICU and post hospital discharge.
Meesen et al [33]	Electrical muscle stimulation delivered during ICU admission significantly attenuated muscle atrophy measured indirectly via circumferential measurements

Table E7. Individual RCTs from excluded systematic reviews

SR → / RCT ↓	Adler *et al* [3]	Casey *et al* [4]	Hellweg *et al* [21]	Li *et al* [6]	Mehlhorn *et al* [7]	Parry *et al* [8]	Thomas *et al* [9]	Williams *et al* [10]	Ydemann *et al* [11]	Choi *et al* [12]	Clini *et al* [13]	Truong *et al* [14] #	Da Silva *et al* [23]	Castro-Avila *et al* [16]
Bouletreau *et al* [34] #						*								
Brummel *et al* [28]														*
Burtin *et al* [35]	*	*		*					*				*	*
Caruso *et al* [25]										*				
Chang *et al* [29]				*										
Chen *et al* [30]				*										
Chen *et al* [31]				*										
Chiang *et al* [36]		*		*			*		*	*			*	
Cuthbertson *et al* [26]					*									
Denehy *et al* [32]														*
Elliott *et al* [37]					*									
Gerovasili *et al* [38]						*		*						
Gruther *et al* [39]						*		*						
Jones *et al* [27]					*									
Karatzanos *et al* [40]						*								
Meesen *et al* [33]						*								
Nava *et al* [41]		*		*			*		*	*	*		*	*
Porta *et al* [42]				*					*	*			*	
Poulsen *et al* [43]						*								
Rodriguez *et al* [44]						*								
Routsi *et al* [45] #						*			*					*
Salisbury *et al* [46]					*									
Schweickert *et al* [47]	*	*	*	*					*					*
Zanotti *et al* [48]		*					*		x	*	x		*	

[#]No RCTs reported in Truong et al. [#]Indicates parallel paper to accompany Schweickert et al [47] with detailed description of intervention

E7. Individual trials reported in included systematic reviews

A total of 24 relevant individual RCTs were included across all included systematic reviews, ranging between 2[49] and 10[50] overall. Table E9 presents the individual studies for each systematic review. Six RCTs[35 37 42 46 51 52] overlapped across two SR, and two further separate RCTs[45 47] overlapped across three included SR.

Table E9. Individual studies reported in included systematic reviews

Individual study	# SR reported in	Systematic review				
		Kayambu *et al* [50]	Hermans *et al*[49]	Calvo-Ayala *et al*[53]	Connolly *et al*[54]	Wageck *et al*[55]
Batterham *et al* [56]	1				*	
Bouletreau *et al* [57 a]	1					*
Bouletreau *et al* [34 a]	1					*
Burtin *et al* [35]	2	*		*		
Chiang *et al* [36]	1	*				
Delaney *et al* [58]	1	*				
Denehy *et al* [32]	1			*		
Elliot *et al* [37]	2			*	*	
Gerovasili *et al* [38]	1					*
Gruther *et al* [39]	1					*
Jackson *et al* [51]	2			*	*	
Jones *et al* [52]	2			*	*	
Karatzanos *et al* [40]	1					*
Muehling *et al* [59]	1	*				
Muehling *et al* [60]	1	*				
Nava *et al* [41]	1	*				
Porta *et al* [42]	2	*			*	
Poulsen *et al* [43]	1					*
Rodriguez *et al* [44]	1					*
Routsi *et al* [45]	3	*	*			*
Salisbury *et al* [46]	2			*	*	
Schweickert *et al* [47]	3	*	*	*		
Velmahos *et al* [61]	1					*
Zanotti *et al* [48]	1	*				
TOTAL	-	10	2	7	6	9

[a]Datasets from the same original study therefore characteristic data only reported once in main text

E8. Detail of populations reported in included systematic reviews

Summary details of individual SR population characteristics are reported in Table E10.

Table E10. Description of populations of included systematic reviews

Author	Population: Description/Diagnosis Gender Age
Kayambu *et al* (2013)[50]	Critically ill patients with a range of causes of admission to ICU. Measurement and scores of illness severity varied across studies (n=3 reported APACHE II ranging 18-26; n=3 reported ASA III ranging 7-34) Overall % M:F – Control 69:31 vs. Exercise 73:27 Overall mean age – Control 59.3 years vs. Exercise 63.6 years
Hermans *et al* (2014)[49]	Pre-morbid independent living status; expected to be ventilated for at least one day. Gender % (M) Intervention 41; Control 58. Median age Intervention 58; Control 54 EMS – only 24 EMS and 28 control participants evaluated. Significant baseline differences between the evaluable group in APACHE II, diagnostic category at admission and presence of co-morbid renal disease.
Wageck *et al* (2014)[55]	Gender % (M) Intervention 68; Control 68 Average age Intervention 61± 19; Control 58 ± 18 No overall summary of participant details. These are reported in the individual study characteristics. Heterogeneity across studies. No overall summary of gender or age. These are reported in the individual study characteristics.
Calvo-Ayala *et al* (2013)[53]	Broad distribution of adult ICU patients evidenced by the variations in the mean APACHE (Acute Physiology and Chronic Health Evaluation) II score (range, 9-28) No summary report for gender. Mean age of studies' subjects (48-66 years).
Connolly *et al* (2015)[54]	Baseline characteristics between the control and intervention groups in included studies were similar. Jackson 2012 and Salisbury 2010 reported some differences. No overall summary of participant details, gender or age.

Abbreviations: APACHE = Acute Physiology and Chronic Health Evaluation. ASA = American Society of Anesthesiologists. EMS = electrical muscle stimulation

E9. Interventions evaluated in included systematic reviews

Systematic reviews included individual RCTs evaluating a range of interventions. Further description of the intervention is reported in Table E11.

Table E11. Description of physical rehabilitation interventions reported in included systematic reviews

Author	SR physical rehabilitation criteria	Interventions reported in review studies
Kayambu *et al* (2013)[50]	Physical therapy defined as - Positioning; Stretching; EMS; ROM exercise; Resistive exercises; Ergometry; Walking; Splinting; Mobilization activities; Aerobic training	EMS Early mobilisation with functional activities Limb strengthening Respiratory techniques Ergometry
Hermans *et al* (2014)[49] [a]	Physiotherapy, EMS and rehabilitation programmes	Early physical therapy EMS
Wageck *et al* (2014)[55]	NMES	-
Calvo-Ayala *et al* (2013)[53] [b]	Exercise/physical therapy	Cycle ergometry Intensive rehabilitation protocol Early mobilisation Aerobic training Strength training
Connolly *et al* (2015)[54] [c]	Exercise rehabilitation or training, including any structured or taught programmes with the aim of improving functional ability and quality of life. Interventions focusing solely on respiratory or inspiratory muscle training were excluded	Aerobic training Strength training Cycle ergometry

Abbreviations: EMS = electrical muscle stimulation. ROM = range of motion. LOS = length of stay. CIP = critical illness polyneuropathy. CIM = critical illness myopathy.

Comments: [a]Aim of review to evaluate effectiveness of any form of intervention reported to reduce risk of CIP/CIM. Review also included non-physical rehabilitation interventions e.g. nutritional interventions, antioxidant therapy, hormone therapy, intravenous immunoglobulin. [b]Aim of review to identify therapies effective in improving long-term physical function. Review also included non-physical rehabilitation interventions e.g. nutrition therapy, insulin therapy, nurse-led follow-up, spontaneous awakening and breathing trials, sedation holds, early tracheostomy. [c]Some interventions included other components including patient manuals, or cognitive therapy

E10. Assessment of methodological quality of included systematic reviews

All included systematic reviews underwent assessment using the PRISMA checklist[1] and AMSTAR tool[62]. Further details on the breakdown of PRISMA and AMSTAR scores are reported in Tables E12 and E13.

Table E12. Breakdown of PRISMA scores for individual systematic reviews

Author	Y	N	Partial	Not Applicable	Total
Kayambu *et al*[50]	14	5	6	2	17
Hermans *et al*[49]	25	1	0	1	25
Wageck *et al*[55]	15	5	4	3	17
Calvo-Ayala *et al*[53]	14	5	4	4	16
Connolly *et al*[54]	25	0	0	2	25

Table E13. Breakdown of AMSTAR scores for individual systematic reviews

Author	Y	N	Partial	Not Applicable	Total
Kayambu *et al*[50]	6	5	0	0	6
Hermans *et al*[49]	10	1	0	0	10
Wageck *et al*[55]	6	4	1	0	6.5
Calvo-Ayala *et al*[53]	7	3	0	1	7
Connolly *et al*[54]	8	1	0	2	8

E11. Main findings and conclusions from included systematic reviews

The main findings and conclusions from included systematic reviews are reported in Table E14.

Table E14. Main findings and conclusions from included systematic reviews

Author (year)	Outcome	Finding	Author conclusion
**Kayambu *et al* (2013) [50] SR included meta-analysis	Peripheral muscle strength	MRC score: Small positive effect ([d] pooled Hedges g =0.27, 95%CI 0.02, 0.52, n=2 studies, n=244 patients) Handgrip strength: No significant effect	ICU physical therapy reduces ICU and hospital LOS, increases VFD, improves muscle strength, physical function and HRQL. No mortality benefit.
	Respiratory muscle strength	Moderate positive effect (g = 0.51, 95%CI 0.12, 0.89, 2 studies, n=105 patients)	
	Physical Function	Small positive effect (g=0.46, 95%CI 0.13, 0.78, n=2 studies, n=143 patients)	
	VFD	Small positive effect (g=0.38, 95%CI 0.16, 0.59, n=3 studies, n=334 patients)	
	HRQL	Small positive effect (g=0.40, 95%CI 0.08, 0.71, n=2 studies, n=154 patients)	
	ICU LOS	Small positive effect (g=–0.34, 95%CI –0.51, –0.18, n=6 studies, n=597 patients)	
	Hospital LOS	Small positive effect (g=–0.34, 95%CI –0.53, –0.15, n=5 studies, n=441 patients)	
	Mortality	No significant effect	
	AE	Not reported	
***Hermans *et al* (2014) [49 a] SR included meta-analysis[a]	Incidence of CIP/CIM	Significant difference with early physical therapy at ICU discharge (RR 0.62, 95%CI 0.39, 0.96, n=1 study, n=82 evaluable patients out of 104 recruited)	Moderate quality evidence suggests potential benefit of early rehabilitation on CIP/CIM accompanied by reduced MV. Very low quality evidence suggests no effect of EMS.
		No effect with early physical therapy at hospital discharge	
		No effect with EMS	
	Duration MV	Significant reduction (3.4 (2.3-7.3) vs. 6.1 (4.0-9.6)days, no p value reported) with early physical therapy	
		No effect with EMS	
	ICU LOS	No effect with early physical therapy or EMS	
	Mortality	Not reported for 30d or 180d and no effect on hospital mortality with early	

		physical therapy No effect on ICU, and not reported for 30d or 180d mortality with EMS	
	AE	No significant severe AE with early physical therapy, and not evaluated with EMS	
**Wageck *et al* (2014) [55] SR included meta-analysis[b]	Muscle strength	MRC score: Positive effect (SMD 0.77, 95%CI 0.13, 1.40, p=0.02, n=3 studies, n=66 patients)	NMES has good results when used to maintain muscle mass and muscle strength of critically ill patients in ICU
	Muscle structure	Reduced muscle degradation (waste product elimination, p<0.01, n=2 studies) No effect (n=3 studies)	
	ICU LOS	No effect	
	Duration MV	No effect	
	Complications	No effect on prevention of DVT occurrence	
	AE	No other AE were reported	
**Calvo-Ayala *et al* (2013) [53 c] SR did not include meta-analysis	Long-term physical function	Significant effect with exercise/physical therapy (varied individual results, n=5 studies) No effect (n=2 studies)	Only effective intervention in improving long-term PF is early exercise/physical therapy
	AE	Not reported	
***Connolly *et al* (2015) [54] SR did not include meta-analysis	Functional exercise capacity	Significant effect with exercise-based rehabilitation (varied protocols and outcome measures, n=3 studies) No effect (n=3 studies)	Unable to show an overall effect of exercise based interventions on functional exercise capacity or HRQOL for an exercise based intervention initiated after ICU discharge
	HRQL	No effect	
	Mortality	Mortality reported across studies (n=6) but not formally analysed	
	AE	Minimal AE reported	

Notes: *** denotes high quality AMSTAR rating. ** denotes medium quality AMSTAR rating. [a] Data reported from studies included relating to physical rehabilitation interventions; data for other interventions were meta-analysed. [b]Meta-analysis conducted for only one outcome of interest. [c]Data for exercise/physical interventions only. [d] Pooled Hedges g is a quantitative method to establishing the strength of an effect size

Abbreviations: SR = systematic review. MRC = Medical Research Council. VFD = ventilator free days. HRQL = health-related quality of life. ICU = intensive care unit. LOS = length of stay. AE = adverse events. CIP/CIM = critical illness polyneuropathy/myopathy. MV = mechanical ventilation. EMS = electrical muscle stimulation. NMES = neuromuscular electrical stimulation.

E12. Application of GRADE assessment to summarise the evidence from included systematic reviews

During the GRADE process, four items were considered (risk of bias, inconsistency, indirectness and imprecision). The Cochrane Underlying Methodology was then applied with the following criteria: High quality (randomised controlled trials; or double-upgraded observational studies); Moderate quality (downgraded randomised controlled trials; or upgraded observational studies); Low quality (double-downgraded randomised controlled trials; or observational studies); Very Low quality (triple-downgraded randomised controlled trials; or downgraded observational studies; or case series/care reports)[63].

Tables E15a and E15b present the GRADE data extraction tables for physical therapy and NMES interventions respectively delivered within the ICU.

Table E15a. Comparison: Physical Therapy / Rehabilitation; Setting: Within ICU

Outcome	Review author; N studies: N patients	Risk of bias	Inconsistency	Indirectness	Imprecision	Pooled effect (95%CI)	P
IMPAIRMENT							
Peripheral muscle strength	Kayambu *et al*[50] 2 244	Serious[1]	Not serious	Not serious	Serious[2]	Hedge's g=0.27 (0.02, 0.52)	0.03
Respiratory muscle strength	Kayambu *et al*[50] 2 105	Serious[3]	Not serious	Not serious	Serious[4]	Hedge's g=0.51 (0.12, 0.89)	0.01
CIP/CIM	Hermans *et al*[49] 1 104	Not serious	N/A	N/A	Not serious	RR 0.62 (0.39, 0.96)~	0.03
ACTIVITY LIMITATION							
Physical function[#]	Kayambu *et al*[50] and Calvo-Ayala *et al* [53] 9 821	Serious[5]	Not serious	Not serious	Serious[6]	Hedge's g=0.46 (0.13, 0.78)	0.01
PARTICIPATION RESTRICTION							
Quality of Life	Kayambu *et al*[50] 2 154	Not serious	Not serious	Not serious	Not serious	Hedge's g=0.40 (0.08, 0.71)	0.01
HEALTHCARE UTILISATION							
VFD	Kayambu *et al*[50] 3 334	Not serious	Not serious	Not serious	Serious[8]	Hedge's g=0.38 (0.16, 0.59)	<0.001
ICU LOS	Kayambu *et al*[50] 6 597	Not serious	Not serious	Not serious	Not serious	Hedge's g=-0.34 (–0.51, –0.18)	<0.001
Hospital LOS	Kayambu *et al*[50]	Not serious	Not serious	Not serious	Not serious	Hedge's g=–0.34	<0.001

	Hermans *et al*[49]* 5 441					(–0.53, –0.15)	
Hospital mortality	Kayambu *et al*[50] Hermans *et al*[49]* 3 274	Not serious	Not serious	Not serious	Not serious	OR 1.0. (0.54, 1.85)	1.0
Duration of MV	Hermans *et al*[49] 1 Not reported	Not serious	Not serious	Not serious	Not serious	Median (IQR) 3.4 days (2.3 to 7.3) versus 6.1 days (4.0 to 9.6)	Not reported

Notes:. # GRADE assessment based only on data from Kayambu et al[50] as no pooled data reported in Calvo-Ayala et al[53]. * Outcome from same RCT reported in both reviews. ~ data derived from 82 evaluable patients out of 104 recruited.

1 50% no random allocation; 50% no concealed allocation; 50% no blinded assessors; 50% not reported measures of key outcomes >85% patients
2 Measured at different endpoints
3 50% no concealed allocation; 50% no blinded assessors; 50% not reported measures of key outcomes >85% patients; 100% no ITT
4 Unclear endpoints in 1 study
5 50% no allocation concealment; 50% not reported measures of key outcomes >85% patients; 50% no ITT
6 Measured at different endpoints
7 Risk of bias scores not reported in detail
8 Measured at different endpoints

Abbreviations: WHO = World Health Organisation. CIP/CIM = critical illness polyneuropathy/myopathy. VFD = ventilator-free days. ICU = intensive care unit. LOS = length of stay. MV = mechanical ventilation

Table E15b. Comparison: NMES; Setting: Within ICU

Outcome	Review/s; N studies: N patients	Risk of bias	Inconsistency	Indirectness	Imprecision	Pooled effect (95%CI)	P
IMPAIRMENT							
Muscle strength	Wagek *et al*[55] 3 66	Serious[1]	Serious[2]	Not serious	Serious[2]	SMD 0.77, (0.13, 1.40)	0.02
Muscle structure	Wagek *et al*[55] 6	Not serious	Serious[3]	Serious[4]	Not possible	Not possible to pool	N/A
CIP/CIM	Hermans *et al*[49] 1 52	Serious[5]	N/A	Serious[6]	Not serious	RR 0.32 (0.10, 1.01)	0.05
HEALTHCARE UTILISATION							
ICU LOS	Wagek *et al*[55] 1 Not reported	Serious[7]	N/A	N/A	N/A	Not reported	NS
Duration of MV	Wagek *et al*[55] 1 Not reported	Serious[7]	N/A	N/A	N/A	Not reported	NS

1 Review reported 50% no concealed allocation; 50% no blinded assessors; 50% not reported measures of key outcomes >85% patients; 50% no ITT

2 Mean difference in 1 study does not fall within the 95% CI of the other

3 3 studies reported an effect and 3 did not

4 Different outcome measures used at different time points

5 High ROB reported by review for this study vis-s-vis randomisation, concealment, incomplete outcome data & selective reporting

6 Not all participants were evaluable

7 Review reported no concealed allocation; no blinded assessors; not reported measures of key outcomes >85% patients

Abbreviations: CIP/CIM = critical illness polyneuropathy/myopathy. ICU = intensive care unit. LOS = length of stay. MV = mechanical ventilation

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