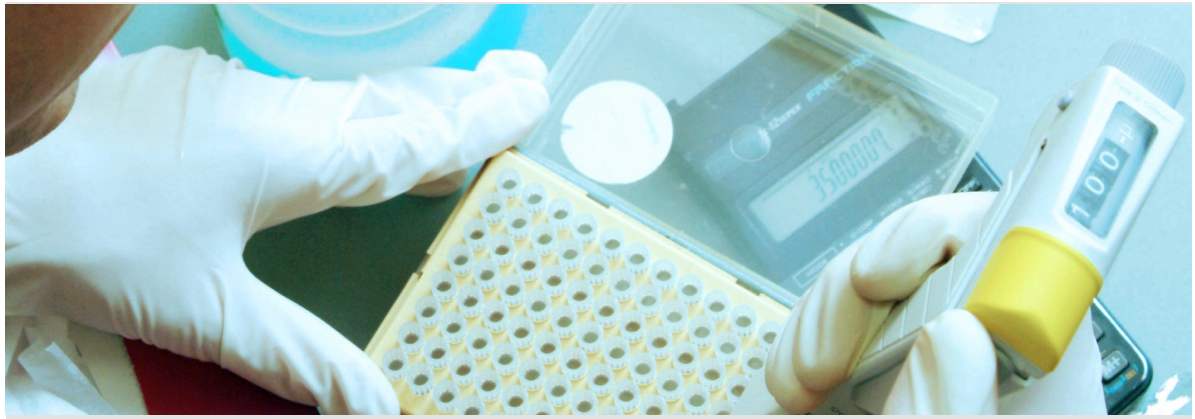
Systematic early rehabilitation in adult, mechanically ventilated intensive care patients



Assessment Report

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Contributions

Coordination: MS, MP; **Conceptualization and methodological approach**: DM, MP, MS, YT, and HY; **Systematic review:** DM, BS, and HY developed the literature search, screened the results, were responsible for data extraction, and graded the risk of bias and the quality of evidence; DM, MP, and HY conducted data analysis and are responsible for data interpretation and wrote this systematic review; **Health economic analyses:** YT conducted the systematic literature search; DM and YT screened the identified literature; YT was responsible for the data extraction, the de novo cost analysis and the budget impact analysis; MS and YT are responsible for data interpretation and wrote the health economic section; **Final report:** DM, MP, MS, YT, and HY agreed upon the content of the final report.

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Contents

Abbreviations

ADL	Activities of Daily Living
AHRQ	Agency for Healthcare Research and Quality
AMSTAR	Assessing the Methodological Quality of Systematic Reviews
APACHE	Acute Physiology, Age, Chronic Health Evaluation
BIA	Budget Impact Analysis
CBA	Cost-Benefit Analysis
CENTRAL	Cochrane Central Register of Controlled Trials
CHEERS	Consolidated Health Economic Evaluation Reporting Standards
CHF	Swiss Franc
CI	Confidence Interval
CHOP	Swiss classification of surgeries
CRD	Centre for Review and Dissemination
COPD	Chronic Obstructive Pulmonary Disease
CUA	Cost-Utility Analysis
DARE	Database of Abstracts of Reviews of Effects
DRG	Diagnosis Related Group
EPICC	Extra Physiotherapy in Critical Care
e.g.	exempli gratia (lat., = for example)
et al.	et alii (lat., = and others)
FIM	Functional Independence Measure (mmFIM=mini-modified FIM)
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
GDP	Gross Domestic Product
HADS	Hospital Anxiety and Depression Score
HIV	Human Immunodeficiency Virus
HTA	Health Technology Assessment
ICD	International Classification of Diseases
ICER	Incremental Cost Effectiveness Ratio
ICU	Intensive Care Unit
ICUAW	ICU-Acquired Weakness
i.e.	id est (lat., = that is)
IQR	Interquartile Range
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
KVG	Swiss health insurance law (“Krankenversicherungsgesetz”)
LOS	Length of Stay
MCS	(SF-36) Mental Health Component Summary Score
MD	Mean Difference
MDC	Major Diagnostic Category
MDSi	Minimum Data Set
MHS	(SF-36) Mental Health Domain Score
MMSE	Mini-Mental State Exam
MRC	Medical Research Council
MRC-SS	MRC Muscle Scale Summary Score
NHS EED	National Health Service Economic Evaluation Database
NMES	Neuro-Muscular Electrical Stimulation
n.r.	not reported
NT$	New Taiwan Dollars

PCS	(SF-36) Physical Health Component Summary Score
PFIT	Physical Function in the ICU test
PFS	(SF-36) Physical Function Domain Score
PICO	Population, Intervention, Comparator, Outcome
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO	International prospective register of systematic reviews
QALY	Quality-Adjusted Life Year
RCT	Randomized Controlled Trial
RR	Risk Ratio
SD	Standard Deviation
SFOPH	Swiss Federal Office of Public Health
SF-36	Short-Form-36 Questionnaire
SHS	Swiss Hospital Statistics
SFSO	Swiss Federal Statistical Office
SIGN	Scottish Intercollegiate Guidelines Network
SwissDRG	Swiss Diagnosis Related Group
TUG	Timed Up-and-Go test
UK	United Kingdom
USA	United States of America
USD	United States Dollars
VAS	Visual Analog Scale
vs.	versus
6MWT	6-Minute Walking Test

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1 Executive summary

1.1 Summary

Background

Intensive care unit (ICU) stays of more than one week are associated with significant functional impairment, increased morbidity and decreased quality of life both in the short and longer term. Patients often take months to recover and to regain full functionality in their daily and professional life. Early rehabilitation may reduce the incidence of ICU-acquired weakness and improve various patient-important outcomes. It is thus current practice in many Swiss hospitals to initiate certain rehabilitative measures during the ICU stay. However, the underlying evidence on the effectiveness of early rehabilitation is uncertain and findings from recent systematic reviews differ. It thus remains unclear how "early" should be defined in this context and whether more systematic early rehabilitation approaches (i.e., indiscriminately in all eligible patients) provide additional benefits compared to less systematic or later rehabilitation approaches. While early rehabilitation might benefit all ICU patients, it might also be associated with higher complication rates and overall costs if the rehabilitation approach is inadequate for the specific patient population.

Aim

This Health Technology Assessment (HTA) aimed to determine the effectiveness, safety, and costs of "systematic early" rehabilitation (i.e., rehabilitation initiated within 7 days after ICU admission systematically in all patients without contraindication) compared with one of the following strategies: “late” rehabilitation (i.e., initiated 7 days or more after ICU admission), “less systematic early" rehabilitation (i.e., initiated within 7 days after ICU admission but later in time and/or not in all patients without contraindications), or “no rehabilitation" (i.e., sham intervention or no intervention) in adult, mechanically ventilated ICU patients in Switzerland.

Clinical effectiveness

We conducted a systematic literature review to determine the clinical effectiveness and safety of systematic early rehabilitation compared to less systematic early rehabilitation, late rehabilitation or no rehabilitation.

Systematic literature search and data synthesis

We used a two-stage systematic literature search process to identify relevant randomized controlled trials (RCTs). In the first stage, we performed a systematic search in Medline and the Cochrane Library to identify recently published high-quality systematic reviews on early rehabilitation in adult ICU patients. We then pooled all publications which were found to potentially fulfill the eligibility criteria by these systematic reviews (i.e., all identified in- and excluded studies of each systematic review). In the second stage, we conducted systematic follow-up searches using the same search strategies used by the high-quality systematic reviews. We searched the Medline, EMBASE, CINAHL, and the Cochrane Central Register of Controlled Trials (CENTRAL) databases to ensure that our review was up to date. Three independent reviewers screened 220 systematic reviews and 2,299 records identified by the follow-up search. We obtained and assessed the full text of 224 potentially relevant studies for inclusion.

Three reviewers extracted relevant information related to study design and characteristics, demographic profiles and characteristics of study participants, details on the intervention and comparators, and outcome measures. We assessed study-level risk of bias according to the Cochrane criteria. Due to the heterogeneity of measured outcomes and reported time points of measurement, we used a narrative synthesis for most of the outcomes. Meta-analyses were conducted for a limited number of outcomes deemed of high importance and where appropriate data were available. We used the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach to evaluate the certainty of evidence for the primary outcomes considered most clinically important for ICU patients and clinicians in Switzerland.

Results

In total, 12 RCTs including 1,304 patients met the inclusion criteria. Two studies compared systematic early vs. late rehabilitation, nine studies compared systematic early vs. less systematic early rehabilitation, and one study compared systematic early vs. no rehabilitation.

We did not find conclusive evidence supporting a beneficial effect of systematic early rehabilitation on muscle strength. While generally Medical Research Council (MRC) Muscle Scale scores were higher in the systematic early rehabilitation groups compared to both late and less systematic early rehabilitation groups, between-group differences were not statistically significant. Similarly, the evidence related to the beneficial effects of systematic early rehabilitation on physical function was inconclusive. While patients in systematic early rehabilitation groups were at lower risk of developing ICU-acquired weakness during the hospital stay compared to patients in both late and less systematic early rehabilitation groups, this effect did not reach statistical significance. Patients receiving systematic early rehabilitation were more

likely to reach independence from assistance during the hospitalization when compared to patients receiving late rehabilitation. Data on independence from assistance for systematic early vs. less systematic early rehabilitation was not available. The time until patients were able to walk was significantly shorter when comparing systematic early with late rehabilitation, but studies investigating systematic early vs. less systematic early rehabilitation reported discordant results. While the maximum achieved walking distance was comparable between intervention and comparator groups, the mean change in walking distance from baseline was larger in patients receiving systematic early rehabilitation compared to those receiving less systematic early rehabilitation. Furthermore, patients receiving systematic early rehabilitation had higher SF-36 Physical Function Domain Scores (PFS) and Physical Health Component Summary Scores (PCS) at 6 months when compared to patients receiving late rehabilitation. However, there was no apparent benefit in SF-36 PFS and PCS as well as other physical function outcomes when comparing systematic early to less systematic early rehabilitation. While there was some evidence for a reduction in delirium duration with systematic early rehabilitation, no positive effect on cognition, mental health or quality of life was found. Importantly, the included RCTs did not allow the conclusion that systematic early rehabilitation reduced ICU or hospital length of stay, duration of mechanical ventilation or mortality for any of the comparator groups. Systematic early rehabilitation appeared safe when implemented under careful monitoring. Of note, the included study by Eggmann et al. was conducted in Switzerland and found no beneficial effects of systematic early rehabilitation on the primary outcomes compared to less systematic early rehabilitation.

In summary, we only found limited evidence in support of a beneficial effect of systematic early rehabilitation for most of the prespecified outcomes. Effect sizes and statistical evidence for a benefit generally tended to be stronger when comparing systematic early with late rehabilitation than when comparing systematic early with less systematic early rehabilitation. Overall, we judged the certainty of the evidence as low or very low.

Health economic analysis

The health economic assessment consisted of a systematic review of the currently published health economic literature, a *de novo* cost analysis with supplemental cost-effectiveness (CE) considerations, and a budget impact analysis (BIA) from a Swiss health insurance law perspective.

Literature search and study selection

The systematic review of the current economic literature aimed to identify literature about costs and cost-effectiveness of systematic early rehabilitative activities in the ICU. Economic search terms were added to the search strategies used in the clinical assessment part, but no time limitation was used. Full texts of 32 potentially relevant articles were obtained and assessed for eligibility.

Systematic literature review and implication

The systematic review of the health economic literature showed that there is currently no cost-effectiveness analysis available for the investigated population, intervention, comparator and outcomes (PICO). Only three studies were considered partially relevant and were therefore reviewed. Morris et al. and Chou et al. estimated that patients receiving early rehabilitation measures cost USD2,500-3,000 less if compared to usual care or no rehabilitation. These results in favor of early rehabilitation were driven by the ICU length of stay (5.5 vs. 6.9 days in Morris et al., 5.8 vs. 9.2 days in Chou et al.) and by the length of the total hospital stay (11.2 vs. 14.5 days in Morris et al., 17.9 vs. 25.4 days in Chou et al.). In contrast, in the study by Wright et al., the intervention group had a longer ICU length of stay (18 vs. 16 days) and a longer hospital stay (42 vs. 41 days) if compared to usual care. Wright et al. did not report information on costs. Nevertheless, they provided information on quality of life (which was similar between intervention and comparator strategy). Considering these discordant results and the limitations of the identified studies, for the *de novo* cost analysis we decided to base the estimation of outcomes relevant as cost drivers on the results of the clinical assessment only.

De novo cost model and results

The *de novo* cost model assumptions were chosen based on the results of the clinical systematic review part, feedback from a group of medical experts involved in this HTA, the results of a survey regarding the supply situation that we conducted among Swiss ICUs, inpatient costs from the Swiss Diagnosis Related Group (DRG) system, and information from the international literature. The survey, conducted among 37 out of 84 Swiss ICUs (response rate 44%), did not allow to elicit information specifically for our exact PICO (focusing on systematic early rehabilitation vs. comparators), but rather on early rehabilitation use in Swiss ICUs in general. This needs to be considered in the interpretation of our economic results.

According to the Swiss ICUs participating in the survey, 82% of ICU patients receive early rehabilitation. Based on the reported frequency and duration of the rehabilitation measures, we

estimated that each patient undergoing early rehabilitation in ICUs receives such measures for a total of 13.3 hours during his or her ICU stay. The average early rehabilitation costs per patient receiving early rehabilitation were estimated to be Swiss Francs (CHF) 863. Most of the costs (88%) were salary costs (CHF763). Estimated material costs (CHF100) accounted for approximatively 12% of the early rehabilitation costs. The results of the clinical assessment did not provide sufficient evidence concerning differences in quality of life, mortality, length of ICU/hospital stay, between early rehabilitation and standard care. There was no information on differences in time to return to work. For these reasons, these variables were not included in the cost analysis.

According to the Swiss Hospital Statistic (SHS), in 2015 there were 4,796 hospitalized cases requiring mechanical ventilation in a Swiss ICU that may be eligible according to the PICO studied in this HTA. The estimated average hospitalization costs of the eligible cases were CHF88,097 (including both patients receiving early rehabilitation and those who did not). Therefore, the costs for providing early rehabilitation (CHF863) represented only a small part of the total hospitalization costs (<1%) in this patient population.

Cost-effectiveness and additional considerations

Considering that the estimated average costs for early rehabilitation in ICUs were low (approximately CHF900 in the base case of the *de novo* cost model), even a small difference in quality of life, in length of stay, or in the time to return to work might have a considerable impact on the cost and cost-effectiveness of early rehabilitation strategies. For example, to achieve an ICER of CHF50,000 or CHF100,000 per QALY gained, early rehabilitation would need to generate 0.018 or 0.009 QALYs more than usual care. Based on a simplified assumption of constant utility differences over time, a utility difference of 0.036 or 0.018 would be required over a 6-month time horizon to meet an ICER threshold of CHF50,000 or CHF100,000, respectively. For a time horizon of 2 years, a utility difference of 0.009 or 0.005 would be necessary. Length of stay (in ICU or hospital) may also have high impact: early rehabilitation might become cost saving if it could reduce the length of stay by less than one single day (assuming hospitalization/ICU costs ranging from CHF1,500 to CHF6,500 per day). Finally, a faster return to work might have a high impact on indirect costs. Assuming a mean GDP per person of CHF79,104 and 220 working days per year, the costs for a single workday lost would be approximatively CHF360. A still professionally active patient receiving early rehabilitation and returning to work earlier might cause considerably lower indirect costs if compared to those not receiving early rehabilitation.

Budget impact analysis

The total costs of early rehabilitation for patients meeting our PICO were estimated to be CHF3.4 million. This represent only 0.8% of the total hospitalization costs for eligible patients, which were estimated to be CHF422 million. It is important to note that the overall number of ICU cases that may receive early rehabilitation may be considerably higher than the population selected for this assessment. According to the SHS, in 2015 there were 14,751 patients requiring mechanical ventilation for at least 24 hours in a Swiss ICU. Assuming the same probability of receiving early rehabilitation and the same average costs per patients, the overall costs may reach CHF10.4 million. Finally, according to the Swiss Society of Intensive Care Medicine, in 2018 there were 85,269 ICU admissions. Although many of these patients may have a very short ICU stay not requiring mechanical ventilation, they may also receive early rehabilitation. Therefore, the total number of patients receiving early rehabilitation and the overall costs of early rehabilitation may be higher.

Conclusion

The evidence regarding the clinical benefits of systematic early rehabilitation of adult and mechanically ventilated ICU patients remains weak and inconsistent. While we found no statistically significant evidence that systematic early rehabilitation improves outcomes related to muscle strength, there were some indications that systematic early rehabilitation could have a positive effect on individual outcomes related to physical function when compared to late rehabilitation. However, we found no statistical evidence for a beneficial effect of systematic early rehabilitation when compared to less systematic early rehabilitation, and no effect on a diverse set of outcomes related to mental and cognitive health, quality of life, duration of mechanical ventilation, hospital and ICU length of stay, as well as mortality. Systematic early rehabilitation appeared to be safe when implemented with adequate monitoring.

The systematic review of the economic literature found no cost-effectiveness study for the predefined PICO. Our analytical options were also substantially restricted given very sparse data. As a result, the available information did not allow us to assess the cost-effectiveness of early rehabilitation in comparison with standard care. A *de novo* cost analysis suggested that the costs of early rehabilitation are low and represent only a small part of the total hospitalization costs of eligible ICU patients. Consequently, the BIA results suggested that an increased or decreased use of early rehabilitation would only have little impact on the total cost burden.

These findings need to be considered within the context of the literature and the current situation in Switzerland. In most studies, especially the most recent ones, systematic early rehabilitation approaches or protocols were compared to standard care, which already consisted of an early, but

less systematic rehabilitation approach. As a result, the timing difference between groups was minimal, as for example in the included Swiss study by Eggmann et al. While our analysis did not find statistical evidence for a beneficial effect when comparing systematic early with such less systematic early approaches, the earliest included high-quality RCT found large effects for systematic early rehabilitation when compared with late rehabilitation. It might thus be reasonable to assume that a transition in standard care towards earlier rehabilitation approaches has taken place in recent years, resulting in incremental benefits that are substantially smaller or more difficult to measure. Our survey among Swiss ICUs suggested that currently most of the ICU patients in Switzerland (about 80%) receive some early rehabilitation measures, which may be reflected in the reported results by Eggmann et al.

1.2 Zusammenfassung

Hintergrund

Intensivstationsaufenthalte von mehr als einer Woche sind sowohl kurz- wie auch längerfristig mit erheblichen Funktionsstörungen, erhöhter Morbidität und verminderter Lebensqualität verbunden. Patienten brauchen oft Monate, um sich zu erholen und die volle Funktionalität im täglichen und beruflichen Leben wiederzuerlangen. Eine frühzeitige Rehabilitation kann die Häufigkeit des Auftretens einer erworbenen Muskelschwäche (*intensive care unit-acquired weakness*, ICUAW) verringern und diverse patientenrelevante Endpunkte verbessern. In vielen Schweizer Spitälern gehört es daher zur Standardbehandlung, gewisse rehabilitative Massnahmen bereits während des Intensivstationsaufenthaltes einzuleiten. Die zugrunde liegenden Erkenntnisse über die Wirksamkeit einer Frührehabilitation sind jedoch unsicher und die Ergebnisse der jüngsten systematischen Übersichtsarbeiten sind heterogen. Es bleibt daher unklar, wie "früh" in diesem Zusammenhang definiert werden sollte und ob systematischere Ansätze der Frührehabilitation (d.h. strikt bei allen Patienten) einen zusätzlichen Nutzen gegenüber weniger systematischen oder späteren Rehabilitationsansätzen bieten. Prinzipiell ist davon auszugehen, dass eine systematische Frührehabilitation allen Patienten auf der Intensivpflegestation (IPS) zugute kommt. Sie könnte aber bei gewissen Patienten auch zu höheren Komplikationsraten und Gesamtkosten führen, falls ein solcher systematischer Rehabilitationsansatz für jene Patientenpopulation unpassend ist.

Ziele

Dieses Health Technology Assessment (HTA) zielte darauf ab, die Effektivität, Sicherheit und Kosten einer "systematischen Frührehabilitation" (d.h. rehabilitative Massnahmen, welche innerhalb von 7 Tagen nach Aufnahme auf der IPS und bei allen Patienten ohne Kontraindikationen eingeleitet werden) bei erwachsenen, mechanisch beatmeten IPS-Patienten in der Schweiz im Vergleich zu einer der folgenden Strategien zu bestimmen: "späte" Rehabilitation (d.h. Beginn 7 Tage oder mehr nach der Aufnahme auf der IPS), "weniger systematische Frührehabilitation" (d.h. Beginn innerhalb von 7 Tagen nach Aufnahme auf der IPS, aber zeitlich verzögert und/oder nicht bei allen Patienten ohne Kontraindikationen) oder "keine Rehabilitation" (d.h. Scheinintervention oder keine rehabilitative Massnahme).

Klinische Wirksamkeit

Wir führten eine systematische Übersichtsarbeit durch, um die klinische Wirksamkeit und Sicherheit einer systematischen Frührehabilitation im Vergleich zu einer weniger systematischen Frührehabilitation, einer späten Rehabilitation oder keiner Rehabilitation zu ermitteln.

Systematische Literaturrecherche und Datensynthese

Für die Literaturrecherche verwendeten wir einen zweistufigen, systematischen Prozess, um relevante randomisierte kontrollierte Studien (*randomized controlled trials*, RCTs) zu identifizieren. In der ersten Phase führten wir eine systematische Literatursuche in Medline und der Cochrane Library durch, um kürzlich veröffentlichte, qualitativ hochwertige, systematische Übersichtsarbeiten bezüglich einer Frührehabilitation von erwachsenen Patienten auf der IPS zu identifizieren. Anschliessend erfassten wir alle Publikationen, welche die Auswahlkriterien dieser systematischen Übersichtsarbeiten potenziell erfüllten (d.h. alle identifizierten Studien, welche von diesen entweder ein- oder ausgeschlossen wurden). In der zweiten Phase führten wir systematische Literatursuchen durch, unter Verwendung derselben Suchstrategien, welche auch von den hochwertigen systematischen Übersichtsarbeiten verwendet wurden. Wir durchsuchten die Datenbanken Medline, EMBASE, CINAHL und das Cochrane Central Register of Controlled Trials (CENTRAL) um sicherzustellen, dass unsere Übersichtsarbeit auf dem neuesten Stand ist. Drei Prüfer untersuchten unabhängig die insgesamt 220 systematischen Übersichtsarbeiten sowie 2'299 Referenzen, welche bei der systematischen Literatursuche identifiziert wurden. Insgesamt wurden 224 potentiell relevante Studien im Volltext bezüglich der Erfüllung der Einschlusskriterien untersucht.

Drei Prüfer extrahierten relevante Informationen über Studiendesign und -merkmale, demographische Charakteristika der Studienteilnehmer, Details über die Intervention und die Vergleichsintervention (Komparator) sowie die evaluierten Endpunkte. Zudem wurde das Verzerrungsrisiko (*risk of bias*) gemäss der Cochrane Kriterien bewertet. Aufgrund der hohen Heterogenität in den gemessenen Ergebnissen und berichteten Evaluationszeitpunkten verwendeten wir für den Grossteil der Resultate eine narrative Synthese. Wir führten Meta-Analysen für eine begrenzte Anzahl von Ergebnissen durch, wo wir diese als wichtig erachteten sowie geeignete Daten verfügbar waren. Wir verwendeten die GRADE-Methodik (*Grading of Recommendations Assessment, Development, and Evaluation*), um die Qualität der Evidenz für jene primären Endpunkte zu bewerten, welche für Patienten und Kliniker in der Schweiz als die klinisch relevantesten angesehen wurden.

Resultate

Insgesamt erfüllten 12 RCTs einschliesslich 1'304 Patienten die Einschlusskriterien. Zwei Studien verglichen systematische Frührehabilitation mit späte Rehabilitation, neun Studien verglichen systematische Frührehabilitation mit weniger systematischer Frührehabilitation, und eine Studie verglich systematische Frührehabilitation mit keiner Rehabilitation.

Wir fanden keine schlüssigen Evidenz für einen positiven Effekt einer systematischen Frührehabilitation auf die Muskelkraft der Patienten. Während Patienten, welche eine systematische Frührehabilitation erhielten, im Allgemeinen höhere Werte auf der *Medical Research Council (MRC) Muscle Scale* erreichten als Patienten mit einer späten oder weniger systematischen Frührehabilitation, waren die Unterschiede zwischen den Gruppen statistisch nicht signifikant. Ebenso war die Evidenz hinsichtlich potenzieller positiver Auswirkungen einer systematischen Frührehabilitation auf die körperliche Funktion nicht eindeutig. Während Patienten mit systematischer Frührehabilitation ein geringeres Risiko hatten, während des Krankenhausaufenthaltes eine ICUAW zu entwickeln als Patienten in den Vergleichsgruppen, war auch dieser Effekt nicht statistisch signifikant. Patienten, welche eine systematische Frührehabilitation erhielten, erreichten im Vergleich zu Patienten mit später Rehabilitation während des Krankenhausaufenthaltes eher wieder ihre Unabhängigkeit. Für den Vergleich von systematischer Frührehabilitation gegenüber einer weniger systematischen Frührehabilitation lagen bezüglich des Erreichens der Unabhängigkeit keine Daten vor. Patienten mit systematischer Frührehabilitation benötigten eine statistisch signifikant kürzere Zeit, bis sie zum ersten Mal gehen konnten verglichen mit Patienten, welche eine späte Rehabilitation erhielten. Studien, welche eine systematische Frührehabilitation mit einer weniger systematischen Frührehabilitation verglichen, wiesen diese Effekte allerdings nicht nach. Die maximal erreichte Gehstrecke war in den verschiedenen Studien und zu verschiedenen Messzeitpunkten vergleichbar zwischen Interventions- und Kontrollgruppen. Allerdings war die mittlere Zunahme der Gehstrecke gegenüber den Anfangswerten statistisch signifikant höher bei Patienten, die eine systematische Frührehabilitation erhielten gegenüber Patienten, welche eine weniger systematische Frührehabilitation erhielten. Darüber hinaus hatten Patienten der Interventionsgruppe, nach 6 Monaten signifikant höhere *SF-36 Physical Function Domain Scores* (PFS) und *SF-36 Physical Health Component Summary Scores* (PCS) als Patienten, die eine späte Rehabilitation erhielten. Es gab jedoch keinen offensichtlichen Nutzen für eine systematische Frührehabilitation verglichen mit einer weniger systematischen Frührehabilitation bezüglich SF-36 PFS und PCS, sowie bezüglich anderer Endpunkte zur körperlichen Funktion. Während es in den eingeschlossenen Studien einige Hinweise für eine Verkürzung der Dauer von Delirium durch eine systematische Frührehabilitation gab, wurden keine positiven Auswirkungen auf Kognition, psychische Gesundheit oder Lebensqualität festgestellt. Zudem liessen die eingeschlossenen

Studien nicht den Schluss zu, dass eine systematische Frührehabilitation die Dauer des Aufenthalts auf der IPS oder im Krankenhaus, die Dauer der mechanischen Beatmung oder die Mortalität für eine der Vergleichsgruppen reduziert. Eine systematische Frührehabilitation erschien sicher, sofern sie unter sorgfältiger Überwachung durchgeführt wird. Es ist zu beachten, dass die in der Schweiz durchgeführte Studie von Eggmann et al. keine positiven Auswirkungen einer systematischen Frührehabilitation im Vergleich zu einer weniger systematischen Frührehabilitation in Bezug auf die primären Endpunkte zeigen konnte.

Zusammenfassend lässt sich sagen, dass wir nur begrenzte Hinweise für einen positiven Effekt einer systematischen Frührehabilitation für die meisten der vordefinierten Ergebnisse finden konnten. Die Effektgrössen sowie die statistische Evidenz für einen Nutzen waren im Allgemeinen tendenziell höher für den Vergleich zwischen systematischer Frührehabilitation und später Rehabilitation, gegenüber dem Vergleich zwischen systematischer Frührehabilitation und weniger systematischer Frührehabilitation. Insgesamt beurteilten wir die Qualität der Evidenz als niedrig oder sehr niedrig.

Gesundheitsökonomische Analyse

Die gesundheitsökonomische Analyse bestand aus einer systematischen Übersicht der aktuell publizierten gesundheitsökonomischen Literatur, einer *de novo* Kostenanalyse mit ergänzenden Kosteneffektivitätsüberlegungen (*cost-effectiveness,* CE) und einer Budget impact-Analyse (BIA) aus der Perspektive des Schweizerischen Krankenversicherungsgesetzes.

Systematische Literaturrecherche und Studienauswahl

Die systematische Überprüfung der aktuellen gesundheitsökonomischen _Literatur zielte darauf ab, die aktuelle Literatur bezüglich der Kosten und Kosteneffektivität systematischer Frührehabilitation auf der IPS zu identifizieren. Die im Rahmen der systematischen Übersichtsarbeit zur klinischen Wirksamkeit und Sicherheit verwendeten Suchstrategien wurden hierfür um zusätzliche gesundheitsökonomische Suchbegriffe ergänzt. Zweiunddreissig potenziell relevante Artikel wurden im Volltext untersucht und bezüglich der Erfüllung der Einschlusskriterien bewertet.

Studienübersicht und Bewertung

Die systematische Übersicht der aktuellen gesundheitsökonomischen Literatur zeigte, dass es derzeit keine Kosteneffektivitäts-Analyse gibt, welche der vordefinierten Zielpopulation, Intervention, Vergleichsgruppe (Komparator) und Endpunkte (PICO) entspricht. Drei Studien

wurden als teilweise relevant erachtet und untersucht. Morris et al. und Chou et al. schätzten, dass Patienten, die Frührehabilitationsmassnahmen auf der IPS erhalten, im Vergleich zur Standardbehandlung bzw. keiner Rehabilitation 2'500-3'000 USD weniger kosten. Diese Ergebnisse zugunsten einer systematischen Frührehabilitation wurden hauptsächlich durch eine verringerte Verweildauer auf der IPS (5.5 vs. 6.9 Tage in Morris et al.; 5.8 vs. 9.2 Tage in Chou et al.) sowie durch eine verringerte Gesamtverweildauer im Krankenhaus (11.2 vs. 14.5 Tage in Morris et al.; 17.9 vs. 25.4 Tage in Chou et al.) bestimmt. Im Gegensatz dazu hatte die Interventionsgruppe in der Studie von Wright et al. im Vergleich zur Standardbehandlung eine längere Verweildauer auf der IPS (18 vs. 16 Tage) und einen längeren Krankenhausaufenthalt (42 vs. 41 Tage). Wright et al. gaben in ihrer Studie keine Informationen bezüglich der Kosten. Allerdings lieferten sie Informationen über die Lebensqualität, für welche sie ähnliche Werte in der Interventions- und Vergleichsgruppe fanden. In Anbetracht der Einschränkungen der identifizierten Studien und der teilweise widersprüchlichen Ergebnisse entschieden wir uns, die *de novo* Kostenanalyse bezüglich der als Kostentreiber wirkenden Endpunkte nur auf die systematische Übersichtsarbeit zur klinischen Wirksamkeit und Sicherheit zu stützen.

De novo Kostenmodell und Resultate

Die Annahmen für das *de novo* Kostenmodell wurden auf der Grundlage der Ergebnisse der systematischen Übersichtsarbeit zur klinischen Wirksamkeit und Sicherheit, des Feedbacks einer Gruppe von an diesem HTA beteiligten medizinischen Experten, der Ergebnisse einer separat durchgeführten Umfrage zur Versorgungssituation auf den Schweizer IPS, der stationären Kosten aus dem Swiss Diagnosis Related Group (SwissDRG) System, sowie von zusätzlichen Informationen aus der internationalen Literatur getroffen. Die Umfrage zur Versorgungssituation, bei welcher 37 von 84 Schweizer IPS teilnahmen (Rücklaufquote 44%), erlaubte es uns nicht, detaillierte Informationen spezifisch im Rahmen unserer PICO-Kriterien (respektive differenzierte Information bezüglich einer systematischen Frührehabilitation und weiteren Rehabilitationsansätzen) zu sammeln, sondern diente eher der Informationsgewinnung bezüglich der aktuell und allgemein angewandten Ansätzen zur Frührehabilitation auf Schweizer IPS. Dies muss bei der Interpretation unserer gesundheitsökonomischen Ergebnisse berücksichtigt werden.

Gemäss den an der Umfrage teilnehmenden Schweizer IPS erhalten 82% der IPS-Patienten eine Frührehabilitation. Basierend auf der angegebenen Häufigkeit und des angegebenen Zeitaufwands für verschiedene Rehabilitationsmassnahmen schätzten wir, dass für jeden Patienten, welcher eine Frührehabilitation erhält, insgesamt etwa 13.3 Stunden für die Frührehabilitation aufgewendet werden. Die resultierenden durchschnittlichen Kosten der

Frührehabilitation wurden auf 863 Schweizer Franken (CHF) pro Patient geschätzt. Der grösste Anteil (88%) der Kosten stellten die Lohnkosten (763 CHF) für das involvierte Personal dar. Die geschätzten Materialkosten (100 CHF) machten somit rund 12% der Frührehabilitationskosten aus. Die Ergebnisse der systematischen Übersicht zur klinischen Wirksamkeit lieferten keine ausreichende Evidenz für Unterschiede in der Lebensqualität, der Mortalität oder der Dauer des Krankenhausaufenthaltes zwischen systematischer Frührehabilitation und Standardversorgung. Es gab zudem keine Informationen über Unterschiede in der Zeit bis zur Rückkehr an den Arbeitsplatz. Aus diesen Gründen wurden diese potenziell kostenrelevanten Variablen nicht in die Kostenanalyse einbezogen.

Gemäss der Schweizerischen Krankenhausstatistik (SKS) gab es im Jahr 2015 in der Schweiz 4'796 Fälle, welche eine mechanische Beatmung auf IPS erforderten und welche die Einschlusskriterien (PICO) dieses HTA erfüllen. Die geschätzten durchschnittlichen Hospitalisationskosten dieser Fälle beliefen sich auf 88'097 CHF (einschliesslich der Patienten, welche eine Frührehabilitation erhielten, und der Patienten, welche keine Rehabilitation erhielten). Die Kosten für die Frührehabilitation (863 CHF) machten daher nur einen kleinen Teil der gesamten Hospitalisationskosten (<1%) dieser Patientenpopulation aus.

Kosteneffektivität und zusätzliche Überlegungen

In Anbetracht der Tatsache, dass die geschätzten durchschnittlichen Kosten für eine Frührehabilitation auf der IPS niedrig waren (ca. 900 CHF in der Basisanalyse des *de novo* Kostenmodells), könnte selbst ein kleiner Unterschied in der Lebensqualität, der Verweildauer oder der Zeit bis zur Rückkehr an den Arbeitsplatz einen erheblichen Einfluss auf die Kosten und Kosteneffektivität von Frührehabilitation haben. Um beispielsweise einen ICER von 50'000 CHF oder 100'000 CHF pro QALY zu erreichen, müsste die Frührehabilitation 0,018 oder 0.009 QALYs mehr als eine Standardversorgung generieren. Unter einer vereinfachenden Annahme von konstanten Effekten im Zeitverlauf wäre über einen Zeitraum von 6 Monaten eine Nutzwert-Differenz (*utility difference*) von 0.036 bzw. 0.018 erforderlich, um einen ICER-Schwellenwert von 50'000 CHF bzw. 100'000 CHF zu erreichen. Über einen Zeithorizont von 2 Jahren wäre hierfür eine Nutzwert-Differenz von 0.009 bzw. 0.005 erforderlich. Auch eine Veränderung in der Verweildauer (auf der IPS oder im Krankenhaus) hätte hohe Auswirkungen: Eine Frührehabilitation könnte bereits zu Kosteneinsparungen führen, wenn sie die Verweildauer um weniger als einen Tag verkürzen würde (wenn Hospitalisationskosten zwischen 1'500 CHF und 6'500 CHF pro Tag angenommen werden). Schliesslich könnte auch eine raschere Rückkehr an den Arbeitsplatz einen hohen Einfluss auf die indirekten Kosten haben. Bei einem durchschnittlichen Brutto-Inland-Produkt (BIP) von 79'104 CHF pro Person und 220

Arbeitstagen pro Jahr betragen die Kosten für einen einzelnen verlorenen Arbeitstag etwa 360 CHF. Ein noch immer berufstätiger Patient, der eine Frührehabilitation erhält und früher an seinen Arbeitsplatz zurückkehrt, könnte im Vergleich zu einem Patienten, der keine Frührehabilitation erhält, erheblich geringere indirekte Kosten verursachen.

Budget Impact-Analyse

Die Gesamtkosten für die Frührehabilitation von Patienten, welche unsere Einschlusskriterien (PICO) erfüllen, wurden auf 3.4 Mio. CHF geschätzt. Dies entspricht nur 0.8% der gesamten Hospitalisationskosten dieser Patienten, welche wir auf 422 Mio. CHF schätzten. Zu beachten ist, dass die Gesamtzahl der Fälle in der Schweiz, für welche eine frühzeitige Rehabilitation in Frage kommt, deutlich höher sein könnte als die Zahl der in unserer Analyse ausgewählten Fälle. Gemäss der SKS gab es im Jahr 2015 in der Schweiz 14'751 Patienten, die eine mechanische Beatmung von mindestens 24 Stunden auf einer IPS benötigten. Angenommen, dass die Wahrscheinlichkeit der Durchführung einer Frührehabilitation und die durchschnittlichen Kosten pro Patient gleich bleiben, könnten die Gesamtkosten 10.4 Mio. CHF erreichen. Schliesslich gab es im Jahr 2018 nach Angaben der Schweizerischen Gesellschaft für Intensivmedizin (SGI-SSMI-SSMI) insgesamt 85'269 Zuweisungen auf eine IPS. Obwohl viele dieser Patienten einen sehr kurzen Aufenthalt auf der IPS hatten und keine mechanische Beatmung benötigten, ist es dennoch möglich, dass auch diese Patienten eine Frührehabilitation erhielten. Somit können die Gesamtzahl der Patienten, welche eine Frührehabilitation erhalten sowie die Gesamtkosten der Frührehabilitation in der Schweiz höher sein.

Fazit

Die Evidenz über den klinischen Nutzen einer systematischen Frührehabilitation von erwachsenen, mechanisch beatmeten IPS-Patienten ist nach wie vor schwach und inkonsistent. Während wir keine statistisch signifikante Evidenz dafür fanden, dass eine systematische Frührehabilitation die Muskelkraft verbessert, gab es Hinweise darauf, dass eine systematische Frührehabilitation verglichen mit einer späten Rehabilitation einen positiven Effekt auf die körperliche Funktion haben könnte. Wir fanden allerdings keinen statistisch signifikanten Effekt zu Gunsten einer systematischen Frührehabilitation verglichen mit einer weniger systematischen Frührehabilitation für eine Vielzahl von Endpunkten bezüglich psychischer und kognitiver Gesundheit, Lebensqualität, Dauer der mechanischen Beatmung, Dauer des Krankenhaus- und Intensivstationsaufenthaltes sowie der Mortalität. Die systematische Frührehabilitation schien bei Umsetzung mit angemessener Überwachung sicher zu sein.

Durch die systematische Übersicht der gesundheitsökonomischen Literatur konnten wir keine Kosteneffektivitäts-Analyse entsprechend unserer Einschlusskriterien identifizieren. Zudem waren unsere Möglichkeiten für eine gesundheitsökonomische Analyse aufgrund der spärlichen Studiendaten stark eingeschränkt. Infolgedessen konnten wir auf Basis der verfügbaren Informationen die Kosteneffektivität der Frührehabilitation im Vergleich zu einer Standardversorgung nicht beurteilen. Die *de novo* Kostenanalyse ergab, dass die Kosten für die Frührehabilitation niedrig sind und nur einen kleinen Teil der gesamten Hospitalisationskosten der eingeschlossenen IPS-Patienten ausmachen. Die BIA deutete daher darauf hin, dass ein erhöhter oder verminderter Einsatz der Frührehabilitation nur geringe Auswirkungen auf die Gesamtkostenbelastung haben würde.

Die Erkenntnisse dieses HTA müssen im Kontext der Literatur und der aktuellen Versorgungssituation in der Schweiz betrachtet werden. In den meisten Studien, insbesondere in denen jüngeren Datums, wurden systematische Frührehabilitations-Ansätze oder Protokolle mit einer Standardversorgung verglichen, welche bereits aus einem als weniger systematisch beurteilten Frührehabilitations-Ansatz bestand. So waren die Unterschiede in diesen Studien bezüglich des Zeitpunkts der ersten Rehabilitationsmassnahme zwischen den Vergleichsgruppen sehr gering (so auch in der Schweizer Studie von Eggmann et al.). Während unsere Analyse keine statistisch signifikante Evidenz für einen positiven Einfluss von systematischer Frührehabilitation verglichen mit weniger systematischer Frührehabilitation fand, berichteten die ältesten qualitativ hochwertigen Studien massgebliche Effekte zu Gunsten einer systematischen Frührehabilitation verglichen mit einer späten Rehabilitation. Es ist davon auszugehen, dass in den letzten Jahren ein Übergang in der Standardversorgung zu früheren Rehabilitationsansätzen stattfand. Dies könnte zu zunehmend kleineren und schwerer messbaren zusätzlichen Vorteilen einer systematischen Frührehabilitation gegenüber späteren respektive weniger systematischen Rehabilitations-Ansätzen geführt haben. Unsere Umfrage unter den Schweizer IPS ergab, dass derzeit die meisten Patienten in der Schweiz (ca. 80%) gewisse Frührehabilitationsmassnahmen erhalten, was sich in den berichteten Ergebnissen von Eggmann et al. widerspiegelt.

1.3 Résumé

Contexte général

Les séjours de plus d'une semaine en unité de soins intensifs (USI) sont associés à une déficience fonctionnelle significative, à une morbidité accrue et à une diminution de la qualité de vie à court terme et à long terme. Les patients ont souvent besoin de longs mois pour se rétablir, pour retrouver une bonne qualité de vie et reprendre leur activité professionnelle. Une réhabilitation précoce permet de réduire l'affaiblissement acquis lors d'un séjour en soins intensifs et permet d'améliorer divers résultats significatifs pour le patient. C'est pourquoi de nombreux hôpitaux suisses ont introduit certaines mesures de réhabilitation pendant le séjour en soins intensifs. Cependant, les données prouvant l'efficacité de la réhabilitation précoce sont incertaines et les conclusions des récentes études systématiques diffèrent. Dans ce contexte il n'est pas clair comment définir le terme « précoce » et si des approches de réhabilitation précoce plus systématiques (c.-à-d. sans distinction pour tous les patients admissibles) offrent des bénéfices supplémentaires par rapport aux approches de réhabilitation moins systématiques ou plus tardives. Bien que la réhabilitation précoce puisse apporter des bénéfices à tous les patients en USI, elle pourrait être aussi synonyme de taux de complications et de coûts globaux plus élevés au cas où l'approche de réhabilitation serait inadaptée pour un groupe spécifique de patients.

Objectif

Cet Health Technology Assessment (HTA) visait à déterminer l'efficacité, la sécurité clinique et à estimer les coûts de la réhabilitation précoce systématique (c.-à-d. la réhabilitation systématique amorcée dans les 7 jours après admission à l'USI pour tous les patients sans contre-indication) comparativement à une des stratégies suivantes : la réhabilitation « tardive » (c.-à-d. amorcée 7 jours ou plus après admission à l'USI), la réhabilitation « précoce moins systématique » (c.-à-d. amorcée dans les 7 jours après admission à l'USI mais plus tard, et/ou pas pour tous les patients sans contre-indications) ou « pas de réhabilitation » (c.-à-d. intervention fictive ou aucune intervention) pour les patients adultes sous ventilation mécanique en USI en Suisse.

Efficacité et sécurité clinique

Nous avons effectué une revue de littérature systématique, pour déterminer l'efficacité et la sécurité clinique de la réhabilitation précoce systématique par rapport à la réhabilitation précoce moins systématique, à la réhabilitation tardive ou à aucune mesure de réhabilitation.

Recherche de littérature systématique et synthèse de données

Nous avons utilisé un processus de recherche de littérature systématique en deux étapes pour identifier les essais contrôlés randomisés pertinents (randomised controlled trials, RCTs). Dans un premier temps, nous avons effectué une recherche systématique dans Medline et dans la Cochrane Library afin d'identifier les revues systématiques de qualité supérieure récemment publiées sur la réhabilitation précoce des patients adultes en soins intensifs. Nous avons ensuite regroupé toutes les publications qui répondaient potentiellement aux critères d'éligibilité selon ces revues systématiques (c.-à-d. toutes les études inclues et exclues de chaque revue systématique). Dans un deuxième temps, nous avons effectué des recherches de suivi systématique à l'aide des mêmes stratégies de recherche que celles utilisées pour les revues systématiques de qualité supérieure. Nous avons consulté les bases de données Medline, EMBASE, CINAHL et Cochrane Central Register of Controlled Trials (CENTRAL) pour nous assurer que notre examen était à jour. Trois examinateurs indépendants ont examiné 220 revues systématiques et 2,299 dossiers identifiés par l'étude de suivi. Nous avons obtenu et évalué le texte intégral de 224 études potentiellement pertinentes selon les critères d'inclusion.

Trois examinateurs ont recueilli les informations pertinentes sur la conception et les caractéristiques de l'étude, les profils démographiques et les caractéristiques des participants à l'étude, les détails de l'intervention et des comparateurs, ainsi que sur l'évaluation des résultats. Nous avons évalué le risque de biais au niveau de l'étude en fonction des critères de Cochrane. En raison de l'hétérogénéité des résultats mesurés et de l'hétérogénéité des points de mesures au cours du temps, nous avons fait une synthèse narrative pour la plupart des résultats. Des méta-analyses ont été effectuées pour un nombre limité de résultats jugés très importants et pour lesquels des données appropriées étaient disponibles. Nous avons utilisé l'approche GRADE (Grading of Recommendations Assessment, Development, and Evaluation) pour évaluer la certitude des données probantes pour les résultats primaires considérés comme les plus importants sur le plan clinique pour les patients et les cliniciens en soins intensifs en Suisse.

Résultats

Au total, 12 RCTs incluant 1'304 patients répondaient aux critères d'inclusion. Deux études ont comparé la réhabilitation précoce systématique par rapport à la réhabilitation tardive, neuf études ont comparé la réhabilitation précoce systématique par rapport à la réhabilitation précoce moins systématique, et une étude a comparé la réhabilitation systématique précoce par rapport à la réhabilitation non systématique.

Nous n'avons pas trouvé de preuves concluantes à l'appui de l'effet bénéfique de la réhabilitation précoce systématique sur la force musculaire. Bien que, de façon générale, les résultats sur

l'échelle musculaire du Medical Research Council (MRC) étaient plus élevés pour les groupes de réhabilitation précoce systématique que pour les groupes de réhabilitation tardive et moins systématique, les différences entre les groupes n'étaient pas statistiquement significatives. De même, les données relatives aux effets bénéfiques de la réhabilitation précoce systématique sur la fonction physique n'étaient pas concluantes. Bien que les patients des groupes de réhabilitation précoce systématique, avaient moins de risque de développer un affaiblissement en soins intensifs pendant leur séjour à l'hôpital que les patients des groupes de réhabilitation précoce tardive et moins systématique, cet effet n'était pas statistiquement significatif. Il était plus probable que les patients qui bénéficient d'une réhabilitation précoce systématique retrouvent leur autonomie pendant l'hospitalisation, par rapport aux patients bénéficiant d'une réhabilitation tardive. On ne disposait pas de données sur l'autonomie des patients bénéficiant d'une réhabilitation précoce systématique par rapport à ceux profitant d'une réhabilitation précoce moins systématique. Le délai avant que les patients soient capables de remarcher était significativement plus court lorsqu'on comparait la réhabilitation précoce systématique et la réhabilitation tardive, mais les études portant sur la réhabilitation précoce systématique par rapport à la réhabilitation précoce moins systématique ont rapporté des résultats discordants. Bien que la distance de marche maximale atteinte soit comparable entre les deux groupes, la différence moyenne de la distance de marche par rapport à la référence était plus importante chez les patients bénéficiant d'une réhabilitation précoce systématique en comparaison à ceux ayant bénéficié d'une réhabilitation précoce moins systématique. De plus, les patients bénéficiant d'une réhabilitation précoce systématique présentaient après 6 mois, des scores SF-36 plus élevés du fonctionnement physique (Physical Function Domain Scores, PFS) et de santé physique (Physical Health Component Summary Scores, PCS) que les patients ayant bénéficié d'une réhabilitation tardive. Cependant, il n'existait aucun avantage apparent pour les SF-36, PFS et PCS ainsi que pour les autres résultats de la fonction physique si l'on comparait la réhabilitation précoce systématique à la réhabilitation précoce moins systématique. Bien qu'il y ait des preuves d'une réduction de la durée du délire avec une réhabilitation précoce systématique, aucun effet cognitif positif, aucune amélioration de la santé mentale ou de la qualité de vie n'a été observé. Il est important de noter que les RCTs ne permettaient pas de conclure que la réhabilitation précoce systématique réduisait la durée du séjour en soins intensifs ou à l'hôpital, ni ne réduisait la durée de la ventilation mécanique ou la mortalité pour aucun des groupes de comparaison. La réhabilitation précoce systématique semblait être sûre lorsqu'elle était pratiquée sous surveillance. Il est à noter que l'étude de Eggmann et coll. a été menée en Suisse et n'a révélé aucun effet bénéfique de la réhabilitation précoce systématique pour les résultats primaires, par rapport à une réhabilitation précoce moins systématique.

En résumé, nous n'avons trouvé que peu d'éléments probants à l'appui d'un effet bénéfique de la réhabilitation précoce systématique vérifiant la plupart des résultats prédéfinis. Le bénéfice mesuré entre la taille de l'effet et les données statistiques, a généralement tendance à être plus élevé, lorsque l'on compare la réhabilitation précoce systématique avec la réhabilitation tardive, que lorsque l'on compare la réhabilitation précoce systématique avec la réhabilitation précoce moins systématique. Dans l'ensemble, nous avons jugé que la certitude des données probantes était faible ou même très faible.

Évaluation économique de la santé

L'évaluation économique de la santé a consisté en un examen systématique de la littérature récemment publiée sur l'économie de la santé, une analyse des coûts *de novo* avec critères supplémentaires de coût-efficacité (CE) et une analyse de l'impact budgétaire (BIA) du point de vue du droit suisse des assurances maladie.

Recherche de la littérature et sélection des études

La revue systématique de la littérature économique actuelle visait à identifier les publications sur les coûts et le rapport coût-efficacité des activités systématiques de réhabilitation précoce en soins intensifs. Des critères de recherche économique ont été ajoutés aux stratégies de recherche utilisées pour l'évaluation clinique, toutefois sans aucune limite de temps. Les textes intégraux de 32 articles potentiellement pertinents ont été rassemblés puis évalués selon leur admissibilité.

Revue systématique de la littérature et implication

La revue systématique de la littérature économique a révélé qu'il n'existe actuellement aucune analyse coût-efficacité pour la population, l'intervention, le comparateur et les résultats (PICO) examinés. Seules trois études ont été jugées partiellement pertinentes et ont donc été examinées. Morris et coll. et Chou et coll. ont estimé que les patients bénéficiant de mesures de réhabilitation précoce coûtent entre 2'500 et 3'000 $US de moins en comparaison aux soins habituels ou à une absence de réhabilitation. Ces résultats en faveur d'une réhabilitation précoce sont attribuables à la durée du séjour en USI (5,5 vs 6,9 jours pour Morris et coll., 5,8 vs 9,2 jours pour Chou et coll.) et à la durée totale du séjour à l'hôpital (11,2 vs 14,5 jours pour Morris et coll., 17,9 vs 25,4 jours pour Chou et coll.). Cependant, dans l'étude de Wright et coll., le groupe d'intervention a eu un séjour plus long en USI (18 vs 16 jours) et un séjour à l'hôpital plus long (42 vs 41 jours) comparativement aux soins habituels. Wright et coll. n'ont pas fourni d'information sur les coûts. Néanmoins, ils ont fourni des informations sur la qualité de vie (qui était semblable comme pour

la stratégie d'intervention et que pour la stratégie de comparaison). Compte tenu de ces résultats discordants et des limites des études identifiées, nous avons décidé, pour l'analyse des coûts de novo, de nous baser seulement sur les résultats de l'évaluation clinique pour l'estimation des résultats pertinents comme inducteurs de coûts.

Model des coûts de novo et résultats

Les hypothèses du modèle de coûts de novo ont été choisies en fonction des résultats de l'examen clinique systématique, des commentaires d'un groupe d'experts médicaux participant à cet HTA, des résultats d'une enquête que nous avons menée auprès des USI suisses sur la situation de l'approvisionnement, des coûts des patients hospitalisés du système Swiss Diagnosis Related Group (DRG) et des renseignements tirés des publications internationales. L'enquête, menée auprès de 37 des 84 USI suisses (taux de réponse de 44%), n'a pas permis d'obtenir d'informations spécifiques pour notre très exact PICO (se concentrant sur la réhabilitation précoce systématique par rapport aux comparateurs), mais plutôt sur l'utilisation de la réhabilitation précoce dans les USI suisses en général. Il faut en tenir compte dans l'interprétation de nos résultats économiques.

Selon les USI suisses participant à l'enquête, 82% des patients des USI bénéficient d'une réhabilitation précoce. D'après la fréquence et la durée des mesures de réhabilitation déclarées, nous avons estimé que chaque patient en réhabilitation précoce dans les USI bénéficient de ces mesures pour un total de 13,3 heures pendant son séjour en USI. Le coût moyen de la réhabilitation précoce par patient bénéficiant d'une réhabilitation précoce a été estimé à 863 francs suisses (CHF). La majeure partie des coûts (88%) étaient des coûts salariaux (763 CHF). Les coûts estimés pour le matériel utilisé (100 CHF) ont représenté environ 12% des coûts de la réhabilitation précoce. Les résultats de l'évaluation clinique n'ont pas fourni suffisamment de données probantes concernant les différences sur la qualité de vie, la mortalité, la durée du séjour en soins intensifs ou en l'hôpital, entre la réhabilitation précoce et les soins standardisés. Il n'y avait pas d'information sur les différences dans les délais de reprise de l'activité professionnelle. Pour ces raisons, ces variables n'ont pas été incluses dans l'analyse des coûts.

Selon la statistique hospitalière suisse (SHS), il y a eu en 2015, 4'796 cas d'hospitalisation nécessitant une ventilation mécanique dans une USI suisse, qui pouvaient être admissibles selon le PICO étudié dans cette HTA. Les coûts d'hospitalisation moyens estimés des cas admissibles s'élevaient à 88'097 CHF (incluant à la fois les patients bénéficiant d'une réhabilitation précoce et ceux qui n'en bénéficiaient pas). Par conséquent, les coûts de réhabilitation précoce (863 CHF) ne représentaient qu'une petite partie des coûts totaux d'hospitalisation (<1%) pour ce groupe de patients.

Rapport coût efficacité et considérations supplémentaires

Étant donné que les coûts moyens estimés pour la réhabilitation précoce dans les USI étaient modestes (environ 900CHF pour le cas de base du modèle de coûts de novo), même une petite différence de la qualité de vie, la durée du séjour ou du délai de la reprise de l'activité professionnelle, pourrait avoir un impact considérable sur les coûts et le coût-efficacité des stratégies de réhabilitation précoce. Par exemple, pour atteindre un rapport coût-efficacité différentiel (Incremental Cost-Effectiveness Ratio, ICER) de 50'000 ou de 100'000 CHF par années de vie pondérée par la qualité (Quality-Adjusted Life Year, QALY), la réhabilitation précoce devrait générer 0.018 ou 0.009 QALY de plus que les soins habituels. Sur la base d'une hypothèse simplifiée de différences d'utilité constantes dans le temps, une différence d'utilité de 0.036 ou 0.018 sur un horizon de six mois serait nécessaire pour atteindre un seuil d'ICER de, respectivement 50'000 ou 100'000 CHF. Sur un horizon de 2 ans, une différence d'utilité de 0.009 ou 0.005 serait nécessaire. La durée du séjour (en soins intensifs ou à l'hôpital) peut également avoir un impact important : la réhabilitation précoce peut devenir rentable si elle permet de réduire la durée du séjour de moins d'une journée (en supposant des frais d'hospitalisation/de soins intensifs allant de 1'500 à 6'500 CHF par jour). Enfin, une reprise plus rapide de l'activité professionnelle pourrait avoir un impact important sur les coûts indirects. En supposant un produit intérieur brut (PIB) moyen par personne de 79'104 et 220 jours de travail par an, le coût d'une journée de travail perdue serait d'environ 360 CHF. Un patient toujours actif sur le plan professionnel, qui bénéficie d'une réhabilitation précoce et qui reprend son travail plus tôt, pourrait entraîner des coûts indirects considérablement moins élevés par rapport à ceux qui ne bénéficient pas de réhabilitation précoce.

Analyse de l'impact budgétaire et résultats

Le coût total de la réhabilitation précoce pour les patients qui répondent à notre PICO, a été estimé à 3,4 millions de CHF. Cela ne représente que 0,8% du total des frais d'hospitalisation des patients admissibles, estimés à 422 millions de CHF. Il est important de noter que le nombre global de cas en soins intensifs qui peuvent bénéficier d'une réhabilitation précoce peut être bien plus élevé, que le groupe de patients sélectionnés pour cette évaluation. Selon le SHS, en 2015, 14'751 patients ont eu besoin de ventilation mécanique pendant au moins 24 heures dans une USI. En supposant, la même probabilité de bénéficier d'une réhabilitation précoce et les mêmes coûts moyens par patient, les coûts globaux peuvent atteindre 10,4 millions de CHF. Enfin, selon la Société suisse de médecine intensive (SGI-SSMI-SSMI), 85'269 admissions ont été dénombrées en 2018. Même si bon nombre de ces patients ont eu un séjour très court en USI ne nécessitant pas de ventilation mécanique, ils ont pu bénéficier d'une réhabilitation précoce. Par conséquent, le

nombre total de patients bénéficiant d'une réhabilitation précoce et les coûts globaux d'une réhabilitation précoce peuvent être plus élevés.

Conclusion

Les données probantes concernant les avantages cliniques de la réhabilitation précoce systématique des patients adultes et des patients sous ventilation mécanique en soins intensifs demeurent peu concluantes et incohérentes. Bien que nous n'ayons trouvé aucune preuve statistiquement significative que la réhabilitation précoce systématique améliore les résultats liés à la force musculaire, il y avait certaines indications que la réhabilitation précoce systématique pourrait avoir un effet positif sur les résultats individuels liés aux fonctions physiques comparativement à la réhabilitation tardive. Cependant, nous n'avons trouvé aucune preuve statistique d'un effet bénéfique de la réhabilitation précoce systématique comparativement à la réhabilitation précoce moins systématique, et aucun effet sur un ensemble diversifié de résultats liés à la santé mentale et cognitive, à la qualité de vie, à la durée de la ventilation mécanique, à la durée du séjour en hôpital et en soins intensifs ainsi qu'à la mortalité. La réhabilitation précoce systématique semblait sûre lorsqu'elle était pratiquée avec un suivi adéquat.

La revue systématique de la littérature économique n'a révélé aucune étude coût-efficacité pour le PICO prédéfini. Nos options analytiques ont également été considérablement restreintes en raison de la rareté des données. Par conséquent, l'information disponible ne nous a pas permis d'évaluer la rentabilité de la réhabilitation précoce par rapport aux soins standardisés. Une analyse des coûts de novo indique que les coûts de la réhabilitation précoce sont peu élevés et ne représentent qu'une petite partie des coûts totaux d'hospitalisation des patients admissibles en USI. Par conséquent, les résultats de la BIA indiquent qu'un recours accru ou réduit à la réhabilitation précoce n'aurait que peu d'incidence sur le fardeau total des coûts.

Ces résultats doivent être considérés dans le contexte de la littérature et de la situation actuelle en Suisse. Dans la plupart des études, en particulier les plus récentes, les approches ou protocoles systématiques de réhabilitation précoce ont été comparés aux soins standardisés, qui consistaient déjà en une approche précoce, mais moins systématique. Bien que notre analyse n'ait pas trouvé de preuves statistiques d'un effet bénéfique en comparant les approches systématiques précoces à des approches moins systématiques, le premier RCT de grande qualité qui a été inclus, a révélé des effets importants pour une réhabilitation précoce systématique comparativement à une réhabilitation tardive. Il pourrait donc être raisonnable de supposer qu'une transition des soins standardisés vers des approches de réadaptation plus précoces ait eu lieu au cours des dernières années, entrainant des bénéfices supplémentaires qui seraient beaucoup plus petits ou plus difficiles à mesurer. Notre enquête auprès des USI suisses a révélé que la plupart des patients des

USI en Suisse (environ 80%) bénéficient actuellement de mesures de réhabilitation précoce, ce qui peut se refléter dans les résultats rapportés par Eggmann et coll.

2 Introduction

Intensive care unit (ICU) stays of more than one week (or perhaps even shorter) are associated with significant functional impairment and decreased quality of life, attributed to proximal muscle weakness, disuse atrophy, delirium and fatigue. In the most extreme cases, patients may develop severe neuromuscular disorder, commonly referred to as ICU-acquired weakness (ICUAW).[1–3] Patients often take months to recover and regain full functionality in their daily and professional life. Moreover, ICU survivors may suffer from suboptimal quality of life, long-term cognitive impairment and an increased risk of death, resulting in higher health care utilization and associated costs.[3–6]

There is evidence that early rehabilitation initiated in the ICU reduces the risks of the negative outcomes mentioned above, but these effects are not consistent across patient-relevant outcomes.[7–10] According to Swiss ICU experts involved in the scoping process of this Health Technology Assessment (HTA), it is current practice in many Swiss hospitals to initiate rehabilitative activities in the ICU, particularly in patients with an expected stay of more than a week. For example, according to data published by the Swiss Federal Office of Public Health (SFOPH), there were 11,369 patients in 2015 who received more than 24 hours of mechanical ventilation (divided among 70 acute-care hospitals, with a mean of 162 cases per hospital).[11] A considerable proportion of these patients may be eligible for early rehabilitation during their ICU stay. A cross-sectional survey conducted by Sibilla et al. in 2014 among 35 ICUs that provide mechanical ventilation in Switzerland reported relevant gaps in the provision of active rehabilitation. It showed that only 33% of 161 adult patients admitted to ICU received active mobilization and 33% did not have any active or passive mobilization. Moreover, patients with endotracheal intubation were less likely to receive active mobilization.[12]

While early rehabilitation is considered important and is widely implemented in Switzerland, it is currently not clear in which patients, when, and how such rehabilitative measures should be initiated.[2] The findings of some systematic reviews suggest that early rehabilitation may reduce the time to wean from mechanical ventilation, improve physical functionality and reduce the risk for ICUAW compared with usual care.[9,13,14] Yet, other reviews have found no evidence for a beneficial effect.[2,15] Arguments to start rehabilitation in the ICU systematically (i.e., in all eligible patients except those with contraindications) and early (within 7 days of ICU admission) are that early activation may prevent muscle loss and dysfunction, as well as reduce delirium and consequences arising post ICU or hospital discharge. On the other side, less systematic rehabilitative approaches that are tailored to the needs of the individual patient may be associated with less complications and lower immediate costs. However, tailored and less protocolized activities might tend to be initiated late, most importantly as fewer patients receive early

rehabilitative activities if the decision is taken late (e.g. upon stabilization of the patient). This might be common practice in many contexts, because ICU patients are often considered as "too sick" to tolerate early mobilization.[6] Moreover, while serious harmful effects are rarely reported, it is important to assess the safety of systematic early rehabilitation in the ICU, because mobilizing critically ill patients (i.e., patients with support monitors, artificial airways and multiple catheters) may not be without risk. Such risks may include adverse cardio-respiratory effects as well as disconnecting catheters or dislodging of supportive equipment (with associated pain due to reinsertion and related infections) and physical injury due to falls.[15–17]

This HTA aims at examining the current evidence base on clinical effectiveness, safety and economic characteristics of systematic early rehabilitation and providing a basis for recommendations for practice and policy in Switzerland. This HTA was complemented by a nationwide companion survey on the definitions, current use and practice variation regarding early rehabilitation in Swiss ICUs (reported separately).

3 Objective

The objective of this HTA was to determine the effectiveness, safety, and economic characteristics of "systematic early" rehabilitation (i.e., rehabilitation initiated within 7 days after ICU admission systematically in all patients without contraindication) compared with “late” rehabilitation (i.e., initiated 7 days or more after ICU admission), “less systematic early" rehabilitation (i.e., initiated within 7 days after ICU admission but later in time and/or not in all patients without contraindications), or “no rehabilitation" (i.e., sham intervention or no intervention) in adult, mechanically ventilated ICU patients in Switzerland.

4 PICO

In this chapter we describe the population, intervention, comparators, and outcomes (PICO) for the current HTA. A brief summary of the PICO is provided in Table 1.

Table 1: Summary description of the population, intervention, comparators, and outcomes (PICO)

			Description
Population		Adult ICU patients (≥18 years) requiring ventilation support (i.e., invasive or non-invasive mechanical ventilation)	
Intervention	•	Systematic early rehabilitation	Rehabilitative activities initiated in all patients without contraindications no later than 7 days after ICU admission
Comparators	I.	Late rehabilitation	Rehabilitative activities initiated 7 days or more after ICU admission (also considered to be less systematic in general)
	II.	Less systematic early rehabilitation	Rehabilitative activities initiated no later than 7 days after ICU admission, but later and/or not in all patients without contraindications (in selected patients only or less protocolized)
	III.	No rehabilitation	No actual rehabilitative measures provided (sham intervention or no intervention)
Outcomes		Primary outcomes	Muscle strength Functional mobility
		Secondary outcomes	Cognitive function and mental health Quality of life Safety outcomes Other outcomes (e.g. length of stay, duration of mechanical ventilation)
		Health economic outcomes	Costs Quality-adjusted life years Incremental cost-effectiveness ratios

4.1 Population

Our population of interest consisted in adult ICU patients (≥18 years) requiring ventilation support (i.e., invasive or non-invasive mechanical ventilation).

We included studies investigating such a patient collective if patients were mechanically ventilated either at study inclusion or before study inclusion during the ICU stay. Studies conducted in post-operative patients only which were ventilated for less than 24 hours on average were excluded. Furthermore, we excluded studies that recruited burn patients, patients with pre-existing neurological illnesses (such as brain trauma, neurosurgery, neuromuscular diseases, stroke, multiple sclerosis, brain tumor, spinal cord injury, patients with para- and tetraplegia) and transplant patients. However, we included studies in which such patients did not contribute to more than 10% of the total study participants.

4.2 Intervention

The experimental intervention of interest was systematic early rehabilitation initiated in the ICU. “Systematic” was defined as rehabilitative measures provided to all patients except those with contraindications. “Early” was defined as rehabilitation starting no later than 7 days after ICU admission.

We included studies that evaluated rehabilitative activities, including physiotherapy or similar activities performed by nursing or physiotherapy staff, that targeted muscle activation, including active range of motion exercises and training, sitting position in bed and tilt table, active side to side turning and exercises in bed, passive and active cycling in bed, sitting on the edge of the bed, transferring from bed to a chair, ambulation, active resistance exercises or bedside training, and neuro-muscular electrical stimulation (NMES). We considered ergotherapy and speech therapy interventions as eligible, if they were performed in conjunction with physical rehabilitation. Similarly, the keeping of an ICU diary (log of patient's history and activities in ICU recorded by relatives or staff), which could help patients to reconstruct ICU experience and prevent post-traumatic stress disorder, was considered as eligible components of early rehabilitative activities. We did not consider interventions exclusively intended to prevent pressure ulcers (e.g., changing position in bed) or to prevent joint stiffness (i.e., joint mobilization but without the goal of activating skeletal muscles) as well as respiratory interventions not aiming at more general muscle activation.

4.3 Comparators

A priori, we defined eligible comparator interventions as (1) the same or similar rehabilitative activities (or passive or active range of motion exercises that were provided as a standard medical or nursing care) starting at a later point in time, (2) rehabilitative activities taking place only in selected patients, (3) a combination of the first two, or (4) no rehabilitative activities. We did not consider studies investigating interventions solely targeted at preventing pressure ulcers or joint stiffness, or targeted at respiratory rehabilitation only.

Based on these criteria and the prespecified cut-off for early interventions (see above), we categorized eligible studies into the following comparator categories: (I) "late" rehabilitation (i.e., rehabilitation initiated 7 days or more after ICU admission), (II) "less systematic early" rehabilitation (i.e., rehabilitative activities initiated within 7 days but later in time and/or not in all patients without contraindications), or "no rehabilitation" (i.e., sham intervention or no intervention). "Late" rehabilitation was considered to be less systematic in general. Comparator group categories defined for this review are summarized in Table 1.

4.4 Outcomes

We considered the following outcomes, even if they were not all reported consistently across studies. We extracted information for the time points of ICU discharge, hospital discharge, as well as 3 months, 6 months and 12 months after hospital discharge, where available.

Primary outcomes

Muscle strength: Medical Research Council (MRC) Muscle Scale Sum Score, hand-held dynamometry, and handgrip strength.

Functional mobility: Barthel Index (BI), Activities of Daily Living (ADL), Functional Independence Measure (FIM), Physical Function in the ICU Test (PFIT), Timed up-and-go test (TUG), 6-minute (6MWT) or other walking tests, distance walked without assistance, time to mobility milestones (e.g., time to first time out of bed, time to standing, time to walking, time to return to work), proportion of patients reaching independence from assistance, SF-36 Physical Function Domain Score (PFS) and Physical Function Component Summary Score (PCS), as well as the proportion of patients developing ICUAW.

Secondary outcomes

Cognitive function and mental health: Delirium duration, delirium-free days, Mini-Mental State Exam (MMSE) scores, Hospital Anxiety and Depression Scale (HADS), as well as SF-36 Mental Health Domain Score (MHS) and Mental Health Component Summary Score (MCS).

Quality of life: Health-related quality of life scores (generic or disease-specific).

Mortality: In-hospital mortality and mortality after hospital discharge.

Other outcomes: Length of ICU stay (ICU LOS), length of hospital stay (Hospital LOS), duration of mechanical ventilation, ventilator-free days.

Safety outcomes: Accidents and fractures (during or outside rehabilitative activities), dislodging of catheters and other installations, hypotension and cardiovascular adverse effects, oxygen desaturation, loss of muscle tone, and complications due to insertion and reinsertion of installations.

Health economic outcomes

Costs: Direct medical, indirect.

Quality of life: Quality-adjusted life years (QALYs).

Incremental cost-effectiveness ratios (ICERs): Cost per QALY gained.

5 Clinical assessment

5.1 Methods

The systematic review was designed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline.[18] The review protocol was reviewed by an expert group installed by the Swiss Medical Board and we made revisions accordingly before registering it on PROSPERO (Registration No. CRD42019122555).[19]

5.1.1 Study types

We considered only randomized controlled trials (RCTs). While we regard observational studies to be important additional information sources to estimate real-world effect estimates and to assess long term outcomes, we did not include such evidence because both our preliminary scoping of the literature and expert input indicated that only limited observational studies with rather small sample sizes (i.e., n<200) would be available.

5.1.2 Information sources and search strategy

As a preliminary search revealed that the number of published RCTs on systematic early rehabilitation in the ICU was limited, we expected the studies would be identified reliably by the most recently published high-quality systematic reviews. We therefore followed a two-stage systematic search process to identify relevant RCTs. First, we identified existing high-quality systematic reviews on early rehabilitation in the ICU, which were used as a source to identify potentially eligible RCTs for our analysis. Second, we performed follow-up searches based on the search strategies of the high-quality systematic reviews selected in the first stage to identify more recently published studies.

In the first stage, we conducted a systematic search in the Medline (PubMed) and Cochrane Library databases for recent systematic reviews on early rehabilitative activities in ICU patients published in the last four years (2015 to 2019). We used variations of the terms “intensive care”, “critical care”, “critical illness”, “mechanical ventilation”, “rehabilitation”, “physiotherapy”, “mobilization”, “muscle training”, “exercise”, “ICU acquired weakness”, and “post-intensive care syndrome” for the search (see Appendix 9.1). Two independent reviewers (DM, HY) screened titles and abstracts of the identified systematic reviews for eligibility. We then analyzed potentially eligible systematic reviews in full-text and assessed them in terms of their quality using the Assessing the Methodological Quality of Systematic Reviews (AMSTAR) 2 checklist,

which is an evaluation tool for the overall quality of systematic reviews.[20] Since we used the systematic reviews to extract individual RCTs, we relied on criteria that focus on the use of clear eligibility criteria (PICO), the quality of the literature search (comprehensiveness, selection, extraction strategies), and risk of bias assessment (AMSTAR criteria 1 and 4–9), which we considered relevant for our purpose. RCTs fulfilling these criteria were considered to be of high quality. We identified three eligible high-quality systematic reviews,[13,15,21] which we used as a basis for the identification of individual RCTs to be included in our analysis. Finally, we assembled all publications which were identified as potentially fulfilling the eligibility criteria by these high-quality systematic reviews (i.e., all identified in- and excluded studies of each systematic review).

In the second stage, we performed a systematic follow-up search of the published literature using the same search strategies as used in those selected high-quality systematic reviews to ensure that our search was up to date. The follow-up searches were conducted in Medline, EMBASE, CINAHL, and CENTRAL. We additionally applied the Cochrane sensitivity and precision-maximizing RCT filter to the search strategies.[22] We set the search timeframe for each strategy starting from two months before the last search was performed in the respective review (to account for a potential lag in the indexing of publications in the relevant databases) and lasting up to the date of the search (see Appendix 9.2).

Furthermore, bibliographies of included studies were searched for additional studies. We considered studies that were published in English, German, French or Italian in our review.

5.1.3 Selection process and data management

The publications identified from the high-quality systematic reviews as well as the follow-up searches were screened in full-text based for their eligibility. We used *DistillerSR*, an online platform for conducting literature reviews, for the entire screening and data extraction process.[23] Three independent reviewers (DM, BS, HY) were involved in the full-text assessment to select eligible RCTs. Disagreements between reviewers were resolved by consensus and the involvement of an experienced senior reviewer (MP).

5.1.4 Data collection

From all relevant RCTs, we extracted information related to study design and characteristics, demographic profiles and other characteristics of study participants, details on the intervention and comparators, and outcome measures. The same reviewers (DM, BS, HY) collected the necessary data independently in consultation with a senior reviewer (MP) for any disagreement

or clarification. Authors of original trials were contacted by email to obtain further information on study design or outcomes where deemed necessary.

5.1.5 Risk of bias (methodological quality) assessment

For all included trials, we assessed the study-level risk of bias related to random sequence generation, allocation concealment, blinding (participants, personnel and outcome assessment), differential loss to follow-up and selective reporting for the finally included studies according to the Cochrane criteria.[24] Overall risk of bias of the included studies was assessed according to the AHRQ standards.[25] As the blinding of patients and personnel was not possible for most interventions, this domain was not considered in the overall assessment.

5.1.6 Data synthesis

Due to the heterogeneity of measured outcomes and time points, we used a narrative synthesis for most of the outcomes or cluster of outcomes (i.e., muscle strength, functional mobility, and health-related quality of life). We conducted meta-analyses (for which we reported both fixed- and random-effects) for a limited number of outcomes deemed of high importance and for which consistent outcome measures were reported by at least three studies. Data reported as medians and interquartile ranges (IQR) were excluded from meta-analyses. We assessed heterogeneity between studies visually using forest plots and statistically using the I^2 statistic. Additionally, we conducted sensitivity analyses in the meta-analyses to assess heterogeneity based on the following factors defined a priori: classification of the comparison (i.e., systematic early vs. late, systematic early vs. less systematic early, and systematic early vs. no rehabilitation), continuation of the intervention post ICU discharge, intervention type (e.g., selective rehabilitation measures), study population characteristics (e.g., selective population), and risk of bias. We did not conduct subgroup analyses according to patient age and ICU LOS as originally planned, as studies did not report results for such populations separately and only analyses across diverse ICU patient populations were possible. However, we report results stratified by our classification of comparators, as outlined above. All statistical analyses were performed in R (version 3.5.2) using the *metafor* package.[26]

5.1.7 Confidence in evidence

We assessed the certainty of the estimates using the standardized Grading of Recommendations Assessment, Development, and Evaluation (GRADE) for those primary outcomes that were

considered the most clinically important and relevant for ICU clinicians and patients in Switzerland.[27–31] These priority outcomes were selected on the basis of the feedback by four Swiss ICU experts who had no prior knowledge of the data.

5.2 Results

In the first stage, our literature search yielded 108 records that were identified via the three high-quality systematic reviews.[13,15,21] In the second stage, we identified 2,299 records through the follow-up search, as well as six additional studies from the reference screening of retrieved RCTs and systematic reviews (Figure 1). Out of these, 12 RCTs fulfilled the eligibility criteria, including data from a total of 679 people randomized to systematic early rehabilitative (experimental) interventions and 625 people randomized to one of the eligible (active) comparator interventions. The reasons for exclusion of studies screened in full-text are provided in Appendix 9.3.

5.2.1 Study characteristics

The baseline characteristics of study participants are presented in Table 2. Participants in the studies were heterogeneous in terms of their demographic characteristics and admission diagnoses. For example, sex distribution between intervention and comparator groups were not well balanced in all studies. Half of the studies included more men than women in both the intervention and comparator groups,[32–37] and the rest had a gender imbalance in one of the comparison groups.[38–42] The age of participants substantially varied between studies, but it was fairly balanced between the intervention and comparator groups in all studies. Most studies included a diverse mix of cases and common admission diagnoses included respiratory problems, cardiovascular disease, sepsis, gastroenterological problems, and trauma, among others. However, some studies were limited to patient collectives with specific conditions: Dong et al. (2016) and Fischer et al. included patients with cardiothoracic surgery only, and Kayambu et al. included sepsis patients only.[34,35,40] The number of study participants varied greatly between studies. While six of the studies included less than 100 participants,[33–35,38,42,43] the other six studies included between 100 and 300 participants.[32,36,37,39–41]

The characteristics of experimental interventions and comparator interventions, as well as outcome measurements are summarized in Table 3. The included studies evaluated various rehabilitative activities mostly consisting of physical therapy targeted at muscle activation. While Brummel et al. additionally evaluated the effect of cognitive therapy combined with physical therapy in one trial arm,[43] none of the studies evaluated interventions consisting of or including diary keeping, ergotherapy or speech therapy.

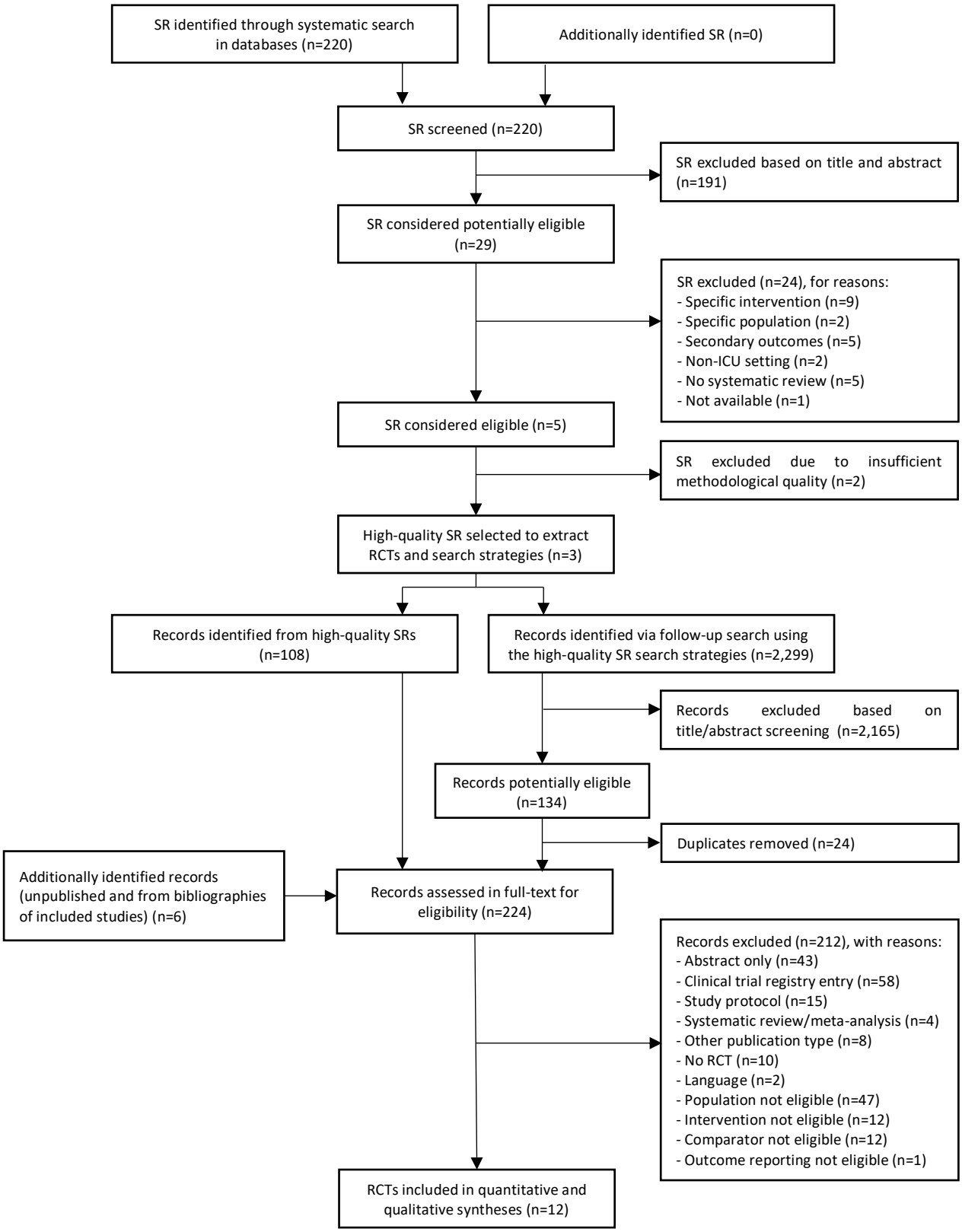


Figure 1. Systematic review study selection process

SR= Systematic Reviews; RCT= Randomized Controlled Trial

We categorized the majority of studies (9/12) as a comparison between systematic early rehabilitation and less systematic early rehabilitation.[32–34,36–38,40,42,43] Schweickert et al.[39] and Morris et al.[41] started the intervention at median 1.5 and 1 day after ICU admission compared to 7.4 and 7 days in their comparator groups, respectively. We therefore considered these two studies as comparisons between systematic early and late rehabilitation (i.e., ≥7 days after admission). All these studies commonly referred to usual or standard care as their comparator groups (which we considered as less systematic by default). Only the study by Fischer et al.[35], which compared systematic early neuromuscular electrical stimulation (NMES) against sham NMES, was categorized as comparing systematic early rehabilitation with no rehabilitation.

Not all studies uniformly reported on how early the intervention started (i.e., time elapsed between ICU admission and the start of first rehabilitative measures). Five studies reported the start time quantitatively, with the time to the first rehabilitative measure taken ranging from 1 to 3 days in intervention groups compared to 2.5 to 7.4 days for the comparator groups.[37,39–41,43] In general, rehabilitation started later in the comparator groups, or were referred to as starting depending on the condition of patients (i.e., less systematic). The other studies did not explicitly report the time to first intervention. Nonetheless, we considered those studies as investigating systematic early rehabilitative interventions based on our contextual assessment of other information provided by the authors. For example, Denehy et al. enrolled patients on the fifth day after ICU admission and designed their intervention to start immediately.[32] While we could not obtain information in the article whether patients actually received early rehabilitation as defined in our review, we decided to include the study based on their protocol according to which they intended to provide early rehabilitation. Furthermore, although we contacted the authors by email, we were unable to obtain information from Dong et al. (2014 and 2016) about the start of the first rehabilitative measure particularly in the comparator groups.[33,40] We therefore categorized their studies as comparing a systematic early against a less systematic intervention, in order to not make an assumption about the timing difference.

Although all studies emphasized on muscle activation, most studies assessed various outcomes, such as mental and cognitive functions beside functional mobility, muscle strength, length of stay, adverse events, and quality of life.

5.2.2 Study-level risk of bias & confidence in evidence

The evaluation of the risk of bias in each included RCT is shown in Figure 2 (for details see Appendix 9.5). In brief, we judged most of the studies to be at high risk of bias in one or more of the assessed criteria. We rated the studies by Schweickert et al.[39] and Eggmann et al.[37] to be of "good overall quality" and the study by Schaller et al.[36] of "fair overall quality", while the rest were

rated as “poor overall quality“. Apart from the impossibility of adequate blinding of patients and personnel, the main reasons for risk of bias were that not all studies reported adequately on all of the relevant dimensions, as well as the lack of a predefined protocol or inconsistency between outcome reporting in the studies and their protocols.

The results from the GRADE assessment regarding our confidence in the evidence on the primary outcomes considered most clinically relevant in Switzerland are presented in Table 9 (page 72). Details on the GRADE evidence profile for these outcomes can be found in Appendix 9.6.

Table 2. Baseline characteristics of study participants

Study	No. of participants		Female [n (%)]		Age, years [Mean(SD)/Median(IQR)]		APACHE II score [Mean(SD)/Median(IQR)]		Baseline diagnoses of patients
	Comparator	Intervention	Comparator	Intervention	Comparator	Intervention	Comparator	Intervention	
(I) Systematic early vs. late rehabilitation									
Schweickert et al. 2009	55	49	23 (41.8)	29 (59.2)	54.4 (46.5–66.4)	57.7 (36.3–69.1)	19.0 (13.3–23.0)	20.0 (15.8–24.0)	Lung injury (55.8%), COPD exacerbation (9.6%), acute exacerbation of asthma (8.7%), sepsis (15.4%), hemorrhage (2.9%), malignancy (2.9%), other (4.8%)
Morris et al. 2016	150	150	82 (54.7)	84 (56.0)	58 (14)	55 (17)	75.0 (27.0)†	76.0 (26.0)†	Acute respiratory failure (without chronic lung disease (67.7%); with chronic lung disease (30.7%)), coma (1.7%)
(II) Systematic early vs. less systematic early rehabilitation									
Dantas et al. 2012	14	14	10 (71.4)	7 (50.0)	50.43 (20.45)	59.07 (15.22)	21.07 (7.23)	23.71 (8.51)	Acute respiratory failure (46.4%), pneumonia (14.3%), cardiomyopathy (0%), collagenosis (3.6%), postoperative period of thoraco-abdominal surgery (10.7%), acute myocardial infarction (7.1%), leptospirosis (3.6%), acute renal insufficiency (3.6%), pulmonary tuberculosis (7.1%), neoplasms (3.6%)
Denehy et al. 2013	76	74	31 (40.8)	24 (32.4)	60.1 (15.8)	61.4 (15.9)	20.7 (7.7)	19.0 (6.0)	Pneumonia (22.7%), cardiac (15.3%), cardiac surgery (30.0%), other surgery (20.7%), liver disease/transplant (14.0%), cardiac arrest (7.3%), sepsis (11.3%), renal (4.7%), other (7.3%)
Brummel et al. 2014‡	22	22	14 (63.6)	9 (40.9)	60 (51–69)	62 (48–67)	27.0 (17.5–31.0)	21.5 (20.0–28.8)	Sepsis/ARDS/pneumonia (59.8%), abdominal surgery (14.9%), other surgery (3.4%), airway protection (9.2%), cirrhosis/GI bleeding (4.6%), CHF/arrhythmia/cardiogenic shock (2.3%), other (5.7%)
		43		15 (34.9)		62 (54–69)		25.0 (19.5–29.5)	
Dong et al. 2014	30	30	10 (33.3)	9 (30.0)	55.5 (16.2)	55.3 (16.1)	16.0 (4.1)	15.0 (4.2)	Abdominal infections (18.3%), ARDS (31.7%), sepsis (6.7%), severe acute pancreatitis (15.0%), community pneumonia (5.0%), aspiration pneumonia (18.3%), COPD exacerbation (5.0%)
Kayambu et al. 2015	24	26	10 (41.7)	8 (30.8)	65.5 (37–85)	62.5 (30–83)	27.0 (6.8)	28.0 (7.6)	Sepsis (100%)
Dong et al. 2016	53	53	31 (58.5)	33 (62.26)	60.2 (15.1)	62.6 (12.8)	17.2 (4.3)	16.3 (4.2)	Coronary artery bypass surgery (100%)
Hodgson et al. 2016	21	29	12 (57.1)	8 (25.9)	53 (15)	64 (12)	15.9 (6.9)	19.8 (9.8)	NA
Schaller et al. 2016	96	104	35 (36.5)	39 (37.5)	64 (45–76)	66 (48–73)	17.0 (11.0–22.0)	16.0 (12.0–22.0)	Visceral surgery (27%), vascular surgery (17%), ENT and ophthalmological surgery (10%), transplant surgery (4%), neurosurgery (3%), orthopedic surgery (3%), thoracic surgery (3%), gynecological surgery (2%), urological surgery (1%), plastic surgery (1%), medical or neurological diagnosis (6%),

Study	No. of participants		Female [n (%)]		Age, years [Mean(SD)/Median(IQR)]		APACHE II score [Mean(SD)/Median(IQR)]		Baseline diagnoses of patients
	Comparator	Intervention	Comparator	Intervention	Comparator	Intervention	Comparator	Intervention	
Eggmann et al. 2018	57	58	16 (28.1)	22 (37.9)	63 (15)	65 (15)	23.0 (7.0)	22.0 (8.0)	Heart surgery (18.3%), neurology/neurosurgery (7.8%), other surgery (12.2%), gastroenterology (12.2%), trauma (3.5%), respiratory insufficiency (21.7%), hemodynamic insufficiency (22.6%), other (1.7%)
(III) Systematic early vs. no rehabilitation									
Fischer et al. 2016	27	27	7 (25.9)	9 (33.3)	69.7 (13.1)	63.3 (15.5)	NA	NA	Cardiothoracic surgery (100%)

† APACHE III score; ‡ three-arm trial; NA= Not available; ARDS=Acute respiratory distress syndrome; COPD=Chronic Obstructive Pulmonary Disease; ENT=Ear, nose and throat; GI: Gastrointestinal; APACHE II= Acute Physiology and Chronic Health Evaluation II score; SD= Standard deviation; IQR= Interquartile range

Table 3. Study interventions, outcome measurements and follow-up timeframes, by comparator group

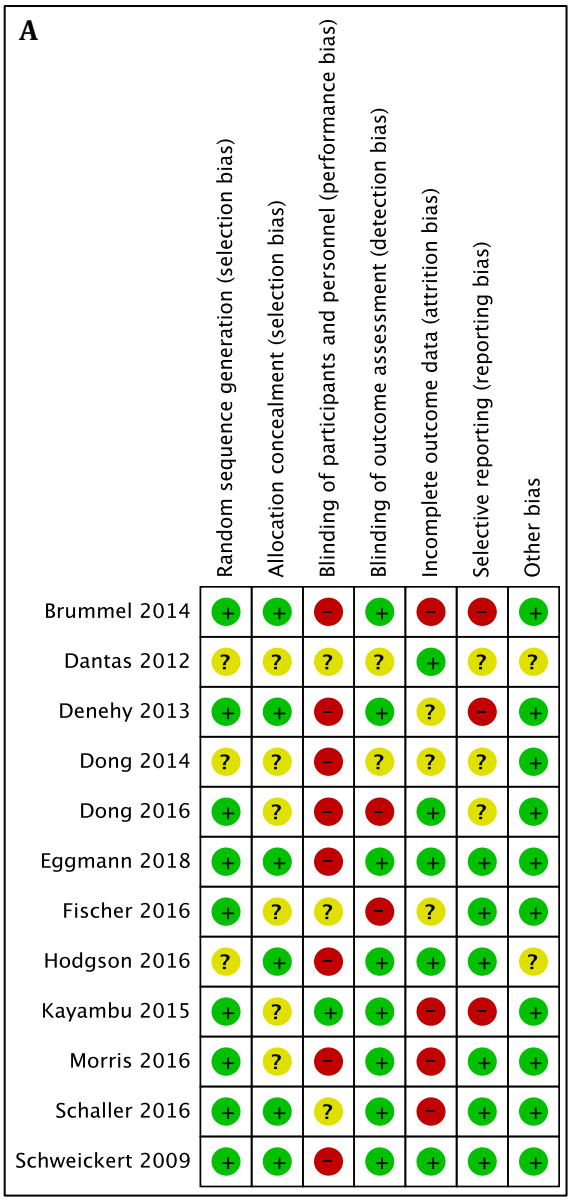
Study	Intervention description		Time to first intervention		Frequency of Intervention		Duration of intervention		Outcomes measured	Follow-up until
	Comparator	Intervention	Comparator	Intervention	Comparator	Intervention	Comparator	Intervention		
(I) Systematic early vs. late rehabilitation										
Schweickert et al. 2009	Standard care: therapy as ordered by the primary care team	Passive range of motion, active range of motion, including bed mobility exercises, ADL and other exercises increasing independency, transfer training (sit to stand, bed to chair, bed to commode), pre-gait exercises, walking	Median 7.4 days (IQR 6.0–10.9) after intubation	Median 1.5 days (IQR 1.0–2.1) after intubation	NA	1X per day	Median 0.0 hrs (IQR 0.0–0.0) per day during ventilation; 0.19 hrs (IQR 0.0–0.38) per day without ventilation	Median 0.32 hrs (IQR 0.17–0.48) per day during ventilation; 0.21 hrs (IQR 0.08–0.33) per day without ventilation	MRC-SS, handgrip force, distance walked without assistance, Barthel Index, ADL, time to first time out of bed, time to standing, time to walking, % of patients reaching independence, % of patients developing ICUAW, hospital mortality, delirium duration, length of hospital stay, duration of mechanical ventilation, ventilator-free days	Hospital discharge
Morris et al. 2016	Usual Care: weekday physical therapy when ordered by the team	Passive range of motions, physical therapy and progressive resistance exercises	Median 7 days (IQR 4–10) after ICU admission	Median 1 days (IQR 0–2) after ICU admission	NA	3X per day, 7 days a week	NA	NA	Hand-held dynamometry, handgrip force, SF-36 PFS, days with delirium, SF-36 MCS, SF-36 overall, in-hospital mortality, MMSE, length of hospital stay, ventilator-free days	Hospital discharge
(II) Systematic early vs. less systematic early rehabilitation										
Dantas et al. 2012	Conventional physical therapy: passive mobilization of the four limbs five times a week and active-assisted exercises according patients' improvements	Passive stretching and mobilization of the four limbs, positioning of the joints, active assisted exercises of the four limbs, transfer from lying to sitting position, active resistive exercises (against gravity or with weight) of upper limbs, cycle ergometry for lower limbs, transfer from sitting to chair, orthostatic posture, counter-resistance exercise on upper limbs, balance exercises, walking	NA (All participants completed first session within 48 hrs after admission)	NA (All participants completed first session within 48 hrs after admission)	5X per week	2X per day	NA	NA	MRC-SS, hospital and ICU LOS, duration of mechanical ventilation	ICU discharge

Study	Intervention description		Time to first intervention		Frequency of Intervention		Duration of intervention		Outcomes measured	Follow-up until
	Comparator	Intervention	Comparator	Intervention	Comparator	Intervention	Comparator	Intervention		
Denehy et al. 2013	Usual care: active bed exercises, sitting out of bed, marching or walking	(a) ICU: Arm and leg active and active resistance movements, moving from sitting to standing, marching in place, (b) Ward: cardiovascular, progressive resistance strength training and functional exercise, (c) Outpatient: cardiovascular, progressive resistance strength training and functional exercise	NA (Enrolment earliest at day 5)	NA (Enrolment earliest at day 5)	NA	1X per day while mechanically ventilated; 2X per day when weaned	NA	15 min per day in mechanically ventilated; 2X15 min per day in weaned; 2X30 min per day on ward; 2X60 min per week as outpatients for 8 weeks	6MWT, TUG test, PFIT, SF-36 PFS, SF-36 PCS, mortality post-discharge, SF-36 MHS, SF-36 MCS, length of hospital stay	Post hospital discharge
Brummel et al. 2014‡	Usual care	Physical therapy: Passive range of motion, sit at the edge of bed, stand, walk, activities of daily living	Median 3 days (IQR 2–6) after enrolment	Median 1 days (IQR 1–1) after enrolment	1-2X per week	1X per day	NA	Median 15.0 min (IQR 10.0–20.0); median 23.0 min (IQR 16.0–26.0)	TUG, ADL, EQ-5D VAS, MMSE, in-hospital mortality, mortality post-discharge, LOS, ventilator-free days	Post hospital discharge
		Cognitive plus physical therapy: same as in physical therapy only + orientation, digit span forward, matric puzzle, real world, digit span reverse, noun list recall, letter-number sequences, pattern recognition		Median 1 days (IQR 1–1) after enrolment, 3 days (IQR 2-4) after ICU admission		Cognitive therapy 2X per day, physical therapy 1X per day		Cognitive therapy 20 min; Physical therapy median 15.0 min for physicians & nurses and median 23.0 min for physiotherapy		
Dong et al. 2014	Control (description not available)	Heading up actively, transferring from supine to sitting position, to sitting at the edge of bed, to sitting in a chair, from sitting to standing, walking bedside	NA	NA	NA	2X per day	NA	Tailored depending on the condition of patients	Time to first time out of bed, duration of mechanical ventilation, in-hospital mortality, ICU LOS	Hospital discharge

Study	Intervention description		Time to first intervention		Frequency of Intervention		Duration of intervention		Outcomes measured	Follow-up until
	Comparator	Intervention	Comparator	Intervention	Comparator	Intervention	Comparator	Intervention		
Kayambu et al. 2015	Standard care: same as in intervention group but less	NMES, passive range of motion, active range of motion, active resistance exercises, sitting up in bed, sitting out of bed, sit to stand, marching on the spot, sitting and standing balance exercises, arm or leg ergometry, tilt table therapy, ambulation	NA (2% completed first session within 48 hrs)	NA (46% completed first session within 48 hrs)	NA	1–2X per day	NA	30 min	MRC-SS, PFIT, SF-36 PFS, SF-36 MHS, HADS in-hospital mortality, mortality post-discharge, hospital LOS, duration of mechanical ventilation, ventilator-free days	ICU discharge
Dong et al. 2016	Therapy only after ICU	Head up, transferring from supine to sitting position, sitting at the edge of bed, sitting in a chair, transferring from sitting to standing, walking along the bed	NA	NA (100% completed first step in first session)	NA	2X per day	NA	NA	In-hospital mortality, hospital LOS, duration of mechanical ventilation	Not specified
Hodgson et al. 2016	Passive movements, same equipment would have been available	Functional activities, active bed exercises, comprising walking as long as possible, standing as long as possible, balance exercises, sitting in or out of bed, sitting balance, sit to stand, rolling	Median 4 days (IQR 3–5)	Median 3 days (IQR 2–4)	1X per day	1X per day	5-10 min per day	30–60 min depending on the condition of patients	MRC-SS, ADL, PFIT, time to standing, time to walking, % of patients developing ICUAW, HADS, EQ-5D VAS, in-hospital mortality, , hospital LOS, duration of mechanical ventilation, ventilator-free days	Post hospital discharge
Schaller et al. 2016	Control	Passive range of motion, sitting, standing, ambulation	NA	NA	NA	1X per day	NA	Tailored depending on the condition of patients	mmFIM, % of patients developing ICUAW, SF-36 (overall score), in-hospital mortality, mortality post-discharge, delirium-free days, hospital LOS, ventilator-free day	Post hospital discharge
Eggmann et al. 2018	Usual care as per the European standard physiotherapy and individually tailored but subject to medical prescription	Motor-assisted bed-cycle, resistant training for upper and lower limbs, sitting on bedside, sitting in a chair, standing, walking	Median 2.2 days (IQR 1.5–2.9) after ICU admission	Median 2.0 days (IQR 1.4–2.8) after ICU admission	1X per day, 5 days per week	Up to 3X per day, 7 days per week	Median 18 min (IQR 14–21)	Median 25 min (IQR 19.5–27)	MRC-SS, handgrip force, 6MWT, TUG, FIM, time to first time out of bed, time to standing, SF-36 PFS, SF-36 PCS, SF-36 MHS, SF-36 MCS, in-hospital mortality, mortality post-discharge, hospital LOS, duration of mechanical ventilation	Post hospital discharge

Study	Intervention description		Time to first intervention		Frequency of Intervention		Duration of intervention		Outcomes measured	Follow-up until
	Comparator	Intervention	Comparator	Intervention	Comparator	Intervention	Comparator	Intervention		
(III) Systematic early vs. no rehabilitation										
Fischer et al. 2016	Sham NMES	NMES	First postoperative day	First postoperative day	2X per day, 7 days a week	2X per day, 7 days a week	30 min per session (i.e., 60 min a day)	30 min per session (i.e., 60 min per day)	ICU mortality, hospital LOS, duration of mechanical ventilation	ICU discharge

‡ Three-arm trial; IQR= Interquartile range; ICU= Intensive care unit; ICUAW= Intensive care unit acquired-weakness; MRC-SS= Medical Research Council Muscle Scale Sum Score; ADL= Activities of Daily Living; 6MWT,= 6-Minute Walking Test; TUG= Timed-up-and-go test; PFIT= Physical Function in the ICU test; FIM= Functional Independence Measure; HADS= Hospital Anxiety and Depression Scale; EQ-5D VAS= EQ-5D visual analogue scale; SF-36= 36-Item Short Form Health Survey; PFS= Physical Function Domain Score; PCS= Physical Health Component Summary Score; MMSE= Mini-Mental State Exam; MHS= Mental Health Domain Score; MCS= Mental Health Component Summary Score; LOS= Length of Stay; NA= Not available.



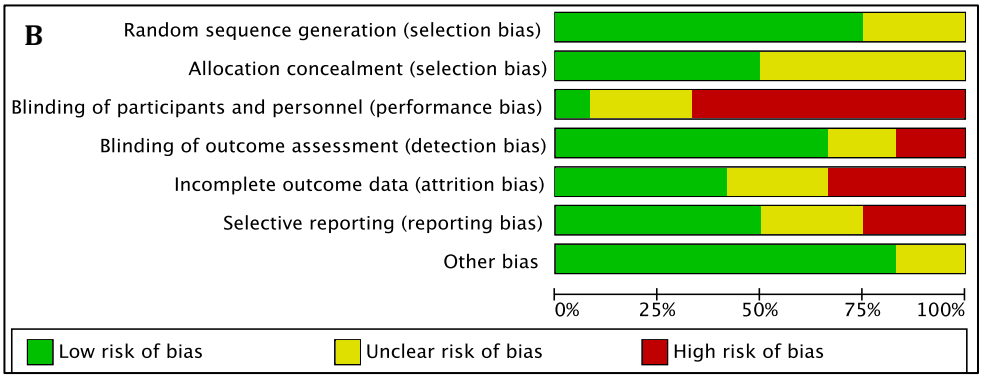


Figure 2. Risk of bias assessment summary

Plot A. Risk of bias summary: review authors' judgments about each risk of bias item for each included study.

Plot B. Risk of bias graph: review authors' judgments about each risk of bias item presented as percentages across all included studies.

5.2.3 Primary outcome: Muscle strength

5.2.3.1 MRC Muscle Scale Sum Score

The MRC Muscle Scale sum score was reported by five studies (Table 4).[34,37–39,42] Dantas et al.[42] found a large and statistically significant difference in MRC score in favor of the systematic early rehabilitation compared with the less systematic early rehabilitation group at ICU discharge. While there was a significant imbalance already at ICU admission, the increase in MRC score was greater in the intervention than the comparator group (6.6 vs. 1.1). Three studies, Kayambu et al.,[34] Hodgson et al.[38] and Eggmann et al.[37] that also compared systematic early with less systematic early rehabilitation, did not find a statistically significant difference in MRC score at ICU discharge. Equally, Schweickert et al.[39], who compared systematic early with late rehabilitation, found no evidence for a difference between groups at hospital discharge.[39]

We performed a pairwise meta-analysis pooling data from the above studies (except Schweickert et al., which reported median estimates), including a total of 203 participants (Figure 3). The mean difference (MD) in MRC scores at ICU discharge was 5.8 (95% confidence interval (CI) -1.4 to 13.0; p=0.12) higher in the intervention group compared to the comparator groups. Heterogeneity was high with an I^2 of 81.7%. Omitting the study by Dantas et al. from the meta-analysis due to the high baseline imbalance resulted in a MD of 2.2 (95% CI -2.5 to 6.9; p=0.36), reducing the heterogeneity to a moderate level (I^2=41.2%; see Appendix 9.4). Overall, we judged the certainty of evidence for a beneficial effect of systematic early rehabilitation on achieved MRC scores to be low compared to late rehabilitation and very low compared to less systematic early rehabilitation (Table 9).

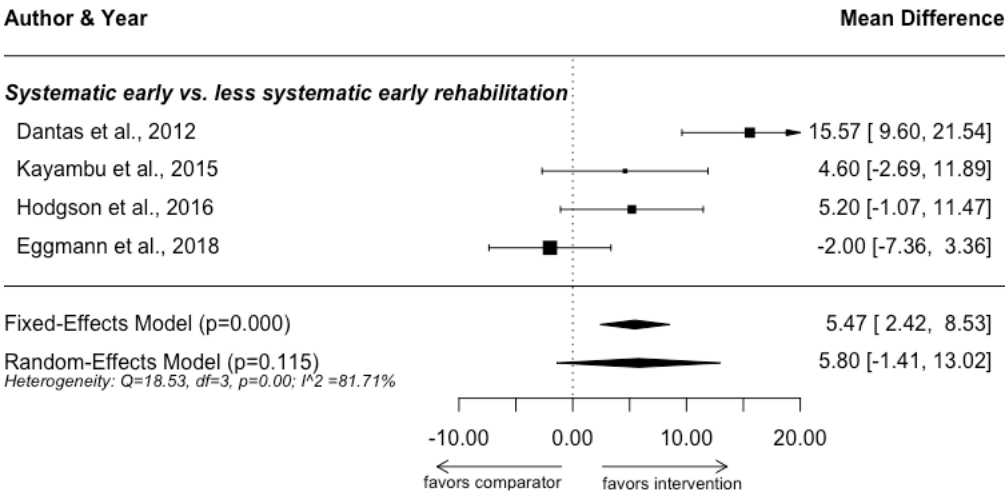


Figure 3. Mean differences in MRC Muscle Scale score at ICU discharge using random- and fixed-effect meta-analyses

5.2.3.2 Hand-held dynamometry

Only Morris et al.[41] published results for hand-held dynamometer strength, which were reported at several time points from ICU discharge up to 6 months post-discharge (Table 4). They observed a steady increase in dynamometer strength in both groups from 20.3 pound (lb) (SD 10.2) to 31.1 lb (SD 10.4) in the systematic early rehabilitation group and from 22.8 lb (SD 10.5) to 30.8 lb (SD 10.5) in the late rehabilitation group from ICU discharge to 6 months of follow-up. However, there was no statistically significant difference between groups in dynamometer strength at any of the reported time points of follow-up.

5.2.3.3 Handgrip strength

Three studies, Schweickert et al.,[39] Morris et al.,[41] and Eggmann et al.,[37] provided data on handgrip strength for various time points (Table 4). None showed a between-group difference in handgrip strength at ICU discharge or at hospital discharge. Handgrip strength was markedly higher in the study by Schweickert et al. [39] compared to the other two studies. In the longer term, Morris et al.[41] reported no difference in handgrip strength between groups up to 6 months of follow-up, while observing an increase from 20.0 kg (calculated SD 10.1) at ICU discharge to 29.3 kg (SD 12.6) at 6 months in the systematic early rehabilitation group and from 20.9 kg (SD 10.5) to 27.2 kg (SD 11.0) in the late rehabilitation group.

Table 4. Outcomes related to muscle strength

Outcome	CG	Study	Follow-up Time Point	Comparator [Mean(SD)/Median(IQR)]	Intervention [Mean(SD)/Median(IQR)]	Reported p-Value
MRC Muscle Scale Sum Score	I	Schweickert et al. 2009	Hospital discharge	48 (0-58)	52 (25-58)	0.38
	II	Dantas et al. 2012	ICU discharge	40.3 (10.5)	55.86 (4.4)	<0.001
		Kayambu et al. 2015	ICU discharge	47.3 (13.6)	51.9 (10.5)	0.24
		Hodgson et al. 2016	ICU discharge	45.2 (13.2)	50.4 (7.5)	0.1
		Eggmann et al. 2018	ICU discharge	44.4 (11.7)	42.4 (13.1)	0.46
Hand-held dynamometry (in lb)	I	Morris et al. 2016*	ICU discharge	22.8 (10.5)	20.3 (10.2)	0.16
			Hospital discharge	23.9 (10.7)	23.7 (10.7)	0.90
			2 months follow-up	28.0 (10.5)	28.5 (10.5)	0.76
			4 months follow-up	29.6 (10.4)	28.8 (10.6)	0.63
			6 months follow-up	30.8 (10.5)	31.1 (10.4)	0.82
Handgrip strength (in kg)	I	Schweickert et al. 2009	Hospital discharge	35 (0-57)	39 (10-58)	0.67
		Morris et al. 2016*	ICU discharge	20.9 (10.5)	20 (10.1)	0.6
			Hospital discharge	24.3 (10.4)	22.6 (10.4)	0.25
			2 months follow-up	26.0 (9.4)	27.2 (9.8)	0.43
			4 months follow-up	27.2 (10.1)	29.0 (10.5)	0.25
			6 months follow-up	27.2 (11.0)	29.3 (10.9)	0.23
	II	Eggmann et al. 2018	ICU discharge	19.6 (13.6)	20.5 (12.6)	0.78

**=SD calculated from 95%CI; CG.=Comparator group: I=systematic early vs. late rehabilitation, II=systematic early vs. less systematic early rehabilitation*

5.2.4 Primary outcome: Functional mobility

5.2.4.1 Barthel Index (BI)

Schweickert et al.[39] was the only trial reporting on the achieved BI (Table 5). While intervention and comparator groups were comparable in BI at baseline prior to ICU admission, the study reported statistical significance for a difference in BI between groups at hospital discharge in favor of the systematic early rehabilitation group.

5.2.4.2 Activities of Daily Living (ADL)

Three studies, Schweickert et al.,[39] Brummel et al.,[43] and Hodgson et al.,[38] reported on the performance of participants in ADL at different time points (Table 5). Schweickert et al. found a higher number in independent ADL achieved with systematic early compared with late rehabilitation at both ICU and hospital discharge, although the difference did not reach statistical significance. Brummel et al. reported no difference in ADL status both at hospital discharge, as well as after 3 months of follow-up between the two intervention groups (physical therapy and cognitive plus physical therapy) and the usual care group, which was considered to consist of less systematic early rehabilitation. Hodgson et al. measured ADL at 6 months of follow-up, but also did not find a difference between groups.

5.2.4.3 Functional Independence Measure (FIM)

Two studies, Schaller et al.[36] and Eggmann et al.[37] provided data on FIM at ICU and hospital discharge (Table 5). Using the mini-modified version of the FIM, Schaller et al. found statistically significant evidence for a difference between the systematic early rehabilitation and the less systematic early comparator group both at ICU and hospital discharge. In contrast, Eggmann et al. found no difference between groups at both time points using the FIM.

5.2.4.4 Physical Function in the ICU Test (PFIT)

Results on the PFIT at ICU discharge were provided by three studies: Denehy et al.,[32] Kayambu et al.,[34] and Hodgson et al.[38] (Table 5). None of them found evidence for a difference between intervention and comparator groups. Denehy et al. showed a similar increase in PFIT scores from baseline at admission to ICU discharge in both groups (from 5.1 (SD 3.1) to 7.7 (SD 1.7) in the intervention group and from 5.2 (SD 3.0) to 8.0 (SD 1.5) in the comparator group).

A pairwise meta-analysis of three studies, Denehy et al., Kayambu et al., and Hodgson et al. including data from 209 participants showed no difference between groups (MD -0.2; 95% CI -0.7 to 0.3; p=0.46; I^2=0.0%) (Figure 4).

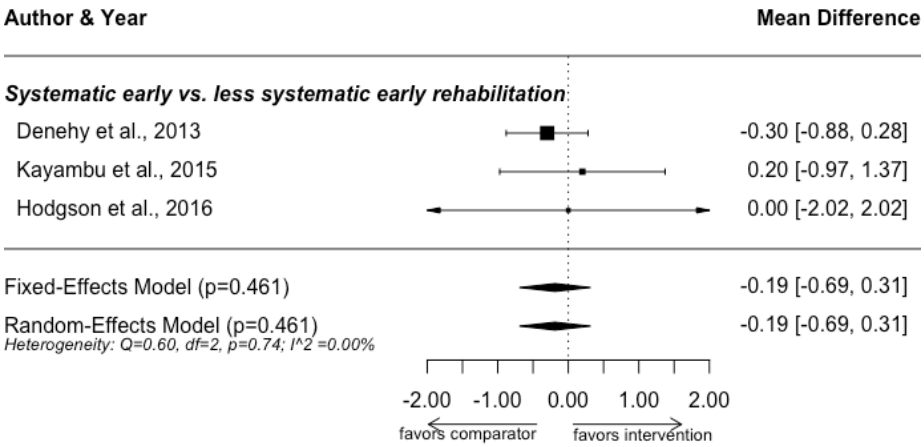


Figure 4. Mean differences in PFIT at ICU discharge using random- and fixed-effect meta-analyses

5.2.4.5 Timed Up-and-Go Test (TUG)

Three studies, Denehy et al.,[32] Brummel et al.,[43] and Eggmann et al.[37], published results on the TUG (Table 5). None of the studies found a difference in TUG time between intervention and comparator groups at ICU or hospital discharge, as well as at 3 months, 6 months, or 12 months post discharge. Denehy et al. observed a rapid improvement in the performance in the TUG between ICU and hospital discharge in both groups, with further improvements occurring until 3 months post-discharge and a stabilization of performance up to 12 months of follow-up. However, they reported no difference between groups in the rate of improvement.

5.2.4.6 6-Minute Walking Test (6MWT) and distance walked without assistance

Denehy et al.[32] and Eggmann et al.[37] provided data on 6MWT, both comparing systematic early rehabilitation with less systematic early rehabilitation (Table 5). On average, the achieved walking distances were comparable between participants of both studies. Denehy et al. found a marked increase in walking distance for both groups from ICU admission until 3 months of follow-up, with a slight further increase until 12 months. While the comparator group had a considerably higher 6MWT distance at ICU discharge, distances did not differ between groups at any later time point. The same study reported a statistically significant difference in the mean change from baseline at both 3 months (MD 63.67 meters; 95% CI 14.17 to 113.18) and 12 months of follow-

up (MD 72.65 meters; 95% CI 9.29 to 135.81) in favor of systematic early rehabilitation compared with less systematic early rehabilitation. Eggmann et al. did not find evidence for a difference in 6MWT distance between groups at hospital discharge (MD 22.75 meters; 95% CI -81.66 to 36.16). Overall, we judged the certainty of evidence to be low for this outcome when comparing systematic early vs. less systematic early rehabilitation (Table 9).

Additionally, Schweickert et al.[39] measured the total distance walked without assistance at hospital discharge, for which they reported a statistically significant difference in favor of the systematic early rehabilitation group (33.4 meters; IQR 0-91.4) compared with the late rehabilitation group (0 meters; IQR 0-30.4).

5.2.4.7 Mobility milestones

Time to first time out of bed

Three studies, Schweickert et al.,[39] Dong et al. (2014),[33] and Eggmann et al.,[37] reported on the time to first time out of bed (Table 5). Both Schweickert et al. and Dong et al. (2014) observed a marked difference between intervention and comparator groups with significantly shorter times needed to first time out of bed in the intervention groups, comparing systematic early with late rehabilitation and less systematic early rehabilitation, respectively. In contrast, Eggmann et al. found no evidence of a between-group difference when comparing systematic early vs. less systematic early rehabilitation.

Time to standing

Results for the time needed to standing were reported by three studies, including Schweickert et al.,[39] Eggmann et al.,[37] and Hodgson et al.[38] (Table 5). While Schweickert et al. found a statistically significant difference between groups in favor of systematic early rehabilitation compared to late rehabilitation, Hodgson et al. did not find a difference comparing systematic early with less systematic early rehabilitation. Eggmann et al. reported a longer time needed for patients in the intervention group, but did not draw a conclusion due to the very limited amount of data (n=3).

Time to walking

Schweickert et al.,[39] Eggmann et al.,[37] and Hodgson et al.[38] also reported data on the time needed for patients to start walking (Table 5). Schweickert et al. reported a statistically significant difference between groups, with a shorter time until patients were able to walk when receiving systematic early rehabilitation compared with late rehabilitation. Hodgson et al. found no

difference between groups and Eggmann et al. provided insufficient data to come to a conclusion, both comparing systematic early with less systematic early rehabilitation. We judged the certainty of the evidence for a decrease in the time necessary until patients are able to walk with systematic early rehabilitation to be low compared to late rehabilitation, and very low compared to less systematic early rehabilitation (Table 9).

5.2.4.8 Return to independence from assistance

Schweickert et al.[39] was the only study reporting on the proportion of patients returning to independence from assistance until hospital discharge (Table 5). They found statistically significant evidence that a higher proportion of patients in the systematic early rehabilitation group reached independence compared with the late rehabilitation group. We judged the certainty of evidence for a beneficial effect on the return to independence to be low for this comparator (Table 9).

5.2.4.9 SF-36 Physical Function Domain Score (PFS) & SF-36 Physical Component Summary Score (PCS)

Four studies reported on SF-36 PFS (Denehy et al.,[32] Kayambu et al.,[34] Morris et al.,[41] and Eggmann et al.[37]) and three studies presented results on SF-36 PCS (Denehy et al., Morris et al., and Eggmann et al.) at various time points (Table 5). SF-36 PFS reported by Kayambu et al. and Eggmann et al. were substantially higher than scores measured by Denehy et al. and Morris et al. While Morris et al. observed a marked increase in SF-36 PFS up to 6 months, Denehy et al. reported only a minimal increase from baseline up to 12 months of follow-up. However, Denehy et al. found a statistically significant difference in the change in SF-36 PFS from baseline to 3 months post discharge in favor of the intervention group (MD 6.8; 95% CI 1.2 to 12.5), which was no longer evident after 12 months. Morris et al. and Kayambu et al. found statistically significantly higher SF-36 PFS in the intervention group at 6 months follow-up comparing systematic early with later and less systematic early rehabilitation, respectively. There was no between-group difference in these two studies at other time points of measurement, nor in the studies by Denehy et al. and Eggmann et al. investigating systematic early vs. less systematic early rehabilitation. Similar observations were made for the SF-36 PCS, with a slight increase in scores in both groups over time up to 12 months in the studies by Morris et al. and Denehy et al. Denehy et al. found a statistically significantly higher change from baseline in the intervention group at 3 months of follow-up (MD 5.6; 95% CI 0.1 to 11.1), which was no longer significant at 12 months. While Morris et al. reported statistically significantly higher SF-36 PCS at 6 months in the systematic early rehabilitation

group, no between-group difference was reported at any other time point. No between-group difference in SF-36 PCS was found in the study by Eggmann et al.

We performed pairwise meta-analyses for the SF-36 PFS and the SF-36 PCS at 6 months after hospital discharge (Figure 5 and Figure 6). For SF-36 PFS, we included the results from three studies (Denehy et al., Kayambu et al., and Morris et al.) with a total of 287 patients, resulting in a MD of 8.7 (95% CI -4.7 to 22.1; p=0.20) favoring systematic early rehabilitation. The effect was statistically significant for systematic early vs. late rehabilitation, while it was not statistically significant for systematic early vs. less systematic early rehabilitation. Heterogeneity was substantial (I^2=83.1%) and could not adequately be explained in sensitivity analyses based on the prespecified domains. The meta-analysis for SF-36 PCS included results from three studies (Denehy et al., Morris et al., and Eggmann et al.) with data from 313 patients, and showed no difference between groups overall (MD 0.01; 95% CI -3.97 to 3.98; p=0.997). However, when stratifying the results by comparator, there was a statistically significant effect in favor of systematic early rehabilitation compared to late rehabilitation. There was no significant difference when comparing systematic early to less systematic early rehabilitation, with a discrete tendency in favor of the comparator groups. Heterogeneity was moderate with an I^2 of 56.4%. Overall, we found no conclusive evidence for a difference between intervention and comparator groups in both SF-36 PFS and PCS at 6 months after hospital discharge, while a beneficial effect appeared to be present for the comparator of systematic early vs. late rehabilitation. We judged the certainty of evidence regarding SF-36 PFS and SF-36 PCS to be very low for both systematic early vs. late and systematic early vs. less systematic early rehabilitation (Table 9).

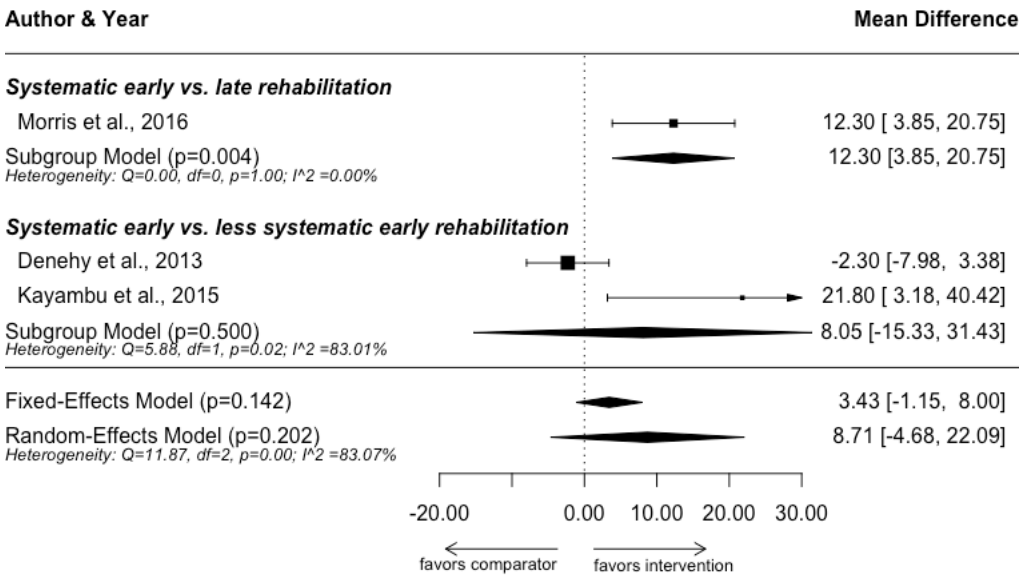


Figure 5. Mean differences in SF-36 Physical Function Domain Score (PFS) at 6 months of follow-up using random- and fixed-effect meta-analyses.

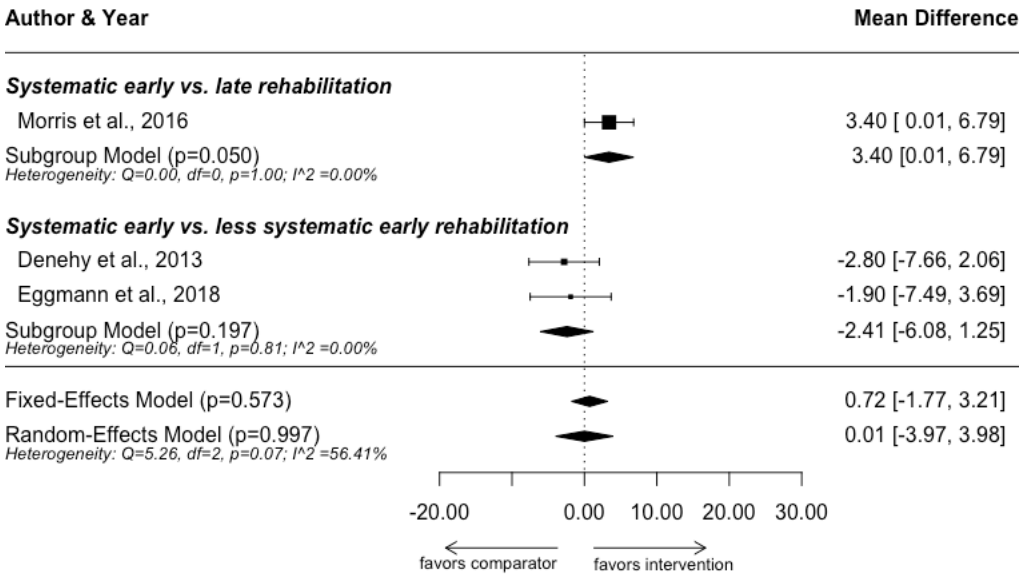


Figure 6. Mean differences in SF-36 Physical Component Summary Score (PCS) at 6 months of follow-up using random- and fixed-effect meta-analyses

5.2.4.10 Patients developing ICU-Acquired Weakness (ICUAW)

Four studies, Schweickert et al.,[39] Denehy et al.,[32] Hodgson et al.,[38] and Schaller et al.,[36] reported on the number of patients who developed ICUAW over the course of hospitalization (Table 5).

None of these studies found a statistically significant difference in the incidence of ICUAW between systematic early rehabilitation and both late or less systematic early rehabilitation groups. Pairwise meta-analyses pooling data from all four studies, with a total of 499 participants, showed an almost 20% risk reduction for the development ICUAW in the intervention groups (risk ratio (RR) 0.82; 95% CI 0.60 to 1.11; p=0.20). However, this effect did not reach statistical significance overall or for the comparator categories individually (Figure 7). We judged the evidence for a beneficial effect of systematic early rehabilitation as low when compared to late rehabilitation, and very low when compared to less systematic early rehabilitation (Table 9).

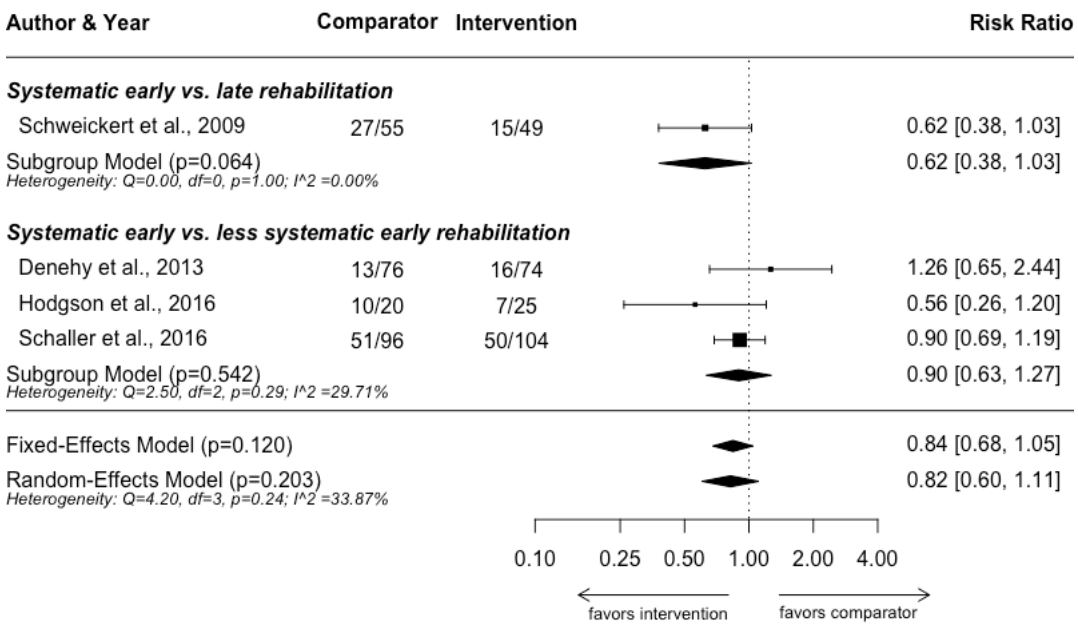


Figure 7. Effects of systematic early rehabilitation (risk ratio) on development of ICUAW using random- and fixed-effect meta-analyses

Table 5. Outcomes related to functional mobility

Outcome	CG	Study	Follow-up Time Point	Comparator [Mean(SD)/ Median(IQR)/n(%)]	Intervention [Mean(SD)/ Median(IQR)/n(%)]	Reported p-Value
Barthel Index	I	Schweickert et al. 2009	Hospital discharge	55 (0-85)	75 (7.5-95)	0.05
Activities of Daily Living (ADL)	I	Schweickert et al. 2009	ICU discharge	0 (0-5)	3 (0-5)	0.15
			Hospital discharge	4 (0-6)	6 (0-6)	0.06
	II	Brummel et al. 2014*	Hospital discharge	1 (0-2.8)	0.5 (0-4.5) / 3 (1-6)	0.25
			3 months follow-up	0 (0-0)	0 (0-1) / 0 (0-2)	0.69
		Hodgson et al. 2016	6 months follow-up	7 (1.3)	6.5 (1.9)	0.81
Functional Independence Measure (FIM)	II	Schaller et al. 2016**	ICU discharge	3 (1-4)	4 (2-5)	0.009
			Hospital discharge	5 (2-8)	8 (4-8)	0.0002
		Eggmann et al. 2018	ICU discharge	28.5 (19.5-41.5)	28.5 (21-42)	0.79
			Hospital discharge	99 (24)	101 (22)	0.66
Physical Function in the ICU Test (PFIT)	II	Denehy et al. 2013	ICU discharge	8 (1.5)	7.7 (1.7)	-
		Kayambu et al. 2015	ICU discharge	5.4 (1.7)	5.6 (2.1)	0.61
		Hodgson et al. 2016	ICU discharge	7.4 (3.6)	7.4 (3.6)	0.83
Timed up-and-go test (TUG; in sec)	II	Denehy et al. 2013	ICU discharge	36.1 (42.9)	41.1 (43.2)	-
			Hospital discharge	12.9 (6.6)	18.8 (24.5)	-
			3 months follow-up	11.6 (11.2)	12.2 (10.0)	-
			6 months follow-up	12.9 (17.9)	9.8 (5.1)	-
			12 months follow-up	14.2 (24.7)	10.3 (6.2)	-
		Brummel et al. 2014*	Hospital discharge	33 (18.5-68.5)	16 (12-22) / 17 (11-27)	0.2
			3 months follow-up	8 (7.5-13.5)	10 (8-13) / 11 (9-13)	0.79
		Eggmann et al. 2018	Hospital discharge	16 (10.3-29)	19.5 (11.5-25)	0.54
6-minute walking test (6MWT; in meters)	II	Denehy et al. 2013	ICU discharge	187.9 (126.1)	146.4 (79.4)	-
			Hospital discharge	266.7 (136.8)	244.2 (124.0)	-
			3 months follow-up	382.1 (139.4)	384.5 (147.9)	-
			6 months follow-up	402.4 (166.6)	394.2 (156.2)	-
			12 months follow-up	409.6 (158.5)	433.8 (150.7)	-
		Eggmann et al. 2018	Hospital discharge	246 (167)	223 (133)	0.45

Distance walked without assistance (in meters)	I	Schweickert et al. 2009	Hospital discharge	0 (0-30.4)	33.4 (0-91.4)	0.004
Time to first time out of bed (in days)	I	Schweickert et al. 2009		6.6 (4.2-8.3)	1.7 (1.1-3)	<0.0001
	II	Dong et al. 2014		14.9 (4.7)	3.8 (1.2)	<0.01
		Eggmann et al. 2018		5 (2-7)	4 (2-7)	0.45
Time to standing (in days)	I	Schweickert et al. 2009		6 (4.5-8.9)	3.2 (1.5-5.6)	<0.0001
	II	Hodgson et al. 2016		3 (2.4-4.5)	3 (2-6)	0.88
		Eggmann et al. 2018		7.5 (3-14)	10 (n=3)	-
Time to walking (in days)	I	Schweickert et al. 2009		7.3 (4.9-9.6)	3.8 (1.9-5.8)	<0.0001
	II	Hodgson et al. 2016		6 (3-8)	6 (3-12)	0.97
		Eggmann et al. 2018		23 (n=2)	8 (n=1)	-
Patients returning to independence from assistance	I	Schweickert et al. 2009	Hospital discharge	29 (59%)	19 (35%)	0.02
SF-36 Physical Function Domain Score (PFS)	I	Morris et al. 2016***	Hospital discharge	38.3 (28.1)	38.4 (27.8)	0.97
			2 months follow-up	43.0 (26.9)	47.4 (27.2)	0.29
			4 months follow-up	47.2 (26.0)	52.2 (26.0)	0.22
			6 months follow-up	43.6 (27.7)	55.9 (27.0)	0.001
	II	Denehy et al. 2013	3 months follow-up	42.3 (12)	39.9 (14.4)	-
			6 months follow-up	42.4 (13.7)	40.1 (14.7)	-
			12 months follow-up	44 (11.2)	41.4 (12.5)	-
		Kayambu et al. 2015	6 months follow-up	60 (29.4)	81.8 (22.2)	0.04
		Eggmann et al. 2018	6 months follow-up	75 (50-85)	75 (45-85)	0.68
SF-36 Physical Health Component Summary Score (PCS)	I	Morris et al. 2016***	Hospital discharge	30.3 (9.7)	30.2 (9.8)	0.96
			2 months follow-up	32.2 (7.6)	33.4 (9.9)	0.43
			4 months follow-up	33.7 (10.3)	36.0 (10.4)	0.16
			6 months follow-up	33.5 (11.1)	36.9 (10.9)	0.05
	II	Denehy et al. 2013	3 months follow-up	42.1 (9.6)	41 (11.4)	-
			6 months follow-up	44.4 (10.7)	41.6 (13.2)	-
			12 months follow-up	46.2 (9.4)	44.7 (10.9)	-
		Eggmann et al. 2018	6 months follow-up	42.7 (10.4)	40.8 (11.1)	0.52
Patients developing ICUAW	I	Schweickert et al. 2009	Hospital discharge	27/55 (49.1%)	15/49 (30.6%)	0.09
	II	Denehy et al. 2013	Hospital discharge	13/76 (17.1%)	16/74 (21.6%)	-
		Hodgson et al. 2016	ICU discharge	10/20 (50%)	7/25 (28%)	0.13
		Schaller et al. 2016	Hospital discharge	51/96 (53.1%)	50/104 (48.1%)	0.95

=physical therapy group / physical+cognitive therapy group, **=mmFIM, *=SD calculated from 95%CI; CG=Comparator group: I=systematic early vs. late rehabilitation, II=systematic early vs. less systematic early* rehabilitation

5.2.5 Secondary outcome: Cognitive function and mental health

5.2.5.1 Delirium duration and delirium-free days

Schweickert et al.[39] and Morris et al.[41] provided data on delirium duration comparing systematic early with late rehabilitation (Table 6). While Schweickert et al. reported a statistically significant reduction in days with delirium in the intervention group both during ICU and hospital stay, Morris et al. found no such difference. Delirium free days (out of 28 days) was reported as an outcome by Schaller et al.[36] only, who found a statistically significantly higher number of delirium free days in the intervention group compared to the comparator group consisting of less systematic early rehabilitation.

5.2.5.2 Mini Mental State Exam (MMSE)

MMSE scores were reported by two studies only (Brummel et al.[43] and Morris et al.[41]) at several time points (Table 6). Brummel et al. measured higher MMSE scores in the physical plus cognitive therapy group at hospital discharge compared with the less systematic early comparator group. However, they did not find a statistically significant difference between groups at hospital discharge or at 3 months follow-up. Morris et al. did not report any difference in performance in the MMSE at any of the measured time points, comparing systematic early with late rehabilitation.

5.2.5.3 Hospital Anxiety and Depression Scale (HADS)

Two studies reported results on the HADS (Table 6). Neither Kayambu et al.[34] nor Hodgson et al.[38] found evidence for reduced HADS scores at ICU discharge or at 6 months follow-up, comparing systematic early with less systematic early rehabilitation.

5.2.5.4 SF-36 Mental Health Domain Score (MHS) & SF-36 Mental Health Component Score (MCS)

Three studies each reported on SF-36 MHS (Denehy et al.,[32] Kayambu et al.,[34] and Eggmann et al.[37]) and SF-36 MCS (Denehy et al.,[32] Morris et al.,[41] and Eggmann et al. [37]) at several time points (Table 6). SF-36 MHS measured by Eggmann et al. were substantially higher than those measured by Denehy et al. and Kayambu et al. Denehy et al. observed relatively stable scores over the 12 months of follow-up. Among the studies comparing systematic early with less systematic early rehabilitation, Eggmann et al. found statistically significantly higher SF-36 MHS in the intervention group at 6 months of follow-up, while both Denehy et al. and Kayambu et al. did not find a difference at any of the measured time points. Regarding SF-36 MCS, both Morris et al. and Denehy et al. found an increase in scores from baseline to 6 and 12 months post discharge, respectively. However, none of the studies found a difference in SF-36 MCS between intervention and comparator groups at any time point.

We performed pairwise meta-analyses for the SF-36 MCS at 6 months after hospital discharge including data from Denehy et al., Morris et al., and Eggmann et al., with a total of 313 patients (Figure 8). The meta-analysis resulted in a MD of 2.1 (95% CI -0.6 to 4.7; p=0.12; I^2=0.0%) in favor of the systematic early rehabilitation groups, while the between-group difference in SF-36 MCS did not reach statistical significance.

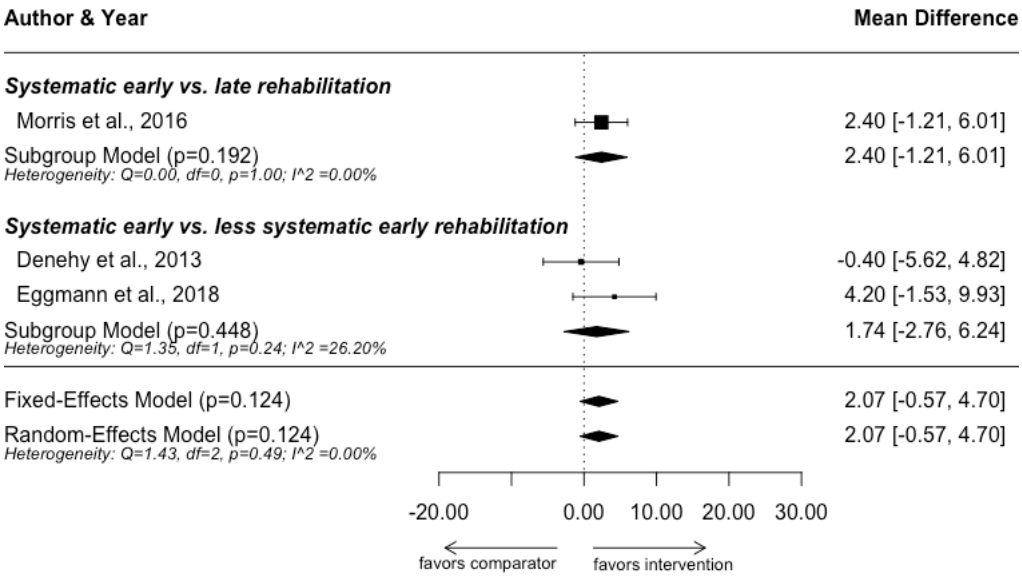


Figure 8. Mean differences in SF-36 Mental Health Component Score at 6 months using random- and fixed-effect meta-analyses

Table 6. Outcomes related to cognitive function and mental health

Outcome	CG	Study	Follow-up Time Point	Comparator [Mean(SD)/ Median(IQR)/n(%)]	Intervention [Mean(SD)/ Median(IQR)/n(%)]	Reported p-Value
Delirium duration (in days)	I	Schweickert et al. 2009	ICU discharge	4 (2-7)	2 (0-6)	0.03
			Hospital discharge	4 (2-8)	2 (0-6)	0.02
		Morris et al. 2016	Hospital discharge	1 (0-3)	1 (0-4)	0.43
Delirium-free days	II	Schaller et al. 2016	Hospital discharge	22 (15-25)	25 (16-27)	0.016
Mini-Mental State Exam (MMSE)	I	Morris et al. 2016**	Hospital discharge	25.1 (3.9)	25.4 (3.8)	0.55
			2 months follow-up	26.8 (3.8)	26.7 (3.8)	0.86
			4 months follow-up	27.2 (2.9)	27.6 (2.8)	0.37
			6 months follow-up	27.0 (2.8)	27.6 (2.8)	0.17
	II	Brummel et al. 2014*	Hospital discharge	25 (24-28)	25.6 (23.2-27.8) / 28 (25.8-29.0)	0.09
			3 months follow-up	28 (26.8-29)	29 (27.0-30.0) / 29 (27.9-29.8)	0.64
Hospital Anxiety and Depression Scale (HADS)	II	Kayambu et al. 2015	ICU discharge	8/19 (42.1%)	6/16 (37.5%)	0.09
		Hodgson et al. 2016	6 months follow-up	11.3 (7.1)	11.6 (9.1)	0.91
SF-36 Mental Health Domain Score (MHS)	II	Denehy et al. 2013	3 months follow-up	44.7 (14.0)	45.67 (14.2)	-
			6 months follow-up	45.6 (13.0)	44.30 (14.8)	-
			12 months follow-up	45.9 (16.5)	46.69 (13.1)	-
		Kayambu et al. 2015	6 months follow-up	37.3 (7.4)	38.6 (11.5)	0.71
		Eggmann et al. 2018	6 months follow-up	70 (64-76)	84 (68-88)	0.023
SF-36 Mental Health Component Summary Score (MCS)	I	Morris et al. 2016**	Hospital discharge	43.3 (11.0)	43.6 (11.1)	0.86
			2 months follow-up	46.2 (11.6)	46.3 (12.0)	0.96
			4 months follow-up	47.7 (11.0)	47.8 (11.1)	0.91
			6 months follow-up	46.4 (11.8)	48.8 (11.6)	0.19
	II	Denehy et al. 2013	3 months follow-up	46.3 (12)	46.0 (13.9)	-
			6 months follow-up	46.2 (12.9)	45.8 (12.9)	-
			12 months follow-up	44.7 (15.7)	47.9 (12.3)	-
		Eggmann et al. 2018	6 months follow-up	45.2 (11.4)	49.4 (10.3)	0.15

**=physical therapy group / physical+cognitive therapy group, **=SD calculated from 95%CI; CG=Comparator group: I=systematic early vs. late rehabilitation, II=systematic early vs. less systematic early rehabilitation*

5.2.6 Secondary outcome: Quality of life and mortality

5.2.6.1 EQ-5D Visual Analog Scale (VAS)

Results on the EQ-5D VAS were reported by Brummel et al.[43] and Hodgson et al.[38] only (Table 7). Both studies found no difference between intervention and comparator groups at 3 months or 6 months, respectively, comparing systematic early with less systematic early rehabilitation.

5.2.6.2 SF-36 overall score

Only Schaller et al.[36] reported the SF-36 overall score, but did not find a difference between intervention and comparator group at 3 months following hospital discharge comparing systematic early with less systematic early rehabilitation (Table 7). Domain-specific and component scores related to physical function and mental health are discussed in the respective chapters above.

5.2.6.3 Mortality

In-hospital mortality

Four studies provided data for ICU mortality[34,35,37,38] and eight for hospital mortality (Table 7).[33,36–41,43] None of the trials individually reported a statistically significant difference in ICU or hospital mortality between the intervention and the comparator groups.

We performed a pairwise meta-analysis for in-hospital mortality pooling data from all eight studies (1,033 participants) (Figure 9). While patients in the intervention groups had a 4% reduction in the risk of dying during hospitalization compared to the comparator groups, we found no statistical evidence in support of such an effect overall (RR 0.96; 95% CI 0.70 to 1.32; p=0.8; I^2 0.0%), nor for any comparator category individually. It is to note that Hodgson et al. and Schaller et al. observed a higher in-hospital mortality in the intervention groups compared to the comparator groups, with the intervention group in the study by Schaller et al. having almost double the mortality of the comparator group.

Mortality after discharge

Mortality after hospital discharge was reported by six studies[32,34,36,37,41,43] (Table 7). None of these studies reported a statistically significant difference between intervention and comparator groups at any time point of follow-up.

We conducted pairwise meta-analyses for mortality at 6 months after hospital discharge, including data from four studies (Denehy et al., Kayambu et al., Morris et al., and Eggmann et al.) and a total of 615 participants (Figure 10). Overall, the mortality after 6 months was increased by 9% in participants randomized to the systematic early rehabilitation groups compared to those in comparator groups; however, the excess risk was not statistically significant (RR 1.09; 95% CI 0.68 to 1.75; p=0.72). Equally, there was no statistically significant difference for the comparators of less systematic early and late rehabilitation individually. However, there was moderate heterogeneity (I^2= 53.6%) due to the surprisingly high mortality in the intervention group reported by Kayambu et al. Omitting this study from the meta-analysis lowered the relative mortality risk to 0.94 (95% CI 0.69 to 1.29; p=0.71), with no further unexplained heterogeneity (I^2=0.0%; see Appendix 9.4). In summary, none of the two models found any statistical evidence for a difference in mortality between groups at 6 months after hospital discharge.

Table 7. Outcomes related to quality of life and mortality

Outcome	CG	Study	Follow-up Time Point	Comparator [Mean(SD)/ Median(IQR)/n(%)]	Intervention [Mean(SD)/ Median(IQR)/n(%)]	Reported p-Value
Quality of life						
EQ-5D VAS	II	Brummel et al. 2014*	3 months follow-up	75 (61-86)	80 (62-89) / 75 (54-80)	0.44
		Hodgson et al. 2016	6 months follow-up	68 (19)	61 (19)	0.25
SF-36 Score (overall)	II	Schaller et al. 2016	3 months follow-up	63.0 (19.9)	61.3 (18.4)	0.69
Mortality						
ICU mortality	II	Kayambu et al. 2015		1/24 (4.2%)	3/26 (11.5%)	0.34
		Hodgson et al. 2016		1/21 (4.8%)	2/29 (6.9%)	0.75
		Eggmann et al. 2018		10/57 (17.5%)	9/58 (15.5%)	0.77
	III	Fischer et al. 2016		3/27 (11.1%)	1/27 (3.7%)	-
In-hospital mortality	I	Schweickert et al. 2009		14/55 (25.5%)	9/49 (18.4%)	0.53
		Morris et al. 2016		18/150 (12.0%)	18/150 (12.0%)	-
	II	Brummel et al. 2014*		6/22 (27.3%)	6/22 (27.3%) / 11/43 (25.6%)	-
		Dong et al. 2014		3/30 (10.0%)	2/30 (6.7%)	1.0
		Dong et al. 2016		3/53 (5.7%)	2/53 (3.8%)	0.65
		Hodgson et al. 2016		1/21 (4.8%)	2/29 (6.9%)	0.75
		Schaller et al. 2016		8/96 (8.3%)	17/104 (16.4%)	0.09
		Eggmann et al. 2018		14/57 (24.6%)	10/58 (17.2%)	0.33
3-month mortality	II	Denehy et al. 2013		13/76 (17.1%)	10/74 (13.5%)	-
		Brummel et al. 2014*		9/22 (40.9%)	7/22 (31.8%) / 16/43 (37.2%)	-
		Kayambu et al. 2015		2/24 (8.3%)	8/26 (30.8%)	0.08
		Schaller et al. 2016		15/96 (15.6%)	21/104 (20.2%)	0.35
6-month mortality	I	Morris et al. 2016		33/150 (22.0%)	33/150 (22.0%)	-
	II	Denehy et al. 2013		14/76 (18.4%)	10/74 (13.5%)	-
		Kayambu et al. 2015		4/24 (16.7%)	12/26 (46.2%)	-
		Eggmann et al. 2018		16/57 (28.1%)	16/58 (27.6%)	0.95
12-month mortality	II	Denehy et al. 2013		19/76 (25.0%)	13/74 (17.6%)	-

**=physical therapy group / physical+cognitive therapy group; CG=Comparator group: I=systematic early vs. late rehabilitation, II=systematic early vs. less systematic early rehabilitation, III=systematic early vs. no rehabilitation*

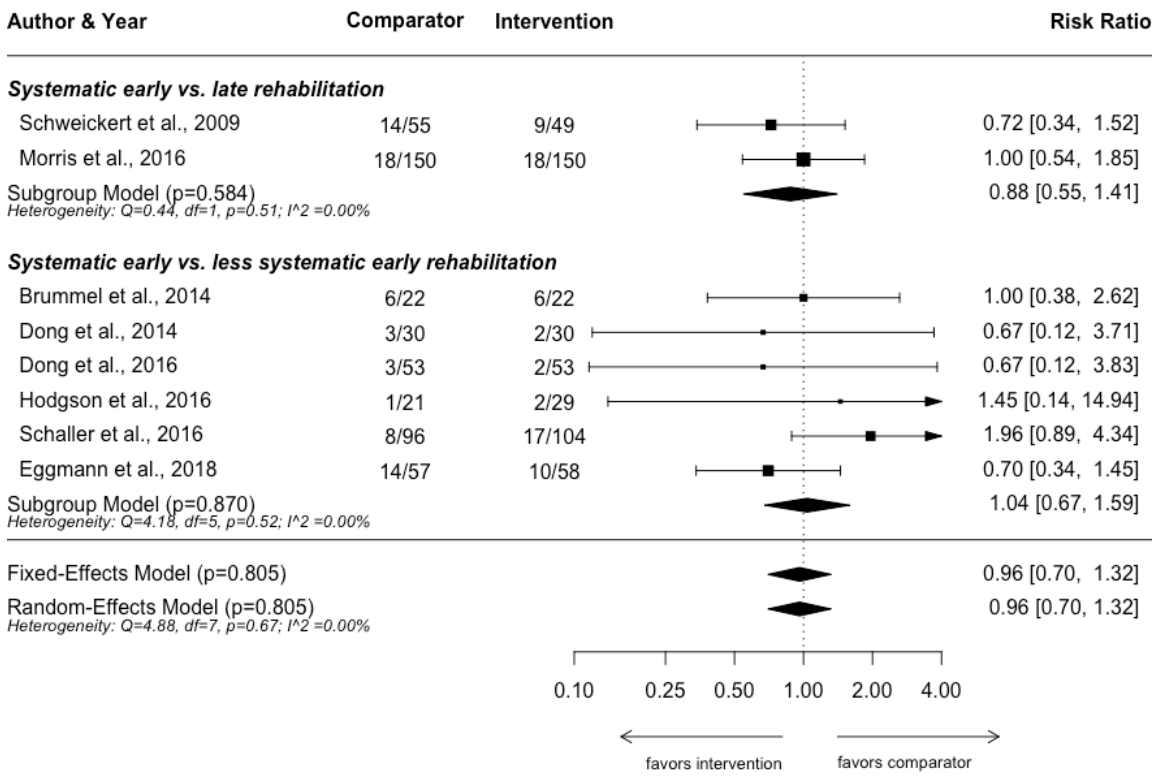


Figure 9. Effects of systematic early rehabilitation (risk ratio) on in-hospital mortality using random- and fixed-effect meta-analyses

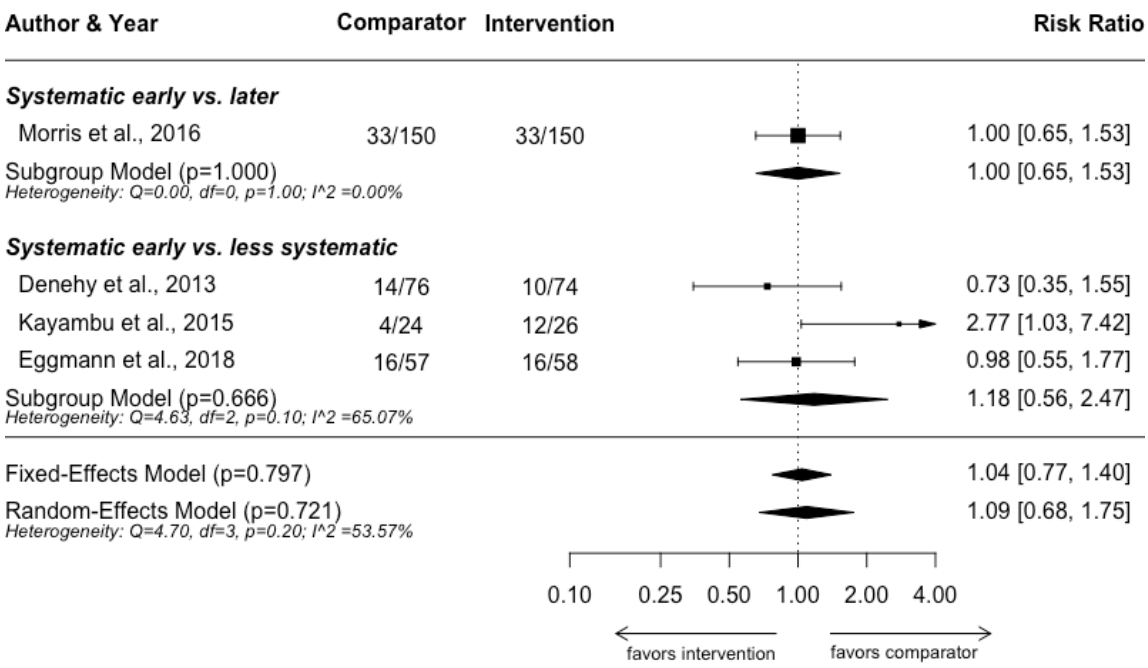


Figure 10. Effects of systematic early rehabilitation (risk ratio) on mortality after 6 months of follow-up using random- and fixed-effect meta-analyses

5.2.7 Other Secondary Outcomes

5.2.7.1 Length of ICU stay (ICU LOS)

Length of ICU stay was the only outcome that was reported in all studies (Table 8). Three studies, Dong et al. (2014),[33] Dong et al. (2016),[40] and Schaller et al.,[36] observed statistically significantly lower ICU LOS in the intervention groups comparing systematic early with less systematic early rehabilitation. However, none of the other nine studies found evidence for a difference between groups for any of the comparators. Since the majority of studies reported median and IQR only and those reporting mean and SD were considerably different from the other studies in terms of ICU LOS, we decided not to conduct a meta-analysis for this outcome.

5.2.7.2 Length of hospital stay (hospital LOS)

All but one study (Dong et al. (2014)[33]) provided information on hospital LOS (Table 8). There was a large variability in hospital LOS between studies. Patients had the lowest hospital LOS in the study by Brummel et al.[43] (median <10 days) and the highest in the study by Kayambu et al.[34] (median >40 days). Mean or median hospital LOS in the intervention groups was reported in the range of 10-19 days in four studies,[36,38,39,41] 20-29 days in four other studies,[32,35,37,40] and 30-39 days in one study.[42] While Dong et al. (2016)[40] and Schaller et al.[35] reported a statistically significantly shorter hospital LOS in the intervention groups comparing systematic early with less systematic early rehabilitation, all the other nine trials reported no difference.

5.2.7.3 Duration of mechanical ventilation

Data from nine studies were available regarding the duration of mechanical ventilation (Table 8). Three out of these reported a statistically significantly shorter duration of mechanical ventilation in the intervention groups.[33,39,40] None of the other six studies that reported the outcome showed a significant difference between groups.[32,34,35,37,38,42] We did not conduct a meta-analysis as the majority of studies reported median and IQR only and as studies allowing a meta-analysis were considerably different from the others (i.e., longest duration of mechanical ventilation of all trials and only trials reporting significant difference).[33,42]

5.2.7.4 Ventilator-free days

Six studies reported on the number of ventilator-free days (Table 8). While Schweickert et al.[39] found a statistically significantly higher number of ventilator-free days in the intervention group, none of the five other studies found such a between-group difference.[34,36,38,41,43]

Table 8. Other secondary outcomes

Outcome	CG	Study	Comparator [Mean(SD)/Median(IQR)]	Intervention [Mean(SD)/Median(IQR)]	Reported p-Value
Length of ICU stay (ICU LOS; in days)	I	Schweickert et al. 2009	7.9 (6.1-12.9)	5.9 (4.5-13.2)	0.08
		Morris et al. 2016	8 (4-13)	7.5 (4-14)	0.68
	II	Dantas et al. 2012	21.4 (17.1)	19.9 (11.7)	0.77
		Denehy et al. 2013	7 (6-11)	8 (6-12)	-
		Brummel et al. 2014*	4 (3.0-6.7)	3.5 (2.3-7.2) / 5 (2.8-9.6)	0.67
		Dong et al. 2014	15.2 (4.5)	12.7 (4.1)	0.01
		Kayambu et al. 2015	8.5 (3-36)	12.0 (4-45)	0.43
		Dong et al. 2016	18.3 (4.2)	11.7 (3.2)	<0.01
		Hodgson et al. 2016	11 (8-19)	9 (6-17)	0.28
		Schaller et al. 2016	10 (6-15)	7 (5-12)	0.005
		Eggmann et al. 2018	6.6 (4.6-14.7)	6.1 (4.0-12.3)	0.57
	III	Fischer et al. 2016	7 (range 3-213)	6 (range 2-23)	0.46
Length of hospital stay (hospital LOS; in days)	I	Schweickert et al. 2009	12.9 (8.9-19.8)	13.5 (8.0-23.1)	0.93
		Morris et al. 2016	10 (7-16)	10 (6-17)	0.41
	II	Dantas et al. 2012	39.7 (17.6)	32.2 (16.4)	0.25
		Denehy et al. 2013	20 (13.0-30.8)	23.5 (16.0-41.5)	-
		Brummel et al. 2014*	8.6 (6.0-16.2)	7.0 (5.0-10.5) / 7.9 (5.1-15.0)	0.46
		Kayambu et al. 2015	45 (14-308)	41 (9-158)	0.8
		Dong et al. 2016	29.1 (4.6)	22.0 (3.8)	<0.01
		Hodgson et al. 2016	29 (16-34)	19 (14-30)	0.33
		Schaller et al. 2016	21.5 (15-30)	15 (11-27)	0.011
		Eggmann et al. 2018	22.0 (15.0-39.2)	25.9 (14.3-37.2)	0.72
	III	Fischer et al. 2016	19 (range 9-213)	22 (range 4-84)	0.6
Duration of mechanical ventilation (in days)	I	Schweickert et al. 2009	6.1 (4-9.6)	3.4 (2.3-7.3)	0.02
	II	Dantas et al. 2012	13.25 (13.5)	10.86 (9.6)	0.6
		Denehy et al. 2013**	98 (47.5-160.5)	105 (52.0-216.5)	-
		Dong et al. 2014	7.3 (2.8)	5.6 (2.1)	0.005
		Kayambu et al. 2015	7 (2-30)	8 (4-64)	0.22
		Dong et al. 2016	13.9 (4.1)	8.1 (3.3)	<0.01
		Hodgson et al. 2016	7.0 (5.0-12.0)	5.4 (3.5-10.0)	0.18
		Eggmann et al. 2018	5.0 (3.6-11.9)	5.4 (3.3-12.9)	0.83
	III	Fischer et al. 2016	2 (range 1-15)	2 (range 1-7)	-
Ventilator-free days	I	Schweickert et al. 2009	21.1 (0-23.8)	23.5 (7.4-25.6)	0.05
		Morris et al. 2016	24 (20-26)	24 (19-26)	0.59
	II	Brummel et al. 2014*	27.4 (0-29.2)	27.1 (1.7-28.7) / 25.3 (0-28.9)	0.81
		Kayambu et al. 2015	21 (0-26)	20 (0-24)	0.71
		Hodgson et al. 2016	17.1 (8.7)	19.2 (7.4)	0.4
		Schaller et al. 2016	22.5 (16-25)	23 (18-25)	0.31

**=physical therapy group / physical+cognitive therapy group, **=in hours; CG=Comparator group: I=systematic early vs. late rehabilitation, II=systematic early vs. less systematic early rehabilitation, III=systematic early vs. no rehabilitation*

5.2.8 Safety

Nine out of twelve studies reported on safety and adverse events outcomes. Schweickert et al.[39] reported one event of oxygen desaturation <80% and one inadvertent removal of an arterial catheter in the intervention group in 498 therapy sessions (both <0.1% of sessions). Denehy et al.[32] reported no adverse events (n=74 in intervention group). Brummel et al. observed hypotensive or tachycardia episodes in 21 of 543 sessions (4%) with one hypertensive urgency with acute backache, while no removal of endotracheal tubes or vascular catheters was reported. Dong et al. observed one event of orthostatic hypotension without serious adverse effects in their

2014 study (n=30 in intervention group). Kayambu et al.[34] reported no adverse events in >600 physiotherapy sessions in the intervention group (visual assessment of presented figure, n=26 in intervention group). Hodgson et al. reported no serious adverse events, while there was one episode of agitation in the intervention group (n=29 in intervention group) as well as two episodes of agitation and one of hypotension in the comparator group (n=21 in comparator group). Morris et al. observed 11 adverse events in the intervention group and 13 in the comparator group, out of which four and three were severe, respectively. The authors considered only one event in the intervention group as potentially related to the intervention and one as life-threatening (n=150 in intervention group). Schaller et al. reported 11 episodes of hypotension, two episodes of oxygen desaturation <90%, one dislodgement of an arterial line and a nasogastric tube in the intervention, while there were five episodes of hypotension, two episodes of desaturation and two occurrences of dislodgement of arterial line in the comparator group.[36] Minor adverse events were more frequent in the intervention group (ten events; n=104 in intervention group) than in the comparator group (one event; n=96 in comparator group). Eggmann et al.[37] reported one episode of oxygen desaturation <85% during cycling exercise in 407 physiotherapy sessions in the intervention group, while there was one episode of desaturation and two episodes of unstable hemodynamics over 377 sessions in the comparator group (all <0.1%).

Table 9. Summary of findings including GRADE assessment for primary outcomes of major interest

Systematic early rehabilitation compared to late or less systematic early rehabilitation interventions for adult ICU patients requiring ventilation support

Patient or population: adult ICU patients requiring ventilation support
Setting: ICUs of any type
Intervention: systematic early rehabilitation
Comparison: late or less systematic early rehabilitation

Outcomes	**Anticipated absolute effects** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Late or less systematic early rehabilitation interventions	**Systematic early rehabilitation interventions**				
MRC Muscle Scale Sum Score (MRC-SS), measured at ICU discharge	(I) Systematic early vs. late rehabilitation		-	104 (1 RCT)	⨁⨁◯◯ LOW [a,b]	
	The median MRC-SS in the comparator group was **48** (0 to 58)	The median MRC-SS in the intervention group was **52** (25 to 58)				
	(II) Systematic early vs. less systematic early rehabilitation		-	203 (4 RCTs)	⨁◯◯◯ VERY LOW [a,c,d]	In a sensitivity analysis, omitting the study by Dantas et al. due to a high baseline imbalance in MRC scores resulted in an MRC-SS in the intervention group, which was 2.2 higher (2.5 lower to 6.9 higher). For that result, the certainty of evidence is judged low (no serious inconsistency).
	The mean MRC-SS in the comparator group in studies ranged from **40.3 to 47.3**	The mean MRC-SS in the intervention group was **5.8 higher** (1.4 lower to 13.0 higher)				
6-Minute Walking Test (6MWT), measured at various time points	(II) Systematic early vs. less systematic early rehabilitation*		-	232 (2 RCTs)	⨁⨁◯◯ LOW [a,e,f]	
	The mean 6MWT distance in the comparator group was 246 meters in Eggmann et al. and 267 meters in Denehy et al. at hospital discharge. The mean change in 6MWT from baseline in the comparator group was 184.3 meters at 3 months and 219.5 meters at 6 months after hospital discharge in Denehy et al.	The mean 6MWT distance in the intervention group was 223 in Eggmann et al. and 244.2 in Denehy et al. at hospital discharge. The mean change in 6MWT from baseline in the intervention group was **63.7 meters higher** (14.2 to 113.2) at 3 months and **72.6 meters higher** (9.3 to 135.8) at 6 months in Denehy et al.				

Systematic early rehabilitation compared to late or less systematic early rehabilitation interventions for adult ICU patients requiring ventilation support

Patient or population: adult ICU patients requiring ventilation support
Setting: ICUs of any type
Intervention: systematic early rehabilitation
Comparison: late or less systematic early rehabilitation

Outcomes	**Anticipated absolute effects** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Late or less systematic early rehabilitation interventions	**Systematic early rehabilitation interventions**				
Time to walking, measured during hospital stay	(I) Systematic early vs. late rehabilitation		-	104 (1 RCT)	⨁⨁◯◯ LOW [a,b]	
	The median time to walking in the comparator group was **7.3 days** (4.9 to 9.6)	The median time to walking in the intervention group was **3.8 days** (1.9 to 5.8)				
	(II) Systematic early vs. less systematic early rehabilitation		-	53 (2 RCTs)	⨁◯◯◯ VERY LOW [a,c,g]	
	The median time to walking in the comparator group was 6 days in Hodgson et al. and 23 days in Eggmann et al.	The median time to walking in the intervention group was 6 days in Hodgson et al. and 8 days in Eggmann et al.				
Patients returning to independence from assistance, measured at hospital discharge	(I) Systematic early vs. late rehabilitation*		**RR 1.71** (1.11 to 2.64)	104 (1 RCT)	⨁⨁◯◯ LOW [a,b]	
	35 per 100	**59 per 100**				
SF-36 Physical Function Domain Score (PFS), measured 6 months after hospital discharge	(I) Systematic early vs. late rehabilitation		-	161 (1 RCT)	⨁◯◯◯ VERY LOW [a,b,c]	
	The mean SF-36 PFS in the comparator group was **43.6**	The mean SF-36 PFS in the intervention group was **12.3 higher** (3.9 to 20.8)				
	(II) Systematic early vs. less systematic early rehabilitation		-	126 (2 RCTs)	⨁◯◯◯ VERY LOW [a,c,d,h]	
	The mean SF-36 PFS in the comparator group in studies ranged from **42.4 to 75.0**	The mean SF-36 PFS in the intervention group was **8.1 higher** (15.3 lower to 31.4 higher)				

Systematic early rehabilitation compared to late or less systematic early rehabilitation interventions for adult ICU patients requiring ventilation support

Patient or population: adult ICU patients requiring ventilation support
Setting: ICUs of any type
Intervention: systematic early rehabilitation
Comparison: late or less systematic early rehabilitation

Outcomes	**Anticipated absolute effects** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Late or less systematic early rehabilitation interventions	**Systematic early rehabilitation interventions**				
SF-36 Physical Health Component Summary Score (PCS), measured 6 months after hospital discharge	(I) Systematic early vs. late rehabilitation		-	161 (1 RCT)	⊕◯◯◯ VERY LOW [a,b,c]	
	The mean SF-36 PCS in the comparator group was **33.5**	The mean SF-36 PCS in the intervention group was **3.4 higher** (0.01 higher to 6.8 higher)				
	(II) Systematic early vs. less systematic early rehabilitation		-	152 (2 RCTs)	⊕◯◯◯ VERY LOW [c,h]	
	The mean SF-36 PCS in the comparator group in studies ranged from **42.7 to 44.4**	The mean SF-36 PCS in the intervention group was **2.4 lower** (6.1 lower to 1.3 higher)				
Patients developing ICUAW, measured at hospital discharge	(I) Systematic early vs. late rehabilitation		**RR 0.62** (0.38 to 1.03)	104 (1 RCT)	⊕⊕◯◯ LOW [a,b]	
	49 per 100	**31 per 100**				
	(II) Systematic early vs. less systematic early rehabilitation		**RR 0.90** (0.63 to 1.27)	395 (3 RCTs)	⊕◯◯◯ VERY LOW [c,h]	
	39 per 100	**36 per 100**				

*Information was available only for one comparator group
CI: Confidence interval; **MD:** Mean difference; **RR:** Risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Downgraded one point due to imprecision (defined as wide confidence intervals including no effect and/or low overall sample size (defined as <400 participants for continuous outcomes or below optimal information size for dichotomous outcomes)).

b. Downgraded one point due to only one study contributing to outcome.

c. Downgraded one point as majority of studies judged as of overall poor quality regarding risk of bias.

d. Downgraded one point due to presence of substantial unexplained heterogeneity.

e. Not downgraded as we judged the risk of bias of studies contributing data as not relevant for outcome.

f. Downgraded one point due to only one study contributing to outcome (change from baseline deemed most important aspect of outcome).

g. Downgraded one point due to only one study contributing to outcome (the second study barely contributed data (n=3).

h. Downgraded two points due to high imprecision (wide confidence intervals for absolute effects including important harm and low overall sample size (see definition above)).

5.3 Discussion

5.3.1 Summary of Findings

We only found limited evidence in support of a beneficial effect of systematic early rehabilitation for most of the prespecified outcomes in this systematic review. While performance related to muscle strength was generally higher in the systematic early rehabilitation groups, we did not find evidence for an effect of systematic early rehabilitation on MRC Muscle Scale sum scores as well as on handgrip or hand-held dynamometer strength compared with both late and less systematic early rehabilitation. A meta-analysis of achieved MRC Muscle Scale scores found no statistically significant difference between systematic early and less systematic early rehabilitation.

Similarly, evidence related to the effects of systematic early rehabilitation on physical function was inconclusive. While patients receiving systematic early rehabilitation were at lower risk of developing ICUAW during the hospital stay compared to patients receiving late or less systematic early rehabilitation, this effect did not reach statistical significance for either comparator. We found statistically significant evidence that more patients receiving early rehabilitation reached independence from assistance during the hospital stay. However, this outcome was only reported by Schweickert et al.,[39] who compared systematic early against late rehabilitation and found exceptionally strong effects in favor of systematic early rehabilitation across several functional mobility outcomes, which stood in contrast to other studies. The time needed until patients were able to walk was significantly shorter among patients receiving early rehabilitation in the same study by Schweickert et al., while studies evaluating systematic early vs. less systematic early rehabilitation found no effect for this mobility milestone. None of the trials reporting on 6MWT found a significant between-group difference at any time point up to one year. However, participants in the systematic early rehabilitation group in the study by Denehy et al.[32] showed a significantly larger increase in walking distance within the first three months. Evidence for SF-36 PFS and PCS was equally conflicting. There was a statistically significant difference in SF-36 PFS and PCS in the study by Morris et al.[41] in favor of systematic early rehabilitation compared to late rehabilitation at 6 months of follow-up. However, there was no difference in the studies evaluating systematic early vs. less systematic early rehabilitation. Furthermore, there was no between-group difference at any earlier time point in both comparator categories, a finding that is challenging to explain physiologically. No trial found a significant difference in achieved ADL, PFIT, and TUG. Overall, we found no evidence in support of systematic early rehabilitation on physical function when compared to less systematic early rehabilitation, while there was slightly stronger evidence in support of systematic early vs. late rehabilitation.

In terms of cognitive function and mental health, two studies found a statistically significant reduction in delirium duration in patients receiving systematic early rehabilitation,[36,39] while another study found no difference between groups.[41] No effect was found on HADS and MMSE, while there was some indication that tailored cognitive therapy is potentially helpful for improving memory function.[43] One study reported improved SF-36 MHS and MCS scores with systematic early rehabilitation,[37] which contrasted with the findings of other studies.[32,34,41] We found no evidence for a positive effect of systematic early rehabilitation on overall quality of life. Furthermore, we found no difference in mortality during hospitalization or after 6 months of follow-up for systematic early vs. both late and less systematic early rehabilitation. The majority of studies reported no effect on ICU and hospital LOS, or on the duration of mechanical ventilation.

We found no evidence that systematic early rehabilitation puts patients at increased risk for adverse events. Adverse events were infrequent and did not differ between groups overall. Most commonly reported adverse events were oxygen desaturation, hypotension, tachycardia and dislodgements of installations (especially arterial catheters). While one trial found that minor adverse events were more frequent in the systematic early rehabilitation group,[36] there was an equal or higher number of adverse events reported for the comparator groups in the other trials.[32,37,38,41] Across all trials, two severe adverse events related to systematic early rehabilitation were reported.[41,43]

5.3.2 Interpretation

Strict comparison and consolidating results was not possible due to considerable heterogeneity between included studies, and findings have to be interpreted taking the differences and respective context of the studies into account. First, study populations varied markedly between studies. While most trials studied a mixed ICU population, some were limited to post-operative[33,35] or septic patients only.[34] Effects found in the latter studies could therefore be specific to the main diagnosis. Furthermore, the average length of ICU and hospital stay, as well as the duration of mechanical ventilation varied strongly, reflecting marked differences in patient recovery between studies. As these measures were barely associated with disease severity (APACHE) scores, we consider it likely that a significant proportion of this variation is attributable to differences in routine practices in the care of ICU patients, or to other patient characteristics.

Second, there were differences between studies in terms of the scope, intensity and nature of rehabilitation interventions delivered. Almost all studies described a varied set of exercises, with increasing difficulty or required effort over time and often tailored to the patient's capabilities and medical stability. However, it is difficult to more accurately compare interventions based on the descriptions on how they were actually performed in the respective studies. While

descriptions are similar, there could have been marked differences in the implementation of the rehabilitation measures. Furthermore, there were differences regarding the continuation of the intervention post ICU discharge, with some even continuing the systematic intervention beyond hospital discharge.[32,43] Although it could be expected that rehabilitation that continues after ICU or even hospital discharge would have stronger effects, this was not apparent in the included studies.

Third, the comparator interventions varied markedly between studies, both in terms of content and timing. While in all studies patients in the comparator groups received a less systematic intervention, the definition and interpretation of “early rehabilitation” was often unclear. As such, the difference in timing until the first rehabilitation session between intervention and comparator groups varied strongly between studies, and not all studies reported these timing differences clearly. The rehabilitation measures provided in "usual” or “standard care” groups were generally poorly described, which does not allow an adequate comparison between trials. The components of usual care are, however, likely to strongly depend on the context, such as ICU and hospital type (i.e., academic centers could be expected to have a structured rehabilitation approach in usual care), as well as regional and health system context. Furthermore, the time of study conduct might be of importance. After the early studies on early rehabilitation (among which the study by Schweickert et al. in 2009),[39] it is likely that standard ICU practices have changed, thus decreasing the size of effect between intervention and usual care groups. This might especially be the case in ICUs that are conducting studies on early rehabilitation, as they appear to have a special awareness of the topic. This might also explain the strong effects found by Schweickert et al., while later studies found no marked effects. It could thus be argued that systematic early rehabilitation appears to have a strong effect when compared to late interventions (≥7 days), but that more recent trials, which we commonly categorized as comparing systematic early vs. less systematic early rehabilitation, failed to show similarly strong results due to an adaptation of standard care. However, other explanations such as, for example, the improvement of ICU care in general or differences in health system contexts may also contribute to our finding of smaller differential effects in more recent studies.

Fourth, we judged the quality of the studies to be rather low in general. Only three studies were considered of good or fair quality in the risk of bias assessment. Resulting from the risk of bias, the generally rather small overall sample sizes and the partially substantial heterogeneity in study results, we judged the certainty of evidence for all of the primary outcomes of major interest as low to very low. Generally, the certainty of evidence was higher for the comparator of systematic early vs. late interventions, while it is important to note that there were less studies included in this comparator category.

And last, some of the included RCTs were markedly different from the others. The study by Denehy et al. enrolled patients on day 5 of mechanical ventilation. While the intervention was designed to begin after enrolment, it was impossible to unequivocally determine whether patients received the first intervention within 7 days after ICU admission. We included the study in our review as we thought it was reasonable to assume that the patients received the intervention early as defined for our review. However, it is possible that patients in that study have received the intervention later than those of the other included trials.[32] We categorized both studies by Dong et al. (2014 and 2016)[33,40] as comparing a systematic early against a less systematic intervention. However, in their 2016 study they stated that control group patients received rehabilitation after ICU discharge on the ward, with the mean ICU LOS being 18.3 days (standard deviation (SD) 4.2). Based on this, it may be likely that there was a substantial difference in timing in both of their studies. If categorized as comparing a systematic early vs. a late intervention, this would have increased the evidence that earlier timing of rehabilitative activities might reduce ICU and hospital LOS as well as duration of mechanical ventilation, but decreased the evidence for such an effect for the comparison of systematic early vs. less systematic early interventions.[33,40] Only Fischer et al. used a sham intervention in the comparator group and was thus categorized as comparing systematic early with no rehabilitation.[35] Furthermore, they studied NMES in a highly selected population of cardiothoracic surgery patients. Therefore, while meeting our eligibility criteria, this study should be interpreted separately from the others.

5.3.3 Results in Context

Other systematic reviews published in the last years have examined the effects of early rehabilitation on muscle strength and physical function in RCTs.[2,15,21] Our results are in line with the findings from the Cochrane Review of four studies by Doiron et al.,[15] which found only uncertain and low-quality evidence in support of early rehabilitation in mechanically ventilated, ICU patients to improve physical function and performance. Moreover, their review also could not find a between-group difference in terms of mortality, delirium, quality of life, as well as ICU and hospital LOS. The systematic review by Fuke et al.[21] found in an analysis of six studies, that early rehabilitation significantly increased MRC Muscle Scale Scores and decreased the incidence of ICUAW in adult ICU patients. The discrepancy with our findings can be explained through the inclusion of other studies in our review, which have found weaker or no effects. Nevertheless, we found some indication of a positive effect of systematic early rehabilitation on MRC scores and ICUAW incidence at hospital discharge, although these effects were not statistically significant. Our findings are in agreement with those by Fuke et al.[21] for cognitive and mental health status-related outcomes, on which they found no effect of early rehabilitation. Similar to this review, Castro-Avila et al.[2] found conflicting results regarding a beneficial effect on physical function and

muscle strength in seven studies. Further systematic reviews have investigated the general use of rehabilitation measures in the ICU[9,16,44] and interventions against ICUAW,[45] all of which came to uncertain conclusions regarding potentially beneficial effects of rehabilitation in ICU patients. In the current context of Switzerland, we consider the study by Eggmann et al., conducted in a Swiss academic hospital center (Inselspital Bern University Hospital) in 2018, to be the most applicable.[37] Although the study was conducted in an academic setting where standard care might include different rehabilitation approaches and resources than in more rural hospitals, their practices and patient population are most likely to reflect the care as it is currently provided in Switzerland. However, further research is still needed to assess current rehabilitation approaches and practice variation regarding systematic early rehabilitation in Switzerland.

5.3.4 Limitations

This systematic review has several limitations. First, we defined "early" rehabilitation in line with the reviews by Fuke et al., and Castro-Avila et al., as systematic rehabilitation started within 7 days of ICU admission. However, there is no universally adapted definition and individual studies might have used different definitions for identifying their intervention as "early".[15,16] It is possible, that a less restrictive definition such as the one used by Doiron et al.,[15] defining early interventions as "designed to commence earlier than the care received by the control group", might have led to the inclusion of further studies and to different conclusions in our review. Second, we excluded trials with a relevant proportion (i.e., >10%) of neurological, burns, or transplant patients, as we considered these patient groups to have different needs or higher risks of adverse events than other ICU patients. We can thus not make a statement related to the rehabilitation of such an ICU population. Including studies that enrolled higher proportions of such patient groups could have yielded more information and might have altered our results. Third, including studies reported in further languages might have provided additional evidence. Fourth, we did not attempt to conduct an analysis of the dose of the interventions (i.e., the frequency, duration or intensity), as we did not find sufficient data to allow an exploration. Moreover, we did not examine specific interventions. Our search strategy was tailored to identify trials encompassing a comprehensive rehabilitation approach and would thus have been inadequate to look at specific interventions individually. For example, only two studies included the use of NMES,[34,35] which do not allow any statement regarding the effectiveness of strategies using NMES alone or as part of a multifaceted intervention. Furthermore, while the keeping of an ICU diary would have met our eligibility criteria, none of the RCTs identified through this systematic review included diary keeping in their rehabilitation approach. Fifth, we did not perform subgroup analyses other than by comparator classification. While it is possible that systematic early rehabilitation would lead to a more pronounced effect in certain population groups (e.g., certain age groups, duration of ICU LOS, or

main diagnosis), the included studies provided insufficient data and information to allow such subgroup analyses. And last, we categorized studies into one of three comparator categories based on a priori defined eligibility criteria. According to the category definition used for "less systematic early" rehabilitation, it is possible that the comparator intervention in one study was equal to the experimental intervention in another study (or vice-versa) due to the heterogeneity in the definitions of "early rehabilitation" in different studies (i.e., of the experimental intervention). As a result, the interpretation of effects in this group is difficult and individual study characteristics need to be considered when comparing results between studies. It is likely that the inclusion of studies that investigated systematic early vs. less systematic early rehabilitation in the overall evaluation of effects may have led to an underestimation of the beneficial effects of systematic early rehabilitation, especially when compared with late rehabilitation or no rehabilitation. However, by analyzing results for each comparator group separately, we were able to draw more detailed conclusions about the potential benefits of systematic early rehabilitation in each of these comparator groups.

5.4 Conclusion

The evidence regarding the benefits of systematic early rehabilitation of adult and mechanically ventilated ICU patients remains weak and inconsistent. A clear statement regarding the usefulness of systematic early rehabilitation is therefore not possible given the available evidence. While we found no statistically significant effect of systematic early rehabilitation on outcomes related to muscle strength, there were some indications that such measures may have a positive effect on physical function when compared with late rehabilitation. However, we did not find a statistically significant effect on physical function when comparing systematic early with less systematic early rehabilitation. Furthermore, we found no evidence for an effect of systematic early rehabilitation on a diverse set of outcomes related to mental and cognitive health, quality of life, duration of mechanical ventilation, hospital and ICU LOS, as well as mortality compared with both late and less systematic early rehabilitation. Systematic early rehabilitation appeared to be safe when implemented with adequate monitoring. It should be emphasized that the earliest included high-quality RCT comparing a systematic early against late rehabilitation found a large effect. This might have resulted in a transition of usual care and difficulties in detecting strong effects in later studies which compared systematic early with less systematic interventions due to smaller differences. It might thus be reasonable to conclude that early rehabilitation may provide a benefit over late rehabilitation, but that there is no evidence that a strict and systematic enforcement provides an additional benefit if standard care rehabilitation commences early within the first days after ICU admission.

6 Health economic assessment

6.1 Methods

The health economic assessment consisted of a systematic review of the currently published literature, a *de novo* cost analysis for Switzerland and a budget impact analysis. In the scoping, options considered for the *de novo* analysis included a cost-effectiveness analysis or a cost analysis with a potentially short time horizon, depending on data availability. Given the limited evidence regarding utilities and longer-term clinical differences, a cost analysis instead of a cost-effectiveness analysis was finally performed.

The systematic review was primarily focused on economic evaluations (i.e. cost-effectiveness, cost-benefit, cost-utility, cost-minimization analyses). In addition, we reviewed costs studies in order to populate the model for the *de novo* cost analysis.

6.1.1 Systematic literature review

The systematic review of the current economic literature aimed to identify literature about costs and cost-effectiveness of systematic early rehabilitation vs. late or no rehabilitation in ICU.

All types of economic evaluation studies were considered and checked for relevant content: cost-effectiveness analyses, cost-benefit analyses, cost-utility analyses and cost-minimization analyses. In addition, we reviewed cost studies to identify important input variables and unit costs for the planned *de novo* analysis.

6.1.1.1 Literature search strategy

A search strategy was developed to identify all relevant literature in the following electronic databases: the Medline and EMBASE databases including abstracts by using OvidSP (including Ovid MEDLINE(R), Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily Update, EMBASE), the Cumulative Index to Nursing and Allied Health Literature (CINAHL) database, the Cochrane Library and the Centre for Review and Dissemination (CRD) database including the Database of Abstracts of Reviews of Effects (DARE), Cochrane Reviews, Health Technology Assessments (HTA) and the Economic Evaluation Database from the UK National Health Service (NHS EED). The search string was obtained by integrating and combining the search string used in the clinical part of this assessment report, and published search strings for health economic analyses from the InterTASC Information Specialists' SubGroup.[46] The following filters, described as highly sensitive in Ovid MEDLINE and EMBASE,

were included: The National Health Service Economic Evaluation Database (NHS EED) filter, the NHS Quality Improvement Scotland filter and the Royle filter published in 2003.[47] Additional filters such as the Scottish Intercollegiate Guidelines Network (SIGN) filter (www.sign.ac.uk/methodology/filters.html), the McKinlay et al. filter, the Wilczynski et al. filter, and the Sassi et al. filter were also included.[48–50] Unspecific abbreviations such as CUA (for cost-utility analysis) or CBA (for cost-benefit analysis) were not used. We performed the search between 6-14 March 2019. The search strategies are reported in Appendix 9.7.

6.1.1.2 Screening of the search results

The screening of the literature was divided into two main phases. In the first phase, all results of the literature search were screened by title and abstract. Titles containing relevant keywords such as early rehabilitation, early intensive care mobility, rapid mobilization, early mobility, costs, cost-effectiveness, cost-benefit, cost-utility, health technology assessment, quality of life, or burden were considered as potentially relevant. If the abstract of the potentially relevant titles confirmed the possible presence of relevant information and an adequate PICO, the article proceeded to the second phase.

In the second phase full texts were screened. Articles were then classified as being potentially relevant or as potentially providing important information.

- Relevant articles needed to meet the following criteria:
    - The article reported a full-scale health economic evaluation study (incremental cost-effectiveness analysis, cost-benefit analysis, cost-utility analysis, or cost-minimization analysis.
    - The 'PIC' of the PICO corresponded to the one defined in the scoping document and used in the systematic review part of this assessment report.
    - The analysis was performed for a jurisdiction with broadly similar socioeconomic characteristics as Switzerland (e.g. North, Central and Western European countries, the USA, Canada, Australia and New Zealand).
- 'Partially relevant' articles were defined as studies potentially providing useful additional information concerning effectiveness or costs for the 'relevant' category. Partially relevant articles also had to correspond to the PICO defined in the scoping document.

6.1.1.3 Data extraction, quality assessment, and transferability to Switzerland

For eligible health economic evaluation studies (i.e. relevant articles as defined above), we planned to perform data extraction, covering the following information:

- Study population (including country, age and BMI range of the patients)
- Intervention
- Comparator(s)
- Setting and perspective of the study
- Cost types included and cost year (i.e. year for which the costs were estimated)
- Type of model
- Time horizon
- Discount rate
- Approach to sensitivity analysis
- Effectiveness
- Costs
- Incremental cost-effectiveness ratio (ICER) or equivalent

A brief, qualitative characterization of each relevant study covering methodological approaches taken, main data sources, methodological issues and potential meaningfulness/transferability of the results for Switzerland was planned.

6.1.1.4 Synthesis of findings from potentially relevant articles

The resulting different pieces of information were synthesized. This necessarily involved an element of interpretation, but it was an explicit aim to make all related assumptions transparent. Comparisons of the assumptions and of the data used by different cost-effectiveness analyses were made. The discussion was complemented with a critical review of possible sources of uncertainty.

6.1.2 De novo cost analysis

The available data did not allow us to perform a *de novo* cost analysis using a bottom-up approach: patient-level data indicating, at the same time, diagnoses, treatments, outcomes and costs were not available. The cost analyses performed for this assessment were thus based on a combination of sources. They focused on the costs of early rehabilitation measures and potential cost differences between intervention and comparator resulting from effects of the intervention. This implied a focus on outcomes for which differences between intervention and comparator were expected. The results of a survey we conducted among 37 out of 84 Swiss ICUs (response rate 44%) formed an important basis of the *de novo* cost analysis. However, it did not allow to elicit information specifically for our exact PICO (focusing on systematic early rehabilitation vs.

comparators), but rather on early rehabilitation use in Swiss ICUs in general. The comparison in this part of the health economic analysis, and in the dependent parts, is thus mainly between any rehabilitation in the ICU *vs.* none. This needs to be considered in the interpretation of the economic results.

6.1.2.1 Approach to cost calculation

The *de novo* cost analysis consisted of three major steps: first, frequency and duration of systematic early rehabilitation in Swiss ICUs were investigated; second, early rehabilitation costs were estimated by combining the frequency and duration of early rehabilitation with the costs of personnel (and material); third, outcomes that may be influenced by early rehabilitation and thus trigger cost differences were analyzed and considered if appropriate.

The economic analyses were mainly based on the results of the survey on the current supply situation, which was conducted in parallel to inform this HTA on current use, and variation, and definitions of early rehabilitation in Swiss ICUs (full survey results reported separately) and on the results of the clinical part of this assessment. Given the availability of the Swiss survey as a data source, it made sense to compare the rehabilitation costs of Swiss patients who received systematic early rehabilitation with those not receiving early rehabilitation, although some trials considered in the clinical systematic review part had active comparator arms (representing more than no early rehabilitation). We also made the simplifying assumptions that the proportion of patients receiving early rehabilitation reported in the survey would also apply to the patients meeting our PICO. The impact of this assumption was tested in sensitivity analysis.

Step 1 - Early rehabilitation frequency and duration in Swiss ICUs

In the survey we specifically asked the responding ICU staff to indicate which proportion of ICU patients receive early rehabilitation and, among them, which proportion receive mechanical ventilation. In addition, it was possible to indicate which rehabilitation measures are performed, the proportion of patients receiving them, which profession usually performs a given measure (e.g. nurse, physiotherapist, etc.), the average daily time required for personnel to perform the measure, and the average number of days in which the measure is performed in one patient. This information was used to estimate the frequency and intensity of early rehabilitation among mechanically ventilated Swiss patients.

Step 2 - Early rehabilitation costs

Systematic early rehabilitation mostly consists of relatively simple passive or active mobilization of the patient (e.g. sitting, cycling, walking) and can be directly provided in the bed or a simple chair, in the patients' room. Therefore, the main costs of early rehabilitation consist of personnel costs and some material costs.

Personnel costs were obtained by combining the average number of hours of early rehabilitation, per patient with early rehabilitation, with the average hourly salary of the relevant staff. According to an ICU participating in the survey, average hourly salaries (including vacation and 13th month salary) were CHF68.85 for physicians, CHF47.50 for assistants, CHF50 for nursing staff, CHF47.80 for physiotherapy team, CHF42.90 for ergotherapy, CHF53.10 for speech therapy, and CHF47.50 for nutritional therapy. Another participant to the survey reported that the mean yearly salary of physicians employed in ICU ranged between CHF80,000 and CHF100,000. Assuming 220 working days per year and 8.4 working hours per day (i.e., 42 hours per week), the mean salary per hour would be CHF43.30-CHF54.10. Adding employer contributions assumed to be 15%, we used an average hourly salary of CHF57.50 per hour, for the present analysis.

The material costs required for early rehabilitation measures cannot be quantified easily. This is because first, most early rehabilitation measures do not require additional material (e.g. many exercises are performed in the bed or a chair). Second, specific devices (e.g. cycling devices) can be used over a long time for many patients. According to a rough estimation provided by an ICU participating in the survey, we assumed a flat rate of CHF100 per case for material costs.

Step 3 - Outcomes that may be influenced by early rehabilitation

Outcomes included in the clinical part of this assessment and that may be influenced by systematic early rehabilitation were investigated. The following outcomes were considered as being potentially relevant from a health-economic perspective: quality of life, mortality, length of ICU stay, length of hospital stay, independence at discharge, and time to return to work.

These outcomes and the associated impact on healthcare or societal costs would be considered/included in the cost analyses or cost-effectiveness considerations depending on the results of the clinical assessment. More specifically, they would be included if a statistically significant difference between early rehabilitation and comparator was shown.

6.1.2.2 Early rehabilitation and overall hospitalization costs

To put the costs of early rehabilitation in the context of overall hospitalization costs, the estimated average hospitalization costs of the eligible cases were approximated using the SHS of the SFOPH

and the diagnosis-related case costs statistics ("Statistik diagnosebezogener Fallkosten") of the SFSO (see BIA in section 6.1.3 for more details).[51,52] These costs were compared with the average early rehabilitation costs.

6.1.2.3 Perspectives

In the scoping, the *de novo* cost analysis was planned to be performed from several perspectives:

a) 'Swiss health insurance law ("Krankenversicherungsgesetz"; KVG) perspective' (considering the direct medical costs of all health care services covered by the Swiss statutory health insurance irrespective of the actual payer. In the present case, we interpreted the estimated real costs of the treating hospitals and potentially other healthcare providers as reflecting the KVG perspective)
b) 'Societal perspective' (all medical and non-medical costs including indirect costs resulting from time off work)

6.1.2.4 Time horizon

The time horizons for the cost analyses needed to be longer than the duration of ICU admission in order to capture potential clinical and economic differences during the post-ICU period. Specifics were dependent on how long differences were observed in clinical studies. A time horizon of 12 months was selected for the base case, due to a lack of robust studies with longer-term clinical outcomes.

6.1.2.5 Discounting

Due to the short time horizon, there was no discounting of costs.

6.1.2.6 Sensitivity analyses, scenario analyses and additional considerations

To investigate the robustness of the *de novo* cost analysis, we performed sensitivity analyses (univariate sensitivity analyses and scenario analyses).

In the sensitivity analyses we varied the most important input parameters (e.g. duration of the early rehabilitation measures and the costs for personnel performing physiotherapy) by ±30%.

In one scenario analysis, overhead costs of 30% were added to the estimated personnel and material costs (i.e. a mean hourly salary of CHF74.75 and mean material costs of CHF130 were used).

The conduct of other scenario analyses and additional considerations on costs and cost-effectiveness depended on intermediate results and on the results of the clinical assessment.

6.1.2.7 Cost-effectiveness and additional considerations

Cost-effectiveness and additional considerations were to be made depending on the results of the clinical assessment and of the review of the economic literature, in particular if no or only weak evidence for a difference between systematic early rehabilitation and usual care (i.e., less systematic early or late rehabilitation) would be found, in terms of quality of life, length of ICU or hospital stays, independence at discharge, or time to return to work. The following aspects were to be considered:

- Quality of life: the difference in QALYs between intervention and comparator that would be needed to achieve an ICER of CHF50,000 or CHF100,000 was investigated.
- Length of stay: the difference in ICU or hospital length of stay that would lead to a cost saving situation in favor of early rehabilitation, assuming absence of other cost-saving effects, was investigated. For a single hospitalization day we assumed costs of CHF1,503 (according to an estimation provided by the University Hospital Basel not considering surgical intervention costs). For an ICU day we made a rough estimation by dividing the average costs of few relevant SwissDRG codes by the corresponding mean lengths of stay (e.g. SwissDRG A13A – Complex case with ventilation for 95-250 hours: average costs = CHF127,624, mean hospitalization length = 23.7 days, mean costs/day = CHF5,385). For the SwissDRGs indicating "ventilation in complex cases" (SwissDRG A07-A13, A18) we found average costs per day ranging between CHF4,060 and CHF6,452.[52]
- Independence at discharge and time to return: the difference in workdays lost, and thus in indirect costs, that would be needed to achieve a cost saving situation in favor of early rehabilitation was investigated, again assuming absence of other cost-saving effects. We estimated that the costs for a single workday lost would be approximatively CHF360 (based on a mean GDP per person of CHF79,104 and assuming 220 working days per year).

6.1.3 Budget impact analyses

The aim of the budget impact analyses was to estimate the overall costs of systematic early rehabilitation in Switzerland. The overall costs according to the current use of early rehabilitation were compared to hypothetical scenarios assuming an increased or decreased use. Calculations were for the Swiss healthcare system using a health insurance system (KVG) perspective.

The analysis consisted of two main steps: first, the number of eligible cases was estimated; second, based on annual number of hospitalizations, the estimated percentage of patients receiving early rehabilitation and the estimated costs of rehabilitation calculated in the *de novo* cost analysis, the total annual costs representing the current use of early rehabilitation were estimated.

In addition, overall hospitalization costs according to SwissDRGs assigned to eligible patients were estimated and compared to the early rehabilitation costs.

6.1.3.1 Number of eligible cases

The analysis consisted of three main steps: first, the annual occurrence of hospitalized cases requiring mechanical ventilation in ICUs in Switzerland was investigated using treatment codes (i.e. CHOP codes); second, patients were selected according to the inclusion/exclusion criteria defined in the scoping phase; third, patients were stratified and further selected according to their SwissDRG codes.

First, information on the total number of cases requiring mechanical ventilation in an ICU was obtained from the SHS 2015 provided by the SFSO.[51] The SHS is a collection of data on all patients who were hospitalized in a Swiss hospital during a specific year, covering, e.g., a total of 1,430,201 hospitalizations in 2015. The collected information includes patient characteristics, diagnoses, and performed interventions.

The following CHOP codes indicating main and secondary treatments were used to identify patients receiving mechanical ventilation:

- 93.9: Artificial ventilation
- 96.0: Non-operative gastric tube insertion and intubation of the airways
- 96.A: Mechanical ventilation and respiration support through mask and tube

Each patient may receive one main treatment (i.e. CHOP code) and several secondary treatments during one hospitalization. Moreover, the reporting of the treatment codes is usually performed in decreasing order of importance (from the main treatment, according to physician's judgment, to secondary treatments). This means that mechanical ventilation for a complex case may be reported only after many other treatments. For these reasons, for each case we analyzed the main treatment and up to 50 secondary treatments.

Second, patients were selected according to the inclusion/exclusion criteria defined in the scoping phase. The selection was performed in a multistep approach. In the first step, two variables of the SHS reporting the length of mechanical ventilation and the length of ICU stay were used. Only cases that received mechanical ventilation and stayed in the ICU for more than 24 hours were included. In the second step, all patients younger than 20 years were excluded (since the age in

the SHS is reported in age classes, it was not possible to have a cut-off at 18 years). In the third step, patients reporting at least one diagnosis mentioned as an exclusion criterion in the scoping phase were identified through ICD-10 codes. The following ICD-10 codes were excluded:

- F00-F99: Mental and behavioral disorders
- G00-G99: Diseases of the nervous system
- I60-I69: Cerebrovascular diseases
- M62.3: Immobility syndrome (paraplegic)
- S00-S09: Injuries to the head
- T20-T32: Burns and corrosions

For each case we considered the main diagnosis ("Hauptdiagnose"), the addition to the main diagnosis ("Zusatz zu Hauptdiagnose"), and up to ten secondary diagnoses ("1.-10. Nebendiagnose").

Third, the Swiss diagnosis related group (SwissDRG) codes indicating the main reason for hospitalization for each case were analyzed to further differentiate between relevant and non-relevant cases. The following SwissDRG groups were considered as relevant:

- Pre-MDC (Major Diagnostic category) - Ventilation in complex cases (SwissDRG A07-A13, A18)
- Pre-MDC - Intensive care complex treatments (SwissDRG A36)
- Diseases or disorders of the respiratory organs (SwissDRGs E01-E77A)
- Diseases or disorders of the circulatory system (SwissDRG F01-F98)
- Diseases or disorders of the digestive organs (SwissDRG G02-G73)
- Diseases or disorders of the hepatic system and pancreas (SwissDRG H01-H64)
- Diseases or disorders of the musculoskeletal system and connective tissue (SwissDRG I02-I98)
- Polytrauma (SwissDRG W01-W61)

In contrast, the following SwissDRG groups or codes were excluded:

- Transplantations or events related transplantation (e.g. SwissDRGs A01-A06, A15-A17, A60, E77B-E77D, F04, F28, H61, H63, I02, I46)
- Geriatric early rehabilitating complex treatments after 7 treatment days (e.g. SwissDRGs A95)
- Diseases or disorders of the nervous system (SwissDRGs B01-B86)
- Diseases or disorders of the eyes (SwissDRGs C01-C64)
- Diseases or disorders of the ear, nose, mouth, and throat (SwissDRGs D01-D67)
- Diseases or disorders of the skin, hypoderm, and breast (SwissDRG J01-J68)

- Endocrine, nutrition, and metabolism diseases (SwissDRGs K01-K64)
- Diseases or disorders of the urinary organs (SwissDRG L02-L72)
- Diseases or disorders of the male and female sexual organs (SwissDRG M01-M64, N01-N62)
- Pregnancy, birth and childbed (SwissDRG O01-O65)
- Diseases of blood, blood-building organs and immune system (SwissDRG Q01-Q61)
- Hematological and solid neoplasms (SwissDRG R01-R65)
- HIV (SwissDRG S01-S65)
- Infectious and parasitic diseases (SwissDRG T01-T64)
- Mental illness and disorders (SwissDRG U01-U66)
- Mental disorders due to alcohol and drugs (SwissDRG V60A-V64Z)
- Injuries, poisoning, and toxic effects of drugs and medicaments (SwissDRG X01-X64)
- Burns (SwissDRG Y01-Y63)
- Other factors influencing the health status (SwissDRG Z01-Z66)
- Error-DRGs und other DRGs (e.g. SwissDRGs 901A-D)

6.1.3.2 Total early rehabilitation costs of eligible cases

Based on the annual number of eligible cases and the estimated costs of rehabilitation calculated in the *de novo* cost analysis, the total annual costs of systematic early rehabilitation were estimated. The annual costs of early rehabilitation for eligible cases were compared with the estimated annual costs of rehabilitation for all hospitalized patients requiring mechanical ventilation for at least 24 hours in a ICU (according to the SHS) and with the estimated annual costs of early rehabilitation for all ICU patients (according to the overall number of ICU admissions reported by the Swiss Society of Intensive Care Medicine).[53]

In a scenario analysis we investigated the overall early rehabilitation costs in case of an increased or decreased use. The frequency of early rehabilitation was varied from 0% (i.e. no use) to 100% (application for all eligible ICU patients).

6.1.3.3 Contextualization of early rehabilitation costs

To better contextualize early rehabilitation costs, we estimated the overall hospitalization costs of the eligible population. The costs reported by the diagnosis-related case costs statistics 2014, adjusted to 2017 according to the increasing costs of healthcare in Switzerland, were applied to the identified cases.[52] Overall costs and costs per SwissDRG group (e.g. Pre-MDC - Ventilation in

complex cases, diseases or disorders of the respiratory organs, or diseases or disorders of the circulatory system) were calculated.

6.1.4 Summary of data collection for cost and budget impact analyses

Table 10 summarizes the sources that were considered for the health economic analyses.

Table 10. Swiss resource use and cost sources

Element	Source
Overall number eligible cases in 2015 identified through SwissDRG, ICD-10, and CHOP codes	SHS 2015 of the SFSO
Overall number of patients admitted to a Swiss ICU in 2018	The minimum data set (MDSi) of the Swiss Society of Intensive Care Medicine
Outcomes that may be influenced by early rehabilitation measures (e.g. length of stay in hospital/ICU, mortality, quality of life, time to return to work)	Clinical part of this assessment Results of the systematic literature review of cost studies
Hospitalization costs for eligible cases according to SwissDRGs	Diagnosis-related case costs statistics ("Statistik diagnosebezogener Fallkosten") of the SFSO
Costs for a single hospitalization day	Estimate provided by University Hospital Basel
Costs for a single ICU day	Diagnosis-related case costs statistics ("Statistik diagnosebezogener Fallkosten") of the SFSO
Early rehabilitation frequency and intensity	Survey conducted within the scope of this HTA
Early rehabilitation costs (personnel and material costs)	Feedback from two ICUs participating in the survey
Physiotherapy tariff	Tarmed (specific physiotherapy tariff: physio swiss)
GDP per capita	SFSO

Abbreviations: CHOP= Swiss classification of surgeries; GDP= Gross domestic product; HTA= Health Technology assessment; ICD-10= International Classification of Disease 10th revision; ICU= Intensive care unit; MDSi= Minimum data set; SFOPH= Swiss Federal Office of Public Health; SFSO= Swiss Federal Statistical Office, SHS= Swiss Hospital Statistics, SwissDRG= Swiss Diagnosis Related Groups

6.2 Results

6.2.1 Health economic literature review

6.2.1.1 Literature search

A total of 11,738 citations were identified from the electronic database searches. Following the removal of duplicates (n=3,903), full citations were reviewed. Based on the titles and abstracts, 7,833 citations were excluded due to inappropriate comparator or non-comparative design, character of a review or commentary piece, inappropriate outcome measure, or no relevant cost information given. A total of 32 citations were included for full text review.

Of these 32 citations there was no relevant study (i.e. cost-effectiveness analysis, cost-benefit analysis, cost-minimization analysis, cost-utility analysis, or HTA). Twenty-nine studies were excluded due to inappropriate PICO or other reasons (Figure 11), whereas three studies were considered partially relevant and were reviewed to identify input variables or unit costs for the *de novo* cost analysis.

- Morris et al. 2008, Early intensive care unit mobility therapy in the treatment of acute respiratory failure.[54]
- Chou et al. 2019, Effectiveness of early rehabilitation on patients with chronic obstructive lung disease and acute respiratory failure in intensive care units: A case–control study.[55]
- Wright et al. 2018, Intensive vs. standard physical rehabilitation therapy in the critically ill (EPICC): a multicenter, parallel-group, randomized controlled trial.[56]

It should be noted that the RCT of Wright et al. was not included in the clinical assessment. Two reasons led to this decision. First, the fact that patients were randomized at a median of 5-6 days after admission and received first intervention at a median of 3 days after randomization.[56] Rehabilitation starting 9 days after admission was not considered as early rehabilitation. Second, this trial compared rehabilitation intensities rather than systematic early vs. late or less systematic early rehabilitation. Despite these discrepancies with the assessment PICO, this study was reviewed in the health economic part because it was the only study reporting outcomes in terms of QALY gained.

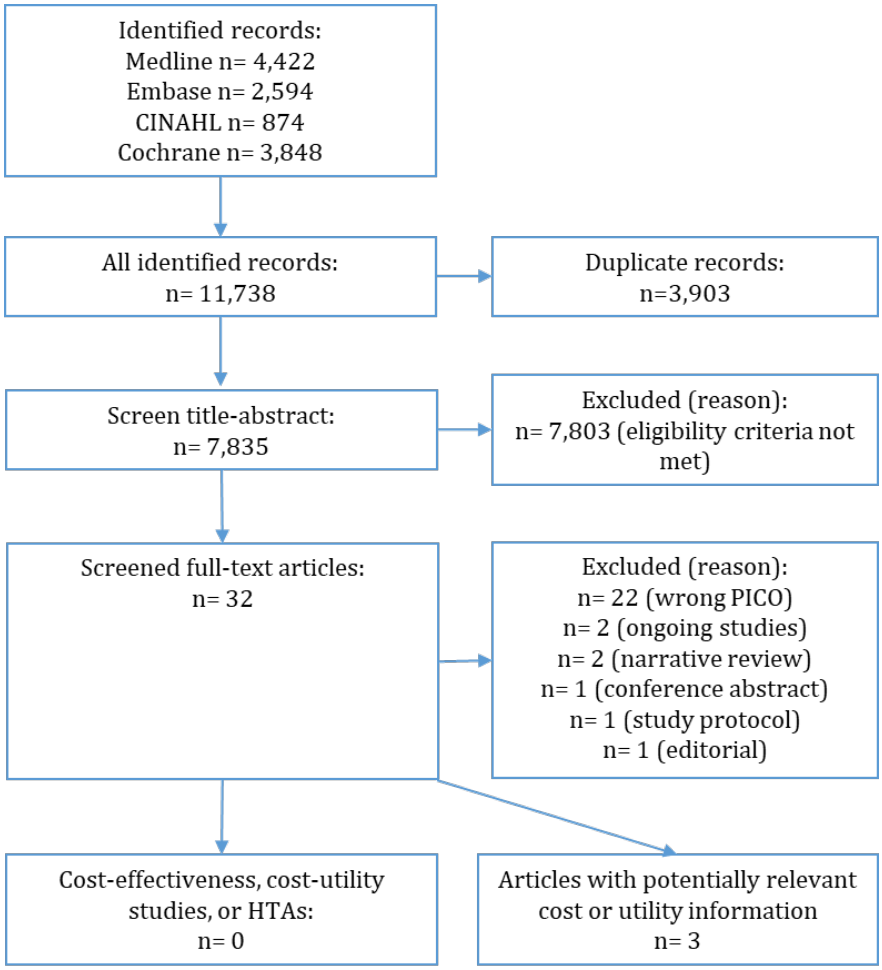


Figure 11. Results of the health economic literature search and study selection process

CINAHL=Cumulative Index to Nursing and Allied Health Literature; HTA=Health Technology Assessment; PICO=Population, Intervention, Comparator, Outcomes.

6.2.1.2 Synthesis of characteristics and findings from potentially relevant articles

This section will briefly summarize the characteristics and findings from the potentially relevant articles.

All identified studies included ICU patients requiring mechanical ventilation and compared early/intensive rehabilitation with standard care, but were considerably heterogeneous in terms of study designs, patient characteristics, and intervention (i.e. rehabilitation program) (Table 11).

Morris et al.[54] conducted a prospective cohort study in a university medical ICU in the UK. They included 370 patients aged 54-55 years with acute respiratory failure (e.g. due to acute lung injury, coma, congestive heart failure, cardiac arrest). The protocol intervention included four levels, ranging from passive mobility in unconscious state (level I) to physical therapy and active transfer to chair (level IV). The analyses were adjusted for confounding factors like body mass index, APACHE II score and vasopressor use. If compared to standard care, patients in the intervention group reported shorter duration of mechanical ventilation (8.8 vs. 10.2 days, p=0.16), shorter ICU length of stay (5.5 vs. 6.9 days, p=0.025), and shorter overall hospital stay (11.2 vs. 14.5 days, p=0.006). The average medical cost per patient was USD44,302 for the usual care group and USD41,142 for the intervention group (p=0.26) (Table 12). Utilities or QALYs were not reported. Morris et al. concluded that implementing a mobility protocol to initiate earlier physical therapy was feasible, safe, did not increase costs, and was associated with decreased ICU and hospital length of stay in survivors who received physical therapy during ICU treatment compared with patients who received usual care.

Chou et al.[55] described their study as a retrospective, observational, case-control study in a medical center with a 19-bed medical ICU in Taiwan. Overall, the records of 105 patients aged 75 years with COPD and acute respiratory failure who required mechanical ventilation in 2011 were examined. Out of 105 patients, 35 received early rehabilitation within 72 hours of mechanical ventilation. The rehabilitation protocol included passive extremity movement for unconscious patients (stage I) and active extremity movement and interaction with physical therapist (stage II). Physiotherapy was provided twice daily 5 days per week. If compared with no rehabilitation, patients receiving rehabilitation reported shorter duration of mechanical ventilation (5.7 vs. 6.7 days, p=0.40), shorter ICU length of stay (5.8 vs. 9.2 days, p=0.033), and shorter overall hospital stay (17.9 vs. 25.4 days, p=0.10). The average medical cost per patient was USD5,066 in the rehabilitation group and USD7,633 in the no rehabilitation group (p=0.06) (Table 12). Utilities or QALYs were not reported. After adjusting for potential confounders (e.g. age, sex, COPD stage, comorbidities), Chou et al. concluded that early rehabilitation was significantly associated with a shorter duration of mechanical ventilation (p=0.037) but was not significantly associated with length of ICU stay (p=0.99) or hospital stay (p=0.57), nor with medical costs (p=0.67).

Wright et al.[56] reported the results of a multicenter RCT conducted in the UK and including 308 ICU patients aged 60-64 years who required invasive or non-invasive ventilation for at least 48 hours. The intervention group had a delivery target of 90 minutes of physical rehabilitation per day (Monday to Friday), whereas the comparator group received standard therapy (i.e. no more than 30 minutes of physiotherapy per day during the week). Both study groups had a duration of ventilation of 4 days. If compared to the standard care group, the intervention group had a longer ICU length of stay (18 vs. 16 days) and a longer hospital stay (42 vs. 41 days). The authors mentioned in the methods section that health economic analysis compared the costs of the standard care and intervention groups from the health service perspective as well as a societal perspective. However, costs were not reported in the results nor in the supplementary table S4 entitled "Health economic analysis". The author simply mentioned that the resource use during participants' primary hospital admission was greater in the intervention group due to the increased physiotherapy time. In contrast to the previously mentioned studies, Wright et al. reported utility scores and QALYs calculated from responses to the SF-6D and EQ-5D instruments collected at 3 and 6 months after discharge. In general, QALYs were similar between groups: according to the QALY estimation based on the SF-6D instrument they amounted to 0.269 QALYs and 0.250 QALYs (difference 0.018, 95% CI -0.006 to 0.043) over six months in the intervention and standard care groups, respectively (Table 12). The estimations based on the EQ-5D were very similar with 0.208 QALYs and 0.184 QALYs (difference 0.018, 95% CI -0.022 to 0.070) over six months in the intervention and standard care groups, respectively. It should be emphasized that the utility estimations were based on a very restricted number of patients. Out of 308 randomized patients, only 116 provided utility data, whereas the majority died during the hospital stay (n=99), was lost to follow-up (n=77), or withdrew from the trial (n=16).

Wright et al. concluded that ICU-based physical rehabilitation did not appear to improve physical outcomes at 6 months compared with standard physical rehabilitation.[56] It should be noted that this study did not fully respect the PICO of the present assessment, as the investigated intervention and comparator were both early rehabilitation therapies (i.e. the difference consisted in the intensity). Nevertheless, we decided to review this study as it was the only one providing QALY estimates.

Table 11. Population demographics and characteristics of the identified studies

Study	Country Population	Age and gender	Intervention	Comparator	Perspective	Cost types considered Cost year	Approach to analysis Time horizon Discounting
Morris et al. 2008	US 370 patients with acute respiratory failure requiring mechanical ventilation on admission to ICU	Intervention: 54.0±16.8 years 56.4% males Comparator: 55.4±16.8 years 53.3% males	Mobility protocol 7 days/week, starting with passive mobility in unconscious state	Usual care including physical therapy initiated on a physician's patient-specific order.	Healthcare (hospital) perspective	Direct inpatient costs n.r.	Prospective cohort study n.r. n.r.
Chou et al. 2019	Taiwan 105 ICU patients with COPD and acute respiratory failure requiring mechanical ventilation	Intervention: 74.9±10.5 years 80.0% males Comparator: 74.7±10.7 years 75.7% males	Early rehabilitation program within 72 hours of mechanical ventilation. Starting with passive mobility in unconscious state (twice daily, 5 days/week)	No rehabilitation	Healthcare (hospital) perspective	Direct inpatient costs 2011	Retrospective case-control study n.r. n.r.
Wright et al. 2018	UK 308 ICU patients who received 48 hours or more of either invasive or non-invasive mechanical ventilation	Intervention: 60±16 years 54% males Comparator: 64±16 years 63% males	90 min physical rehabilitation per day (from Monday to Friday)	Usual care including max 30 min physiotherapy per day (from Monday to Friday)	Healthcare perspective Hospital	n.r. * n.r.	Randomized controlled trial 6 months n.r.

*The authors mentioned a health economic analysis in the supplementary table S4. However, the table reports only resource use (not monetary) and utility values. Abbreviations: COPD=chronic obstructive pulmonary disease; ICU=intensive care unit; n.r.= not reported; UK=United Kingdom, US=United States.

Table 12. Cost and utility results of the identified studies

Study, perspective (currency)	Costs int.	Costs comp.	Incremental cost	QALY int.	QALY comp.	Incremental QALYs	ICER (costs per QALY)
Morris et al. 2008, Healthcare (USD)	41,142	44,302	-3,160	n.r.	n.r.	n.r.	n.r.
Chou et al. 2019, Healthcare (USD)	5,066	7,633	-2,567	n.r.	n.r.	n.r.	n.r.
Wright et al. 2018, Healthcare (USD)	n.r.	n.r.	n.r.	0.208[a]-0.269[b]	0.184[a]-0.250[b]	0.019-0.024	n.r.

*Costs were originally reported in New Taiwan Dollars (NT$). However, an exchange rate to USD was also provided (USD 1 = NT$ 30); a estimation based on the EQ-5D questionnaire; b estimation based on the SF-6D questionnaire. Abbreviations: int.= intervention; comp.= comparator; EQ-5D= EuroQol 5 Dimensions; ICER=incremental cost-effectiveness ratio; n.r.=not reported; QALY=quality-adjusted life years; SF-6D=Short-Form-Six Dimension; USD=United States Dollar.

6.2.1.3 Limitations of the potentially relevant articles

The three studies considered above had several limitations restricting their transferability to Switzerland.

First, the sample size was generally small, especially in the study conducted in Taiwan.[54–56] Second, the populations differed substantially: Morris et. al included patients with acute respiratory failure with a mean age of 54-55 years, Chou et al. included patients with similar condition (COPD and acute respiratory failure) but a considerably higher mean age (75 years), whereas the ICU population in Wright et al. was broader (patients 60-64 years old who received mechanical ventilation for 48 hours; excluding end-of-life care, acute brain or spinal cord injury, multiple trauma if mobilization therapy was judged unlikely to be possible, burns, rapidly progressive neuromuscular disease). Third the early rehabilitation interventions differed between the studies and may not be representative for those currently adopted in the Swiss ICUs. Fourth, cost collection and calculation were not described in enough detail[55,57] or were not reported at all.[56] Fifth, the identified studies did not exactly report when early rehabilitation was initiated. Only in the study by Morris et al. rehabilitation was conducted during the whole week. In contrast, Chou et al. and Wright et al. reported that physiotherapy was conducted only 5 days per week (Wright et al. specified from Monday to Friday). This approach may have an impact on patients recruiting at the end of the week (e.g. on Thursday or Friday), as they'll not be able to profit from early rehabilitation.

The studies conducted by Morris et al. and Chou et al. included patients from a single ICU, whereas Wright et al. recruited patients from four hospitals in the UK. Considering the designs used by Morris et al. (prospective cohort study) and Chou et al. (retrospective case-control study), residual confounding cannot be excluded.

The study by Morris et al. included patients recruited between 2004 and 2006: it could be argued that rehabilitation approaches may have changed/improved considerably over time. The study by Chou et al. was conducted in Taiwan. Although the cost difference between intervention and

comparator was similar to that reported by Morris et al. for the US (i.e. intervention was less expensive by approximatively USD2,500-3,000), the total costs were quite different. The costs of early rehabilitation were USD41,142 in Morris et al. and USD5,066 in Chou et al. Although a price correction based on country-specific purchasing power parities and considering cost changes over time might reduce this difference, it is evident that the results of Chou et al. are not comparable to the Swiss reality. Obviously, this does not only apply to costs, but also to the population characteristics and healthcare use.

The study by Wright et al. compared intensive vs. standard rehabilitation therapy. Both interventions were defined as "early rehabilitation therapies" (although rehabilitation started nine days after admission). Therefore, intervention and comparator didn't fully respect the PICO of the present assessment. As already mentioned, we decided to review this study since it was the only one providing information on QALYs, whereas costs were not reported. It is worth emphasizing that in this RCT, the intervention group had a longer ICU length of stay (18 vs. 16) and a longer hospital stay (42 vs. 41 days) if compared to the comparator. This means that in a cost calculation the intervention group would probably have been more expensive (in contradiction to the other two studies included in this review of health economic studies).

Considering the above-mentioned limitations and partially discordant results, the clinical evidence of the studies included in the economic review was judged to not provide a sufficient basis for implementation in the *de novo* cost analysis. This implies that the *de novo* cost analysis would need to rely on the results of the clinical systematic review. Given that the latter provided no evidence for an incremental benefit of systematic early rehabilitation activities in the ICU, the health economic analysis presented is a cost analysis.

6.2.2 *De novo* cost analysis

6.2.2.1 Early rehabilitation frequency and duration in Swiss ICUs

According to the ICUs participating to the survey, all ICUs in Switzerland perform early rehabilitation in their patients during the first 7 days after admission (i.e. all participating ICUs reported that they do so). However, the proportion of patients receiving early rehabilitation varies between ICUs (ranging from 30% to 100%, with a mean of 82±21%). Table 13 summarizes the types and duration of early rehabilitation measures reported by the participating ICUs. According to the survey results, most of the adopted early rehabilitation measures were performed in a collaboration between nursing and physiotherapy staff. Ergotherapy staff, ICU physicians, and patients' relatives were rarely involved in the adopted early rehabilitation measures.

Based on the reported frequencies and durations of the rehabilitation measures we estimated that on average, each patient undergoing early rehabilitation in ICUs receives rehabilitation measures during a total of 13.3 hours during their ICU stay.

Table 13. Early rehabilitation measures performed in the ICUs participating to the survey

Early rehabilitation measure	ICUs providing the measure (% (n/N))	Proportion of patients receiving the measure (% (SD))	Average daily time dedicated to providing the measure (minutes (SD))	Average number of days in which the measure is provided (days (SD))
Passive range of motion	97.3 (36/37)	71.5 (32.9)	28.5 (16.8)	3.8 (3.3)
Neuro-muscular electro-stimulation	10.8 (4/37)	33.0 (45.3)	46.7 (23.1)	2.3 (2.5)
Passive chair position in bed, tilt table	97.3 (36/37)	54.3 (38.9)	57.9 (46.3)	3.5 (1.7)
Passive cycling in bed	48.6 (18/37)	12.0 (13.5)	33.8 (30.5)	3.8 (2.5)
Active range of motion muscle activation and training	89.2 (33/37)	59.3 (35.6)	34.2 (19.5)	4.3 (1.5)
Active side to side turning	91.9 (34/37)	71.2 (33.2)	42.3 (36.7)	4.0 (2.0)
Active cycling in bed	59.5 (22/37)	11.8 (13.1)	39.2 (30.7)	4.5 (2.0)
Other active exercises in bed	67.6 (25/37)	55.2 (39.1)	44.6 (37.1)	4.7 (2.3)
Sitting on the edge of the bed	94.6 (35/37)	83.0 (24.5)	47.7 (35.2)	3.6 (1.5)
Transfers from bed to a chair	97.3 (36/37)	76.7 (25.8)	59.4 (50.8)	3.5 (1.7)
Ambulation (walking with patient)	89.2 (33/37)	26.6 (23.0)	25.2 (12.1)	3.7 (1.7)
Active resistance exercises, bedside cycling	45.9 (17/37)	19.5 (25.5)	33.8 (10.6)	3.8 (1.4)

Abbreviations: CHF= Swiss Francs; ICU= Intensive Care Unit

6.2.2.2 Early rehabilitation costs

Overall, average early rehabilitation costs per patient receiving early rehabilitation were estimated at CHF863. Most of the costs (88%) were related to salaries (CHF763). Material costs (CHF100) accounted for approximatively 12% of the early rehabilitation costs.

6.2.2.3 Outcomes that may be influenced by early rehabilitation

This section addresses the parameters considered as potential modifiers of costs, and thus potentially relevant for the cost model, or as potentially relevant for cost-effectiveness considerations. The clinical systematic review did not find sufficiently strong evidence for any of them, which would have formed a sufficient basis for actually taking them into account. Thus, none of them was finally used in this context. See sections 5.2.4, 5.2.6, and 5.2.7 for more details.

6.2.2.4 Early rehabilitation and overall hospitalization costs

In the BIA the number and distribution of eligible cases identified using the SHS of the SFOPH were combined with the diagnosis-related case costs statistics of the SFSO to estimate the total average hospitalization costs (more details are provided in the BIA in section 6.1.3).[51,52] The

average hospitalization costs per eligible case were estimated at CHF88,097 (including patients receiving early rehabilitation and those who did not receive them). This means that the costs for early rehabilitation (CHF863) represented only a small part of the total hospitalization costs (<1%).

6.2.2.5 Sensitivity and scenario analyses

The approach to the *de novo* cost analysis, dictated by sparse data, did not allow for particularly detailed sensitivity and scenario analyses. According to the results of the clinical systematic review, there was no statistically significant evidence for a difference between systematic early and late or less systematic early rehabilitation for the outcomes that may potentially be influenced by early rehabilitation and relevant from an economic perspective, or studies did not provide useful information.

In the sensitivity analyses we varied the duration of the early rehabilitation measures and the costs for physiotherapy and personnel by ±30%. The variation of duration and cost only had a small impact on the costs of early rehabilitation (Table 14).

In a scenario analysis overhead costs of 30% were added to the estimated personnel and material costs. The average early rehabilitation costs increased from CHF863 to CHF1,122 (+30%).

Table 14. Sensitivity and scenario analyses of per-patient cost of early rehabilitation

Sensitivity analysis	**Base case**	**Sensitivity Analysis**	
		-30%	**+30%**
Duration of early rehabilitation measures (CHF)	863	634	1092
Personnel costs (CHF)	863	634	1092
Duration of early rehabilitation measures AND personnel costs (CHF)	863	474	1390
Scenario analysis	**Base case**	**Scenario Analysis**	
Personnel costs including 30% overhead (CHF)	863	1,122	

Abbreviations: CHF= Swiss Francs
NB: the sensitivity analyses varying duration of early rehabilitation measures or personnel costs by ±30% show identical results because the costs were calculated using the formula: (duration of rehabilitation x personnel costs) + material costs.

6.2.2.6 Cost-effectiveness and additional considerations

As previously reported, the clinical review only found weak and inconsistent evidence for differences between systematic early and late (or less systematic) rehabilitation in terms of quality of life, length of ICU or hospital stays, and time to return to work. Nevertheless, it cannot

be excluded that specific subgroup of patients (e.g. patients in a specific age, diagnosis, or treatment group) may show significantly better (or worse) outcomes.

Considering that the estimated average costs for early rehabilitation in ICUs were low (approximately CHF900 per patient receiving it, in the base case of the *de novo* cost model), even a small difference in quality of life, in length of stay, or in the time to return to work might have a considerable impact on the cost and cost-effectiveness of early rehabilitation strategies (as explained in section 6.1.2, the estimate of approximately CHF900 refers to early rehabilitation vs. no rehabilitation in the ICU, with the implication that the incremental costs of systematic early compared with late or less systematic early rehabilitation might even be smaller).

For example, to achieve an ICER of CHF50,000 or CHF100,000 per QALY gained, early rehabilitation would need to generate 0.018 or 0.009 QALYs more than usual care. Based on a simplified assumption of constant utility differences over time, a utility difference of 0.036 or 0.018 would be required over a 6-month time horizon to meet an ICER threshold of CHF50,000 or CHF100,000, respectively. For a time horizon of 2 years, a utility difference of 0.009 or 0.005 would be necessary.

Length of stay (in ICU or hospital) may also have high impact: systematic early rehabilitation might even become cost saving if it could reduce the length of stay by less than one single day (assuming hospitalization/ICU costs ranging from CHF1,500 to CHF6,500 per day).

Finally, a faster return to work may have a high impact on indirect costs. Assuming a mean GDP per person of CHF79,104 and 220 working days per year, the costs for a single workday lost would be approximatively CHF360. A still professionally active patient receiving systematic early rehabilitation and returning to work earlier might cause considerably lower indirect costs if compared to those not receiving systematic early rehabilitation.

6.2.3 Budget impact analysis

The analysis consisted of two main steps: first, the number of eligible cases was estimated. In the second step, the annual number of hospitalizations, the estimated percentage of patients receiving systematic early rehabilitation and the estimated costs of rehabilitation calculated in the *de novo* cost analysis were used to estimate total annual costs representing the current use of early rehabilitation. In sensitivity analysis we investigated the total costs of hypothetical scenarios in which the use of early rehabilitation was varied. Finally, overall hospitalization costs according to SwissDRGs assigned to eligible patients were estimated and compared to the early rehabilitation costs.

6.2.3.1 Number of eligible cases

First, the annual occurrence of hospitalized cases requiring mechanical ventilation in Swiss ICUs was investigated. According to the treatment codes (i.e. CHOP codes) reported in the SHS, there were 51,115 hospitalized cases requiring mechanical ventilation in 2015.

Second, patients were further selected according to the inclusion/exclusion criteria defined in the scoping phase. The number of eligible cases decreased to 14,751 cases when a minimum length of mechanical ventilation (24 hours) and of length of ICU stay (24 hours) were used as additional filters. The exclusion of all patients younger than 20 years led to a total number of 12,365 cases. Finally, 5,812 eligible cases remained after excluding patients with at least one diagnosis (represented by a relevant ICD-10 code) mentioned as an exclusion criterion in the scoping phase.

Third, SwissDRG codes indicating the main hospitalization reason for each case were analyzed to further differentiate between relevant and non-relevant cases. Table 15 illustrates the results of the final case identification process using the SwissDRGs of the patients. Overall, 4,796 cases were considered relevant, whereas 1,016 cases were excluded. Among the included cases, two SwissDRG code groups were particularly frequent: the pre major diagnostic code (pre-MDC) indicating a ventilation in complex cases (n=2,041) and the diseases or disorders of the circulatory system (n=1,328).

6.2.3.2 Total early rehabilitation costs of eligible cases

As reported in the *de novo* cost analysis, we estimated that the average costs of systematic early rehabilitation may reach CHF863 per patient. Assuming that 82% of the ICU patients meeting the PICO receive early rehabilitation during their ICU stay (as suggested by the survey results), it can be estimated that the yearly total costs for early rehabilitation in patients meeting the PICO may reach CHF3.4 million.

To better contextualize the yearly total costs for early rehabilitation in patients meeting the PICO, we compared them with the estimated total costs for all hospitalized patients requiring mechanical ventilation for at least 24 hours in a Swiss ICU. The estimated total cost of systematic early rehabilitation in patients requiring mechanical ventilation for at least 24 hours in a Swiss ICU was CHF10.4 million (i.e. 14,751 cases times 82% probability of receiving early rehabilitation times CHF863 per case). This means that the estimated costs of CHF3.4 million for patients meeting the PICO were equivalent to 33% of the estimated total costs of early rehabilitation in all patients requiring mechanical ventilation for at least 24 hours in a Swiss ICU.

Table 15. Number of finally included/excluded cases according to SwissDRG groups/codes

Included SwissDRG groups/codes	N
Pre-MDC (Major Diagnostic category) - Ventilation in complex cases (SwissDRG A07-A13, A18)	2,041
Pre-MDC (Major Diagnostic category) - Intensive care complex treatments (SwissDRG A36)	282
Diseases or disorders of the respiratory organs (SwissDRGs E01-E77A)	540
Diseases or disorders of the circulatory system (SwissDRG F01-F98)	1,328
Diseases or disorders of the digestive organs (SwissDRG G02-G73)	337
Diseases or disorders of the hepatic system and pancreas (SwissDRG H01-H64)	94
Diseases or disorders of the musculoskeletal system and connective tissue (SwissDRG I02-I98)	89
Polytrauma (SwissDRG W01-W61)	85
Total	**4,796**

Excluded SwissDRG groups/codes	N
Transplantations or events related transplantation (e.g. SwissDRGs A01-A06, A15-A17, A60, E77B-E77D, F04, F28, H61, H63, I02, I46)	164
Geriatric early rehabilitating complex treatments after 7 treatment days (e.g. SwissDRGs A95)	18
Diseases or disorders of the nervous system (SwissDRGs B01-B86)	45
Diseases or disorders of the ear, nose, mouth, and throat (SwissDRGs D01-D67)	98
Diseases or disorders of the skin, hypoderm, and breast (SwissDRG J01-J68)	14
Endocrine, nutrition, and metabolism diseases (SwissDRGs K01-K64)	19
Diseases or disorders of the urinary organs (SwissDRG L02-L72)	58
Diseases or disorders of the male and female sexual organs (SwissDRG M01-M64, N01-N62)	44
Pregnancy, birth and childbed (SwissDRG O01-O65)	25
Diseases of blood, blood-building organs and immune system (SwissDRG Q01-Q61)	6
Hematological and solid neoplasms (SwissDRG R01-R65)	37
HIV (SwissDRG S01-S65)	2
Infectious and parasitic diseases (SwissDRG T01-T64)	443#
Injuries, poisoning, and toxic effects of drugs and medicaments (SwissDRG X01-X64)	29
Other factors influencing the health status (SwissDRG Z01-Z66)	1
Error-DRGs und other DRGs (e.g. SwissDRGs 901A-D)	13
Total	**1,016**

This group was excluded since most of the identified cases (77%) were related to transplantation. Abbreviations: HIV= Human Immunodeficiency Virus; SwissDRG= Swiss Diagnosis Related Groups

6.2.3.3 Sensitivity analyses

In sensitivity analysis we investigated the overall costs in case of an increased or decreased use of systematic early rehabilitation. The frequency of early rehabilitation was varied from 0% (i.e. no use) to 100% (application for all ICU patients).

The overall early rehabilitation costs for all eligible cases according to the PICO would decrease to CHF0 if nobody would receive early rehabilitation measures. In contrast, in case of application of early rehabilitation measures to all eligible cases, the overall costs of early rehabilitation would increase to CHF4.1 million (+CHF 0.7 million if compared to the current use). This suggests that the application of early rehabilitation measures to all eligible cases would have a modest impact (+22%).

6.2.3.4 Contextualization of early rehabilitation costs

Average and total hospitalization costs of eligible cases

The average hospitalization costs per eligible case were estimated using the diagnosis-related case costs statistics. The selected 4,796 cases were distributed across 197 different SwissDRG codes and eight main groups. As reported in Table 16, the mean costs per case ranged from CHF27,309 for patients with diseases or disorders of the respiratory organs (SwissDRGs E01-E77A) to CHF140,802 for complex cases requiring ventilation (SwissDRGs A07-A13, A18). Overall, the mean costs per eligible case were estimated at CHF88,097 (including patients receiving early rehabilitation and those who do not). Overall, we estimated that the yearly total hospitalization costs for ICU patients requiring mechanical ventilation and meeting the inclusion criteria of the PICO reached CHF422 million. Table 16 illustrates the total costs according to different SwissDRG categories. The SwissDRG group including complex cases requiring ventilation (SwissDRG A07-A13, A18) was by far the biggest (43% of the total number of cases) and most expensive (CHF287 million, 68% of the total costs).[52] Diseases or disorders of the circulatory system (SwissDRG F01-F98) were also very frequent but less expensive (CHF52,725 per case, CHF70 million in total). Cases with intensive care complex treatments and polytrauma were less frequent but more expensive compared to diseases or disorders of the respiratory organs or of the digestive organs.

Table 16. Average and total hospitalization costs per eligible patients according to SwissDRG groups

SwissDRG groups/codes	N	Average costs (CHF)	Total costs (CHF)
Pre-MDC (Major Diagnostic category) - Ventilation in complex cases (SwissDRG A07-A13, A18)	2,041	140,802	287,377,205
Pre-MDC (Major Diagnostic category) - Intensive care complex treatments (SwissDRG A36)	282	85,579	24,133,282
Diseases or disorders of the respiratory organs (SwissDRGs E01-E77A)	540	27,309	14,747,048
Diseases or disorders of the circulatory system (SwissDRG F01-F98)	1,328	52,725	70,018,260
Diseases or disorders of the digestive organs (SwissDRG G02-G73)	337	42,713	14,394,284
Diseases or disorders of the hepatic system and pancreas (SwissDRG H01-H64)	94	30,219	2,840,579
Diseases or disorders of the musculoskeletal system and connective tissue (SwissDRG I02-I98)	89	29,196	2,598,471
Polytrauma (SwissDRG W01-W61)	85	75,358	6,405,423
Total	**4,796**	**88,097**	**422,514,552**

Abbreviations: CHF= Swiss Francs; SwissDRG= Swiss Diagnosis Related Groups

Comparison of total early rehabilitation costs with total hospitalization costs of eligible cases

The estimated overall costs of systematic early rehabilitation in the eligible population (CHF 3.4 million) represented only a small part of the overall hospitalization costs (0.8%).

6.3 Discussion

The health economic assessment consisted of a systematic review of the currently published economic literature, a *de novo* cost analysis for Switzerland, and a budget impact analysis. For the *de novo* cost analysis and the budget impact analysis, we investigated the current practice in Switzerland.

6.3.1 Systematic review of economic literature

The systematic review of the health economic literature showed that there is currently no cost-effectiveness analysis for the investigated PICO. Only three studies were considered partially relevant and were therefore reviewed.[54–56] Morris et al. and Chou et al. estimated that patients receiving early rehabilitation measures costed USD2,500-3,000 less if compared to usual care or no rehabilitation. The results in favor of early rehabilitation were driven by the ICU length of stay (5.5 vs. 6.9 days in Morris et al., 5.8 vs. 9.2 days in Chou et al.) and by the length of the total hospital stay (11.2 vs. 14.5 days in Morris et al., 17.9 vs. 25.4 days in Chou et al.). In the study by Wright et al., the intervention group had a longer ICU length of stay (18 vs. 16 days) and a longer hospital stay (42 vs. 41 days) if compared to standard care. These results are not in line with those reported by Morris et al. and by Chou et al. Wright et al. did not report information on costs (despite mentioning a cost analysis in the main document). Nevertheless, they provided information on quality of life (which was similar between intervention and comparator strategy). Considering these discordant results and the limitations of the above-mentioned studies (see section 6.2.1.3), for the present *de novo* cost analysis we decided to base the estimation of outcomes relevant as cost drivers on the results of the clinical assessment only.

6.3.2 De novo cost analysis

According to the Swiss ICUs participating to the survey, 82% of ICU patients receive early rehabilitation. Based on the reported frequency and duration of the rehabilitation measures we estimated that each patient undergoing early rehabilitation in ICUs receive such measures for a total of 13.3 hours during their ICU stay.

The average costs per patient receiving systematic early rehabilitation were estimated at CHF863. Most of the costs (88%) were salary costs (CHF763). Estimated material costs (CHF100) accounted for approximatively 12% of the early rehabilitation costs.

The results of the clinical assessment did not provide sufficient evidence concerning differences in quality of life, mortality, length of ICU/hospital stay, nor time to return to work between early

rehabilitation and standard care. For these reasons, these variables were not included in the cost analysis. Consequently, the cost difference between strategies in our analysis (ca. CHF900 in favor of standard care), are not consistent with those reported by Morris et al. and Chou et al. (USD2,500-3,000 in favor of early rehabilitation) who assumed longer lengths of ICU/hospital stays in the standard care strategies.[54,55] Nevertheless, we approximated which effect sizes in favor of early rehabilitation might be required to lead to a cost-effective or cost-saving situation. First, to achieve an ICER of CHF50,000 or CHF100,000 per QALY gained, early rehabilitation would need to generate 0.018 or 0.009 QALYs more than usual care. Although the difference was not significant, Wright et al. reported that patients undergoing intensive rehabilitation accrued 0.208 QALYs over 6 months, whereas patients with standard care accrued 0.184 QALYs (i.e. 0.024 QALYs less).[56] It should be considered that Wright et al. compared intensive vs. standard early rehabilitation. Therefore, the reported difference in QALYs may not reflect the difference between early rehabilitation and late/no rehabilitation. It cannot be excluded that trials with a longer follow-up period and a sample size powered to identify small between-group differences might demonstrate QALY differences of 0.009-0.018 in favor of early rehabilitation vs. late/no rehabilitation. Second, the length of stay (in ICU or hospital) may also have a high impact: early rehabilitation may become cost-saving if it could reduce the length of stay by one single day (assuming ICUs/hospitalization costs ranging from CHF1,500 to CHF4,000). Finally, difference in time to return to work was not included in the calculations due to lacking information. However, it is important to emphasize that indirect costs relating to longer periods of absenteeism from work may have a considerable economic impact.

According to the SHS, in 2015 there were 4,796 hospitalized cases requiring mechanical ventilation in a Swiss ICU that may be eligible according to the PICO studied in this HTA.[51] The average costs per eligible case were estimated at CHF88,097 (including patients receiving early rehabilitation and those who do not receive it). This means that the costs for early rehabilitation (CHF863) represented only a small part of the total hospitalization costs (<1%).

6.3.3 Budget impact analysis

In the BIA we estimated the total early rehabilitation costs as well as the total hospitalization costs of eligible cases. As reported in the *de novo* cost analysis, we estimated that the average costs of systematic early rehabilitation may be CHF863 per patient. Assuming that 82% of the ICU patients receive early rehabilitation during their ICU stays (as suggested by our survey results), the total costs of early rehabilitation for patients meeting our PICO were estimated to be CHF3.4 million. The total hospitalization costs for eligible patients were estimated to be CHF422 million. This means that the estimated overall costs of early rehabilitation in the eligible population

represented only a small part of their overall hospitalization costs (0.8%). Sensitivity analyses confirmed that the administration of early rehabilitation measures has a minimal impact on the overall costs of ICU patients requiring mechanical ventilation.

It is important to note that the overall number of ICU cases receiving early rehabilitation may be considerably higher than the population selected for this assessment. According to the SHS, in 2015 there were 14,751 patients requiring mechanical ventilation for at least 24 hours in a Swiss ICU.[51] Assuming the same probability of receiving early rehabilitation and the same average costs per patients, the overall costs may reach CHF10.4 million.

According to the Swiss Society of Intensive Care Medicine, in 2018 there were 85,269 ICU admissions.[53] Although many of these patients may have a very short ICU stay not requiring mechanical ventilation, they may also receive early rehabilitation. Therefore, the total number of patients receiving early rehabilitation and the overall costs of early rehabilitation may be higher.

6.3.4 Strengths and limitations

One of the main strengths of the *de novo* cost analysis and BIA was the use of the results of the clinical assessment to decide whether potentially relevant economic outcomes could be included or not in the main analysis. Another strength was the use of Swiss data to derive a series of inputs variables. In particular, data from the SFSO (e.g. SHS and Diagnosis-related case costs statistics) were combined to identify eligible cases and derive average hospital costs for eligible cases in Switzerland. Through CHOP codes it was possible to identify patients that received mechanical ventilation during their hospitalization. Through ICD-10 codes, SwissDRG codes, age class and variables indicating the length of ventilation and ICU stay it was possible to further select cases according to the studied PICO.

The *de novo* cost analysis and the BIA also have several limitations. First, several assumptions were based on the results of the systematic review of the clinical part of the assessment. The clinical assessment was based exclusively on RCTs reflecting the PICO under investigation. These studies were very heterogeneous in terms of population (e.g. had different age or gender distribution, different sample size, different diagnoses of the patients), intervention and comparator (e.g. regarding time elapsed from ICU admission and rehabilitation start, type of rehabilitation measure), and outcomes. Outcomes relevant from an economic perspective showed no evidence for significant differences in favor of early rehabilitation or were not reported adequately. It cannot be excluded that early rehabilitation for specific subgroups of patients may lead to significant improvements (in terms of length of stay or mortality reduction, increase of quality of life, faster return to work). On the other hand, it is also possible that early rehabilitation may lead to increased adverse events if applied to the wrong patients or if performed too early.

Furthermore, it is important to consider that other elements post-ICU care may have a significant impact on the total costs of ICU patients. These include for example institutionalization for patients unable to return to independency, home modifications for those with impaired mobility, and caregiver support (from specific institutions or relatives). The fact that relatives may be forced to become caregivers may lead to additional psychological burden, financial difficulties, and indirect costs. It should also be emphasized that the identified RCTs had in general a very short follow-up (in many cases until ICU/hospital discharge, in few cases until 6/12 months). Longer-term follow-up data might provide important information concerning mortality, readmissions due to complications, working capacity, and quality of life.

Another limitation concerns the estimation of the frequency of use of early rehabilitation. In the survey we could only collect information on early rehabilitation measures for ICU patients in general. However, ICU patients are an extremely heterogeneous population. The eligibility criteria of the PICO of the present assessment restricted the patient selection to those requiring mechanical ventilation, but excluding burn patients, patients with pre-existing neurological illnesses (such as brain trauma, neurosurgery, neuromuscular diseases, stroke, multiple sclerosis, brain tumor, spinal cord injury, patients with para- and tetraplegia) and transplant patients. The combination of information from both types of sources (i.e. survey results applying to all ICU patients and published evidence for the more restricted PICO) imply a risk of lack of compatibility. It is e.g. not guaranteed that the use of early rehabilitation in 82% of ICU patients, as reported by the survey participants, also applies to the patients meeting our PICO, as we assumed.

The estimation of the costs of systematic early rehabilitation was affected by substantial uncertainty. We based our calculation on the estimated time used to provide early rehabilitation combined with the estimated salary of the personnel involved. Following survey results, we assumed that early rehabilitation is mostly provided by the nursing staff or by a physiotherapy team. It is possible that the involvement of other specialists in the rehabilitation process may lead to higher personnel costs. Moreover, we assumed that one single nurse or physiotherapist will provide the treatment. However, it cannot be excluded that some specific rehabilitation measures or certain patient subgroups (e.g. particularly fragile or heavy) may require the simultaneous involvement of two or more persons.

Finally, it is important to remember that the cost analyses compared systematic early rehabilitation with no rehabilitation for reasons of data availability, thus deviating from the main PICO used in in the clinical and economic systematic review parts. It could be argued that a comparison with an active comparator (such as late rehabilitation or less systematic early rehabilitation) would lead to smaller differences in costs and effects. In this optic, the calculation of the costs for early rehabilitation vs. no rehabilitation, combined with treatment effects from

trials comparing early rehabilitation with active comparator, can be considered a conservative approach.

6.4 Conclusion

The systematic review of the economic literature suggested that there is currently no cost-effectiveness study for the predefined PICO.

Our own analytical options were also substantially restricted given very sparse data. The available information did not allow us to assess the cost-effectiveness of systematic early rehabilitation in comparison with standard care. The *de novo* cost analysis suggested that the costs of early rehabilitation are low and represent only a small part of the total hospitalization costs of eligible ICU patients. Consequently, the BIA results suggested that an increased or decreased use of early rehabilitation would have a little impact on the total cost burden.

Given the paucity of high-quality and long-term data on clinical outcomes and health related quality of life, it remains unclear whether an analysis over a longer period of observation or including indirect costs resulting from productivity losses might lead to substantially different health economic results. Moreover, it should be emphasized that the study population according to the predefined PICO was very heterogeneous (in terms of age, gender, diagnoses, and treatments). Although there were no or only few significant differences between systematic early rehabilitation and eligible comparators in general, it cannot be excluded that specific subgroups may profit from early rehabilitation. On the other side, certain subgroups may as well have additional complications due to early rehabilitation, leading to increased costs.

Ultimately, it is not possible to judge based on currently available data if systematic early rehabilitation might meet frequently assumed cost-effectiveness thresholds (e.g. CHF 50,000 or CHF 100,000 per QALY gained). In this optic, long-term studies investigating treatment effectiveness and the quality of life of ICU patients requiring mechanical ventilation and receiving early rehabilitation or late/no rehabilitation would be desirable.

It should be remembered that the published literature often compared "early rehabilitation" or specific early rehabilitation protocols with standard care. In several cases standard care already included early rehabilitation as defined for this HTA. The main differences between interventions and comparators were the intensity of rehabilitation and the rehabilitation pathway (i.e. whether a protocol or a care team decide when a patient should start rehabilitation). It could be argued that in many cases, standard care may already provide good support for ICU patients. According to the survey we conducted among Swiss ICUs, most of the patients in ICU in Switzerland (82%) already receive early rehabilitation treatments.

7 Overall conclusion

The findings of this report need to be considered within the context of the literature and the current situation in Switzerland. In most studies, especially the most recent ones, specific early rehabilitation measures or protocols were compared to standard care already consisting of an early, but less systematic rehabilitation approach. This implies that the timing difference between groups was minimal, as for example in the study by Eggmann et al.[37] conducted in Switzerland. While our analysis mostly did not find evidence for a beneficial effect when comparing systematic early with such less systematic early rehabilitation approaches, the earliest included high-quality RCT found large effects on several outcomes comparing systematic early vs. late rehabilitation. It might thus be reasonable to assume that a transition in standard care towards earlier rehabilitation approaches has taken place in recent years. Consequently, additional benefits against such a comparator of already implemented, albeit less systematic early rehabilitation can be expected to be substantially smaller and more difficult to measure. More recent trials might thus be underpowered to detect such small differences statistically due to their limited sample sizes. Our survey among Swiss ICUs suggested that most of the patients in ICU in Switzerland (82%) receive early rehabilitation measures, which may be reflected in the reported results reported by Eggmann et al.[37] Our economic analyses could not answer the question of cost-effectiveness, due to lack of suitable data, but indicated the costs of early rehabilitation to contribute to only a small fraction of the hospitalization costs of ICU patients.

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9 Appendix

9.1 Search Strategies for Systematic Reviews

Medline (Pubmed) strategy

("intensive care"[tiab] OR "ICU"[tiab] OR "critical care"[tiab] OR "critically ill"[tiab] OR "mechanical ventilation"[tiab] OR "ventilation support"[tiab] OR "PICS"[tiab] OR "ICUAW"[tiab]) AND ("exercise"[tiab] OR "rehabilitation"[tiab] OR "physical therapy"[tiab] OR "physiotherapy"[tiab] OR "mobilisation"[tiab] OR "mobilization"[tiab] OR "early mobility"[tiab] OR "physical fitness"[tiab] OR "muscle training"[tiab] OR "diary"[tiab]) AND (Meta-Analysis[ptyp] OR systematic[sb] OR "meta-analysis"[tiab] OR "systematic review"[tiab]) AND ("2015/01/01"[PDAT] : "2018/12/04"[PDAT])
Date: 04 Dec 2018
Results: 220

Cochrane Reviews (The Cochrane Library) strategy

("intensive care":ti,ab OR ICU:ti,ab OR "critical care":ti,ab OR "critically ill":ti,ab OR "mechanical ventilation":ti,ab OR "ventilation support":ti,ab OR PICS:ti,ab OR ICUAW:ti,ab) AND (exercise:ti,ab OR rehabilitation:ti,ab OR "physical therapy":ti,ab OR physiotherapy:ti,ab OR mobilisation:ti,ab OR mobilization:ti,ab OR "early mobility":ti,ab OR "physical fitness":ti,ab OR "muscle training":ti,ab OR diary:ti,ab) AND (meta-analysis:ti,ab OR "systematic review":ti,ab)
Further filter: publications from 01/01/2015 to 04/12/2018
Date: 04 Dec 2018
Results: 220

9.2 Search Strategies for Follow-Up Searches

Medline (Ovid) strategy based on Doiron et al. 2018

1 exp Intensive Care Units/ or Critical Illness/ or exp Critical Care/ or (critical* adj3 (ill* or care*)).tw. or intensive care.tw. or (icu or icuaw).tw.

2 exp Exercise Therapy/ or exp Physical Therapy Modalities/ or Occupational Therapy/ or (mobilizat* or mobilisat* or mobility).tw. or exercis*.tw. or (therap* adj3 (physical or exercise or occupation*)).tw. or ((bed or daily living) adj3 activit*).tw. or (training or pregait or pre-gait or walk* or adl or physiotherap* or ambulation).tw. or ((cycle or bicycle) adj1 ergomet*).tw.

3 ((randomized controlled trial or controlled clinical trial).pt. or clinical trial.sh. or (randomized or randomised or randomly).ti,ab. or trial.ti. or placebo.ti,ab.) not (animals not humans).sh.

4 1 and 2 and 3

5 4 and (201706* or 201707* or 201708* or 201709* or 201710* or 201711* or 201712* or 2018* or 2019*).dp,ed,ep,ez.

Date: 17 Jan 2019

Results: 264

Medline (Ovid) strategy based on Fuke et al. 2018

1 ("critical ill" or "critical illness" or "critical care" or "intensive care" or "mechanical ventilation" or "mechanical ventilated" or "postoperative care").mp.

2 (rehabilitation or "physical therapy" or physiotherapy or exercise or mobilization or "mobility intervention" or "muscle training").mp.

3 ("Activities of Daily Living" or "Quality of Life" or "postintensive care syndrome" or "motor function" or "Physical Functioning" or "functional status" or "physical function" or "ventilator days" or "quality of life" or (walking or walk) or muscle or polyneuromyopathy or "length of stay" or "length of ICU stay" or "length of hospital stay" or "intubation period" or "duration of mechanical ventilation" or re-admission or "functional outcome" or "ICU-acquired weakness" or "ICU-acquired paresis" or ICUAW or "ICUAW" or "intensive care unit acquired weakness" or "critical illness polyneuropathy" or "critical illness myopathy" or "critical illness neuromyopathy" or "acute quadriplegic myopathy" or "thick filament myopathy" or "acute necrotizing myopathy of intensive care" or "acute corticosteroid myopathy" or "critical illness neuromuscula syndromes" or "Tower test" or "Timed Up and Go Test" or "dysexecutive questionnaire" or FAQ or "EQ-5D VAS" or 6MWD or "6-min walking distance" or "Quadriceps force, and self-perceived functional status" or "SF-36 PF" or MRC or "Medical Research Council" or "AQoL utility" or "EQ-5D" or PFIT or "physical functional ICU test" or "Hospital Anxiety and Depression Scale" or "Hand-grip strength").mp.

4 ((randomized controlled trial or controlled clinical trial).pt. or clinical trial.sh. or (randomized or randomised or randomly).ti,ab. or trial.ti. or placebo.ti,ab.)) not (animals not humans).sh.

5 1 and 2 and 3 and 4

6 5 and (201604* or 201605* or 201606* or 201607* or 201608* or 201609* or 201610* or 201611* or 201612* or 2017* or 2018* or 2019*).dp,ed,ep,ez.

Date: 17 Jan 2019

Results: 232

Medline (Ovid) strategy based on Castro-Avila et al. 2015

1 Critical Care/ or critical care.mp. or intensive care units/ or intensive care unit?.mp. or burn units/ or burn unit?.mp. or coronary care units/ or coronary care unit?.mp. or recovery room/ or recovery room?.mp. or respiratory care units/ or respiratory care unit?.mp. or Critical Illness/rh or Critical Illness/ or (critical illness or critically ill).mp. or *Intensive Care/ or intensive care.mp. or intensive treatment unit?.mp. or intensive therapy unit?.mp. or high dependency unit?.mp. or ICU.mp. or HDU.mp.

2 exp Rehabilitation/ or rehabilitat*.mp. or exp Physical Therapy Modalities/ or physical therapy modalit?.mp. or physical therap*.mp. or physiotherap*.mp. or kinesiotherap*.mp. or exp Exercise Therapy/ or exercise therap*.mp. or physical exertion/ or physical exertion.mp. or Early

Ambulation/ or Early Ambulation.mp. or mobilization.mp. or mobilisation.mp. or Muscle Weakness/rh or Muscle Weakness/th or Neuromuscular Diseases/rh

3 ((randomized controlled trial or controlled clinical trial).pt. or clinical trial.sh. or (randomized or randomised or randomly).ti,ab. or trial.ti. or placebo.ti,ab.) not (animals not humans).sh.

4 1 and 2 and 3

5 4 and (201402* or 201403* or 201404* or 201405* or 201406* or 201407* or 201408* or 201409* or 201410* or 201411* or 201412* or 2015* or 2016* or 2017* or 2018* or 2019*).dp,ed,ep,ez.

Date: 17 Jan 2019

Results: 420

Embase (Embase.com/Elsevier) strategy based on Doiron et al. 2018

#1 icu:ab,ti OR icuaw:ab,ti OR 'intensive care':ab,ti OR ((critical* NEAR/3 (ill* OR care)):ab,ti) OR 'intensive care'/exp OR 'critical illness'/de OR 'intensive care unit'/de

#2 training:ab,ti OR pregait:ab,ti OR 'pre-gait':ab,ti OR walk*:ab,ti OR adl:ab,ti OR physiotherapy*:ab,ti OR (((cycle OR bicycle) NEAR/1 ergomet*):ab,ti) OR ambulation:ab,ti OR (((bed OR 'daily living') NEAR/3 activity):ab,ti) OR ((therap* NEAR/3 (physical* OR exercise OR occupation*)):ab,ti) OR exercis*:ab,ti OR mobiliz*:ab,ti OR mobilis*:ab,ti OR mobility:ab,ti OR 'occupational therapy'/de OR 'physiotherapy'/exp OR 'kinesiotherapy'/exp

#3 ('controlled clinical trial'/exp OR randomized:ti,ab OR randomised:ti,ab OR randomly:ti,ab OR trial:ti OR placebo:ti,ab) NOT ([animals]/lim NOT [humans]/lim)

#4 #1 AND #2 AND #3

#5 #4 AND [1-6-2017]/sd NOT [conference abstract]/lim

Date: 17 Jan 2019

Results: 690

Embase (Embase.com/Elsevier) strategy based on Fuke et al. 2018

#1 'critical ill':ab,ti OR 'critical illness':ab,ti OR 'critical care':ab,ti OR 'intensive care':ab,ti OR 'mechanical ventilation':ab,ti OR 'mechanical ventilated':ab,ti OR 'postoperative care':ab,ti

#2 rehabilitation:ab,ti OR 'physical therapy':ab,ti OR physiotherapy:ab,ti OR exercise:ab,ti OR mobilization:ab,ti OR 'mobility intervention':ab,ti OR 'muscle training':ab,ti

#3 'activities of daily living':ab,ti OR 'post-intensive care syndrome':ab,ti OR 'motor function':ab,ti OR 'physical functioning':ab,ti OR 'functional status':ab,ti OR 'physical function':ab,ti OR 'ventilator days':ab,ti OR 'quality of life':ab,ti OR walking:ab,ti OR walk:ab,ti OR muscle:ab,ti OR polyneuromyopathy:ab,ti OR 'length of stay':ab,ti OR 'length of icu stay':ab,ti OR 'length of hospital stay':ab,ti OR 'intubation period':ab,ti OR 'duration of mechanical ventilation':ab,ti OR 'readmission': ab,ti OR 'functional outcome':ab,ti OR 'icu-acquired weakness':ab,ti OR 'icu-acquired paresis':ab,ti OR icuaw:ab,ti OR 'icu-aw':ab,ti OR 'intensive care unit acquired weakness':ab,ti OR 'critical illness polyneuropathy':ab,ti OR 'critical illness myopathy':ab,ti OR 'critical illness

neuromyopathy':ab,ti OR 'acute quadriplegic myopathy':ab,ti OR 'thick filament myopathy':ab,ti OR 'acute necrotizing myopathy of intensive care':ab,ti OR 'acute corticosteroid myopathy':ab,ti OR 'critical illness neuromuscula syndromes':ab,ti OR 'tower test':ab,ti OR 'timed up and go test':ab,ti OR 'dysexecutive questionnaire':ab,ti OR faq:ab,ti OR 'eq-5d vas':ab,ti OR 6mwd:ab,ti OR '6-min walking distance':ab,ti OR 'quadriceps force, and self-perceived functional status':ab,ti OR 'sf-36 pf':ab,ti OR mrc:ab,ti OR 'medical research council':ab,ti OR 'aqol utility':ab,ti OR 'eq-5d':ab,ti OR pfit:ab,ti OR 'physical functional icu test':ab,ti OR 'hospital anxiety and depression scale':ab,ti OR 'hand-grip strength':ab,ti

#4 ('controlled clinical trial'/exp OR randomized:ti,ab OR randomised:ti,ab OR randomly:ti,ab OR trial:ti OR placebo:ti,ab) NOT ([animals]/lim NOT [humans]/lim)

#5 #1 AND #2 AND #3 AND #4

#6 #5 AND [1-4-2017]/sd NOT [conference abstract]/lim

Date: 17 Jan 2019

Results: 78

Embase (Embase.com/Elsevier) strategy based on Castro-Avila et al. 2015

#1 'intensive care'/de OR 'critical care':de,lnk,ab,ti OR 'intensive care unit'/de OR 'intensive care unit*':de,lnk,ab,ti OR 'burn unit'/de OR 'burn unit*':de,lnk,ab,ti OR 'coronary care unit'/de OR 'coronary care unit*':de,lnk,ab,ti OR 'recovery room'/de OR 'recovery room*':de,lnk,ab,ti OR 'respiratory care unit*':de,lnk,ab,ti OR 'critical illness'/de OR 'critical illness':de,lnk,ab,ti OR 'critically ill':de,lnk,ab,ti OR 'intensive care'/mj OR 'intensive care':de,lnk,ab,ti OR 'intensive treatment unit*':de,lnk,ab,ti OR 'intensive therapy unit*':de,lnk,ab,ti OR 'high dependency unit*':de,lnk,ab,ti OR icu:de,lnk,ab,ti OR hdu:de,lnk,ab,ti

#2 'rehabilitation'/exp OR rehabilitat*:de,lnk,ab,ti OR 'physiotherapy'/exp OR 'physical therapy modalit*':de,lnk,ab,ti OR 'physical therap*':de,lnk,ab,ti OR physiotherap*:de,lnk,ab,ti OR kinesiotherap*:de,lnk,ab,ti OR 'kinesiotherapy'/exp OR 'exercise therap*':de,lnk,ab,ti OR 'exercise'/de OR 'physical exertion':de,lnk,ab,ti OR 'mobilization'/de OR 'early ambulation':de,lnk,ab,ti OR mobilization:de,lnk,ab,ti OR mobilisation:de,lnk,ab,ti OR 'muscle weakness'/dm_rh,dm_th OR 'neuromuscular disease'/dm_rh

#3 ('controlled clinical trial'/exp OR randomized:ti,ab OR randomised:ti,ab OR randomly:ti,ab OR trial:ti OR placebo:ti,ab) NOT ([animals]/lim NOT [humans]/lim)

#4 #1 AND #2 AND #3

#5 #4 AND [1-2-2014]/sd NOT [conference abstract]/lim

Date: 17 Jan 2019

Results: 468

CINAHL (EBSCOhost) strategy based on Doiron et al. 2018

(TI ((cycle or bicycle) N1 ergomet*) OR AB ((cycle or bicycle) N1 ergomet*) OR TI (training or pregait or pre-gait or walk* or adl or physiotherap* or ambulation) OR AB (training or pregait or pregait or walk* or

adl or physiotherap* or ambulation) TI ((bed or daily living) N3 activit*) OR AB ((bed or daily living) N3 activit*) TI (therap* N3 (physical or exercise or occupation*)) OR AB (therap* N3 (physical or exercise or occupation*)) TI exercis* OR AB exercis* TI (mobilizat* or mobilisat* or mobility) OR AB (mobilizat* or mobilisat* or mobility) (MH "Occupational Therapy+") (MH "Physical Therapy+") (MH "Therapeutic Exercise+")) AND (TI (icu or icuaw) OR AB (icu or icuaw) OR TI intensive careOR AB intensive care OR TI (critical*N3 (ill* or care*)) OR AB (critical* N3 (ill* or care*)) OR (MH "Critical Care") OR (MH "Critical Illness") OR (MH "Intensive Care Units+")) AND ((MH "Randomized Controlled Trials+") OR TI (randomized or randomised or randomly or trial or placebo) OR AB (randomized or randomised or randomly or placebo) NOT ((MH "Animals+") NOT (MH "Human")))
Limiters: Published Date: 20170601; Search modes: Find all my search terms
Date: 17 Jan 2019
Results: 12

CINAHL (EBSCOhost) strategy based on Fuke et al. 2018

(("critical ill" OR "critical illness" OR "critical care" OR "intensive care" OR "mechanical ventilation" OR "mechanical ventilated" OR "postoperative care")) AND ((rehabilitation OR "physical therapy" OR physiotherapy OR exercise OR mobilization OR "mobility intervention" OR "muscle training")) AND (("Activities of Daily Living" OR "Quality of Life" OR "post-intensive care syndrome" OR "motor function" OR "Physical Functioning" OR "functional status" OR "physical function" OR "ventilator days" OR "quality of life" OR (walking OR walk) OR muscle OR polyneuromyopathy OR "length of stay" OR "length of ICU stay" OR "length of hospital stay" OR "intubation period" OR "duration of mechanical ventilation" OR re-admission OR "functional outcome" OR "ICU-acquired weakness" OR "ICU-acquired paresis" OR ICUAW OR "ICU-AW" OR "intensive care unit acquired weakness" OR "critical illness polyneuropathy" OR "critical illness myopathy" OR "critical illness neuromyopathy" OR "acute quadriplegic myopathy" OR "thick filament myopathy" OR "acute necrotizing myopathy of intensive care" OR "acute corticosteroid myopathy" OR "critical illness neuromuscula syndromes" OR "Tower test" OR "Timed Up and Go Test" OR "dysexecutive questionnaire" OR FAQ OR "EQ-5D VAS" OR 6MWD OR "6-min walking distance" OR "Quadriceps force, and self-perceived functional status" OR "SF-36 PF" OR MRC OR "Medical Research Council" OR "AQoL utility" OR "EQ-5D" OR PFIT OR "physical functional ICU test" OR "Hospital Anxiety and Depression Scale" OR "Hand-grip strength")) AND ((MH "Randomized Controlled Trials+") OR TI (randomized or randomised or randomly or trial or placebo) OR AB (randomized or randomised or randomly or placebo) NOT ((MH "Animals+") NOT (MH "Human")))
Limiters: Published Date: 20160401; Search modes: Find all my search terms
Date: 17 Jan 2019
Results: 100

CINAHL (EBSCOhost) strategy based on Castro-Avila et al. 2015

((MH "Critical Care") OR "critical care" OR (MH "Intensive Care Units") OR "intensive care unit? " OR (MH "Burn Units") OR "burn unit? " OR (MH "Coronary Care Units") OR "coronary care unit?" OR (MH "Post

Anesthesia Care Units") OR "recovery room?" OR (MH "Respiratory Care Units") OR "respiratory care unit?" OR (MH "Critical Illness") OR (MH "Critical Illness/RH") OR "critical illness" OR "critically ill" OR "intensive care" OR "intensive treatment unit?" OR "intensive therapy unit?" OR "high dependency unit?" OR ICU OR HDU) AND ((MH "Rehabilitation+") OR rehabilitat* OR (MH "Physical Therapy+") OR "physical therapy modalit?" OR "physical therap*" OR physiotherap* OR kinesiotherap* OR (MH "Therapeutic Exercise") OR "exercise therap*" OR "physical exertion" OR (MH "Early Ambulation") OR "Early Ambulation" OR mobilization or mobilisation OR (MH "Muscle Weakness/RH/TH") OR (MH "Neuromuscular Diseases/RH")) AND ((MH "Randomized Controlled Trials+") OR TI (randomized or randomised or randomly or trial or placebo) OR AB (randomized or randomised or randomly or placebo) NOT ((MH "Animals+") NOT (MH "Human")))

Limiters: Published Date: 20140201; Search modes: Find all my search terms

Date: 17 Jan 2019

Results: 256

CENTRAL (The Cochrane Library) strategy based on Doiron et al. 2018

#1 ([mh "Intensive Care Units"] OR [mh ^"Critical Illness"] OR [mh "Critical Care"] OR (critical* NEAR3 (ill* OR care*)):ti,ab OR "intensive care":ti,ab OR (icu OR icuaw):ti,ab)

#2 ([mh "Exercise Therapy"] OR [mh "Physical Therapy Modalities"] OR [mh "Occupational Therapy"] OR (mobilizat* OR mobilisat* OR mobility):ti,ab OR exercis*:ti,ab OR (therap* NEAR3 (physical OR exercise OR occupation*)):ti,ab OR ((bed OR "daily living") NEAR3 activit*):ti,ab OR (training OR pregait OR pre-gait OR walk* OR adl OR physiotherap* OR ambulation):ti,ab OR ((cycle OR bicycle) NEAR1 ergomet*):ti,ab)

#3 #1 AND #2

Limiter: from June 2017

Date: 17 Jan 2019

Results: 628

CENTRAL (The Cochrane Library) strategy based on Fuke et al. 2018

#1 ("critical ill" OR "critical illness" OR "critical care" OR "intensive care" OR "mechanical ventilation" OR "mechanical ventilated" OR "postoperative care"):kw,ti,ab

#2 (rehabilitation OR "physical therapy" OR physiotherapy OR exercise OR mobilization OR "mobility intervention" OR "muscle training"):kw,ti,ab

#3 ("Activities of Daily Living" OR "Quality of Life" OR "post-intensive care syndrome" OR "motor function" OR "Physical Functioning" OR "functional status" OR "physical function" OR "ventilator days" OR "quality of life" OR (walking OR walk) OR muscle OR polyneuromyopathy OR "length of stay" OR "length of ICU stay" OR "length of hospital stay" OR "intubation period" OR "duration of mechanical ventilation" OR re-admission OR "functional outcome" OR "ICU-acquired weakness" OR "ICU-acquired paresis" OR ICUAW OR "ICU-AW" OR "intensive care unit acquired weakness" OR "critical illness polyneuropathy" OR "critical illness myopathy" OR "critical illness neuromyopathy"

OR "acute quadriplegic myopathy" OR "thick filament myopathy" OR "acute necrotizing myopathy of intensive care" OR "acute corticosteroid myopathy" OR "critical illness neuromuscula syndromes" OR "Tower test" OR "Timed Up and Go Test" OR "dysexecutive questionnaire" OR FAQ OR "EQ-5D VAS" OR 6MWD OR "6-min walking distance" OR "Quadriceps force, and self-perceived functional status" OR "SF-36 PF" OR MRC OR "Medical Research Council" OR "AQoL utility" OR "EQ-5D" OR PFIT OR "physical functional ICU test" OR "Hospital Anxiety and Depression

#4 #1 AND #2 AND #3

Limiter: from Apr 2016

Date: 17 Jan 2019

Results: 461

CENTRAL (The Cochrane Library) strategy based on Castro-Avila et al. 2015

#1 ("critical care" OR "intensive care unit? " OR "burn unit? " OR "coronary care unit?" OR "recovery room?" OR "respiratory care unit?" OR "critical illness" OR "critically ill" OR "intensive care" OR "intensive treatment unit?" OR "intensive therapy unit?" OR "high dependency unit?" OR ICU OR

#2 (rehabilitat* OR "physical therapy modalit?" OR "physical therap*" OR physiotherap* OR kinesiotherap* OR "exercise therap*" OR "physical exertion" OR "Early Ambulation" OR mobilization or mobilisation):kw,ti,ab

#3 #1 AND #2

Limiter: from Feb 2014

Date: 17 Jan 2019

Results: 622

9.3 List of Excluded Studies, with Reason

Excluded References, with Reasons
Abstract only (n=43)
Schweickert W, Poston J, Esbrook C, et al. Temporal Relation of Early Mobilization on Recovery of Functional Independence in Mechanically Ventilated Patients. A92 FIVE RANDOMIZED CLINICAL TRIALS WITH EDITORIAL DISCUSSION 2009;:A2168. doi:10.1164/ajrccm-conference.2009.179.1_MeetingAbstracts.A2168
Hanekom S., Louw Q., Coetzee A. Physiotherapy management of critically ill patients guided by an evidence based protocol is safe and effective: A preliminary study. Intensive Care Med 2010;36:S324. doi:10.1007/s00134-010-2000-8
Malicdem M.G., Cruz B.O.-D., Punzal P., et al. Outcome of pulmonary rehabilitation among difficult to wean patients admitted at the philippine heart center - A randomized controlled study. Respirology 2010;15:99. doi:10.1111/j.1400-1843.2010.01865.x
Patel B, Poston J, Pohlman A, et al. Complications Of Critical Illness In Mechanically Ventilated Patients In A Randomized Controlled Trial Of Early Mobilization. D49 CLINICAL TRIALS IN CRITICAL CARE 2010;:A6033–A6033. doi:10.1164/ajrccm-conference.2010.181.1_MeetingAbstracts.A6033
Arikan H, Turan HN, Degirmenci B, *et al.* Comparison in the efficacy of mobilization and active cycle of breathing technique in coronary artery bypass greft surgery. *European Respiratory Journal* 2011;**38**:2979.
Berney SC, Haines K, Warrillow S, et al. The Safety And Feasibility Of Exercise Rehabilitation In The ICU. A104 INTENSIVE CARE UNIT ORGANIZATION, OUTCOMES, AND RESEARCH 2011;:A2385–A2385. doi:10.1164/ajrccm-conference.2011.183.1_MeetingAbstracts.A2385
Denehy L, Berney S, Skinner E, et al. Evaluation Of Exercise Rehabilitation For Survivors Of Intensive Care: An Assessor Blinded Randomised Controlled Trial. B25 MONITORING AND NON-PULMONARY CRITICAL CARE 2011;:A2642–A2642. doi:10.1164/ajrccm-conference.2011.183.1_MeetingAbstracts.A2642
Evans J, Tsekouras C, Johnson K, *et al.* Effect of Early Mobilization Efforts on Postoperative Length of Stay After Cardiac Transplant and Left Ventricular Assist Device Surgery. *Critical Care Nurse* 2011;**31**:e50-1.
Gerovasili V., Karatzanos L., Zervakis D., et al. Electrical muscle stimulation is an effective form of exercise and early mobilization in ICU patients. Am J Respir Crit Care Med 2011;183.http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L70848092
Ali MS, Talwar D, Singh RK, et al. Controlled Trial Of Short Term (3 Weeks) Pulmonary Rehabilitation In COPD Following Acute Exacerbation. B45 EXACERBATIONS OF COPD: PREVENTION, TREATMENT AND OUTCOMES 2012;:A3034–A3034. doi:10.1164/ajrccm-conference.2012.185.1_MeetingAbstracts.A3034
Brummel NE, Jackson JC, Girard TD, et al. Feasibility Of An Early Physical And Cognitive Rehabilitation Protocol For Critically Ill Patients: The Activity And Cognitive Therapy In The ICU (ACT-ICU) Trial. C14 CLINICAL TRIALS IN CRITICAL CARE 2012;:A3885–A3885. doi:10.1164/ajrccm-conference.2012.185.1_MeetingAbstracts.A3885
Paternostro-Sluga T, Gruther W. Intensive Physical Therapy Reduces Length of Hospital Stay in Critically Ill Patients. PM&R 2012;4:S310–1. doi:10.1016/j.pmrj.2012.09.965
Paternostro-Sluga T, Hiesmayr M, Janda D, et al. Early Neuromuscular Electrical Stimulation for Intensive Care Unit Patients: Effect on Muscle Strength and Urinary Nitrogen Excretion. PM&R 2012;4:S310. doi:10.1016/j.pmrj.2012.09.964
Beros J, Khadka G, Duffner L, et al. Does Neuromuscular Electric Stimulation Of The Quadriceps Affect Mobility In Patients Weaning From Prolonged Ventilation? B104 ICU WEAKNESS ON THE RUN: EXERCISE, ELECTRICAL STIMULATION, AND PHARMACOTHERAPY 2013;:A3618–A3618. doi:10.1164/ajrccm-conference.2013.187.1_MeetingAbstracts.A3618
Files D, Morris P, Shrestha S, et al. Randomized, controlled pilot study of early rehabilitation strategies in acute respiratory failure. Critical Care 2013;17:P540. doi:10.1186/cc12478
Goodman J, Walker W, Wright J, et al. Project PIX (Post Intensive care eXercise): impact on physical fitness and focus group analysis of quality of life following exercise rehabilitation. Crit Care 2013;17:P534. doi:10.1186/cc12472
Kho ME, Martin RA, Toonstra AL, et al. Le Tour De ICU: Feasibility And Safety Of Routine Use Of In-Bed Cycling For Physical Rehabilitation In The Intensive Care Unit (ICU). B104 ICU WEAKNESS ON THE RUN: EXERCISE, ELECTRICAL STIMULATION, AND PHARMACOTHERAPY 2013;:A3620–A3620. doi:10.1164/ajrccm-conference.2013.187.1_MeetingAbstracts.A3620
Wolfe KS, Wendlandt BN, Patel SB, et al. Long-Term Survival And Health Care Utilization Of Mechanically Ventilated Patients In A Randomized Controlled Trial Of Early Mobilization. D16 RANDOMIZED AND OBSERVATIONAL STUDIES IN CRITICAL CARE 2013;:A5235–A5235. doi:10.1164/ajrccm-conference.2013.187.1_MeetingAbstracts.A5235
Emerson K, Hu BB, Smith C, *et al.* Impact Of A Collaborative Multidisciplinary Team On ICU Delirium. *Critical Care Medicine* 2014;**42**:A1501–2.
Kho ME, Truong AD, Zanni JM, et al. Neuromuscular Electrical Stimulation (NMES) In Mechanically Ventilated Patients: A Randomized, Sham-Controlled Pilot Trial With Blinded Outcome Assessment. B109 ICU ACQUIRED MUSCLE WEAKNESS: MAKING PROGRESS? 2014;:A3881–A3881. doi:10.1164/ajrccm-conference.2014.189.1_MeetingAbstracts.A3881
Eggmann S, Verra ML, Luder G, et al. Physiological effects and safety of an early, combined endurance and resistance training in mechanically ventilated, critically ill patients. Physiotherapy 2015;101:e344–5. doi:10.1016/j.physio.2015.03.553
Fares S, Laghi F, Duffner LA, et al. Impact of Neuromuscular Electrical Stimulation on Quadriceps Size and Functional Activity in Patients Weaning from Prolonged Ventilation. A104 MOVING THE NEEDLE ON ICU-ASSOCIATED NEUROMUSCULAR WEAKNESS 2015;:A2294–A2294. doi:10.1164/ajrccm-conference.2015.191.1_MeetingAbstracts.A2294
Goll M, Wollersheim T, Haas K, et al. Randomised controlled trial using daily electrical muscle stimulation (EMS) in critically ill patients to prevent intensive care unit (icu) acquired weakness (ICUAW). Intensive Care Med Exp 2015;3. doi:10.1186/2197-425X-3-S1-A809
Hadjibalassi M, Lambrinou E, Papastavrou E, *et al.* Effects of a psycho-cognitive nursing intervention on critical care patients: pain and anxiety levels. *CONNECT: The World of Critical Care Nursing* 2015;**9**:158–158.
Kayambu G, Boots R, Paratz J. Early physical rehabilitation in intensive care patients with sepsis syndromes—a randomised controlled trial. Physiotherapy 2015;101:e735. doi:10.1016/j.physio.2015.03.3597
Santos L, Lemos F, Bianchi T, et al. Early ambulation using a cycle ergometer on quadriceps muscle morphology in mechanically ventilated critically ill patients in the intensive care unit: a randomized controlled trial. Intensive Care Med Exp 2015;3. doi:10.1186/2197-425X-3-S1-A551

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Bissett B, Leditschke IA, Neeman T, et al. Inspiratory Muscle Training to Enhance Recovery from Prolonged Mechanical Ventilation: A Randomized Trial. A95 CRITICAL CARE: RECOVERY OF PHYSICAL FUNCTION AFTER CRITICAL ILLNESS 2016;:A2613–A2613. doi:10.1164/ajrccm-conference.2016.193.1_MeetingAbstracts.A2613
Hodgson C. A pilot randomised controlled trial of early goal directed mobilisation. *Anaesth Intensive Care* 2016;**44**:308.
McWilliams D, Jones C, Reeves E, et al. Does enhanced physiotherapy and early mobilisation reduce the degree of muscle loss for patients admitted to critical care? Intensive Care Medicine Experimental 2016;4. doi:10.1186/s40635-016-0100-7
Schaller S.J., Waak K., Edrich T., et al. Goal directed early mobilization reduces ICU length of stay and improves functional mobility: An international multi center, randomized, controlled trial (SOMS Trial). Anesth Analg 2016;122:S418. doi:10.1213/01.ane.0000499505.96779.a0
Wollersheim T, Malleike J, Haas K, et al. Randomized controlled trial using daily protocol based physiotherapy or protocol based physiotherapy with additional electrical muscle stimulation (EMS) in critically ill patients to prevent intensive care unit (ICU) acquired weakness (ICUAW). Intensive care medicine experimental Conference: 29th annual congress of the european society of intensive care medicine, ESICM 2016 Italy 2016;4. doi:10.1186/s40635-016-0099-9
Wright S, Thomas K, Baker C, et al. The extra physiotherapy in critical care (EPICC) multi-centre randomised controlled trial. Intensive care medicine experimental Conference: 29th annual congress of the european society of intensive care medicine, ESICM 2016 Italy 2016;4. doi:10.1186/s40635-016-0099-9
Abruzzi F, Azevedo Peixoto Primo J, Marques Filho P, et al. Ultra early mobilization reduces the time of mechanical ventilation and ICU stay. Critical care Conference: 37th international symposium on intensive care and emergency medicine Belgium 2017;21. doi:10.1186/s13054-017-1630-4
Bryce H, Hudson A, Law T, et al. Improved physiotherapy outcome measures by the use of cycle ergometry in critical care patients. Critical Care (London, England) 2017;Conference: 37th International Symposium on Intensive Care and Emergency Medicine. Belgium. 21. doi:10.1186/s13054-017-1630-4
Carbon N, Wollersheim T, Krebs M, et al. Effects of protocol based physiotherapy and added physiotherapeutic measures on insulin sensitivity in critically ill patients with multiple organ failure. Intensive care medicine experimental Conference: 30th annual congress of the european society of intensive care medicine, ESICM 2017 Austria 2017;5. doi:10.1186/s40635-017-0151-4
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Gandotra S, Lovato J, Case D, et al. Recovery Trajectories of Critically Ill Patients in a Randomized Controlled Trial of Early Rehabilitation. D15 CRITICAL CARE: DO WE HAVE A CRYSTAL BALL? PREDICTING CLINICAL DETERIORATION AND OUTCOME IN CRITICALLY ILL PATIENTS 2017;:A7019–A7019. doi:10.1164/ajrccm-conference.2017.195.1_MeetingAbstracts.A7019
Hickmann J, Castanares-Zapatero D, Deldicque L, et al. Physical therapy during the early course of sepsis is safe and preserves skeletal muscle mass. Annals of intensive care Conference: french intensive care society, international congress - reanimation 2017 France Conference start: 20170111 Conference end: 20170113 2017;7. doi:10.1186/s13613-016-0224-7
Kho ME, Molloy AJ, Clarke F, et al. CYCLE Pilot RCT: A Multicenter Feasibility Study of Early in-Bed Cycling Versus Routine Physiotherapy in Medical-Surgical Ventilated Patients. A104 CRITICAL CARE: IMPROVING ICU EXERCISE, REHABILITATION, RECOVERY, AND SURVIVORSHIP 2017;:A2746–A2746. doi:10.1164/ajrccm-conference.2017.195.1_MeetingAbstracts.A2746
McWilliams D, Jones C, Atkins G, et al. A Comparison of Early and Enhanced Rehabilitation of Mechanically Ventilated Patients in Critical Care Compared to Standard Care (REHAB): A Single Site Feasibility Randomized Controlled Trial. A104 CRITICAL CARE: IMPROVING ICU EXERCISE, REHABILITATION, RECOVERY, AND SURVIVORSHIP 2017;:A2751–A2751. doi:10.1164/ajrccm-conference.2017.195.1_MeetingAbstracts.A2751
Sarfati C, Moore A, Mendialdua P, et al. Study of efficacy on ICU acquired weakness of early standing with the assistance of a tilt table in critically ill patients. Annals of intensive care Conference: french intensive care society, international congress - reanimation 2017 France Conference start: 20170111 Conference end: 20170113 2017;7:206-207. doi:10.1186/s13613-016-0224-7
Wappel SR, Ali O, Serra M, et al. The Effect of an Exercise, Nutrition and Neuromuscular Electrical Stimulation Intervention on Acute Muscle Wasting in Critically Ill Patients Receiving Mechanical Ventilation. A104 CRITICAL CARE: IMPROVING ICU EXERCISE, REHABILITATION, RECOVERY, AND SURVIVORSHIP 2017;:A2747–A2747. doi:10.1164/ajrccm-conference.2017.195.1_MeetingAbstracts.A2747
Kho M, Molloy A j., Clarke F j., et al. Outcomes from a Multicentre Pilot Randomized Clinical Trial of Early In-Bed Cycling with Mechanically Ventilated Patients: CYCLE Pilot RCT. C104 CRITICAL CARE: BODY AND MIND IN AND OUT OF THE ICU - SEDATION, DELIRIUM, MOBILIZATION, AND LONG TERM FUNCTIONAL AND COGNITIVE OUTCOMES 2018;:A6031–A6031. doi:10.1164/ajrccm-conference.2018.197.1_MeetingAbstracts.A6031
Clinical trial registry entry (n=58)
A Study Promoting Critical Illness Recovery in the Elderly - Pilot (NCT02963558)
ACT-ICU Study: Activity and Cognitive Therapy in the Intensive Care Unit (NCT01270269)
Assessing The Effects of Exercise, Protein, and Electric Stimulation On Intensive Care Unit Patients Outcomes (NCT02509520)
Being Awake, Upright and Moving as the Basis for Early ICU Physiotherapy (NCT02301273)
CYCLE: A Randomized Clinical Trial of Early In-bed Cycling for Mechanically Ventilated Patients (NCT03471247)
Cycling Exercise in Mechanical Ventilation (NCT03581760)
Dose of Early Therapeutic Mobility: Does Type or Frequency Matter? (NCT00999011)
E-Vent: Electrical muscle stimulation in mechanical Ventilation (ISRCTN35179428)
Early Chair Sitting Exercise in Mechanically Ventilated Critically Ill Patients (NCT02021227)

Excluded References, with Reasons
Early Cycloergometric Physiotherapy in Critically Ill Patients With Invasive Mechanical Ventilation (NCT02478411)
Early Directed Physical Therapy in the Management of Mechanically Ventilated Patients in a Medical Intensive Care Unit (NCT00322010)
Early Exercise Training in Critically Ill Patients (NCT00695383)
Early Mobilisation in Intensive Care Unit : Interest of Cyclo-ergometry in Patients With Septic Chock (NCT02872792)
Early Mobilization and Intensive Rehabilitation in the Critically Ill (NCT02864745)
Early Mobilization in Intensive Therapy (NCT01549808)
Early Mobilization in the ICU (NCT01777035)
Early Neurocognitive Rehabilitation in Intensive Care (NCT02078206)
Early Physical Therapy in Patients With Sepsis (NCT01787045)
Early Rehabilitation in Critical Illness Survivors (NCT02754505)
Early Rehabilitation of COPD Patients in ICU (NCT00628992)
Early Rehabilitation Program is Feasible and Safe in ICU in Liver Transplanted Patients (NCT01960868)
Effect Of Acute Inflammatory Mediators On Functional Limitations In Patients With Acute Respiratory Failure (NCT01707303)
Effect of early mobilisation on respiratory complications following abdominal surgery (ISRCTN28048472)
Effects of early, combined endurance and resistance training on mechanically ventilated, critically ill patients – a randomised controlled trial (DRKS00004347)
Effects of Neuromuscular Electrical Stimulation on Exercise Capacity in Respiratory Critically Ill Patients (NCT03083652)
Efficacy and Safety of a Multicomponent Physical Therapy Program in Mechanically Ventilated Patient With Sepsis (NCT03406494)
Electrical Muscle Stimulation (EMS), a Preventive and Therapeutic Tool for Critical Illness Polyneuromyopathy (CIPNM) (NCT00882830)
Electrical Muscle Stimulation and Bicycling Combined to Early Standard Rehabilitation in the ICU (NCT02185989)
Electro-Neuro-Muscular Stimulation in ICU (NCT02011282)
eStimCycle: Early Rehabilitation in Critical Care (ACTRN12612000528853)
Exercise in Critically Ill Patients With Sepsis (NCT01364909)
Extra physiotherapy in critical care: intensive versus standard physical rehabilitation therapy in the critically ill (ISRCTN20436833)
High Protein Intake and Early Exercise in Adult Intensive Care Patients (NCT03469882)
Impact of Early Mobilization on Mechanical Ventilation Duration in Intubated Critically Ill Patients (NCT02520193)
Impact of the Erigo Machine on Functional Recovery in ICU Patients (NCT02615990)
Mobilising Critically Ill patients: Physiological and Functional Outcomes following Early Rehabilitation in Sepsis (ACTRN12610000808044)
Mobilization With Neuromuscular Electrical Stimulation in Critical Care Patients (NCT02298114)
Neuromuscular Electrical Stimulation in the Critically Ill (NCT02566941)
Nutrition and Exercise in Critical Illness (NCT03021902)
Progressive Mobility Program and Technology to Improve the Level of Physical Activity and Functionality of ICU Patients (NCT02889146)
Progressive Mobilization With Dose Control and Training Load in in Critically Ill Patients (NCT03596853)
Project 4B: Lower Extremity Strength Training in ICU Patients (NCT02467023)
Rehabilitation After Intensive Care (NCT01770821)
Rehabilitation Following Critical Illness (NCT00976807)
Safety and Performance of Muscle Activation for Critical Care Patients (NCT01552616)
Standardized Rehabilitation for Intensive Care Unit (ICU) Patients With Acute Respiratory Failure (NCT00976833)
Study of Safety and Efficacy on Neuromyopathy of Early Standing With the Assistance of Tilt Table in Critically Patients (NCT02047617)
Systematic Team Approach to Guide Early Mobilization in Surgical Intensive Care Unit Patients (NCT01363102)
TEAM: A Trial of Early Activity and Mobility in ICU (NCT01927510)
The EXERCISE trial: Evaluation of exercise rehabilitation for survivors of intensive care (ACTRN12605000776606)
The Impact of Early Mobilization Protocol in Patients in the ICU (NCT01769846)
Transcutaneous Electric Muscle Stimulation (TEMS) in Septic Patients (NCT01071343)
Transcutaneous Electrical Nerve Stimulation Post-thoracic Surgery in a Intensive Care Unit (NCT02438241)

Excluded References, with Reasons
Treatment of Critical Illness Polyneuromyopathy (NCT01058421)
Treatment of Invasively Ventilated Adults With Early Activity and Mobilisation (NCT03133377)
Treatment of Muscle Weakness in Critically Ill Patients (NCT02247895)
Use of de game therapy to assess functionality and upper limb muscle strength in critical patients (RBR-6sz5dj)
Use of Neuromuscular Electrostimulation (NMES) for Treatment or Prevention of ICU-Associated Weakness (NCT00709124)
Study Protocol (n=15)
Kayambu G, Boots RJ, Paratz JD. Early rehabilitation in sepsis: a prospective randomised controlled trial investigating functional and physiological outcomes The i-PERFORM Trial (Protocol Article). BMC Anesthesiology 2011;11:21. doi:10.1186/1471-2253-11-21
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dos Santos LJ, de Aguiar Lemos F, Bianchi T, et al. Early rehabilitation using a passive cycle ergometer on muscle morphology in mechanically ventilated critically ill patients in the Intensive Care Unit (MoVe-ICU study): study protocol for a randomized controlled trial. Trials 2015;16. doi:10.1186/s13063-015-0914-8
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Kho ME, Molloy AJ, Clarke F, et al. CYCLE pilot: a protocol for a pilot randomised study of early cycle ergometry versus routine physiotherapy in mechanically ventilated patients. BMJ Open 2016;6:e011659. doi:10.1136/bmjopen-2016-011659
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Nickels MR, Aitken LM, Walsham J, et al. Critical Care Cycling Study (CYCLIST) trial protocol: a randomised controlled trial of usual care plus additional in-bed cycling sessions versus usual care in the critically ill. BMJ Open 2017;7:e017393. doi:10.1136/bmjopen-2017-017393
Snelson C, Jones C, Atkins G, et al. A comparison of earlier and enhanced rehabilitation of mechanically ventilated patients in critical care compared to standard care (REHAB): study protocol for a single-site randomised controlled feasibility trial. Pilot and Feasibility Studies 2017;3:19. doi:10.1186/s40814-017-0131-1
Thomas S, Mehrholz J. Fitness- und Mobilitätstraining bei Patienten mit auf Intensivstation erworbenem Schwächesyndrom (FITonICU): Protokoll für eine randomisierte kontrollierte Studie. *Zeitschrift fur Physiotherapeuten* 2017;**69**:78–84.
Wassenaar A, Rood P, Schoonhoven L, et al. The impact of nUrsiNg DEliRium Preventive INnterventions in the Intensive Care Unit (UNDERPIN-ICU): A study protocol for a multi-centre, stepped wedge randomized controlled trial. International Journal of Nursing Studies 2017;68:1–8. doi:10.1016/j.ijnurstu.2016.11.018
Lago AF, de Oliveira AS, de Souza HCD, et al. The effects of physical therapy with neuromuscular electrical stimulation in patients with septic shock. Medicine (Baltimore) 2018;97. doi:10.1097/MD.0000000000009736
Nielsen AH, Angel S, Egerod I, et al. The effect of diaries written by relatives for intensive care patients on posttraumatic stress (DRIP study): protocol for a randomized controlled trial and mixed methods study. BMC Nursing 2018;17:37. doi:10.1186/s12912-018-0306-y
Nydahl P, Diers A, Günther U, et al. PROtokollbasierte MObilisierung auf IntensivstaTIONen [PROtocol-based MObilizaTION on intensive care units : Design of a cluster randomized pilot study]. Med Klin Intensivmed Notfmed 2018;113:581–92. doi:10.1007/s00063-017-0358-x
Schujmann DS, Lunardi AC, Fu C. Progressive mobility program and technology to increase the level of physical activity and its benefits in respiratory, muscular system, and functionality of ICU patients: study protocol for a randomized controlled trial. Trials 2018;19. doi:10.1186/s13063-018-2641-4
Systematic Review/Meta-Analysis (n=4)
Castro-Avila AC, Serón P, Fan E, et al. Effect of Early Rehabilitation during Intensive Care Unit Stay on Functional Status: Systematic Review and Meta-Analysis. PLOS ONE 2015;10:e0130722. doi:10.1371/journal.pone.0130722
Connolly B, Salisbury L, O'Neill B, et al. Exercise rehabilitation following intensive care unit discharge for recovery from critical illness. Cochrane Database of Systematic Reviews Published Online First: 2015. doi:10.1002/14651858.CD008632.pub2
Elkins M, Dentice R. Inspiratory muscle training facilitates weaning from mechanical ventilation among patients in the intensive care unit: a systematic review. J Physiother 2015;61:125–34. doi:10.1016/j.jphys.2015.05.016
Mehrholz J, Pohl M, Kugler J, et al. Physical rehabilitation for critical illness myopathy and neuropathy. Cochrane Database of Systematic Reviews Published Online First: 2015. doi:10.1002/14651858.CD010942.pub2
Other publication type (n=8)
Melchers P., Maluck A., Suhr L., *et al.* An early onset rehabilitation program for children and adolescents after traumatic brain injury (TBI): Methods and first results. *Restor Neurol Neurosci* 1999;**14**:153–60.
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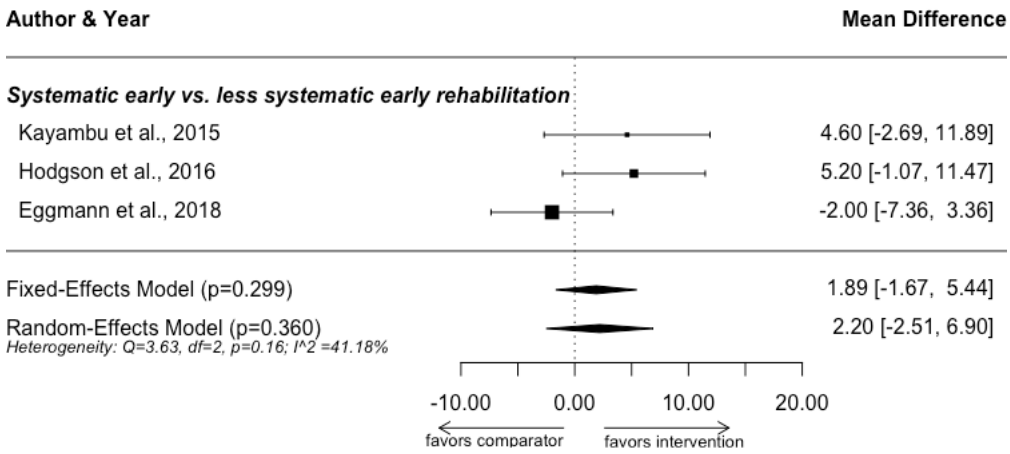
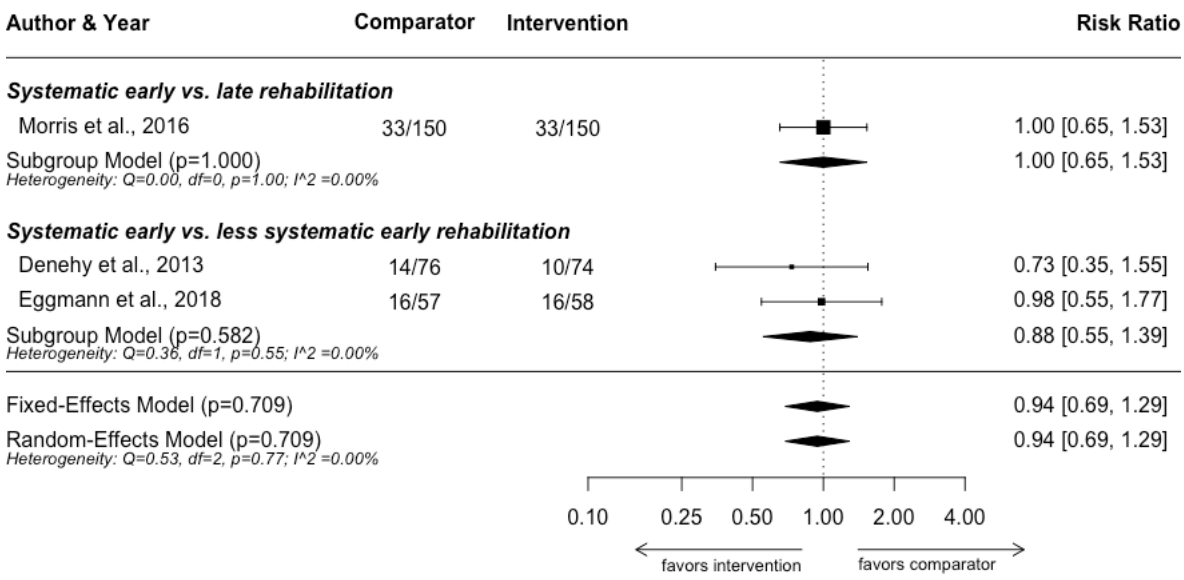
9.4 Meta-Analyses: Heterogeneity Assessment



Mean differences in MRC Muscle Scale score at ICU discharge using random- and fixed-effect meta-analyses; excluding the study by Dantas et al. 2012 for high baseline imbalance in MRC Muscle Scale score.



Effects of systematic early rehabilitation (risk ratio) on mortality at 6 months of follow-up after hospital discharge using random- and fixed-effect meta-analyses; excluding the study by Kayambu et al. 2015 for unexpectedly high mortality in the intervention group.

9.5 Cochrane Risk of Bias Assessment Details

Study	Sequence Generation	Allocation Concealment	Blinding of Patients and Personnel	Blinding of Outcome Assessors	Incomplete Outcome Data	Selective Reporting	Other Risk of Bias	Overall Assessment*
Schweickert et al. 2009	Low	Low	High	Low	Low	Low	-	good
Comment			"the nature of the intervention prevented any blinding from patient and health-care providers"					
Dantas et al. 2012	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Present	poor
Comment	Randomization strategy not stated.	Allocation concealment strategy not stated.	No information on blinding of participants available.	No information on blinding of outcome assessors available.		No protocol available.	Extreme baseline imbalance (age and gender).	
Denehy et al. 2013	Low	Low	High	Low	Unclear	High	-	poor
Comment			"maintained (single) blinding"		Different n for each outcome measure reported (Table 3).	No information provided for some prespecified outcomes and time points.		
Brummel et al. 2014	Low	Low	High	Low	High	High	-	poor
Comment			"inability to blind patients or those performing the interventions"		Follow-up occurred less frequently in the cognitive plus physical therapy group because of withdrawals.	No information provided for some prespecified outcomes and time point.		
Dong et al. 2014	Unclear	Unclear	High	Unclear	Unclear	Unclear	-	poor
Comment	Randomization strategy not stated.	Allocation concealment not mentioned.	"this study [...] is not double blinded"	No information on blinding of outcome assessors available.	No information on attrition available.	No protocol available.		
Kayambu et al. 2015	Low	Unclear	Low	Low	High	High	-	poor
Comment		Allocation concealment strategy not stated.			Differentially more losses in intervention group.	No information provided for some prespecified outcomes and time points.		

Study	Sequence Generation	Allocation Concealment	Blinding of Patients and Personnel	Blinding of Outcome Assessors	Incomplete Outcome Data	Selective Reporting	Other Risk of Bias	Overall Assessment*
Dong et al. 2016	Low	Unclear	High	High	Low	Unclear	-	poor
Comment		Allocation concealment not mentioned.	"Blinding could not be performed in this randomized study"	"Blinding could not be performed in this randomized study"		Outcomes not clearly prespecified. No muscle strength or functional mobility outcome reported.		
Fischer et al. 2016	Low	Unclear	Unclear	High	Unclear	Low	-	poor
Comment		Allocation concealment not mentioned.	Blinding attempted but potentially broken, depends on communication with patients.	"Nonblinded assessors performed the ultrasound scans, [...]"; Results are at high risk of bias due to unblinded performance of ultrasound scans.	Significant attrition (>30%), but no missing outcome data for outcomes of interest. Intention-to-treat analysis, no imputation used.			
Hodgson et al. 2016	Unclear	Low	High	Low	Low	Low	Present	poor
Comment	Randomization not mentioned.		"all clinicians involved in their care were aware of study-group assignments"; Specifically mentioned as assessor-blinded, no mentioning of blinding of patients.				Potential issues related to study design: imbalance in group size (21 vs. 29 under randomized allocation).	
Morris et al. 2016	Low	Unclear	High	Low	High	Low	-	poor
Comment		Allocation concealment not mentioned.	Specifically mentioned as assessor-blinded, no mentioning of blinding of patients.		High amount of missing data at several timepoints.			
Schaller et al. 2016	Low	Low	Unclear	Low	High	Low	-	fair
Comment			"Patients were not made aware of their assignment."		Significant loss to follow-up (38% of patients). Multiple imputation for SF-36 at 3 months			

Study	Sequence Generation	Allocation Concealment	Blinding of Patients and Personnel	Blinding of Outcome Assessors	Incomplete Outcome Data	Selective Reporting	Other Risk of Bias	Overall Assessment*
					performed as sensitivity analysis.			
Eggmann et al. 2018	Low	Low	High	Low	Low	Low	-	good
Comment			"Blinding the responsible ICU staff was impossible"; "blinding of participants and physiotherapists was impossible."					

*blinding of personnel not considered for the overall assessment, as judged almost impossible to perform.

9.6 GRADE Evidence Profile Details

Outcome	Certainty assessment							Certainty	Importance
Comparator	№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		
MRC Muscle Scale Sum Score (MRC-SS), measured at ICU discharge									
(I) systematic early vs. late	1	randomised trials	not serious	not serious	not serious	serious [a]	only one study contributing to results [b]	⊕⊕◯◯ LOW	critical
(II) systematic early vs. less systematic early	4	randomised trials	serious [c]	serious [d]	not serious	serious [a]	none	⊕◯◯◯ VERY LOW	critical
6-Minute Walking Test (6MWT), measured at various time points									
(II) systematic early vs. less systematic early	2	randomised trials	not serious [e]	not serious	not serious	serious [a]	mainly one study contributing to results [f]	⊕⊕◯◯ LOW	critical
Time to walking, measured during the hospital stay									
(I) systematic early vs. late	1	randomised trials	not serious	not serious	not serious	serious [a]	only one study contributing to results [b]	⊕⊕◯◯ LOW	critical
(II) systematic early vs. less systematic early	2	randomised trials	serious [c]	not serious	not serious	serious [a]	mainly one study contributing to results [g]	⊕◯◯◯ VERY LOW	critical
Patients returning to independence from assistance, measured at hospital discharge									
(I) systematic early vs. late	1	randomised trials	not serious	not serious	not serious	serious [a]	only one study contributing to results [b]	⊕⊕◯◯ LOW	critical
SF-36 Physical Function Domain Score (PFS), measured 6 months after hospital discharge									
(I) systematic early vs. late	1	randomised trials	serious [c]	not serious	not serious	serious [a]	only one study contributing to results [b]	⊕◯◯◯ VERY LOW	critical

Outcome	Certainty assessment							Certainty	Importance
Comparator	№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		
(II) systematic early vs. less systematic early	2	randomised trials	serious [c]	serious [d]	not serious	serious [a,h]	none	⊕◯◯◯ VERY LOW	critical
SF-36 Physical Health Component Summary Score (PCS), measured 6 months after hospital discharge									
(I) systematic early vs. late	1	randomised trials	serious [c]	not serious	not serious	serious [a]	only one study contributing to results [b]	⊕◯◯◯ VERY LOW	critical
(II) systematic early vs. less systematic early	2	randomised trials	serious [c]	not serious	not serious	very serious [h]	none	⊕◯◯◯ VERY LOW	critical
Patients developing ICUAW, measured at hospital discharge									
(I) systematic early vs. late	1	randomised trials	not serious	not serious	not serious	serious [a]	only one study contributing to results [b]	⊕⊕◯◯ LOW	critical
(II) systematic early vs. less systematic early	3	randomised trials	serious [c]	not serious	not serious	very serious [h]	none	⊕◯◯◯ VERY LOW	critical

CI: Confidence interval; MD: Mean difference; RR: Risk ratio

Explanations

a. Downgraded one point due to imprecision (defined as wide confidence intervals including no effect and/or low overall sample size (defined as <400 participants for continuous outcomes or below optimal information size for dichotomous outcomes)).
b. Downgraded one point due to only one study contributing to outcome.
c. Downgraded one point as majority of studies judged as of overall poor quality regarding risk of bias.
d. Downgraded one point due to presence of substantial unexplained heterogeneity.
e. Not downgraded as we judged the risk of bias of studies contributing data as not relevant for outcome.
f. Downgraded one point due to only one study contributing to outcome (change from baseline deemed most important aspect of outcome).
g. Downgraded one point due to only one study contributing to outcome (the second study barely contributed data (n=3).
h. Downgraded two points due to high imprecision (wide confidence intervals for absolute effects including important harm and low overall sample size (see definition above)).

9.7 Search Strategies for the Health Economic Assessment

Medine (Pubmed) strategy based on Doiron et al. 2018

1 intensive care unit$ OR critical illness OR critical care or critical adj3 (ill$ or care$) or intensive care or icu or icuaw

2 Exercise Therapy or Physical Therapy Modalities or Occupational Therapy or mobilizat$ or mobilisat$ or mobility or exercis$ or therap$ adj3 (physical or exercise or occupation$)

3 Afford$ OR Budget$ OR Capital expenditure$ OR cost$ OR cost-benefit OR Cost-consequence$ OR Cost-effectiveness OR Cost-minimization OR Cost-utility OR Economic$ OR Economic-evaluation OR Expenditure$ OR Fee$ OR Finance$ OR Financial OR Financing OR Health expenditure$ OR Health resource allocation OR Health resource utilization OR Health-economic$ OR Medical savings accounts OR Monetary OR Pharmaco-economic analyses OR Pharmaco-economic analysis OR Pharmacoeconomic$ OR Pharmacoeconomic-analyses OR Pharmacoeconomic-analysis OR Price$ OR Socioeconomic$

4 1 and 2 and 3

Date: 06 Mar 2019

Results: 664

Medine (Pubmed) strategy based on Fuke et al. 2018

1 "critical ill" or "critical illness" or "critical care" or "intensive care" or "mechanical ventilation" or "mechanical ventilated" or "postoperative care"

2 rehabilitation or "physical therapy" or physiotherapy or exercise or mobilization or "mobility intervention" or "muscle training"

3 "Activities of Daily Living" or "Quality of Life" or "postintensive care syndrome" or "motor function" or "Physical Functioning" or "functional status" or "physical function" or "ventilator days" or "quality of life" or (walking or walk) or muscle or polyneuromyopathy or "length of stay" or "length of ICU stay" or "length of hospital stay" or "intubation period" or "duration of mechanical ventilation" or re-admission or "functional outcome" or "ICU-acquired weakness" or "ICU-acquired paresis" or ICUAW or "ICUAW" or "intensive care unit acquired weakness" or "critical illness polyneuropathy" or "critical illness myopathy" or "critical illness neuromyopathy" or "acute quadriplegic myopathy" or "thick filament myopathy" or "acute necrotizing myopathy of intensive care" or "acute corticosteroid myopathy" or "critical illness neuromuscula syndromes" or "Tower test" or "Timed Up and Go Test" or "dysexecutive questionnaire" or FAQ or "EQ-5D VAS" or 6MWD or "6-min walking distance" or "Quadriceps force, and self-perceived functional status" or "SF-36 PF" or MRC or "Medical Research Council" or "AQoL utility" or "EQ-5D" or PFIT or "physical functional ICU test" or "Hospital Anxiety and Depression Scale" or "Hand-grip strength"

4 Afford$ OR Budget$ OR Capital expenditure$ OR cost$ OR cost-benefit OR Cost-consequence$ OR Cost-effectiveness OR Cost-minimization OR Cost-utility OR Economic$ OR Economic-evaluation OR Expenditure$ OR Fee$ OR Finance$ OR Financial OR Financing OR Health expenditure$ OR

Health resource allocation OR Health resource utilization OR Health-economic$ OR Medical savings accounts OR Monetary OR Pharmaco-economic analyses OR Pharmaco-economic analysis OR Pharmacoeconomic$ OR Pharmacoeconomic-analyses OR Pharmacoeconomic-analysis OR Price$ OR Socioeconomic$

5 1 and 2 and 3 and 4

Date: 06 Mar 2019

Results: 1349

Medine (Pubmed) strategy based on Castro-Avila et al. 2015

1 "Critical Care" or "intensive care units" or "intensive care unit?" or "burn units" or "burn unit" or "coronary care units" or "coronary care unit?" or "recovery room" or "recovery room?" or "respiratory care units" or "respiratory care unit?" or "Critical Illness" or "critically ill" or "Intensive Care" or "intensive treatment unit?" or "intensive therapy unit?" or "high dependency unit?" or ICU or HDU

2 Rehabilitation or rehabilitat* or "Physical Therapy Modalities" or "physical therapy modalit?" or "physical therap*" or physiotherap* or kinesiotherap* or exp "Exercise Therapy" or "exercise therap*" or "physical exertion" or "physical exertion" or "Early Ambulation" or mobilization or mobilisation or "Muscle Weakness" or "Neuromuscular Diseases"

3 Afford$ OR Budget$ OR Capital expenditure$ OR cost$ OR cost-benefit OR Cost-consequence$ OR Cost-effectiveness OR Cost-minimization OR Cost-utility OR Economic$ OR Economic-evaluation OR Expenditure$ OR Fee$ OR Finance$ OR Financial OR Financing OR Health expenditure$ OR Health resource allocation OR Health resource utilization OR Health-economic$ OR Medical savings accounts OR Monetary OR Pharmaco-economic analyses OR Pharmaco-economic analysis OR Pharmacoeconomic$ OR Pharmacoeconomic-analyses OR Pharmacoeconomic-analysis OR Price$ OR Socioeconomic$

4 1 and 2 and 3

Date: 06 Mar 2019

Results: 2409

Embase (Embase.com/Elsevier) strategy based on Doiron et al. 2018

#1 icu:ab,ti OR icuaw:ab,ti OR 'intensive care':ab,ti OR ((critical* NEAR/3 (ill* OR care)):ab,ti) OR 'intensive care'/exp OR 'critical illness'/de OR 'intensive care unit'/de

#2 training:ab,ti OR pregait:ab,ti OR 'pre-gait':ab,ti OR walk*:ab,ti OR adl:ab,ti OR physiotherapy*:ab,ti OR (((cycle OR bicycle) NEAR/1 ergomet*):ab,ti) OR ambulation:ab,ti OR (((bed OR 'daily living') NEAR/3 activity):ab,ti) OR ((therap* NEAR/3 (physical* OR exercise OR occupation*)):ab,ti) OR exercis*:ab,ti OR mobiliz*:ab,ti OR mobilis*:ab,ti OR mobility:ab,ti OR 'occupational therapy'/de OR 'physiotherapy'/exp OR 'kinesiotherapy'/exp

#3 'budget':ab,ti OR 'health care cost':ab,ti OR 'cost':ab,ti OR 'cost benefit analysis':ab,ti OR 'cost consequence analysis':ab,ti OR 'cost effectiveness analysis':ab,ti OR 'cost minimization

analysis':ab,ti OR 'cost utility analysis':ab,ti OR 'economics':ab,ti OR 'economic evaluation':ab,ti OR 'expenditures':ab,ti OR 'finance':ab,ti OR 'financial':ab,ti OR 'financing':ab,ti OR 'resource allocation':ab,ti OR 'health economics':ab,ti OR 'pharmacoeconomics':ab,ti OR 'price':ab,ti OR 'socioeconomics':ab,ti

#4 #1 AND #2 AND #3

#5 #4 NOT [conference abstract]/lim NOT ([animals]/lim NOT [humans]/lim)

Date: 06 Mar 2019

Results: 1869

Embase (Embase.com/Elsevier) strategy based on Fuke et al. 2018

#1 'critical ill':ab,ti OR 'critical illness':ab,ti OR 'critical care':ab,ti OR 'intensive care':ab,ti OR 'mechanical ventilation':ab,ti OR 'mechanical ventilated':ab,ti OR 'postoperative care':ab,ti

#2 rehabilitation:ab,ti OR 'physical therapy':ab,ti OR physiotherapy:ab,ti OR exercise:ab,ti OR mobilization:ab,ti OR 'mobility intervention':ab,ti OR 'muscle training':ab,ti

#3 'activities of daily living':ab,ti OR 'post-intensive care syndrome':ab,ti OR 'motor function':ab,ti OR 'physical functioning':ab,ti OR 'functional status':ab,ti OR 'physical function':ab,ti OR 'ventilator days':ab,ti OR 'quality of life':ab,ti OR walking:ab,ti OR walk:ab,ti OR muscle:ab,ti OR polyneuromyopathy:ab,ti OR 'length of stay':ab,ti OR 'length of icu stay':ab,ti OR 'length of hospital stay':ab,ti OR 'intubation period':ab,ti OR 'duration of mechanical ventilation':ab,ti OR 'readmission':ab,ti OR 'functional outcome':ab,ti OR 'icu-acquired weakness':ab,ti OR 'icu-acquired paresis':ab,ti OR icuaw:ab,ti OR 'icu-aw':ab,ti OR 'intensive care unit acquired weakness':ab,ti OR 'critical illness polyneuropathy':ab,ti OR 'critical illness myopathy':ab,ti OR 'critical illness neuromyopathy':ab,ti OR 'acute quadriplegic myopathy':ab,ti OR 'thick filament myopathy':ab,ti OR 'acute necrotizing myopathy of intensive care':ab,ti OR 'acute corticosteroid myopathy':ab,ti OR 'critical illness neuromuscula syndromes':ab,ti OR 'tower test':ab,ti OR 'timed up and go test':ab,ti OR 'dysexecutive questionnaire':ab,ti OR faq:ab,ti OR 'eq-5d vas':ab,ti OR 6mwd:ab,ti OR '6-min walking distance':ab,ti OR 'quadriceps force, and self-perceived functional status':ab,ti OR 'sf-36 pf':ab,ti OR mrc:ab,ti OR 'medical research council':ab,ti OR 'aqol utility':ab,ti OR 'eq-5d':ab,ti OR pfit:ab,ti OR 'physical functional icu test':ab,ti OR 'hospital anxiety and depression scale':ab,ti OR 'hand-grip strength':ab,ti

#4 'budget':ab,ti OR 'health care cost':ab,ti OR 'cost':ab,ti OR 'cost benefit analysis':ab,ti OR 'cost consequence analysis':ab,ti OR 'cost effectiveness analysis':ab,ti OR 'cost minimization analysis':ab,ti OR 'cost utility analysis':ab,ti OR 'economics':ab,ti OR 'economic evaluation':ab,ti OR 'expenditures':ab,ti OR 'finance':ab,ti OR 'financial':ab,ti OR 'financing':ab,ti OR 'resource allocation':ab,ti OR 'health economics':ab,ti OR 'pharmacoeconomics':ab,ti OR 'price':ab,ti OR 'socioeconomics':ab,ti

#5 #1 AND #2 AND #3 AND #4

#6 #5 NOT [conference abstract]/lim NOT ([animals]/lim NOT [humans]/lim)

Date: 06 Mar 2019

Results: 143

Embase (Embase.com/Elsevier) strategy based on Castro-Avila et al. 2015

#1 'intensive care'/de OR 'critical care':de,lnk,ab,ti OR 'intensive care unit'/de OR 'intensive care unit*':de,lnk,ab,ti OR 'burn unit'/de OR 'burn unit*':de,lnk,ab,ti OR 'coronary care unit'/de OR 'coronary care unit*':de,lnk,ab,ti OR 'recovery room'/de OR 'recovery room*':de,lnk,ab,ti OR 'respiratory care unit*':de,lnk,ab,ti OR 'critical illness'/de OR 'critical illness':de,lnk,ab,ti OR 'critically ill':de,lnk,ab,ti OR 'intensive care'/mj OR 'intensive care':de,lnk,ab,ti OR 'intensive treatment unit*':de,lnk,ab,ti OR 'intensive therapy unit*':de,lnk,ab,ti OR 'high dependency unit*':de,lnk,ab,ti OR icu:de,lnk,ab,ti OR hdu:de,lnk,ab,ti

#2 'rehabilitation'/exp OR rehabilitat*:de,lnk,ab,ti OR 'physiotherapy'/exp OR 'physical therapy modalit*':de,lnk,ab,ti OR 'physical therap*':de,lnk,ab,ti OR physiotherap*:de,lnk,ab,ti OR kinesiotherap*:de,lnk,ab,ti OR 'kinesiotherapy'/exp OR 'exercise therap*':de,lnk,ab,ti OR 'exercise'/de OR 'physical exertion':de,lnk,ab,ti OR 'mobilization'/de OR 'early ambulation':de,lnk,ab,ti OR mobilization:de,lnk,ab,ti OR mobilisation:de,lnk,ab,ti OR 'muscle weakness'/dm_rh,dm_th OR 'neuromuscular disease'/dm_rh

#3 'budget':ab,ti OR 'health care cost':ab,ti OR 'cost':ab,ti OR 'cost benefit analysis':ab,ti OR 'cost consequence analysis':ab,ti OR 'cost effectiveness analysis':ab,ti OR 'cost minimization analysis':ab,ti OR 'cost utility analysis':ab,ti OR 'economics':ab,ti OR 'economic evaluation':ab,ti OR 'expenditures':ab,ti OR 'finance':ab,ti OR 'financial':ab,ti OR 'financing':ab,ti OR 'resource allocation':ab,ti OR 'health economics':ab,ti OR 'pharmacoeconomics':ab,ti OR 'price':ab,ti OR 'socioeconomics':ab,ti

#4 #1 AND #2 AND #3

#5 #4 NOT [conference abstract]/lim

Date: 06 Mar 2019

Results: 582

CINAHL (EBSCOhost) strategy based on Doiron et al. 2018

((TI ((cycle or bicycle) N1 ergomet*) OR AB ((cycle or bicycle) N1 ergomet*) OR TI (training or pregait or pre-gait or walk* or adl or physiotherap* or ambulation) OR AB (training or pregait or pregait or walk* or adl or physiotherap* or ambulation) TI ((bed or daily living) N3 activit*) OR AB ((bed or daily living) N3 activit*) TI (therap* N3 (physical or exercise or occupation*)) OR AB (therap* N3 (physical or exercise or occupation*)) TI exercis* OR AB exercis* TI (mobilizat* or mobilisat* or mobility) OR AB (mobilizat* or mobilisat* or mobility) (MH "Occupational Therapy+") (MH "Physical Therapy+") (MH "Therapeutic Exercise+")) AND (TI (icu or icuaw) OR AB (icu or icuaw) OR TI intensive careOR AB intensive care OR TI (critical*N3 (ill* or care*)) OR AB (critical* N3 (ill* or care*)) OR (MH "Critical Care") OR (MH "Critical Illness") OR (MH "Intensive Care Units+"))) AND (Afford$ OR Budget$ OR Capital expenditure$ OR cost$ OR cost-benefit OR Cost-consequence$ OR Cost-effectiveness OR Cost-minimization OR Cost-utility OR Economic$ OR Economic-evaluation OR Expenditure$ OR Fee$ OR Finance$ OR Financial OR Financing OR Health expenditure$ OR Health resource allocation OR Health resource utilization OR Health-economic$ OR

Medical savings accounts OR Monetary OR Pharmaco-economic analyses OR Pharmaco-economic analysis OR Pharmacoeconomic$ OR Pharmacoeconomic-analyses OR Pharmacoeconomic-analysis OR Price$ OR Socioeconomic$) NOT ((MH "Animals+") NOT (MH "Human")))
Date: 07 Mar 2019
Results: 95

CINAHL (EBSCOhost) strategy based on Fuke et al. 2018

(("critical ill" OR "critical illness" OR "critical care" OR "intensive care" OR "mechanical ventilation" OR "mechanical ventilated" OR "postoperative care")) AND ((rehabilitation OR "physical therapy" OR physiotherapy OR exercise OR mobilization OR "mobility intervention" OR "muscle training")) AND (("Activities of Daily Living" OR "Quality of Life" OR "post-intensive care syndrome" OR "motor function" OR "Physical Functioning" OR "functional status" OR "physical function" OR "ventilator days" OR "quality of life" OR (walking OR walk) OR muscle OR polyneuromyopathy OR "length of stay" OR "length of ICU stay" OR "length of hospital stay" OR "intubation period" OR "duration of mechanical ventilation" OR re-admission OR "functional outcome" OR "ICU-acquired weakness" OR "ICU-acquired paresis" OR ICUAW OR "ICU-AW" OR "intensive care unit acquired weakness" OR "critical illness polyneuropathy" OR "critical illness myopathy" OR "critical illness neuromyopathy" OR "acute quadriplegic myopathy" OR "thick filament myopathy" OR "acute necrotizing myopathy of intensive care" OR "acute corticosteroid myopathy" OR "critical illness neuromuscula syndromes" OR "Tower test" OR "Timed Up and Go Test" OR "dysexecutive questionnaire" OR FAQ OR "EQ-5D VAS" OR 6MWD OR "6-min walking distance" OR "Quadriceps force, and self-perceived functional status" OR "SF-36 PF" OR MRC OR "Medical Research Council" OR "AQoL utility" OR "EQ-5D" OR PFIT OR "physical functional ICU test" OR "Hospital Anxiety and Depression Scale" OR "Hand-grip strength")) AND (Afford$ OR Budget$ OR Capital expenditure$ OR cost$ OR cost-benefit OR Cost-consequence$ OR Cost-effectiveness OR Cost-minimization OR Cost-utility OR Economic$ OR Economic-evaluation OR Expenditure$ OR Fee$ OR Finance$ OR Financial OR Financing OR Health expenditure$ OR Health resource allocation OR Health resource utilization OR Health-economic$ OR Medical savings accounts OR Monetary OR Pharmaco-economic analyses OR Pharmaco-economic analysis OR Pharmacoeconomic$ OR Pharmacoeconomic-analyses OR Pharmacoeconomic-analysis OR Price$ OR Socioeconomic$) NOT ((MH "Animals+") NOT (MH "Human")))
Date: 07 Mar 2019
Results: 280

CINAHL (EBSCOhost) strategy based on Castro-Avila et al. 2015

((MH "Critical Care") OR "critical care" OR (MH "Intensive Care Units") OR "intensive care unit? " OR (MH "Burn Units") OR "burn unit? " OR (MH "Coronary Care Units") OR "coronary care unit?" OR (MH "Post Anesthesia Care Units") OR "recovery room?" OR (MH "Respiratory Care Units") OR "respiratory care unit?" OR (MH "Critical Illness") OR (MH "Critical Illness/RH") OR "critical illness" OR "critically ill" OR "intensive care" OR "intensive treatment unit?" OR "intensive therapy unit?" OR "high dependency unit?" OR ICU OR HDU) AND ((MH "Rehabilitation+") OR rehabilitat* OR (MH "Physical Therapy+") OR "physical therapy

modalit?" OR "physical therap*" OR physiotherap* OR kinesiotherap* OR (MH "Therapeutic Exercise") OR "exercise therap*" OR "physical exertion" OR (MH "Early Ambulation") OR "Early Ambulation" OR mobilization or mobilisation OR (MH "Muscle Weakness/RH/TH") OR (MH "Neuromuscular Diseases/RH")) AND (Afford$ OR Budget$ OR Capital expenditure$ OR cost$ OR cost-benefit OR Cost-consequence$ OR Cost-effectiveness OR Cost-minimization OR Cost-utility OR Economic$ OR Economic-evaluation OR Expenditure$ OR Fee$ OR Finance$ OR Financial OR Financing OR Health expenditure$ OR Health resource allocation OR Health resource utilization OR Health-economic$ OR Medical savings accounts OR Monetary OR Pharmaco-economic analyses OR Pharmaco-economic analysis OR Pharmacoeconomic$ OR Pharmacoeconomic-analyses OR Pharmacoeconomic-analysis OR Price$ OR Socioeconomic$) NOT ((MH "Animals+") NOT (MH "Human")))

Date: 07 Mar 2019

Results: 499

CENTRAL (The Cochrane Library) strategy based on Doiron et al. 2018

#1 ('Intensive Care Units' OR 'critical illness' OR 'critical care' OR 'intensive care' OR ICU OR ICUAW)

#2 'Exercise Therapy' OR 'Physical Therapy Modalities' OR 'Occupational Therapy' OR (mobilizat* OR mobilisat* OR mobility) OR exercis* OR (therap* NEAR/3 (physical OR exercise OR occupation*)) OR ((bed OR 'daily living') NEAR/3 activit*) OR (training OR pregait OR pre-gait OR walk* OR adl OR physiotherap* OR ambulation) OR ((cycle OR bicycle) NEAR/1 ergomet*)

#3 Afford$ OR Budget$ OR Capital expenditure$ OR cost$ OR cost-benefit OR Cost-consequence$ OR Cost-effectiveness OR Cost-minimization OR Cost-utility OR Economic$ OR Economic-evaluation OR Expenditure$ OR Fee$ OR Finance$ OR Financial OR Financing OR Health expenditure$ OR Health resource allocation OR Health resource utilization OR Health-economic$ OR Medical savings accounts OR Monetary OR Pharmaco-economic analyses OR Pharmaco-economic analysis OR Pharmacoeconomic$ OR Pharmacoeconomic-analyses OR Pharmacoeconomic-analysis OR Price$ OR Socioeconomic$

#4 #1 AND #2 and #3

Date: 13 Mar 2019

Results: 1434

CENTRAL (The Cochrane Library) strategy based on Fuke et al. 2018

#1 'critical ill' OR 'critical illness' OR 'critical care' OR 'intensive care' OR 'mechanical ventilation' OR 'mechanical ventilated' OR 'postoperative care'

#2 rehabilitation OR 'physical therapy' OR physiotherapy OR exercise OR mobilization OR 'mobility intervention' OR 'muscle training'

#3 'Activities of Daily Living' OR 'Quality of Life' OR 'post-intensive care syndrome' OR 'motor function' OR 'Physical Functioning' OR 'functional status' OR 'physical function' OR 'ventilator days' OR 'quality of life' OR walking OR walk OR muscle OR polyneuromyopathy OR 'length of stay' OR 'length of ICU stay' OR 'length of hospital stay' OR 'intubation period' OR 'duration of mechanical

ventilation' OR 're-admission' OR 'functional outcome' OR 'ICU-acquired weakness' OR 'ICU-acquired paresis' OR ICUAW OR 'ICU-AW' OR 'intensive care unit acquired weakness' OR 'critical illness polyneuropathy' OR 'critical illness myopathy' OR 'critical illness neuromyopathy' OR 'acute quadriplegic myopathy' OR 'thick filament myopathy' OR 'acute necrotizing myopathy of intensive care' OR 'acute corticosteroid myopathy' OR 'critical illness neuromuscular syndromes' OR 'Tower test' OR 'Timed Up and Go Test' OR 'dysexecutive questionnaire' OR 'FAQ' OR 'EQ-5D VAS' OR '6MWD' OR '6 min walking distance' OR 'Quadriceps force and self-perceived functional status' OR 'SF-36 PF' OR 'MRC' OR 'Medical Research Council' OR 'AQoL utility' OR 'EQ-5D' OR PFIT OR 'physical functional ICU test' OR 'Hospital Anxiety and Depression'

#4 Afford$ OR Budget$ OR Capital expenditure$ OR cost$ OR cost-benefit OR Cost-consequence$ OR Cost-effectiveness OR Cost-minimization OR Cost-utility OR Economic$ OR Economic-evaluation OR Expenditure$ OR Fee$ OR Finance$ OR Financial OR Financing OR Health expenditure$ OR Health resource allocation OR Health resource utilization OR Health-economic$ OR Medical savings accounts OR Monetary OR Pharmaco-economic analyses OR Pharmaco-economic analysis OR Pharmacoeconomic$ OR Pharmacoeconomic-analyses OR Pharmacoeconomic-analysis OR Price$ OR Socioeconomic$

#5 #1 AND #2 AND #3 AND #4

Date: 14 Mar 2019

Results: 1151

CENTRAL (The Cochrane Library) strategy based on Castro-Avila et al. 2015

#1 'critical care' OR 'intensive care unit?' OR 'burn unit? ' OR 'coronary care unit?' OR 'recovery room?' OR 'respiratory care unit?' OR 'critical illness' OR 'critically ill' OR 'intensive care' OR 'intensive treatment unit?' OR 'intensive therapy unit?' OR 'high dependency unit?' OR ICU OR HDU

#2 rehabilitat* OR 'physical therapy modalit?' OR 'physical therap*' OR physiotherap* OR kinesiotherap* OR 'exercise therap*' OR 'physical exertion' OR 'Early Ambulation' OR mobilization or mobilisation

#3 Afford$ OR Budget$ OR Capital expenditure$ OR cost$ OR cost-benefit OR Cost-consequence$ OR Cost-effectiveness OR Cost-minimization OR Cost-utility OR Economic$ OR Economic-evaluation OR Expenditure$ OR Fee$ OR Finance$ OR Financial OR Financing OR Health expenditure$ OR Health resource allocation OR Health resource utilization OR Health-economic$ OR Medical savings accounts OR Monetary OR Pharmaco-economic analyses OR Pharmaco-economic analysis OR Pharmacoeconomic$ OR Pharmacoeconomic-analyses OR Pharmacoeconomic-analysis OR Price$ OR Socioeconomic$

#4 #1 AND #2 AND #3

Date: 14 Mar 2019

Results: 1263