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Systematic early rehabilitation in adult, mechanically ventilated intensive care patients

Report of the Council of experts of the Swiss Medical Board

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Executive summary

Prolonged stays in the intensive care unit (ICU) are associated with functional impairment, increased morbidity, and reduced quality of life (QoL) in survivors. Early rehabilitation, beginning in the ICU, may reduce these morbidities and improve patient outcomes. In recent years, rehabilitation during an ICU stay has been widely introduced, but evidence of conclusive benefit remains controversial while associated potential harms and costs have not been well described.

The Swiss Medical Board (SMB) assessed whether systematic early rehabilitation *versus* less systematic early, late, or no rehabilitation delivered to patients in ICU is associated with better patient-relevant outcomes and/or is cost-effective. The assessment was based on standard methods for systematic reviews and health economic analysis supplemented by a cross-sectional survey among leaders of Swiss ICUs. Based on this assessment, the present Appraisal Report was drafted using the Evidence-to-Decision (EtD) framework.

The systematic review included 12 randomized, controlled trials (RCTs) in a total of 1304 patients. Most studies reported outcomes limited to the time of discharge from ICU or hospital. Overall, there was minimal or no evidence of a benefit or meaningful clinical relevance of systematic early rehabilitation *versus* less systematic early rehabilitation. However, systematic early rehabilitation may be more beneficial than late rehabilitation. Results of the cross-sectional survey among Swiss ICU leaders illustrated significant heterogeneity of practice regarding early rehabilitation in the ICU. This echoes the uncertainties highlighted by the systematic review.

The Council of experts concluded that the differences in both desirable and undesirable effects of systematic early rehabilitation were small. Overall, the level of evidence was low. Major sources of potential bias included impossibility of blinding, lack of complete reporting of relevant dimensions, lack of predefined protocols, high variability in interventions delivered, and inconsistency in reporting between outcomes and protocols. The Council of experts concluded that the balance between desirable and undesirable effects of systematic early rehabilitation in the ICU could not be determined. Both benefits and harms appear to be small and have little overall clinical relevance. However, the relative benefits and harms of the various rehabilitation interventions in specific patient subgroups are unknown.

The health economic analysis included a *de novo* cost analysis and a budget impact analysis. Both analyses were limited by the lack of available data. The Council of experts determined that the resources required to deliver systematic early rehabilitation and the potential cost savings are likely to be small relative to total ICU hospitalization costs, although robust data are lacking. The Council of experts concluded that these resource requirements favored neither the intervention nor the comparator for outcomes assessed at hospital discharge. Longer-term cost-benefit implications are unknown.

The Council of experts concluded that early rehabilitation may be valued variably by different stakeholders, while improved outcomes post-ICU would clearly be valued by patients. The Council of experts deemed early rehabilitation in the ICU to be both acceptable and feasible in Switzerland. There was no major concern with respect to health equity. Based on the limited and low-quality evidence available, the Council of experts issued a conditional recommendation in favor of systematic early rehabilitation in the ICU.

Kurzfassung

Ein prolongierter Aufenthalt auf der Intensivstation ist für überlebende Patienten mit funktioneller Beeinträchtigung, erhöhter Morbidität und verringerter Lebensqualität assoziiert. Durch die im intensivmedizinischen Bereich beginnende Frührehabilitation könnten Morbiditäten dieser Art reduziert und bessere Therapieergebnisse erzielt werden. In den letzten Jahren wurde die Rehabilitation im Intensivbereich auf breiter Ebene eingeführt. Die Evidenz für einen eindeutigen Nutzen bleibt jedoch umstritten und potenziell assoziierte Schäden und Kosten nicht differenziert beschrieben.

Das Swiss Medical Board (SMB) hat untersucht, ob eine systematische Frührehabilitation im Vergleich zu weniger systematischen Früh-, Spät- bzw. Nichtrehabilitation von Intensivpatienten, mit besseren patientenrelevanten Behandlungsergebnissen verbunden und/oder kosteneffizient ist. Die Untersuchung basierte auf standardisierten Verfahrensweisen für systematische Übersichtsarbeiten und gesundheitsökonomischen Analysen. Ergänzt wurde die Untersuchung durch eine Querschnittserhebung unter Leitern und Leiterinnen von Schweizer Intensivstationen. Der mithilfe des Evidence-to-Decision (EtD)-Modells erstellte Bewertungsbericht ist das Ergebnis dieser Untersuchung.

In die systematische Übersichtsarbeit einbezogen wurden 12 randomisierte, kontrollierte Studien (RCTs) mit insgesamt 1.304 Patienten. Bei den meisten Studien beschränkten sich die erfassten Outcomes auf den Zeitraum bis zur Entlassung aus der Intensivstation bzw. dem Spital. Zusammenfassend gab es wenig bzw. keine Evidenz für einen Nutzen oder eine bedeutsame klinische Relevanz der systematischen gegenüber einer weniger systematischen Frührehabilitation. Dagegen kann die systematische Frührehabilitation sinnvoller sein als die Spätrehabilitation. Die Ergebnisse der Querschnittserhebung unter Leitern und Leiterinnen von Schweizer Intensivstationen hinsichtlich der klinischen Praxis der Frührehabilitation im intensivmedizinischen Umfeld, zeigen eine signifikante Heterogenität. Dies spiegelt die in der systematische Übersichtsarbeit aufgeworfenen offenen Fragen wider.

Der Expertenrat kam zu dem Schluss, dass sich sowohl bei erwünschten als auch bei unerwünschten Auswirkungen einer systematischen Frührehabilitation nur geringfügige Differenzen abzeichnen. Das Evidenzniveau war insgesamt niedrig. Die wichtigsten möglichen Verzerrungsquellen umfassten die Unmöglichkeit der Verblindung, die Unvollständigkeit der Berichte zu relevanten Dimensionen, das Fehlen vordefinierter Protokolle, die hohe Variabilität erfolgter Interventionen und die Uneinheitlichkeit zwischen Outcome-Erhebung und Protokollen. Der Expertenrat kam zu dem Schluss, dass sich das Gleichgewicht zwischen erwünschten und unerwünschten Auswirkungen einer systematischen Frührehabilitation auf der Intensivstation nicht bestimmen lässt. Sowohl Nutzen als auch Schäden scheinen gering zu sein und generell nur eine geringe klinische Relevanz zu haben. Der relative Nutzen und Schaden verschiedener rehabilitativer Interventionen bei spezifischen Patientensubgruppen ist allerdings nicht bekannt.

Die gesundheitsökonomische Analyse umfasste eine *De-novo*-Auswertung der Kosten sowie eine Analyse der Budgetauswirkungen. Aufgrund unzureichender Daten hatten beide Analysen nur eine bedingte Aussagekraft. Obgleich solide Daten fehlen, dürfte laut Feststellung des Appraisal-Komitees die für eine systematische Frührehabilitation erforderlichen Ressourcen und potenziellen Kostenersparnisse im Vergleich zu den Gesamtkosten der intensivmedizinischen Versorgung relativ gering sein. Nach dem Dafürhalten des Appraisal-Komitees spricht dieser Ressourcenbedarf anhand der zum Entlassungszeitpunkt aus dem Spital ermittelten Outcomes weder für eine Intervention noch für den Komparator. Die längerfristigen Kosten-Nutzen-Aspekte sind nicht bekannt.

Der Expertenrat folgerte, dass die Frührehabilitation von einzelnen Stakeholdern unterschiedlich bewertet wird. Patienten begrüssen ein besseres Outcome nach der Versorgung auf der Intensivstation eindeutig. Der Expertenrat erachtet die Frührehabilitation auf der Intensivstation in der Schweiz als akzeptabel und realisierbar. Hinsichtlich der Chancengleichheit bei der Gesundheitsförderung gab es keine grösseren Bedenken. Auf Grundlage der begrenzten Nachweise und Evidenz von geringer Qualität erteilte der Expertenrat eine bedingte Empfehlung zugunsten einer systematischen Frührehabilitation im intensivmedizinischen Setting.

Résumé

Pour les patients qui ont survécu, un séjour prolongé en soins intensifs entraîne une altération fonctionnelle, une augmentation de la morbidité et une réduction de la qualité de vie. Une réadaptation précoce, débutée en soins intensifs, pourrait réduire ces morbidités et améliorer la situation des patients. La réadaptation pendant un séjour en soins intensifs s'est largement développée au cours des dernières années, mais les preuves concluantes des bénéfices qu'elle pourrait apporter restent controversées alors même que des nuisibilités potentielles et les coûts associés n'ont pas été bien décrits.

Le Swiss Medical Board (SMB) a évalué la corrélation entre une réadaptation précoce systématique par rapport à une réadaptation précoce moins systématique, tardive ou aucune réadaptation en soins intensifs, et une amélioration de la situation des patients et/ou si cette solution serait rentable. Cette évaluation a été réalisée selon des méthodes d'examen systématique et d'analyse économique de la santé, complétées par une étude transversale menée auprès des dirigeants des unités de soins intensifs suisses. Le présent Rapport d'appréciation a été rédigé sur la base de cette évaluation à l'aide du cadre de preuves (*Evidence-to-Decision Framework, EtD*).

Douze (12) essais contrôlés randomisés, pour un total de 1 304 patients, ont été utilisés dans le cadre de cet examen. La plupart des études fait état de résultats limités au moment de la sortie de réanimation ou de l'hôpital des patients. Globalement, on n'a que peu ou pas de preuve que la réadaptation précoce systématique apporte des bénéfices ou ait une pertinence clinique probante par rapport à une réadaptation précoce moins systématique. Cependant, la réadaptation précoce systématique pourrait apporter plus de bénéfices qu'une réadaptation tardive. Les résultats de l'étude transversale menée auprès des dirigeants des unités de réanimation suisses a démontré qu'il existait une grande diversité de pratiques en matière de réadaptation précoce en soins intensifs. Ceci fait écho aux incertitudes mises en exergue par l'examen systématique.

Le Conseil d'experts a conclu que les différences en termes d'effets désirés et indésirables d'une réadaptation précoce systématique étaient peu importantes. Le niveau de preuve était globalement faible. Les principales sources de biais potentielles incluaient l'impossibilité de faire des essais en aveugle, l'absence de reporting complet des dimensions pertinentes, l'absence de protocoles pré-établis, d'importantes variations dans les interventions et des incohérences de reporting entre les résultats et les protocoles. Le Conseil d'experts a conclu qu'on ne pouvait pas établir l'équilibre entre les effets désirés et indésirables d'une réadaptation précoce systématique en soins intensifs. Les bénéfices et la nuisibilité semblent être faibles et n'avoir que peu de pertinence clinique. Toutefois, on ne connaît pas les bénéfices et la nuisibilité relatifs des diverses interventions de réadaptation dans des sous-groupes de patients spécifiques.

L'analyse économique de la santé incluait une analyse de coût *de novo* et une analyse d'impact budgétaire. Les deux analyses étaient limitées par le manque de données disponibles. Le Conseil d'experts a établi que les ressources requises pour la mise en œuvre d'une réadaptation précoce systématique et les économies potentielles étaient susceptibles d'être relativement faibles au regard du coût total d'une hospitalisation en soins intensifs, bien qu'on manque de données fiables. Le Conseil d'experts a conclu que ces exigences de ressources ne favorisaient ni l'intervention, ni le comparateur de résultats évalués à la sortie de l'hôpital. On ne connaît pas les implications de coût-bénéfices à plus long terme.

Le Conseil d'experts a conclu que la valeur d'une réadaptation précoce pourrait être estimée différemment par différentes parties prenantes, bien qu'il soit évident que les patients attacheraient

une valeur importante à une amélioration de leur résultats post-soins intensifs. Le Conseil d'experts a jugé que la réadaptation précoce en soins intensifs est acceptable et faisable en Suisse. Aucune préoccupation majeure n'a été mise en évidence quant à l'équité en matière de santé. Sur la base du nombre limité et de la mauvaise qualité des preuves disponibles, le Conseil d'experts émet une recommandation conditionnelle en faveur de la réadaptation précoce systématique en soins intensifs.

Abbreviations

ADL	Activities of daily living
APACHE	Acute Physiology, Age, Chronic Health Evaluation
BI	Barthel Index
CHOP	Schweizerische Operationsklassifikation (Swiss classification of surgical interventions)
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
EQ-5D VAS	European Quality of Life 5 Dimensions visual analog scale
EtD	Evidence-to-Decision
FIM	Functional Independence Measure (mmFIM=mini-modified FIM)
GRADE	Grading of Recommendations, Assessment, Development, and Evaluation
HADS	Hospital Anxiety and Depression Score
HTA	Health technology assessment
ICD	International Classification of Diseases
ICER	Incremental cost -effectiveness ratio
ICU	Intensive care unit
ICUAW	ICU-acquired weakness
KVG	Swiss health insurance law (Krankenversicherungsgesetz)
LOS	Length of stay
MCS	(SF-36) Mental Health Component Summary score
MD	Mean difference
MHS	(SF-36) Mental health component summary score
MID	Minimal important difference
MMSE	Mini-Mental State Exam
MRC	Medical Research Council
MRC-SS	MRC Muscle Scale Sum Score
NMES	Neuromuscular electrical stimulation
NR	not reported
PCS	(SF-36) Physical Component Summary Score
PFIT	Physical function in the ICU test
PFS	(SF-36) Physical Functioning Score
PICO	Population, Intervention, Comparator, Outcome
QALY	Quality-adjusted life year
QoL	Quality of life
RCT	Randomized controlled trial
RR	Risk ratio

SD	Standard deviation
SF-36	Short-Form-36 questionnaire
SHS	Swiss hospital statistics
SFSO	Swiss Federal Statistical Office
SMB	Swiss Medical Board
TUG	Timed up-and-go test
VAS	Visual analog scale
6MWT	6-Minute walk test

Definitions

Medical Research Council Muscle Scale Sum Score (MRC-SS) – scale (0 to 5) for muscle power; a higher score indicates stronger muscles [minimal important difference 3.53 or 4[1]]

Barthel Index (BI) – assessment of functional independence (maximum 100 points; a higher score indicates greater functional ability)

Functional Independence Measure (FIM) – evaluates functional status (18 items scored 1-7; higher scores indicate greater independence)

Physical function in the ICU test (PFIT) - measures functional level in mechanically ventilated patients (range 0-12; a higher score indicates greater physical function)

Timed up-and-go test (TUG) – measures mobility and balance (time ≥ 12 seconds indicates high risk for falling [cdc.gov])

SF-36 – measure of health-related quality of life (range 0 – 100; a higher score indicates a better state of health)

SF-36 Physical Functioning Score (PFS) – [minimal important difference 4.14 or 5[1,2]]

SF-36 Physical Component Summary Score (PCS)

6-Minute (6MWT) – distance walked over 6 minutes [minimal important difference 35 meters[2,3]]

1. Background

Prolonged stays in the intensive care unit (ICU) are associated with significant functional impairment and reduced quality of life (QoL) in survivors, attributed at least in part to proximal muscle weakness, disuse atrophy, delirium, and fatigue.[4,5] Return to full functionality in daily and professional life may take months after an ICU stay. ICU survivors may suffer from suboptimal QoL and cognitive impairment resulting in higher healthcare utilization and associated costs. In addition, such patients have an increased risk of death over the longer term.[6-8] According to the Swiss classification of surgical interventions (Schweizerische Operationsklassifikation, CHOP) codes, 51,115 patients required mechanical ventilation in Switzerland in 2015. Of these, 14,751 required ventilation in ICUs for at least 24 hours. Large numbers of patients are therefore at risk for suboptimal outcomes after an ICU stay, which may have important clinical and social consequences.

Initiation of early rehabilitation in patients in the ICU has been suggested as an intervention to improve long-term outcomes.[9] It is plausible that such interventions, by improving survivor function, could also have a positive impact on long-term QoL, mortality, and healthcare costs. As such, implementation of early rehabilitation has been widely adopted in ICUs based on the assumptions that this could reduce ICU-related morbidity (i.e. loss of muscle function, delirium, and duration of ventilation) and improve patient outcomes. Early rehabilitation in ICUs is generally considered an intervention associated with low risk and low cost.

Rehabilitation in the ICU may be either systematic (i.e. in all ICU patients who do not have any contraindication) and early (commonly defined as initiation within 7 days of admission), non-systematic (i.e. as and when indicated in individual patients) and early, or late (initiation beyond 7 days of ICU admission). A potential advantage of systematic over less systematic early rehabilitation may be that standardized initiation in all eligible patients is less subjective, and therefore, more patients may benefit. Potential advantages of less systematic early rehabilitation (i.e. initiated as indicated and/or tolerated in stronger or less sick patients, or at later time points) may be the better tailoring of rehabilitation to patients' needs and possibly a lower risk of adverse events. Early rehabilitation may potentially limit debilitation more than late rehabilitation. Potential immediate risks of rehabilitation in the ICU include cardiorespiratory destabilization, dislodging of catheters or supportive equipment, pain, anxiety, and physical injury due to falls.[10-12] Rehabilitation provided in the ICU may take various forms, may be of varying frequency and intensity, and may be delivered by core ICU staff or external therapists.

It is, however, unclear whether systematic early rehabilitation provided to patients in the ICU does indeed confer important benefits compared with less systematic early or late rehabilitation, and if so, when and how this should best be implemented and in which patients.[13] The findings from recent systematic reviews differ with regard to these questions.[10,13-16] To provide a basis for recommendations for practice and policy in Switzerland, this health technology assessment (HTA) examined the available evidence of clinical effectiveness, safety, and costs of systematic early rehabilitation as compared with less systematic early rehabilitation, late rehabilitation, or no rehabilitation in adult patients over 18 years of age who required ventilation support (invasive or noninvasive) for at least 24 hours in the ICU.

2. Methods

In the formal scoping process, the PICO (population, intervention, comparison, outcome) questions were defined in consultation with stakeholders. Evidence of clinical effectiveness and safety as well as

health economic evidence were assessed using the methods described in detail in the corresponding Assessment Report.

First, a 2-stage systematic review identified 12 eligible randomized controlled trials (RCTs) published between 2009 and 2018. Studies including patients ventilated for less than 24 hours or those including >10% of patients with burns, pre-existing neurologic illnesses, or transplantation were excluded. The 12 RCTs comprised a total of 1304 patients over 18 years of age, of whom 679 were randomized to systematic early rehabilitation (intervention) and 625 were randomized to less systematic early or late rehabilitation or no interventions (comparators). Six studies included fewer than 100 patients, and 6 included between 100 and 300 patients. One study was from a single center in Switzerland.

Systematic early rehabilitation was defined as rehabilitative activities initiated no later than 7 days after ICU admission in all patients who did not have any contraindications.

Comparator interventions were defined as:

- late rehabilitation - the same or similar rehabilitative activities initiated 7 days or more after ICU admission;
- less systematic early rehabilitation - the same or similar rehabilitative activities initiated no later than 7 days after ICU admission, but later than the systematic early rehabilitation group and/or not in all patients who did not have any contraindication;
- no rehabilitation - sham or no intervention provided during ICU stay.

The following rehabilitation interventions were variably considered across included studies: physiotherapy (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 neuromuscular electrical stimulation [NMES]); occupational and speech therapy if combined with physiotherapy; or keeping of an ICU diary. Studies investigating interventions solely targeted at preventing pressure ulcers or joint stiffness or targeted at respiratory rehabilitation only were excluded.

Second, the health economic assessment consisted of a systematic review of the health economic literature, a *de novo* cost analysis with supplemental cost-effectiveness considerations, and a budget impact analysis based on the perspective of the Swiss health insurance law (Krankenversicherungs-gesetz, KVG) i.e. considering all direct medical costs irrespective of payer, and the societal perspective over a 12-month time horizon. Detailed methods and assumptions are outlined in the corresponding Health Economic Assessment Report. To determine the frequency, variability, and practices of ICU rehabilitation in Switzerland, a supplemental survey was conducted among leaders of Swiss ICUs to provide inputs for the *de novo* cost and budget impact analyses.

The Council of experts discussed the results of the assessment in meetings held in November 2019 and January 2020 using the Evidence-to-Decision (EtD) framework.[17] Recommendations were formulated based on the available evidence and additional considerations including feedback from stakeholders. The EtD framework considers several domains such as the balance between desirable and undesirable effects, quality of evidence, cost utility/resource requirements, patient values, health equity, and acceptability/feasibility of the intervention. Differences in desirable and undesirable effects were categorized as large, moderate, small, or trivial. The resulting recommendations were formulated as 'strong' or 'conditional' in favor of a given intervention, in favor of either the intervention or

comparator, or against the intervention. Recommendations were supplemented by considerations regarding subgroups, implementation aspects, monitoring and evaluation, and research priorities.

3. Results of the appraisal

3.1 Evidence of clinical effectiveness and harm

Of the 12 RCTs included in the systematic review of clinical effectiveness, 2 studies compared systematic early rehabilitation with late rehabilitation[9,18], 9 compared systematic early with less systematic early rehabilitation[2,19-26], and 1 compared systematic early rehabilitation with no rehabilitation (NMES with sham NMES)[27]. Results of the systematic review are predominantly reported as narrative summaries given the high heterogeneity and small numbers of studies addressing each outcome/endpoint.

3.1.1 Desirable effects

3.1.1.1 Evidence from randomized studies

The primary outcome of *muscle strength* was assessed using the Medical Research Council Muscle Scale Sum Score (MRC-SS) in 5 studies (347 participants)[9,19,22,24,26], hand-held dynamometry in 1 study (300 participants)[18], and handgrip strength in 3 studies (519 participants)[9,18,26]. There were no statistically significant between-group differences for systematic early vs. less systematic early rehabilitation at ICU discharge, or for early vs. late rehabilitation at hospital discharge using any of these measures. However, the minimal important difference (MID)[9] in MRC-SS (mean difference in MRC-SS of 5.8; 95% CI, -1.4 to 13.0), based on meta-analysis, exceeded the published MID values of 4 or 3.53[1].), suggesting potential clinical benefit of systematic early rehabilitation over less systematic early rehabilitation (Table 1). However, after exclusion of one study (28 participants)[19] with high baseline imbalance in MRC-SS, the overall mean difference (2.2; 95% CI, -2.5 to 6.9) fell below the MID, suggesting low clinical relevance.

The primary outcome of *functional mobility* was assessed using various measures. A significant between-group difference in the Barthel Index (BI, 1 study, 104 participants[9]) was reported, favoring systematic early rehabilitation over late rehabilitation. Functional Independence Measure (FIM) was assessed in 2 studies (315 participants)[25,26], one of which found a significantly higher score favoring systematic over less systematic early rehabilitation, whereas the second study found no difference.

Two studies (265 participants)[2,26] examined the impact of systematic vs. less systematic early rehabilitation on the 6-minute walk test (6MWT). Overall, there were no significant between-group differences in 6MWT distance in either study (Table 1). One study (150 participants)[2] reported an improvement in the mean difference in 6MWT from baseline in both the systematic early rehabilitation group and the less systematic early rehabilitation group at 3, 6, and 12 months (72.55 meters; 95% CI, 9.29 to 135.8 at 12 months). This value exceeded the published MID (35 meters[2,3]), suggesting an overall benefit of rehabilitation, although there was no control group without rehabilitation for comparison. The differences between the intervention and comparator groups in this study related primarily to the intensity of rehabilitation. Despite the lack of significant between-group differences in the 6MWT, the mean within-group change from first to last assessments was greater in the intervention group suggesting a benefit of systematic early rehabilitation.

Time to mobility milestones were assessed in 4 studies (329 participants, Table 1)[9,21,24,26]. Time to first time out of bed, time to walking, time to returning to independence, and the distance walked without assistance at hospital discharge favored systematic early rehabilitation over late rehabilitation in a single study (104 participants)[9]. No significant differences in these parameters (when studied) were reported between systematic and less systematic early rehabilitation in the remaining studies, with the exception of a shorter time to first time out of bed in one study favoring systematic early rehabilitation (60 participants)[21].

Meta-analyses of both the *SF-36 Physical Functioning Score* (PFS) in 4 studies (615 participants)[2,18,22,26] and the *SF-36 Physical Component Summary Score* (PCS) in 3 studies (565 participants)[2,18,26] did not reveal any statistically significant between-group differences at 6 months of follow-up. However, subgroup analysis did find a significant difference favoring systematic early rehabilitation compared with late rehabilitation for both scores in one study (300 participants)[18]. The published MID for the SF-PFS (5 or 4.14[1,2]) was exceeded for both the comparisons of systematic early rehabilitation with less systematic early rehabilitation (mean difference 8.05; 95% CI, -15.33 to 31.33) and systematic early rehabilitation with late rehabilitation (mean difference 12.30; 95% CI, 3.85 to 20.75) based on the meta-analysis, suggesting potential clinical relevance (Table 1).

There were no significant between-group differences for systematic early rehabilitation compared with either less systematic early or late rehabilitation for *activities of daily living* (ADL, 3 studies, 241 participants[9,20,24]), *physical function in the ICU test* (PFIT, 3 studies, 250 participants[2,22,24]), *timed up-and-go test* (TUG, 3 studies, 352 participants[2,20,26]), or the proportion of patients developing *ICU-acquired weakness* (ICUAW, 4 studies, 504 participants[2,9,24,25]) at multiple time points after ICU discharge.

Secondary outcomes included measures of cognitive function and mental health-related QoL, mortality, length of ICU stay (ICU LOS), length of hospital stay (hospital LOS), duration of mechanical ventilation, ventilator-free days, and various safety outcomes. Delirium duration was reported in 3 studies (604 participants)[9,18,25]. Two studies found a significant reduction in days with delirium or a greater number of delirium-free days, whereas the 3rd study found no difference. Three studies (315 participants)[2,22,26] examined the SF-36 mental health component summary score (MHS). One study found a significantly higher SF-36 MHS at 6 months after systematic early rehabilitation whereas the remaining 2 studies found no effect. No between-group differences were observed for the Mini-Mental State Exam (MMSE) in 2 studies (387 participants[18,20]), Hospital Anxiety and Depression Score (HADS) in2 studies (100 participants[22,24]), SF-36 Mental Health Component Summary score (MCS) in 3 studies (565 participants[2,18,26]), European Quality of Life 5 Dimensions visual analog scale (EQ-5D VAS) in 2 studies (137 participants[20,24]), or the SF-36 overall score (1 study, 200 participants[25]).

Three of 12 studies reported a significant reduction in ICU length of stay (LOS) comparing systematic early vs. less systematic early rehabilitation. Two of 11 studies reported a significant reduction in hospital LOS comparing systematic early vs. less systematic early rehabilitation. Three of 9 studies reported a significantly shorter duration of ventilation with systematic early rehabilitation compared with less systematic or late rehabilitation. One of 6 studies reported a higher number of ventilator-free days associated with systematic early rehabilitation vs. late rehabilitation.

3.1.1.2 Additional considerations

A single study (54 particiants[27]) investigated the effects of rehabilitation compared with no rehabilitation. This study evaluated NMES or sham intervention on muscle layer thickness in patients

after cardiothoracic surgery but did not find any effect. This study had a very narrow research question and therefore limited generalizability. No systematic comparison of rehabilitation with a no-rehabilitation control was possible in the other RCTs. Therefore, no conclusions about potential benefits of rehabilitation versus no rehabilitation can be drawn.

Overall, there was minimal or no evidence for a benefit of systematic early rehabilitation vs. less systematic early rehabilitation. Systematic early rehabilitation may be beneficial compared with late rehabilitation when assessed at hospital discharge. This conclusion is based on 2 studies (404 participants); however, there was overlap in timing of rehabilitation initiation in the 1st study and no data on frequency of the comparator intervention or duration of either intervention in the 2nd study, which may have modified the outcomes. Given the study sample sizes, stratified analysis to identify potential patient subgroups who benefited from systematic early rehabilitation or to identify the rehabilitation strategy that was most effective was not possible. Furthermore, the impact of subsequent or ongoing rehabilitation after ICU discharge may have contributed to unmeasured confounding in some studies. Only 1 study (150 participants[2]) followed patients for 1 year. Thus, the longer-term impact of systematic early rehabilitation could not be assessed.

3.1.1.3 Judgment

The Council of experts concluded that the differences in desirable effects between systematic early rehabilitation compared with less systematic early rehabilitation or late rehabilitation are small.

3.1.2 Undesirable effects

3.1.2.1 Evidence from randomized studies

No statistically significant between-group difference was observed for ICU mortality (4 studies, 269 participants[22,24,26,27]) or hospital mortality (8 studies, 1022 participants[9,18,20,21,23-26]). Pairwise meta-analysis of these 8 studies revealed a nonsignificant 4% reduction in hospital mortality favoring systematic early rehabilitation over less systematic early or late rehabilitation. No statistically significant between-group difference was observed for mortality after hospital discharge (6 studies, 902 participants[2,18,20,22,25,26]). In contrast, pairwise meta-analysis of 4 studies (615 participants)[2,14,18,26] found a nonsignificant 9% increase in the risk of death at 6 months post-discharge in the systematic early rehabilitation group compared with less systematic early or late rehabilitation groups.

Adverse events were reported in 9 studies (1116 participants[2,9,18,20-22,24-26]). These events included episodes of desaturation, hypotension, tachycardia, agitation, hypertension, and dislodgement of arterial lines and a nasogastric tube. These events were infrequent, and 2 were reported as severe, including one that was life-threatening. The potentially increased risk of healthcare-associated infection or transmission of nosocomial pathogens was not assessed in any study.

3.1.2.2 Additional considerations

Two studies[24,25] reported higher in-hospital mortality in the systematic early rehabilitation groups compared to the comparator groups. In one of these studies (300 participants[25]), mortality in the systematic early rehabilitation groups was double that in the less systematic early rehabilitation group. Similarly, 6-month mortality was four times higher in the systematic early rehabilitation group compared with the comparator in another study (50 participants[22]). Although the effect size was large,

considerable uncertainty remains about the true effect size because of large CIs related to small numbers of events.

Adverse events and their consequences, including whether these may have increased the costs or LOS, were not reported in detail in most studies, which limited further analysis.

3.1.2.3 Judgment

The Council of experts concluded that the risk of mortality was not significantly different in the various rehabilitation groups (although power concerns likely contributed to imprecision of estimates) and that the number of adverse events was small. Overall, the differences in undesirable effects between systematic early rehabilitation and less systematic early or late rehabilitation were judged to be small.

3.1.3 Certainty of evidence

Of the 12 RCTs included in the systematic review of clinical effectiveness, 2 were considered of high quality, 1 of fair quality, and 9 of low quality.

Table 1 summarizes the findings including GRADE assessment for primary outcomes of major interest. The quality of evidence was rated as low or very low for all primary and secondary outcomes studied because most studies were judged to have a high risk of bias in one or more domains. These ratings were based on multiple limitations which included the following:

1) studies tended to be small;
2) the definition of early rehabilitation was not standardized;
3) the exclusion criteria applied to studies limited generalizability;
4) despite APACHE II scores being comparable between treatment groups, studies were heterogeneous with respect to gender balance, ICU admission diagnosis/case mixes, patient numbers, type of rehabilitation intervention, frequency and intensity of interventions, adequate description of comparator group interventions, timing of initiation of experimental and comparator interventions, outcomes studied, and duration of follow-up;
5) components of comparator group interventions were generally not reported;
6) confounding by indication could not be ruled out especially in less systematic or late rehabilitation groups where physically stronger patients may have tended to receive more rehabilitation, which may have biased towards the null;
7) overlap of timing of systematic and less systematic early rehabilitation in some studies may have led to confounding;
8) given that rehabilitation has been widely taken up in ICUs, a change in standard of care over time likely biased later studies towards the null;
9) stratification of analysis by specific interventions or patient subgroups was not possible because of small patient numbers and lack of data;
10) mortality outcomes and safety data were not presented in detail.

3.1.3.1 Judgment

The Council of experts concluded that the overall certainty of evidence of effects from the systematic review was low.

3.1.4 Stakeholder values

A search of published evidence of patient values in relation to systematic early rehabilitation in the ICU was not part of the assessment. ICU patients are at risk of delayed return to full functionality in daily and professional life and may suffer from longer-term suboptimal QoL, cognitive impairment, and increased risk of death. Therefore, it is not unreasonable to anticipate that relatively simple interventions that may positively impact these outcomes would be valued by patients, families, and the society. Is not clear how specific outcomes measured in various studies are valued *per se* or relative to one another, e.g. muscle strength vs. cognitive functioning. The large heterogeneity of interventions and outcomes and limited survivor follow-up evidenced by the systematic review highlight many remaining knowledge gaps in terms of clinical utility and stakeholder values.

3.1.4.1 Additional considerations

A cross-sectional exploratory survey among ICU leaders and senior attending physicians was conducted to understand current practices and attitudes in connection with early rehabilitation in Swiss ICUs. The survey served as a background for contextual interpretation of the findings of the systematic review, and to provide evidence for the cost analyses. Table 2 summarizes the major findings. The survey response rate was 44% (37 of 84 ICUs), with the majority of respondents being from the German-speaking part of Switzerland (28 of 37 respondents, 76%) and from ICUs caring for adult patients (34 of 37 respondent ICUs, 91.9%). All respondents stated that they provided "early" mobilization in their ICU suggesting that this practice is valued by the Swiss ICU leaders who completed the survey. Six of 37 ICUs (16%) conducted routine follow-up of ICU survivors; 3 at hospital discharge and 4 over the longer term.

Although all respondents stated that they provided "early" mobilization, fewer ICUs reported providing rehabilitation "in general" (87%). The estimated mean proportions of ICU patients receiving early mobilization or rehabilitation in general were 82% and 53%, respectively. Disproportionately large numbers of ventilated and post-operative patients received early mobilization compared to other ICU patients (62% vs. 33%, respectively, for ventilated patients, and 77% vs. 60%, respectively, for post-operative patients vs. all patients), suggesting proportionately lower provision to other ICU patients (Table 2). Reasons for these discrepancies are unclear and could imply differences in clinician perceptions of the value of early rehabilitation in different patient groups. Lack of awareness, lack of motivation, lack of formal protocols/standardized practices, and lack of data were cited as additional barriers, which may suggest that early rehabilitation is valued differently by funders and practitioners across ICUs.

3.1.4.2 Judgment

The Council of experts concluded that there was possibly important uncertainty or variability in how stakeholders' value early rehabilitation outcomes in ICUs.

3.1.5 Balance between desirable and undesirable effects

The benefits and harms of systematic early rehabilitation in ICU compared to no rehabilitation remain unknown. Overall, there is little evidence of clinical benefit of systematic early rehabilitation compared with less systematic early rehabilitation. The evidence of benefit of systematic early rehabilitation compared with late rehabilitation may be more favorable. The findings for some clinically relevant outcomes (i.e. MIDs were exceeded for the 6MWT and the SF-36 PFS) may suggest a small benefit of

systematic early rehabilitation over less systematic or late rehabilitation, but the certainty of evidence was low. For other patient-relevant outcomes, the limited data available did not show any significant differences between rehabilitation groups. There is little evidence of substantial harm, although mortality and long-term data are unclear because of large CIs and lack of follow-up data. Adverse events were poorly reported. The relative benefits vs. harms of the various rehabilitation interventions studied and their impact in specific patient subgroups are unknown.

3.1.5.1 Additional considerations

Since rehabilitation is practiced in many Swiss ICUs, there appears to be a *de facto* presumption that benefit outweighs harm. Given the paucity of long-term follow-up in both studies and clinical practice, this presumption remains to be tested.

3.1.5.2 Judgment

The Council of experts concluded that the balance of desirable and undesirable effects of systematic early rehabilitation compared with less systematic early rehabilitation or late rehabilitation is unknown.

3.2 Considerations regarding resource requirements

3.2.1 Evidence

No relevant studies were identified in the literature regarding cost-effectiveness, cost-benefit analysis, cost-minimization analysis, cost-utility analysis, or HTA. Given the limited evidence regarding utilities and longer-term clinical differences, a cost analysis was performed instead of a cost-effectiveness analysis. The analysis was conducted from the perspective of the Swiss health insurance law (KVG) and the societal perspective over a time horizon of 12 months. The various data inputs and assumptions are described in detail in the Assessment Report.

Estimates of the proportion of patients receiving early rehabilitation in Swiss ICUs, mean duration (daily time and days) per patient, distribution of actual rehabilitation interventions, and the providers of these interventions (e.g. bedside nurses or physiotherapists) were obtained from the ICU leader survey results. The variety of early mobilization measures and variability in practices are outlined in the Survey Report. All respondents reported that early rehabilitation was practiced in their ICUs. The reported duration of early mobilization was 13.3 hours per patient but was not reported relative to ICU LOS. Significant differences in early mobilization practice in ICUs (i.e. routine involvement of rehabilitation specialists, rehabilitation activities, and use of protocols, Table 2) were identified across the spectrum of ICU characteristics (i.e. language, size, university, private, cantonal). Lack of resources (i.e. personnel, time, and financial resources) was cited as a barrier to implementation of early rehabilitation.

3.2.1.1 De novo cost analysis

Available data did not permit a bottom-up cost analysis using patient-level data. Estimated per-patient costs were derived from the costs of early rehabilitation and the potential cost differences between early rehabilitation and no rehabilitation. Given the lack of evidence from the clinical systematic review regarding outcomes with potential relevance to costs, costs associated with QoL, mortality, LOS, independence at time of discharge, and time to return to work were not included in the analysis. The

cost for 13.3 hours of early mobilization delivered per ICU stay was estimated at CHF 863 per patient. This cost comprised a flat rate of CHF 100 for rehabilitation materials, and the balance was accounted for by estimated proportion of staff time required. These costs are applicable to the ICU stay only and would amount on average to <1% of the total hospitalization costs per patient (average total hospitalization cost CHF 88,097).

3.2.1.2 Budget impact analysis

For the budget impact analysis, the total annual costs were calculated based upon the number of patients eligible for systematic early rehabilitation (i.e. those meeting the patient eligibility criteria used in the clinical systematic review, derived from Swiss hospital statistics, SHS 2015), the reported proportion of patients receiving systematic early rehabilitation in Swiss ICUs (responses from the survey of ICU leaders), and the estimation of cost per patient determined in the *de novo* cost analysis. The budget impact analysis was restricted to costs estimated for early rehabilitation of ICU patients, relative to total hospitalization costs.

Applying the patient eligibility criteria outlined in the Assessment Report, 4796 of 51,115 patients (9.4%) who had received any mechanical ventilation in 2015 were considered eligible for early rehabilitation in the ICU. Based on the survey results, approx. 82% of eligible patients receive early rehabilitation. Thus, considering the per-patient cost of CHF 863, the total annual cost for early rehabilitation among eligible patients would reach CHF 3.4 million. If, however, systematic early rehabilitation was to be extended to 82% of all patients ventilated for >24 hours and had an ICU LOS >24 hours (i.e. 14,751 patients in 2015), the annual cost would rise to around CHF 10.4 million. The mean hospitalization cost per eligible patient was estimated at CHF 88,097. Therefore, the total annual hospitalization costs for patients meeting the eligibility criteria applied in the RCTs included in the clinical systematic review would be around CHF 422 million. The cost of CHF 3.4 million for early rehabilitation would therefore amount to 0.8% of total annual hospitalization costs.

3.2.1.3 Additional considerations

The survey among ICU leaders used in the cost analysis has several limitations which likely impact the robustness of the input data used: 1) low response rate which may suggest response bias and overestimation of rehabilitation use; 2) lack of standardized definition of “early” rehabilitation or mobilization; 3) proportions of patients receiving early mobilization were estimated by respondents; 4) differences between perceived and actual practices were not determined; 5) self-reporting may have led to social desirability bias; 6) variability of practices and persons who deliver them reduce generalizability of cost assumptions.

Since ICU rehabilitation is performed by bedside nurses in many ICUs, it is unclear whether additional costs for nursing time are relevant. The use of a flat rate of CHF 100 per patient for rehabilitation materials is an assumption. From the survey, the proportion of patients in the ICU who receive early rehabilitation in Switzerland ranged from 30% to 100%. Therefore, the total costs may be variable. The impact of costs incurred or saved through adverse events, changes in LOS or duration of post-hospital rehabilitation required, or costs incurred or saved by caregivers and family members were not included in the analysis.

Despite the lack of eligible studies for formal systematic review, costs associated with early and/or intensive rehabilitation in ICUs reported in 3 partially relevant studies[28-30] from the United Kingdom and Taiwan were additionally considered. In 2 studies[28,30] including patients with primarily

cardiorespiratory disorders, there was a tendency towards reduced duration of ventilation and reduced hospital LOS when compared with usual care or no rehabilitation. However, in adjusted analyses, direct inpatient costs were not significantly lower in the early rehabilitation groups. In Switzerland, the cost of one hospitalization day was assumed to be CHF 1503, while the costs for "ventilation in complex cases" range from CHF 4060 to CHF 6452, and the cost for a single workday lost is around CHF 360. Given the relatively low cost of early rehabilitation in ICU compared to the cost of a single hospitalization day, the cost analysis would favor early rehabilitation in Switzerland if rehabilitation indeed reduces LOS. In contrast, the third study[29] reported longer ICU and hospital stays and greater resource use in the patients receiving intensive rehabilitation compared with standard physical rehabilitation in ICU. This study did not report costs but analyzed utility scores (i.e. quality-adjusted life years, QALYs) in a small number of patients (calculated from SF-6D and EQ-5D scores at 3 and 6 months after discharge) and found no significant difference between treatment groups (difference 0.018, 95% CI -0.022 to 0.070)[29]. In Switzerland, an incremental cost-effectiveness ratio (ICER) of CHF 50,000 or CHF 100,000 is regarded as relevant; therefore, early rehabilitation would need to generate 0.018 or 0.009 QALYs more than usual care to be cost-effective. These 3 studies had several limitations including variability in study populations, small patient numbers, study design, nature and timing of interventions and outcomes measured, and lack of reporting of detailed costing information. In addition, UK and Taiwan have different health financing mechanisms, which limits the generalizability to the Swiss context.

3.2.1.5 Judgment

The Council of experts concluded that the costs and potential savings associated with implementation of systematic early rehabilitation in the ICU are small relative to total hospitalization costs. This judgment excludes any consideration of broader long-term health system costs, societal costs, or cost-effectiveness.

3.2.2 Certainty of evidence with regard to resource requirements

Determination of the number of ICU patients potentially eligible for early rehabilitation based on SHS data is probably reliable. Given the lack of clear short-term or long-term benefits determined in the clinical systematic review and in the absence of real costing data, the cost analyses were based on multiple assumptions. Per-patient costs and current practice of early rehabilitation in the ICU in Switzerland are subjective and associated with substantial uncertainty. The true extent of utilization (i.e. proportion of patients, frequency, duration, intensity, and source of delivery) of early rehabilitation in eligible patients is unknown. The eligibility criteria used in the clinical systematic review would have applied to only 9.4% of all patients who received any mechanical ventilation or 32.5% of those who were ventilated for >24 hours. Whether the cost analysis should be restricted to this group is unclear. Similarly, it is not known whether specific patient subgroups or additional patient groups (e.g. those not ventilated in the ICU) may benefit substantially, or whether some patient subgroups may potentially be harmed. All these factors are relevant for accurate cost analyses. Given that some form of rehabilitation is being delivered in many ICUs, current per-patient hospitalization cost estimates may already include rehabilitation costs. Furthermore, most studies included in the clinical systematic review compared systematic early rehabilitation with less systematic early rehabilitation, whereas the cost analysis considered only early ICU rehabilitation compared with no ICU rehabilitation.

Additional limitations that impact the certainty of cost analysis include lack of long-term follow-up, costs of post-ICU rehabilitation in hospital or post-hospital discharge, costs of caregiver time, costs of patient days lost from work, disability, large heterogeneity of interventions (which may be associated with variable resource costs or requirement of specialist input), and lack of utility data.

3.2.2.1 Judgment

The Council of experts concluded that the certainty of evidence regarding resources required to implement systematic early rehabilitation in the ICU is low.

3.3 Health equity

A search of published evidence of health equity in relation to systematic early rehabilitation in the ICU was not part of the assessment. Findings from the survey among Swiss ICU leaders suggested high variability in utilization and practices of early rehabilitation in the ICU between geographic region/language groups, ICU size, ICU location (i.e. university, canton, private), and adult and pediatric units. In addition, ventilated and post-operative patients may be favored over other patient groups. Patients therefore have different access to early rehabilitation given the lack of standardization across units and the lack of standardized rehabilitation protocols. Furthermore, the potential impact of systematic early rehabilitation in the ICU for patients not meeting the eligibility criteria applied to the systematic clinical review and economic assessment is not known.

3.3.1 Judgment

The Council of experts concluded that there is probably no impact on health equity since the costs and resource requirements for systematic early rehabilitation are low and the certainty of benefit is not confirmed.

3.4 Acceptability

Swiss ICU directors (44% response rate in the survey) stated that early mobilization is practiced in their ICUs. Thus, this practice appears to be accepted by clinicians. Acceptability by other stakeholders (including patients) is unknown.

3.4.1 Judgment

The Council of experts concluded that early mobilization in the ICU is acceptable to key stakeholders (clinicians). This judgment excludes any consideration of effectiveness or safety of the intervention.

3.5 Feasibility

Given that there has been wide uptake of rehabilitation practices in ICUs, early rehabilitation in the ICU seems feasible. However, the survey among ICU leaders found significant differences in practice (i.e. routine involvement of rehabilitation specialists, rehabilitation activities, use of protocols) depending on the geographic and language zones, ICU size, and ICU location (i.e. university, private, cantonal). Therefore, the generalizability of these findings is limited. Existence of a specialized ICU physiotherapy team was reported by 49% of ICUs (15 of 35 respondents), with 30% reporting regular visits by other therapists (occupation, speech, nutrition). Written rehabilitation protocols exist in 46% of ICUs (15 of 32 respondents). Lack of resources was cited as a major barrier to implementation of

early rehabilitation (i.e. personnel, time, and financial resources). Lack of awareness, lack of motivation, lack of formal protocols/standardized practices, and lack of data were cited as additional barriers.

3.5.1 Judgment

The Council of experts concluded that early rehabilitation is feasible in the subpopulation of ICU patients meeting the eligibility criteria applied in the clinical systematic review.

4. Recommendations

The Council of experts issued a conditional recommendation in favor of systematic early rehabilitation in patients aged at least 18 years who require ventilation in the ICU for over 24 hours and who meet the eligibility criteria applied in the RCTs that formed the basis of the clinical systematic review.

4.1 Justification

Return to maximum functionality for ICU patients is desirable. Early rehabilitation is already frequently implemented in Swiss ICUs and is unlikely to be discontinued in the absence of evidence of overt harm. The committee's recommendation is however conditional, given that the certainty of the evidence of clinical effectiveness and safety of systematic early rehabilitation is low, and that the patients to whom the recommendations may apply is limited to those meeting the eligibility criteria applied in the RCTs included in the systematic review. In this patient population, systematic early rehabilitation may confer marginal benefit over less systematic rehabilitation for some prespecified outcomes, and early rehabilitation may confer greater benefit than late rehabilitation. Evidence of significant harm is lacking, but given the overall low grade of evidence and paucity of data, the true balance between desirable and undesirable effects remains unknown. Although data on cost-effectiveness are extremely limited, the additional cost of delivering early rehabilitation in the ICU is likely to be low compared to total hospitalization costs. However, the absolute costs of systematic early rehabilitation may become high if rehabilitation is widely scaled up, making it imperative to better understand the cost-effectiveness and social value of the interventions.

4.2 Subgroup considerations

The available studies did not report any subgroup effects of patient factors or rehabilitation interventions on outcomes. The supplemental survey among Swiss ICU leaders suggested that current practice appears to favor early rehabilitation activities for ventilated and post-operative patients. The clinical systematic review was restricted to RCTs which included patients aged 18 years or older who required ventilation for over 24 hours and who met specified inclusion criteria. It remains unknown whether systematic early rehabilitation is of benefit to the wider ICU population. Moreover, it remains unknown if any patient subgroups may be disproportionately placed at risk of harm by early rehabilitation in the ICU.

4.3 Implementation considerations

Effective and transparent communication with patients is necessary to enable shared decision making. Patients' perception of treatment options and their preferences and values should be considered before a decision is made. Given the lack of safety data, caution must be exercised to minimize potentially avoidable harms associated with delivery of early rehabilitation in the ICU. The survey

highlighted that lack of resources, awareness, motivation, and protocols were barriers to implementation. A standardized approach should be developed by consensus by ICU practitioners in Switzerland such that similar practices are carried out across ICUs. This approach would facilitate prospective monitoring and evaluation of the benefits, harms, and costs of systematic early rehabilitation in the ICU.

4.4 Monitoring and evaluation

Although the quality of evidence of possible benefit and of long-term ICU follow-up are limited, early rehabilitation in ICUs in Switzerland is frequently implemented. Thus, it is imperative that interventions and outcomes are better understood. The widespread use of detailed electronic health records in the ICU should permit standardized data collection of patient characteristics to monitor timing, frequency, intensity, and type of rehabilitation measures used in current practice across ICUs. In addition, it should be possible to evaluate the positive and negative outcomes over the short and the long terms. Robust evidence is required to determine cost-effectiveness.

4.5 Research priorities

Long-term studies investigating clinical benefit, cost-effectiveness, and safety of both systematic and less systematic early rehabilitation in the ICU are needed. Given the low cost and the potential long-term benefits in terms of QoL, survival, reduced healthcare costs, and lower post-ICU morbidity, this topic is of clinical, social, and economic importance. However, because the ICU population is highly heterogeneous, large patient numbers will be required to determine which patient subgroups are most likely to benefit and which may be harmed by early rehabilitation. Similarly, given the broad range of ICU rehabilitation interventions currently practiced, stratified analyses in large multicenter cohorts are required to establish which specific interventions may be most beneficial for which patients to inform development of standardized practices. Long-term outcomes must be determined. Simultaneously, stakeholder values should be investigated to ensure that research efforts (and clinical care) address relevant outcomes.

Consequently, the Council of experts recommends a joint research effort by specialized centers (e.g. in a sufficiently large multicenter RCT or large prospective observational cohorts) to fill the many existing knowledge gaps. Furthermore, well-designed cost-effectiveness studies should provide a more reliable database for future health economic assessments.

5. References

1. Merkies IS, van Nes SI, Hanna K, Hughes RA, Deng C. Confirming the efficacy of intravenous immunoglobulin in CIDP through minimum clinically important differences: shifting from statistical significance to clinical relevance. *Journal of Neurology, Neurosurgery, and Psychiatry* 2010; **81**(11): 1194-9.
2. Denehy L, Skinner EH, Edbrooke L, et al. Exercise rehabilitation for patients with critical illness: a randomized controlled trial with 12 months of follow-up. *Critical Care (London, England)* 2013; **17**(4): R156.
3. Puhan MA, Mador MJ, Held U, Goldstein R, Guyatt GH, Schunemann HJ. Interpretation of treatment changes in 6-minute walk distance in patients with COPD. *The European Respiratory Journal* 2008; **32**(3): 637-43.
4. Desai SV, Law TJ, Needham DM. Long-term complications of critical care. *Critical Care Medicine* 2011; **39**(2): 371-9.
5. Iwashyna TJ, Ely EW, Smith DM, Langa KM. Long-term cognitive impairment and functional disability among survivors of severe sepsis. *JAMA* 2010; **304**(16): 1787-94.
6. Girard TD, Kress JP, Fuchs BD, et al. Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients in intensive care (Awakening and Breathing Controlled trial): a randomised controlled trial. *Lancet (London, England)* 2008; **371**(9607): 126-34.
7. Sosnowski K, Lin F, Mitchell ML, White H. Early rehabilitation in the intensive care unit: an integrative literature review. *Australian critical care : official journal of the Confederation of Australian Critical Care Nurses* 2015; **28**(4): 216-25.
8. Shehabi Y, Riker RR, Bokesch PM, Wisemandle W, Shintani A, Ely EW. Delirium duration and mortality in lightly sedated, mechanically ventilated intensive care patients. *Critical Care Medicine* 2010; **38**(12): 2311-8.
9. Schweickert WD, Pohlman MC, Pohlman AS, et al. Early physical and occupational therapy in mechanically ventilated, critically ill patients: a randomised controlled trial. *Lancet (London, England)* 2009; **373**(9678): 1874-82.
10. Doiron KA, Hoffmann TC, Beller EM. Early intervention (mobilization or active exercise) for critically ill adults in the intensive care unit. *The Cochrane Database of Systematic Reviews* 2018; **3**: Cd010754.
11. Fuest K, Schaller SJ. Recent evidence on early mobilization in critical-Ill patients. *Current Opinion in Anaesthesiology* 2018; **31**(2): 144-50.
12. Nydahl P, Sricharoenchai T, Chandra S, et al. Safety of patient mobilization and rehabilitation in the intensive care unit. Systematic review with meta-analysis. *Annals of the American Thoracic Society* 2017; **14**(5): 766-77.
13. Castro-Avila AC, Seron P, Fan E, Gaete M, Mickan S. Effect of early rehabilitation during intensive care unit stay on functional status: Systematic review and meta-analysis. *PloS one* 2015; **10**(7): e0130722.
14. Kayambu G, Boots R, Paratz J. Physical therapy for the critically ill in the ICU: a systematic review and meta-analysis. *Critical Care Medicine* 2013; **41**(6): 1543-54.
15. Calvo-Ayala E, Khan BA, Farber MO, Ely EW, Boustani MA. Interventions to improve the physical function of ICU survivors: a systematic review. *Chest* 2013; **144**(5): 1469-80.
16. Hermans G, De Jonghe B, Bruyninckx F, Van den Berghe G. Interventions for preventing critical illness polyneuropathy and critical illness myopathy. *The Cochrane Database of Systematic Reviews* 2014; (1): Cd006832.

17. Alonso-Coello P, Schunemann HJ, Moberg J, et al. GRADE Evidence to Decision (EtD) frameworks: a systematic and transparent approach to making well informed healthcare choices. 1: Introduction. *BMJ (Clinical Research Ed)* 2016; **353**: i2016.

18. Morris PE, Berry MJ, Files DC, et al. Standardized rehabilitation and hospital length of stay among patients with acute respiratory failure: A randomized clinical trial. *JAMA* 2016; **315**(24): 2694-702.

19. Dantas CM, Silva PF, Siqueira FH, et al. Influence of early mobilization on respiratory and peripheral muscle strength in critically ill patients. *Revista Brasileira de Terapia Intensiva* 2012; **24**(2): 173-8.

20. Brummel NE, Girard TD, Ely EW, et al. Feasibility and safety of early combined cognitive and physical therapy for critically ill medical and surgical patients: the activity and cognitive therapy in ICU (ACT-ICU) trial. *Intensive Care Medicine* 2014; **40**(3): 370-9.

21. Dong ZH, Yu BX, Sun YB, Fang W, Li L. Effects of early rehabilitation therapy on patients with mechanical ventilation. *World Journal of Emergency Medicine* 2014; **5**(1): 48-52.

22. Kayambu G, Boots R, Paratz J. Early physical rehabilitation in intensive care patients with sepsis syndromes: a pilot randomised controlled trial. *Intensive Care Medicine* 2015; **41**(5): 865-74.

23. Dong Z, Yu B, Zhang Q, et al. Early rehabilitation therapy is beneficial for patients with prolonged mechanical ventilation after coronary artery bypass surgery. *International Heart Journal* 2016; **57**(2): 241-6.

24. Hodgson CL, Bailey M, Bellomo R, et al. A binational multicenter pilot feasibility randomized controlled trial of early goal-directed mobilization in the ICU. *Critical Care Medicine* 2016; **44**(6): 1145-52.

25. Schaller SJ, Anstey M, Blobner M, et al. Early, goal-directed mobilisation in the surgical intensive care unit: a randomised controlled trial. *Lancet (London, England)* 2016; **388**(10052): 1377-88.

26. Eggmann S, Verra ML, Luder G, Takala J, Jakob SM. Effects of early, combined endurance and resistance training in mechanically ventilated, critically ill patients: A randomised controlled trial. *PloS one* 2018; **13**(11): e0207428.

27. Fischer A, Spiegl M, Altmann K, et al. Muscle mass, strength and functional outcomes in critically ill patients after cardiothoracic surgery: does neuromuscular electrical stimulation help? The Catastim 2 randomized controlled trial. *Critical Care (London, England)* 2016; **20**: 30.

28. Morris PE, Goad A, Thompson C, et al. Early intensive care unit mobility therapy in the treatment of acute respiratory failure. *Critical Care Medicine* 2008; **36**(8): 2238-43.

29. Wright SE, Thomas K, Watson G, et al. Intensive versus standard physical rehabilitation therapy in the critically ill (EPICC): a multicentre, parallel-group, randomised controlled trial. *Thorax* 2018; **73**(3): 213-21.

30. Chou W, Lai CC, Cheng KC, Yuan KS, Chen CM, Cheng AC. Effectiveness of early rehabilitation on patients with chronic obstructive lung disease and acute respiratory failure in intensive care units: A case-control study. *Chronic Respiratory Disease* 2019; **16**: 1479973118820310.

Table 1. Summary of findings including GRADE assessment for primary outcomes of major interest derived from the Assessment Report

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)	p values, comments
	Late or less systematic early rehabilitation interventions	Systematic early rehabilitation interventions				
MRC Muscle Scale Sum Score (MRC-SS), measured at ICU discharge	**Systematic early vs. late rehabilitation**		-	104 (1 RCT[9])	⨁⨁OO LOW [a,b]	p = 0.38
	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)				
	Systematic early vs. less systematic early rehabilitation		-	203 (4 RCTs[19,22,24,26])	⨁OOO VERY LOW [a,c,d]	p =0.115** In a sensitivity analysis, omitting the study by Dantas et al.[19] 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	**Systematic early vs. less systematic early rehabilitation***		-	232 (2 RCTs[2,26])	⨁⨁OO LOW [a,e,f]	In the study by Denehy et al.[2] the rate of change was greater in the intervention group compared with the usual-care group (group × time; p = 0.049). Between-group effects did not exceed the MID.
	The mean 6MWT distance in the comparator group was 246 meters in Eggmann et al.[26] and 267 meters in Denehy et al.[26] 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.[2]	The mean 6MWT distance in the intervention group was 223 in Eggmann et al.[26] and 244.2 in Denehy et al.[2] 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.[2]				

Outcomes	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	p values, comments
	Late or less systematic early rehabilitation interventions	Systematic early rehabilitation interventions				
Time to walking, measured during hospital stay	**Systematic early vs. late rehabilitation**		-	104 (1 RCT[9])	⊕⊕OO LOW [a,b]	p < 0.0001
	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)				
	Systematic early vs. less systematic early rehabilitation		-	53 (2 RCTs[24,26])	⊕OOO VERY LOW [a,c,g]	p = 0.97 and ND
	The median time to walking in the comparator group was 6 days in Hodgson et al.[24] and 23 days in Eggmann et al.[26]	The median time to walking in the intervention group was 6 days in Hodgson et al.[24] and 8 days in Eggmann et al.[26]				
Patients returning to independence from assistance, measured at hospital discharge	**Systematic early vs. late rehabilitation***		**RR 1.71** (1.11 to 2.64)	104 (1 RCT[9])	⊕⊕OO LOW [a,b]	p = 0.02
	35 per 100	**59 per 100**				
SF-36 Physical Function Domain Score (PFS), measured 6 months after hospital discharge	**Systematic early vs. late rehabilitation**		-	161 (1 RCT[18])	⊕OOO VERY LOW [a,b,c]	p = 0.202** In the subgroup analysis Morris et al.[18] showed a statistically significant difference between systematic early versus late rehabilitation. The overall effect and the estimates for comparator subgroups exceeded the MID cut-off from published studies suggesting clinical importance.
	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)				
	Systematic early vs. less systematic early rehabilitation		-	126 (2 RCTs[2,22])	⊕OOO 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)				

Outcomes	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	p values, comments
	Late or less systematic early rehabilitation interventions	Systematic early rehabilitation interventions				
SF-36 Physical Component Summary Score (PCS), measured 6 months after hospital discharge	**Systematic early vs. late rehabilitation**		-	161 (1 RCT[18])	⊕OOO VERY LOW [a,b,c]	p = 0.997**
	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)				
	Systematic early vs. less systematic early rehabilitation		-	152 (2 RCTs[2,26])	⊕OOO 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	**Systematic early vs. late rehabilitation**		**RR 0.62** (0.38 to 1.03)	104 (1 RCT[9])	⊕⊕OO LOW [a,b]	p = 0.203**
	49 per 100	**31 per 100**				
	Systematic early vs. less systematic early rehabilitation		**RR 0.90** (0.63 to 1.27)	395 (3 RCTs[2,24,25])	⊕OOO VERY LOW [c,h]	
	39 per 100	**36 per 100**				

*Information was available only for one comparator group; ** p values derived from random effects model meta-analyses reported in the Systematic Review. CI: Confidence interval; MD: Mean difference; RR: Risk ratio; NR – not reported

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 CIs 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 CIs for absolute effects including important harm and low overall sample size; see definition above).

Table 2. Implementation of early mobilization and distribution of measures utilized in Swiss ICUs*

	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 for which the measure is provided (days [SD])
Frequency:				
Regular structured interdisciplinary rounds	54.1 (20/37)	-	-	-
ICUs providing any rehabilitation	86.5 (32/37)	53.1 (33.3)	-	-
ICUs with general rehabilitation protocol	46.9 (15/32)	-	-	-
Early mobilization protocol available	45.9 (17/37)	-	-	-
Proportion of patients receiving early mobilization	-	81.8 (21.3)	-	-
Mechanically ventilated patients as a proportion of all those receiving early mobilization (%)[a]	-	63.0 (32.8)	-	-
Post-operative patients as a proportion of all those receiving early mobilization (%)[b]	-	76.7 (27.1)	-	-
Early mobilization measures:				
Passive range of motion	97.3 (36/37)	71.5 (32.9)	28.5 (16.8)	3.8 (3.3)
Neuromuscular electrostimulation	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)
Routine evaluation of patient outcomes	16.2 (6/37)	-	-	-

*compiled from Tables 4,5,6 &7 of Early rehabilitation in Swiss ICU survey report. Legend: ICU - Intensive Care Unit; SD - standard deviation. [a]Ventilated patients constituted 33% of the ICU population overall; [b]Post-operative patients constituted 60% of the ICU population overall.