Supplementary Appendix

to paper Waldauf et. al.: Functional Electrical Stimulation-Assisted Cycle Ergometry-Based Progressive Mobility Programme for Mechanically Ventilated Patients: Randomised Controlled Trial with Six Months Follow Up

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Supplementary Methods

Full list of Enrolment Criteria

Inclusion Criteria:

(1) ≥18 years;

(2) mechanical ventilation, or imminent need of it at presentation;

(3) predicted ICU length of stay ≥7 days;

Exclusion Criteria:

(1) known primary systemic neuromuscular disease or spinal cord lesion at admission.

(2) severe lower limb injury or amputation;

(3) bedridden premorbid state (Charleston Comorbidity Score >4)

(4) approaching imminent death or withdrawal of medical treatment within 24 h;

(5) pregnancy;

(6) presence of external fixator or superficial metallic implants in lower limb;

(7) open wounds or skin abrasions at electrode application points;

(8) presence of pacemaker, implanted defibrillator or another implanted electronic medical device;

(9) predicted as unable to receive first rehabilitation session within 72 hours of admission or transferred from another ICU after more than 24 hours of mechanical ventilation;

(10) Presence of other condition preventing the use of FESCE or considered unsuitable for the study by a responsible medical team;

(11) prior participating in another functional outcome-based intervention research study.

Individualised Rehabilitation Protocol

Protocolised rehabilitation in the intervention group (EMIR Trial)

Stage and RASS score	Progressive mobility component	Supine cycle component (incl. the use of FESCE)	Total
0 unstable RASS -5 to -3 +/- neuromuscular blocking agents	2x15 minutes Passive/active exercises: passive and active range of motion, application of stretch reflex to upper and lower extremities and activation of global motor response, positioning in bed Respiratory-related activity	2x20 minutes Warm-up phase: about 5 minutes of passive cycling Therapeutic phase: functional electric stimulation (duration to aim for 90 min of total exercise per day, typically 10 min per session) Relaxation phase: about 5 minutes of passive cycling	Aim for 2 sessions a day and total 90 min of exercise a day (both FESCE and progressive mobility component)
1 sedated RASS -5 to -3	1x30 minutes Passive/active exercises: passive and active range of motion, application of stretch reflex to upper and lower extremities and activation of global motor response, positioning in bed Respiratory-related activity	2x20 minutes Warm-up phase: about 5 minutes of passive cycling Therapeutic phase: functional electric stimulation (duration to aim for 90 min of total exercise per day, typically 10 min per session) Relaxation phase: about 5 minutes of passive cycling	Aim for 2 sessions a day and total 90 min of exercise a day (both FESCE and progressive mobility component)
2 transition phase RASS -1 or 1, borderline cooperation	If cooperative: 2x10 minutes Passive/active exercises: active range of motion/lightly resisted upper and lower extremities, activation of global motor response, positioning in bed Respiratory-related activity 2x5 minutes Passive/active exercises (sit up in bed) If delirious: Individualise approach max. 30 minutes	2x20 minutes Warm-up phase: about 5 minutes of passive cycling Therapeutic phase: duration to aim for 20 minutes of functional electric stimulation (typically 10 min per session), attempt active cycling if cooperative Relaxation phase: about 5 minutes of passive cycling	Aim for 2 sessions a day and total 90 min of exercise a day (both FESCE and progressive mobility component)

	If resedated: 1x15 minutes Passive/active exercises: passive and active range of motion, application of stretch reflex to upper and lower extremities and activation of global motor response, positioning in bed Respiratory-related activity		
3 weak RASS 0, cooperative	2x10 minutes Active exercises: active range of motion/lightly resisted upper and lower extremities 2x5 minutes Progressive mobility: mobility activities progressing from less difficult activity in bed, active sitting on the bed 2x60 minutes Active exercise: sit out with assistance**	2x20 minutes Warm-up phase: about 5 minutes of passive cycling Therapeutic phase: active cycling if able or functional electric stimulation (duration to aim for 90 min of total exercise per day, typically 10 min per session) Relaxation phase: about 5 minutes of passive cycling	Aim for 2 sessions a day and total 90 min of exercise a day (both FESCE and progressive mobility component)
4 able to stand with assistance RASS 0, cooperative	2x10 minutes Active exercises: active range of motion, low to moderate resistance against upper and lower extremities 2x30 minutes Progressive mobility: mobility activities progressing from less difficult activity in bed to more difficult out of bed activities such as up to chair and ambulation	Warm-up phase: about 5 minutes of passive cycling Therapeutic phase: active cycling if able or functional electric stimulation (duration to aim for 90 min of total exercise per day, typically 10 min per session) Relaxation phase: about 5 minutes of passive cycling	Aim for 2 sessions a day and total 90 min of exercise a day (both FESCE and progressive mobility component)

Table S1: Protocolised rehabilitation in the intervention group. Notes: FESCE functional electrical stimulation-assisted cycle ergometry; RASS = Richmond agitation and sedation scale. Categories of interventions were re-defined according to Consensus on exercise reporting template in the intensive care unit (Reid et al., 2018), dose and intensity according to Perme C, Chandrashekar R., 2009; * The setup of FES cycling is not included in FESCE time. This (e.g., electrode placement, achieve muscle contractions, start cycling) took the physiotherapists about 10 - 15 minutes. Take down time was approximately 10 minutes. ** Mobilisation into a chair is included in exercise time, sitting out time is not unless further exercise in sitting position.

Details of rehabilitation delivered per treatment day and per study day

	Groups	n	mean	SD	min	max	range	Q0.25	median	Q0.75	Wilcoxon
ICU [Days]	Intervention	75	13.7	8.5	1	31	30	7	12	20.5	0.674
	Control	75	13.9	10.5	2	63	61	5.5	12	19	
Number of treatment days/patient	Intervention	75	10.8	8.1	0	27	27	4	10	16	0.052
	Control	75	8.2	6.9	0	22	22	2	7	13	
Number of FESCE treatment days/patient	Intervention	75	6.5	6.1	0	24	24	2	5	9	N/A
	Control	N/A									
FESCE [min/treatment day]:	Intervention	63	31.1	10.1	8.7	50	41.3	22	33.1	39	N/A
	Control	N/A									
FESCE [min/study day]:	Intervention	75	14.7	11.5	0	41.7	41.7	5.7	14	23.7	N/A
	Control	N/A									
Physiotherapy duration [min/ treatment day]	Intervention	69	56.9	15	21.3	104.4	83	48.1	55	63.8	0.381
	Control	66	54.5	10	29.5	78.8	49.2	50.1	53.3	57.1	
Physiotherapy duration [min/ study day]	Intervention	75	45.4	21.2	0	94.2	94.2	36.1	48.8	54.6	<0.001
	Control	75	33.2	17.5	0	67.4	67.4	22.7	37.1	45.3	
Total duration of rehabilitation [min/ treatment day]	Intervention	71	79.6	24	15	139.1	124.1	65.6	82.2	96.6	<0.001
	Control	66	54.5	10	29.5	78.8	49.2	50.1	53.3	57.1	
Total duration of rehabilitation [min/ study day]	Intervention	75	60.2	27.2	0	121.4	121.4	48.7	61.9	77.7	<0.001
	Control	75	33.2	17.5	0	67.4	67.4	22.7	37.1	45.3	

Table S2A: Duration of rehabilitation calculated either per treatment day (i.e. excluding days without rehabilitation in analogy with Wright et al., 2018) or per study day (i.e. including days without rehabilitation).

	Groups	n	mean	SD	min	max	range	Q0.25	median	Q0.75	Wilcoxon
Passive exercise [min/treat.day]	Intervention	69	22.3	10	0	60.1	60.1	15	23.7	27	<0.001
	Control	66	15.7	8.5	0	30	30	10.1	15	23.2	
Passive exercise [min/study day]	Intervention	75	17.7	10.8	0	60.1	60.1	11.4	18.9	23.9	<0.001
	Control	75	9.5	7.1	0	30	30	4.3	8.5	15	
Supine resistance exercises [min/treat.day]	Intervention	69	23.3	9.6	0	44.3	44.3	17.7	24	30	0.104
	Control	66	26.9	7.9	8.2	50	41.8	22.8	27.1	30	
Supine resistance exercises [min/study day]	Intervention	75	18	10	0	44.3	44.3	12.2	18.3	25.5	0.25
	Control	75	16.1	9	0	35.3	35.3	10.7	17.3	22.3	
Supine aerobic exercise [min/treat.day]	Intervention	69	8.9	12.2	0	51.7	51.7	0	3	14	0.255
	Control	66	8.7	7.4	0	30	30	0.1	7.5	15	
Supine aerobic exercise [min/study day]	Intervention	75	7.6	11.4	0	50.7	50.7	0	2.4	12.2	0.714
	Control	75	5.5	5.9	0	30	30	0	5	8.7	

Exercise whilst sitting [min/treat.day]	Intervention	69	0.5	1.2	0	7.3	7.3	0	0	0	0.179
	Control	66	0.4	1.5	0	7.7	7.7	0	0	0	
Exercise whilst sitting [min/treat.day]	Intervention	75	0.4	1.1	0	6.8	6.8	0	0	0	0.138
	Control	75	0.3	1.2	0	7.5	7.5	0	0	0	
Mobilising into chair [min/treat.day]	Intervention	69	1.8	4.1	0	25	25	0	0	1.7	0.161
	Control	66	2.7	3.9	0	15	15	0	0	4	
Mobilising into chair [min/study day]	Intervention	75	1.6	3.8	0	25	25	0	0	1.1	0.379
	Control	75	1.8	3	0	13.1	13.1	0	0	2.2	
Stand-up and/or walking exercise [min/treat.day]	Intervention	69	0.2	0.6	0	2.9	2.9	0	0	0	0.656
	Control	66	0.2	0.5	0	2.2	2.2	0	0	0	
Stand-up and/or walking exercise [min/study day]	Intervention	75	0.2	0.5	0	2.9	2.9	0	0	0	0.574
	Control	75	0.1	0.4	0	1.8	1.8	0	0	0	

Table S2B: Detailed description of phases of protocolised rehabilitation calculated either per treatment day (i.e. excluding days without rehabilitation in analogy with Wright et al., 2018) or per study day (i.e. including days without rehabilitation).

Reasons for days without rehabilitation

The intervention occurred in 817/932 days; standard care occurred on 615/895 days. The reasons for no-physiotherapy days were:

1. Day of enrollment was recorded as the day in the study, but no rehabilitation was delivered as the study subjects were usually randomized in the afternoon.

2. Day where rehabilitation was considered unsafe (patient not meeting safety criteria) or not feasible (e.g. patient transferred to operating room)

3. Out-of-bed mobilization were occasionally skipped particularly for obese patients, when there was no assistance available to physios from the nurses due to staff shortages or workload on the unit.

4. (In standard of care only): Unlike study physios, hospital physios do not work on Sundays.

Richmond Agitation Sedation Scale (RASS)

Score	Term	Description
+4	Combative	Overtly combative, violent, immediate danger to staff
+3	Very agitated	Pulls or removes tube(s) or catheter(s); aggressive
+2	Agitated	Frequent non-purposeful movement, fights ventilator
+1	Restless	Anxious but movements not aggressive vigorous
0	Alert and calm	
-1	Drowsy	Not fully alert, but has sustained awakening (eye-opening/eye contact) to voice (>10 seconds)
-2	Light sedation	Briefly awakens with eye contact to voice (<10 seconds)
-3	Moderate sedation	Movement or eye opening to voice (but no eye contact)
-4	Deep sedation	No response to voice, but movement or eye opening to physical stimulation
-5	Unarousable	No response to voice or physical stimulation communicate or follow commands

Table S3: Richmond Agitation and Sedation Scale

Reflex locomotion therapy

There are many different physical therapy interventions available and views about what physical therapy entails differ. Some therapists emphasize the role of stimuli application (neuroproprioceptive „facilitation and inhibition“ while others emphasize physical therapy as a problem-solving educational process (Motor/skill acquisitions). Different views could influence both the delivery and outcome of therapy. For example, Vojta reflex locomotion or the Perfetti approach are considered key interventions in one region (Vojte reflex locomotion in the Czech Republic while Perfetti approch in Spain), but may be unknown to some physical therapists in other regions (Rasova et al., 2020).

Reflex locomotion therapy developed by prof. Vojta (Vojta V., 1973) is routinely used in the Czech Republic. Patients are set up into the precisely given initial position with defined angular setting of extremities (prone, supine and kneeling position) and activation zones (trunk, acromion, scapula, epicond. med. humeri, proc. styl. radii, spina iliaca sup. ant., mus. gluteus, epicond. med. femoris, calcaneum) are stimulated with precise localization and pressure direction. This sustained manual pressure stimulation of specific points on the skin surface gradually evokes a widespread involuntarily motor response (reflex creeping, reflex turning and process of verticalization), and moreover sensory and autonomic response is activated [2]. Such approach is implemented not only in bedridden patients, but also in fully active patients with aim to qualitatively improve their movement.

Screening strategy

Research nurses (5 persons in 2.5 full-time working equivalents) were responsible for pre-screening potentially eligible patients and notifying investigators, who were approaching the family at or immediately after the first family meeting with medical team. In case legal representative was not available, eligible patients have been enrolled without consent as per article 38 of the Declaration of Helsinki. In this case, an independent physician confirmed patient's lack of capacity

and fulfilment of the entry criteria. Pre-screening during week days was performed by a research nurse who has always been physically present at morning rounds. During weekend and bank holidays pre-screening research nurses used remote access to clinical information system (MetaVision, IMD Soft, Israel).

Randomisation procedure details

When entering screening baseline data and checking against inclusion and exclusion criteria, the process of randomisation was performed automatically in an electronic case-report form. The computer was programmed to generate a randomisation sequence at http://randomisation.com in permuted blocks of four in each of four strata based on (1.) presence or absence of sepsis and (2.) specific consent to muscle biopsy studies.

Strategy to minimise loss of follow-up

1. Protocol was designed to allow primary outcome be obtained over the phone.
2. Contact details + 2 back-ups: When consenting the relatives, we not only took contact details of patients, but also contact detail of the next of kin and a back-up contact for other family member. Contact details were checked when research nurses performed discharge visits.
3. Plan A: Re-join interview: 4-6 weeks before the 6 months follow up was due the research nurses (who were known to the patients or the family) phoned and arranged the date for the follow up phone call. During this pre-interview, the main objective was to determine who is the best to phone (whether the patient or the carer should be interview) and schedule time and date of this phone call. Patients/carers were also reminded not to disclose whether they used bike or not during their hospital stay when speaking with blinded outcome assessor.
4. Plan B: Use of back-up contacts: In case patients/relatives were not available, the attempts to re-join interview continue, with eventual use of back-up contacts.
5. Plan C: In cases this failed, the blinded study assessors themselves tried to contact patients/carers directly at 6 months.
6. Plan D: Physical visits of patients: In remaining cases (n=6) it was necessary to physically visit patients at their homes or long-term care facilities. In 5 cases, it was in patients who remained hospitalised in long term facilities, whose family agreed with gathering the data but did not know the necessary details about patient's current condition, which nursery personnel refused to give over the phone. In one case, it was necessary to visit a patient suffering from self-neglect in his home.

Details on power analysis and primary outcome measurement

Power analysis is based on the study of Kayambu et al. 2015, who studied a rehabilitation intervention in patients with sepsis and reported in the control group the mean **physical function (PF) score** 60 points with a standard deviation of 29.4 points. We aimed to be able to detect changes of health-related quality of life that are clinically important for patients. In order to determine "moderately clinically important" difference for our patients, we used per analogiam data from a study on patients with COPD, asthma and myocardial infarction (Wyrwich et al., 2005), which determined this difference to be in the range of 15-20 points by a Delphi consensus of stakeholders. In order to get 80% probability to detect (at $p<0.05$) a difference of 15.8 points in the population with physical function score of 60.0±29.4 points, we would require 108 patients (n=54 in each group). We used two-sided test at https://clincalc.com/stats/samplesize.aspx to calculate this. In order to compensate for non-survivors (mortality of unselected patients in our unit in 2014 was 28%), we planned for and also randomised 150 patients.

Please note that although PF is an important determinant of the study primary outcome, **physical component score (PCS)**, there are other elements of physical health, which we believed could also have been influenced by the intervention and thus better reflects the answer to our research question. Namely, **PCS = (10PF+4RP+2BP+5GH)/21,** where RP is role limitation due to physical health, BP=bodily pain and GH = general health. There was no study published in 2014 to report on PCS and its standard deviation in populations similar to our cohort and therefore it should be noted that power analysis of our study is based on surrogate (PF).

Details of secondary outcome measurements

- Four-item Physical Fitness in Intensive Care Test (PFIT-s) was measured as per Denehy et al., 2013 with using ordinal scale ranging from 0 to 12 (see table S4).

Assistance	Cadence [steps/min]	Shoulder Strength	Knee Strength
0=unable	0=unable	0=<gr 3	0=<gr 3
1=assists x 2	1= <49	1=gr 3	1=gr 3
2=assist x 1	2=50-80	2=gr 4	2=gr 4
3=no assistance	3=>80	3=gr 5	3=gr 5

Table S4: Components of PFIT-s test. Note gr.= grade referring to Oxford muscle power scale (see below on MRC score)

- A trained study physiotherapist unblinded to patient's treatment allocation was obtaining these scores at D28 or ICU discharge, whichever occurred earlier. Data were entered into the electronic CRF in the form of scroll-down list.

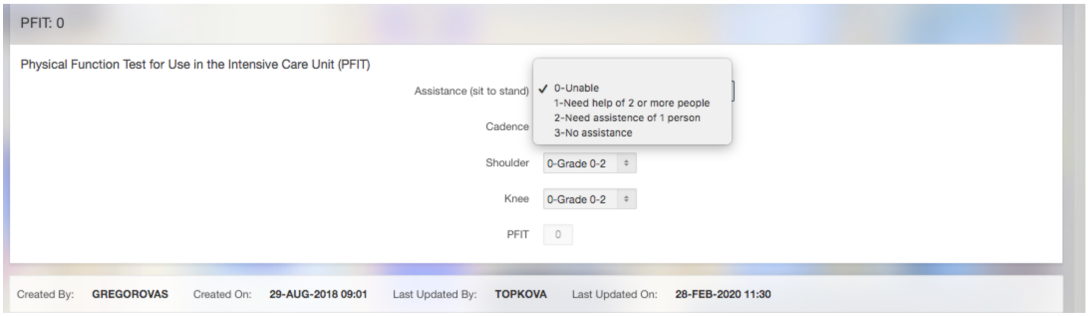


Figure S1: PFIT-s entry into electronic case report form.

- Rectus muscle cross-sectional diameter was measured by ultrasound (Vivid G5, GE Healthcare) as described by Montes R., 2001. Linear 9MHz probe was placed in transverse plane perpendicular to the skin in the midpoint between patella and anterior superior iliac spine and rectus femoris muscle identified and its antero-posterior diameter measured. See Fig. S2.

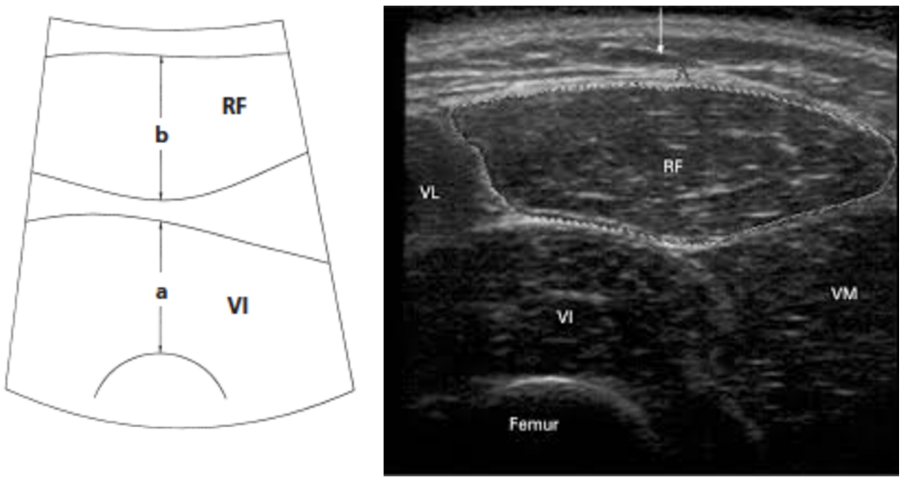


Figure S2: Measurement of rectus femoris cross-sectional diameter – adapted from Montes [6]. Note: RF = rectur femoris muscle, VI = vastus intermedius muscle.

- Daily nitrogen balance was calculated as a difference between nitrogen intake minus nitrogen excretion. Nitrogen intake was calculated automatically (Metavision 5.0, IMD Soft Israel) by multiplying N-content of the feeding formulas and their intake. Nitrogen excretion has been measured by multiplying output of urine (and/or dialysis fluid) and its nitrogen content. Nitrogen content was calculated as a sum of nitrogen in urea, creatinine and

ammonia. No preservation of urine has been used before ammonia measurement. We have not measured nor estimated non-urinary nitrogen losses.

- Muscle power as per the Medical Research Council (MRC) score has been assessed as a sum of 5-grade Oxford scores on 3 muscle groups on four limbs. Oxford score is measured as 0, paralysis; 1, only a trace or flicker of muscle contraction is seen or felt; 2, muscle movement is possible with gravity eliminated; 3, muscle movement is possible against gravity; 4, muscle strength is reduced, but movement against resistance is possible and 5, full power. Therefore, MRC score ranges from 0 (quadriplegia) to 60 (normal muscle strength).
- Number of ventilator-free days has been calculated for each patient as a count of days when a patient in alive and disconnected from invasive or non-invasive mechanical ventilation for entire 24 hours period. This includes patients with tracheostomies ventilating all day long on Ayre T-piece and patients supported by high-flow nasal oxygen cannula. Ventilator-free day is not counted when the patient requires non-invasive ventilation or in patients on end-of-life pathway after terminal extubation.

- ICU length of stay was measured at discharge from ICU or at day 28, whichever occurred earlier.

- Number of episodes of elevated intracranial pressure (Pre-specified safety outcome): Rehabilitation intervention (with or without FESCE) could have been delivered per protocol to patients with ICP measurement in place whos ICP is normal and stable and who are not on second or third-tier therapy for intracranial hypertension. ICP has been measured by intraparenchymal probe (Codman® , Life Sciences, USA) inserted in right midpupillary line and zeroed at tragus. An elevation of ICP has been defined as any elevation above 20 mmHg lasting for 5 or more minutes or requiring any intervention. ICP has been watched carefully during and after rehabilitation interventions and noted in electronic case report form. In addition, ICP waveforms were checked manually in retrospect from clinical information system (Metavision 5, IMD Soft, Israel) in all patients with ICP monitor in place, who were enrolled into the study.

- Number of dialysis interruptions (Pre-specified safety outcome): This was defined as unplanned termination of continuous renal replacement therapy for any reason that requires resetting the circuit or reinsertion of venous access cannula.

Supplementary Results

Recruitment curve

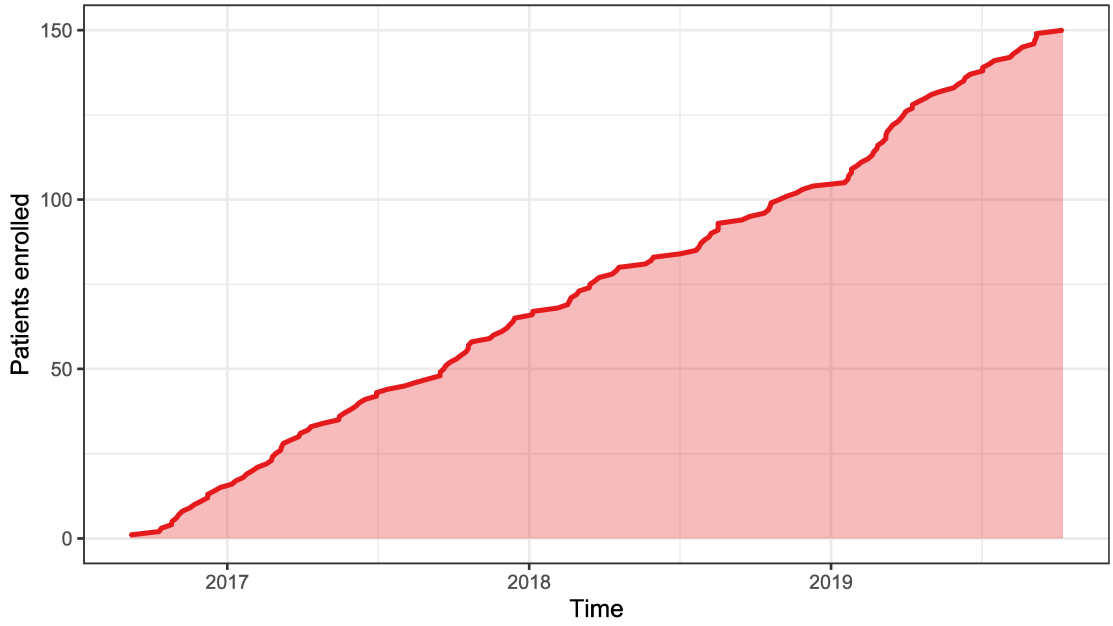


Figure S3: Recruitment curve = number of enrolled patients over time.

Primary outcomes – how it was collected

Eighty eight (59%) out of 150 enrolled patients were alive at 6 month. Primary outcome was collected from 88 (100%) of them following way:

- Eleven out of 31 patients who consented to metabolic substudy came to hospital for follow-up exercise testing, insulin clamp and muscle biopsies.
- 53 patients were interviewed face-to-face at their convenience next to their scheduled unrelated hospital appointment or were visited at home by outcomer assessors
- In 24 patients, primary outcome data were gained by structured telephone interview with patients themselves (n=10) or their carers (n=14).

Primary outcome normality testing and descriptive statistics

Primary outcome = Physical Component Summary Score of SD-36 QoL questionnaire at 6 months deviated from normal distribution in our population.

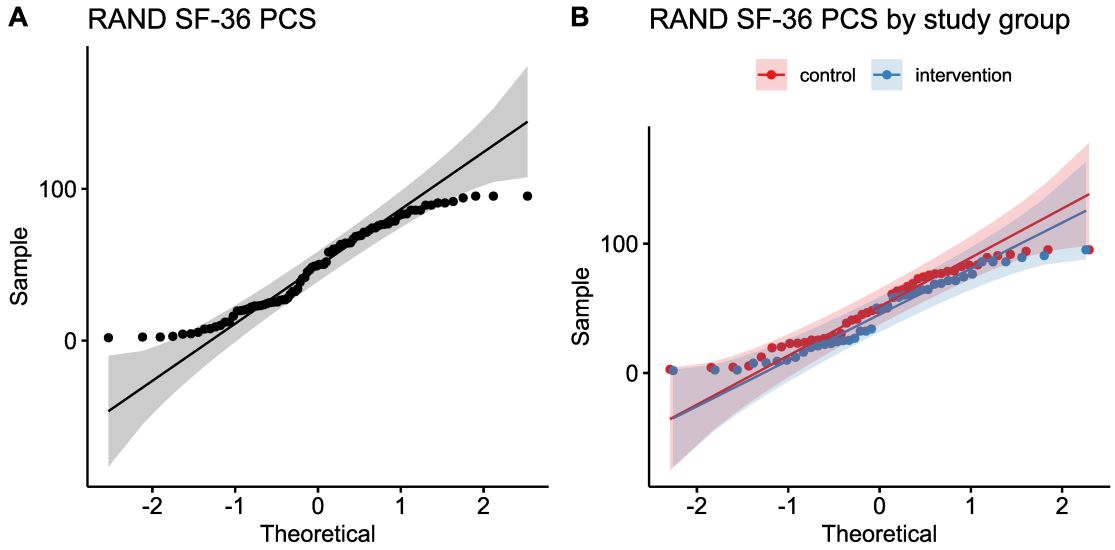


Figure S4: PCS SF-36 (primary outcome) normality of distribution.

In the paper, Wilcoxon test was used to test the differences and results presented as medians (interquartile range).

Group	n	mean	SD	min	max	range	se	Q0.25	Median	Q0.75
Controls	46	51.65	28.81	2.86	95.24	92.38	4.25	25.77	49.17	76.85
Intervention	42	45.3	29.19	1.9	95.24	93.33	4.5	21.25	50.24	69.13

Table S5: Descriptive statistics of the primary outcome (PCS-SF36 at 6 months is as follows)

Means with 95% confidence intervals

Means with 95% Confidence intervals for primary outcome (PCS/SF36) are: Intervention 45.3 (35.1-55.5), Control 51.7 (41.9-61.4)

Physical function score

Median physical function score of SF-36 at 6 months was 47.5 (IQR 20; 84) points and 42.5 (IQR 25; 80) in intervention vs. control groups (p=0.65, Wilcoxon). This was not a prespecified outcome and we report this to enable metanalyses.

RAND SF-36 at 6 months

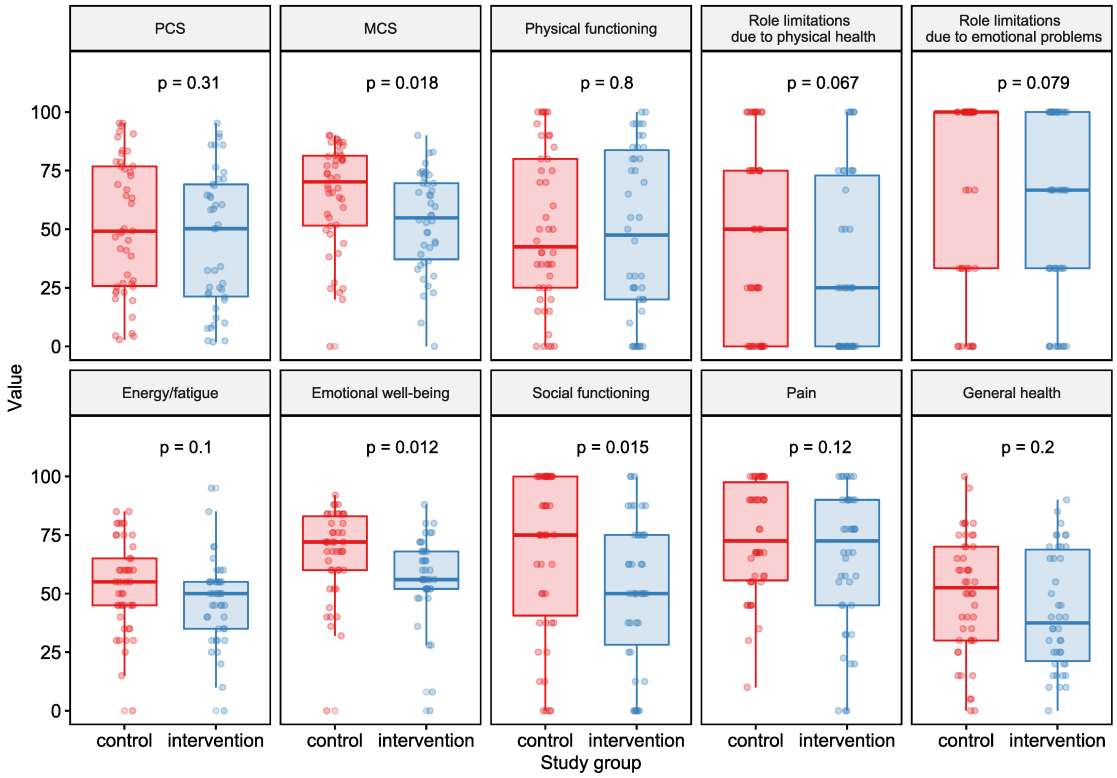


Figure S5: Results of SF-36 at 6 months (p values are from t-test) and data are calculated as per version 1 of RAND methodology https://www.rand.org/health-care/surveys_tools/mos/36-item-short-form/scoring.html

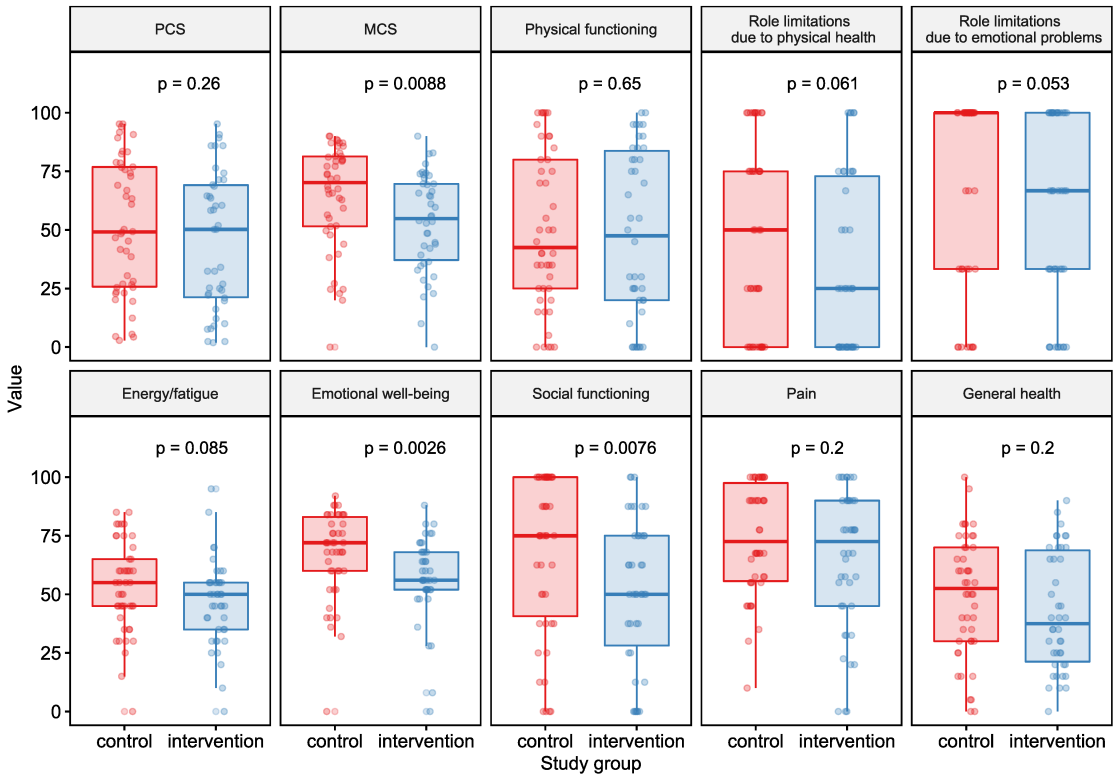


Figure S6: Results of SF-36 at 6 months (p values are from Wilcoxon test) and data are calculated as per version 1 of RAND methodology https://www.rand.org/health-care/surveys_tools/mos/36-item-short-form/scoring.html

Mental component score in subgroups with and without traumatic brain injury

Note: This was not a prespecified outcome and the study was not powered to investigate this. Data below must be interpreted as hypothesis generating only.

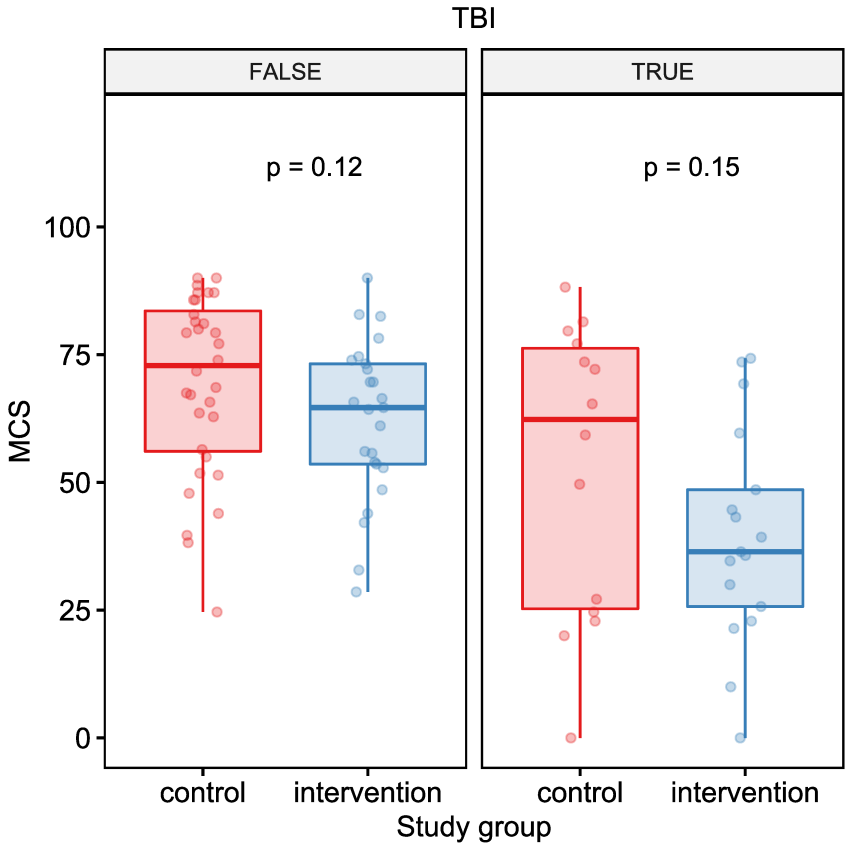


Figure S7: Mental component summary score at 6 months in patients with and without traumatic brain injury. P-values are from Wilcoxon test.

Exploratory data analysis

Groups	n	mean	SD	min	max	range	se	Q0.25	Median	Q0.75
TBI = FALSE, control	32	69.1	17.6	24.6	90.0	65.4	3.1	56.1	72.9	83.6
TBI = FALSE, intervention	25	62.3	15.5	28.6	90.0	61.4	3.1	53.6	64.6	73.2
TBI = TRUE, control	14	52.9	28.6	0.0	88.2	88.2	7.6	25.3	62.3	76.3
TBI = TRUE, intervention	17	39.4	21.1	0.0	74.3	74.3	5.1	25.7	36.4	48.6

Table S7A: Mental component summary scores at 6 months.

term	estimate	std.error	statistic	p.value
(Intercept)	70.181	3.22	21.797	<0.001
group: intervention - control	-9.227	4.252	-2.17	0.033
TBI: TRUE - FALSE	-19.626	4.447	-4.414	<0.001

Table S7B: Linear regression analysis: MCS ~ group + TBI:

Linear regression: MCS ~ group * TBI:

term	estimate	std.error	statistic	p.value
(Intercept)	69.14	3.512	19.688	<0.001
group: intervention - control	-6.854	5.303	-1.293	0.2
TBI: TRUE - FALSE	-16.206	6.366	-2.546	0.013
group intervention : TBI TRUE	-6.711	8.917	-0.753	0.454

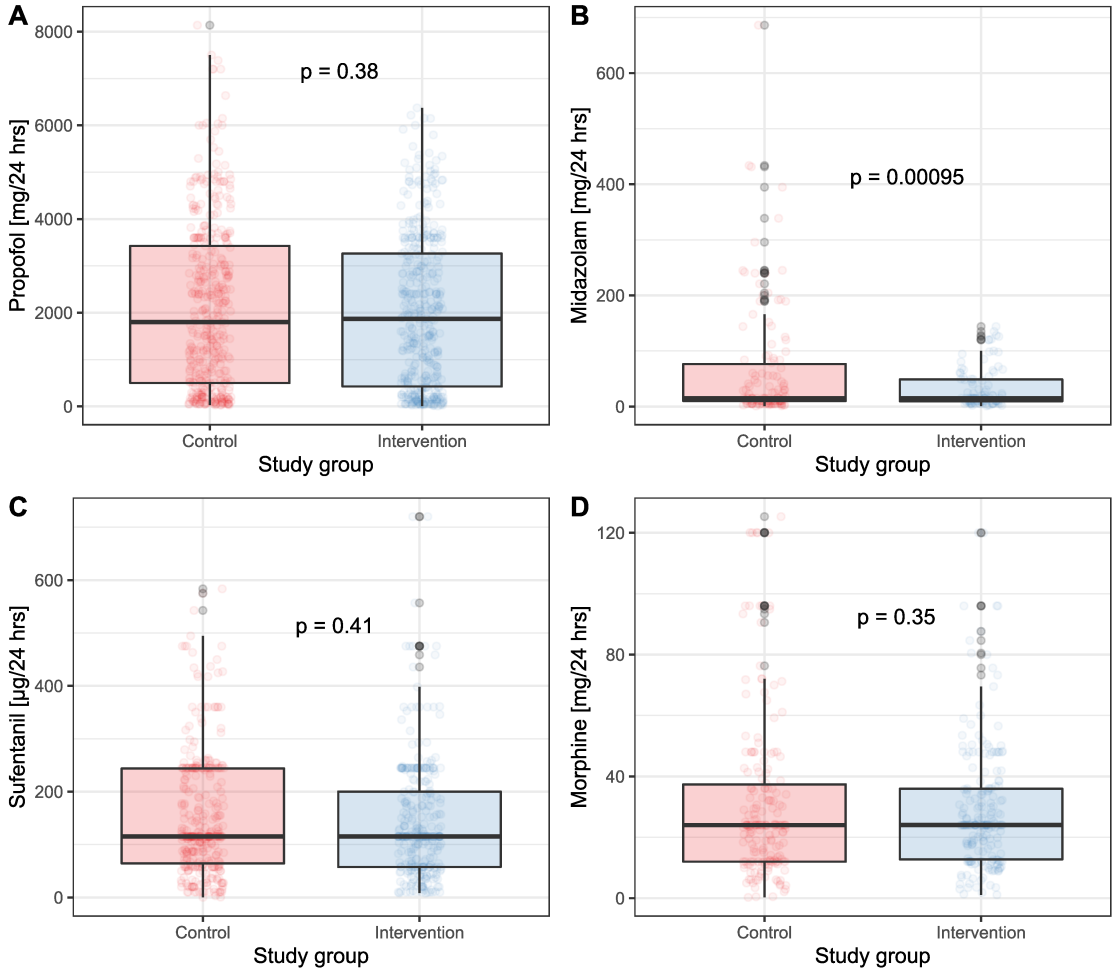
Table S8: Linear regression analysis: MCS ~ group * TBI:

ICU and hospital length of stay – Tabular views of descriptive data

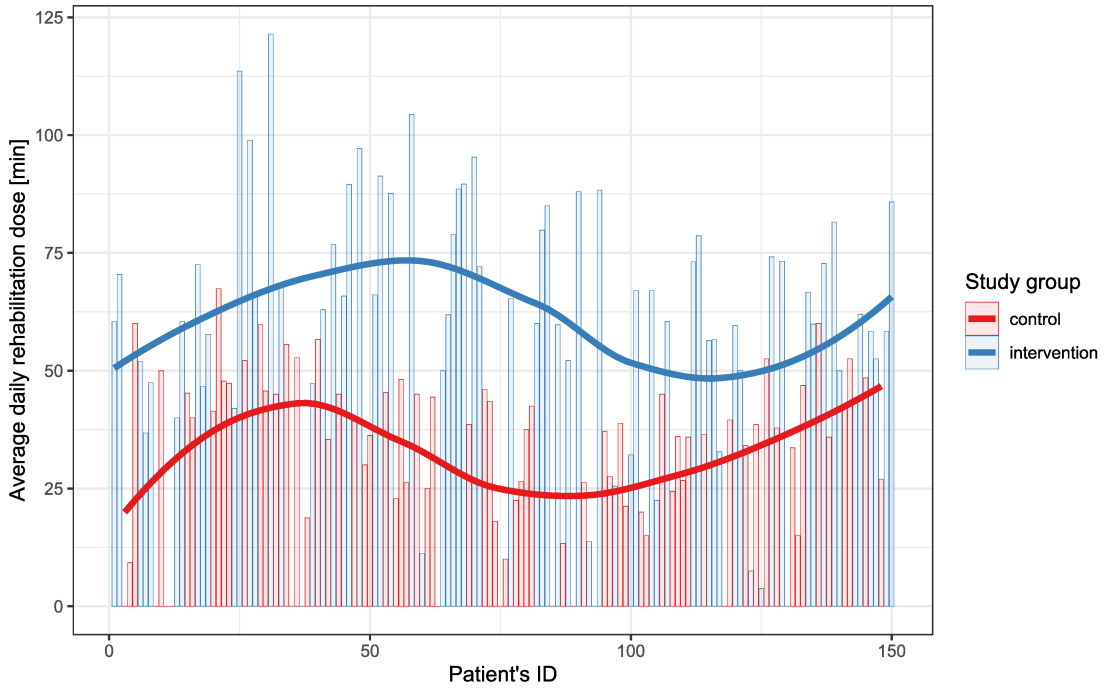
		N	Mean ± SD	Median (IQR)	Min	Max
ICU LOS [days]	Intervention	75	13.7±8.5	12 (7-21)	1	31
	Control	75	13.9±10.5	12 (6-19)	2	63
Hospital LOS [months]	Intervention	70	2.2±2.0	1.4 (0.5-2.6)	0.1	6.0
	Control	69	2.0±1.9	1.4 (0.5-4.0)	0.1	6.2

Table S9: Tabular view of uncensored lengths of stay. Please note that this table contains descriptive uncensored data unlike Figure 3C and 3D of the main manuscript containing death-censored Kaplan-Meier curves.

Doses of drugs used for sedation and analgesia



Supplementary Figure S8: Doses of sedatives



Supplementary Figure S9: Duration of rehabilitation vs. study number that were given consecutively and represent time. Individual bars represent mean rehabilitation duration in individual subjects, the line is Loess curve (local regression).

Sedation heatmap in tabular view

	Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Group	RASS	perc	perc	perc	perc	perc	perc	perc	perc	perc	perc	perc	perc	perc	perc
Control	4	0	0	0	0	0	0		0	0	0	0	0	0	0
	3	0	0	1.4	0	0	0	0	0	0	0	0	0	0	0
	2	2.7	0	1.4	1.6	1.8		2.1	4.5	9.5	2.4	2.6	0	0	3.3
	1	2.7	2.7	4.3	4.9	7.3	8.0	10.6	9.1	4.8	7.1	13.2	8.6	6.2	3.3
	0	10.7	16.4	21.4	19.7	25.5	38.0	38.3	31.8	40.5	47.6	36.8	14.3	6.2	16.7
	-1	10.7	6.8	11.4	11.5	10.9	10.0	14.9	18.2	21.4	14.3	21.1	31.4	46.9	43.3
	-2	12.0	23.3	20.0	21.3	16.4	16.0	12.8	11.4	7.1	4.8	7.9	25.7	21.9	10.0
	-3	28.0	17.8	12.9	13.1	7.3	4.0	4.3	6.8	4.8	2.4	2.6	8.6	3.1	3.3
	-4	21.3	23.3	17.1	18.0	16.4	12.0	6.4	6.8	4.8	4.8	5.3	2.9	9.4	10.0
	-5	12.0	9.6	10.0	9.8	14.5	12.0	10.6	11.4	7.1	16.7	10.5	8.6	6.2	10.0
Intervention	4	1.3	1.4	0	0	0	1.8	2.0	0	0	5.1	0	0	0	0
	3	1.3	2.8	4.4	1.5	3.3	3.6	2.0	2.2	4.8	7.7	5.3	2.8	5.7	3.1
	1	6.7	2.8	5.9	7.6	11.5	7.1	10.2	20.0	2.4	17.9	5.3	2.8	11.4	21.9
	0	6.7	9.9	14.7	18.2	14.8	17.9	20.4	20.0	21.4	15.4	21.1	11.1	11.4	28.1
	-1	4.0	8.5	5.9	12.1	13.1	5.4	14.3	13.3	23.8	23.1	23.7	13.9	22.9	9.4
	-2	14.7	12.7	13.2	10.6	13.1	16.1	14.3	13.3	21.4	7.7	18.4	16.7	22.9	15.6
	-3	13.3	21.1	14.7	16.7	8.2	12.5	6.1	6.7	7.1	7.7	13.2	27.8	14.3	3.1
	-4	32.0	19.7	17.6	10.6	11.5	17.9	16.3	11.1	4.8	5.1	2.6	16.7	2.9	3.1

	-5	20.0	21.1	23.5	22.7	24.6	17.9	14.3	13.3	14.3	10.3	10.5	8.3	8.6	15.6

Table S10: Distribution of patients into Richmond Agitation and Sedation Scale categories. Note: perc = percentage of patients

Detailed description of the influence of intervention on intracranial pressure.

The Protocol followed standard safety criteria (Sommers et al., 2015) for both intervention and control group. This means that planned rehabilitation session was omitted in case patient had unstable ICP or was receiving neuroprotective regimen (i.e. 2nd or 3rd tier of treatments for intracranial hypertension).

There were 15 days with ICP monitoring in place in 3 patients in the control group and 15 days with ICP monitoring in 4 patients in the intervention group. In all patients and intraparenchymatous ICP probe (Codman, Germany) was inserted through a burr hole in right midpupillary line and zeroed at tragus. Sustained ICP elevation was defined as ICP>20 torr for >5 mins or any elevation that required intervention.

All rehabilitation sessions were initiated on patients who were fulfilling safety criteria. There were no ICP elevations in the 3 patients in the control group, but in total 23 elevations were recorded in two out of four patients in the interventional group. These two patients are described in more detail.

Patient A was 27-year-old man with blunt severe TBI. He begun FESCE exercises on day 3 when the decision to wake him up was made. He suffered 3 elevations of ICP, which occurred 4, 6.5 and 22 hours after last FESCE exercise. The patient was alive with severe neurological disability 6 months after

Patient B was 73-year-old man with severe blunt isolated TBI. He was randomised into interventional arm, but was not receiving any exercises due to unstable ICP up until day 6 when his ICP stabilised. Then he received one 15 min FESCE intervention throughout which ICP remained stable. However, 55 mins after this, ICP begun to rise again, requiring reescalation of treatment. Thereafter, there were 20 more ICP elevations, which resulted in the necessity of a decompressive craniectomy. Afterwards, the patients resumed rehabilitation program, but remained comatose and died 2.5 months after the injury.

Consensus on Exercise Reporting Template (CERT) Self-evaluation Result (16 item checklist)

Here we provide the results of paper self-evaluation according to minimum standards published for reporting exercise interventions (Slade et al., 2016). In case some details were not included in the manuscript due to word count restrictions, they can be found here.

1 Detailed description of the type of exercise equipment:

Functional electrical stimulation-assisted cycle ergometry (RT300 System, © Restorative Therapies Inc. 2005-2016. LB100108 Version 37)

2 Detailed description of the qualifications, expertise and/or training

Educated (MSc.), experienced (10 years of clinical practice) and certified (underwent special training how to use Functional electrical stimulation-assisted cycle ergometry) physical therapist delivered the therapy.

3 Describe whether exercises are performed individually or in a group.

Exercises was performed individually.

4 Describe whether exercises are supervised or unsupervised; how they are delivered

Exercise was supervised by senior physical therapist (Ph.D., 20 year of clinical practice, trained in FESCE) and medical doctor (specialised in critical illness, Ph.D., 20 year of clinical practice). The details of therapy are described in Table S1 above.

5 Detailed description of how adherence to exercise is measured and reported

Adherence to exercise was measured by following ways:

- Immediately after the intervention was delivered, the physiotherapist recorded the duration and content of the therapy in electronic case-report form (see Figure S10)
- Throughout the study 20 randomly selected sessions were observed by a hidden observer and objective data on progressive mobility programme time were recorded with physiotherapists self-reported data
- FESCE device automatically records and stores exercise duration, distance travelled (in meters), and energy load (calories).

Figure S10: Electronic Case Report Form to record exercise times

6 Detailed description of motivation strategies

Motivation strategies were dependent on the sedation score. There was no extra motivation for deeply sedated patients, who received passive, reflex and FESCE exercises. Once patients regained consciousness, the therapists talked to them explaining the role of the therapy and gave them psychological support. Motivation strategies, enjoyment of the progress and psychological support were not protocolized in this study. Patients using FESCE had the possibility to observe on the monitor animation of a cyclist and together with the distance travelled, speed and heart rate. Motivation strategies, enjoyment of the progress and psychological support were not protocolized in this study.

7a Detailed description of the decision rule(s) for determining exercise progression

Progression in meeting milestones (such as sitting on the bed, sitting out, stand etc) were dependent on patient's consciousness, cooperativity, muscle power (this can be inferred from Table S1). In addition, the decision to actively mobilise the patient was determined according to consensus recommendations regarding safety criteria for mobilization of adult, mechanically ventilated patients in the ICU (Hodgson et al., 2014).

Most importantly: a fraction of inspired oxygen less than 0.6 with a percutaneous oxygen saturation more than 90% and a respiratory rate less than 30 breaths/minute and normal and stable intracranial pressure were required for in- and out-of-bed mobilization.

7b Detailed description of how the exercise program was progressed

Once the patient was more alert and able to participate, they were encouraged to engage in therapy. To increase the intervention workload, resistance and cycling cadence were increased incrementally. Therapists also corrected the trajectory of the movement by passive corrections or by techniques of neuroproprioceptive “facilitation, inhibition” (e.g. adaptive resistance).

8 Detailed description of each exercise to enable replication

Surface electrodes were applied to the gluteal, hamstrings and quadriceps muscles on both legs according to a regime specified by Parry et al., 2014. In brief, patients underwent warm-up phase (expected length about 5 minutes of passive cycling), therapeutic phase (i.e. functional electrical stimulation or active cycling lasting as driven by meeting daily duration goals and patient’s tolerance), and relaxation phase (expected length about 5 minutes of passive cycling). FES impulses had pulse width 250 μs, pulse frequency 40 Hz, and the lowest output per channel (in a range 0- 60 mA) that allowed locomotive movement of lower extremities60 mA.

9 Detailed description of any home programme component

Not applicable, the program was only delivered at hospital.

10 Describe whether there are any non-exercise components

There are any non-exercise components.

11 Describe the type and number of adverse events that occur during exercise

Pre-specified safety parameters (secondary outcomes) were dialysis interruptions and elevations of intracranial pressure in patients and these are described in the manuscript body.

There were no additional severe periprocedural events such as falls, inadvertent extubations ot line removals in either group.

12 Describe the setting in which the exercises are performed

Face to face individualised physical therapy was delivered at two intensive care unit containing 10 and 11 level 3 beds of a large teaching hospital and admits approximately 1000/year of non-selected medical and surgical critically ill patients.

13 Detailed description of the exercise intervention

Patients were laying supine strapped to a cyclo-ergometer modified for use on a hospital bed. Intervention is in detail described in the Table S!.

14a Describe whether the exercises are generic (one size fits all) or tailored

Details about exercise can be inferred from Table S1. This was a pre-specified exercise programme where physical therapy and FESCE setting was tailored to patients condition.

14b Detailed description of how exercises are tailored to the individual

Interventions were tailored according to consciousness, cooperativity, muscle power and standard safety criteria for mobilization of critically ill patients [9] . Distance and duration of cycling was set by signs of muscle fatigue such as pain, grimace or increase in heart rate.

15 Describe the decision rule for determining the starting level

Starting level was determined according to consensus recommendations regarding safety criteria for mobilization of adult, mechanically ventilated patients in the ICU [9]. Most importantly: a fraction of inspired oxygen less than 0.6 with a percutaneous oxygen saturation more than 90% and a respiratory rate less than 30 breaths/minute and normal and stable intracranial pressure were required for in- and out-of-bed mobilization.

16a Describe how adherence or fidelity is assessed/measured

Adherence to exercise was measured by the FESCE. Parameters as the distance (in meters), the average session duration (seconds) and energy load (calories). Moreover, the therapist recorded detail information about each session into the study protocol. In addition, there was a concealed assessor, who checked the accuracy of self-reported times during 20 random exercises.

16b Describe the extent to which the intervention was delivered as planned

Intervention was delivered in 817 out of 932 (88%) ICU days. During the days where it was delivered, the average daily doses were 80±35, mean daily dose of FESCE was 32±13 min (Figure 2 of the main manuscript).

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