CENTRE HOSPITALIER REGIONAL D'ORLEANS

Study protocol

Clinical trial investigating routine care strategies

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Title

Early and daily electrical muscle stimulation and bedside cycling exercises added to standardized early rehabilitation, compared to standardized early rehabilitation alone. Impact on global muscle strength at intensive care unit discharge. An open-label, single-center, assessor-blinded randomized trial.

Short title : PROMOREA1

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Clinical trial summary

Background: Early mobilization (from the first day if possible), first passive and then passive and active, is recommended for critically ill patients in whom it reduces the duration of mechanical ventilation, length of hospital stay, improves functional status, muscle strength and perceived quality of life in the mid- or long-term. The early addition of muscular work of the lower limbs on a cycle ergometer, and to a lesser extent electrical muscle stimulation of the quadriceps are now part of common practice in some intensive care units (ICU). These interventions should, in theory, through muscle strengthening, further increase the benefits of early mobilization.

Hypothesis: Early electrical stimulation of the quadriceps muscles, and early work on a cycle ergometer associated with a standardized early rehabilitation program (i.e., early passive, then passive/active and as soon as possible fully active mobilization while in the intensive care unit) can improve muscle function and thus reduce the duration of mechanical ventilation, length of ICU stay, readmissions and improve quality of life in the midterm in critically ill patients, as compared with a standardized early rehabilitation program alone.

Primary objective: To show that the adjunction of early electrical stimulation of the quadriceps and early work on a cycle ergometer improves the effects of standardized early rehabilitation, in terms of global muscle strength measured at ICU discharge.

Design: Single-center, pragmatic, add-on, open-label, assessor-blinded, controlled, randomized trial comparing two parallel groups of patients with 1:1 allocation ratio. Analysis will follow a *modified* intention-to-treat approach since the primary endpoint will not be assessable in nonsurvivors at ICU discharge.

Primary endpoint: Global muscle strength assessed by the MRC score (on the day of ICU discharge (+/- 1 day)). A physiotherapist blinded to the randomization group will conduct this assessment.

Key secondary endpoints:

- Functional autonomy at ICU discharge (+/- 1 day) assessed by the *ICU Mobility Scale* (blinded assessment)
- Modification of functional autonomy, as compared to the period before ICU admission, assessed by the Katz index and by the Barthel index at ICU discharge (+/- 1 day) and at six months after ICU discharge.
- Frequency of delirium in the ICU.
- Duration of invasive mechanical ventilation.
- Ventilator-free days from inclusion through Day 28.
- ICU, hospital and Day 28 mortality
- Functional status and perceived quality of life assessed by the SF-36 questionnaire by regular mail or by telephone interview with the patient him/herself at 6 months. Clinical research assistants blinded to the group of randomization will conduct telephone interviews.
- Adverse events during interventions

Inclusion criteria

- Age ≥ 18 years
- Admitted to the ICU less than 72 hours before screening and randomization
- Patient deemed to need more than 48 additional hours of care in the ICU at time of screening
- Sufficient functional autonomy: Barthel's score > 55 within 15 days before ICU admission, assessed by interview of the patient or his/her family/caregivers.

Non-inclusion criteria

- Consent refusal (by patient, family members of legal representative)
- Pregnant Woman
- Cardiac arrest as the cause of ICU admission or cardiac arrest between admission and screening
- Presence of a pacemaker or an implantable defibrillator
- Acute cerebral disease requiring deep sedation for at least 72 hours to prevent secondary brain insult (severe traumatic brain injury, status epilepticus, stroke, and others causes of intracranial hypertension)
- Acute polyradiculoneuropathy (Guillain-Barre syndrome)
- Myasthenia
- Advanced Dementia
- Deep venous thrombosis or pulmonary embolism treated for less than 48 hours
- Contraindication to electrical muscle stimulation and/or leg bicycling, for musculoskeletal and/or dermatological and/or surgical reasons.

- Contraindication to standing and/or transfer to chair
- Amputation of a lower limb

Study population:

We will enroll 157 patients in each arm, i.e. a total of 314 patients, in one single medical-surgical ICU in a 1100-bed teaching regional hospital in France.

Timelines:

Anticipated study duration: 30 months

Anticipated duration of the recruitment period: 24 months

Study duration for a given patient: 1) Intervention period: from inclusion date to ICU discharge; 2) Follow-up period: from inclusion date until six months after ICU discharge.

1. Rationale of the research, expected results and perspectives

1.1 Scope of the clinical problem

Intensive care units are specialized in the care of patients with one or several life-threatening organ failures. About 70-85% of these patients will be discharged alive from the ICU and hospital. Among them, a large proportion will suffer psychological, cognitive and musculoskeletal disorders during weeks, months and even years after ICU discharge (1-4).
Among the survivors of working age only 50% return to work one year after hospital discharge. Cognitive disorders, which occur in about 75% of ICU patients (5), can persist up to several years after returning home, particularly in patients treated for acute respiratory distress syndrome, and are partly responsible for the delayed return to normal activity (6-9).
Musculoskeletal disorders also occur frequently during ICU stay (10,11): A severe and debilitating muscle wasting and decrease in muscle strength occur in 25-50% of ICU patients (10,12,13), particularly in patients treated for severe sepsis, multiple organ failure, or who are subjected to prolonged mechanical ventilation (14).
Several studies have shown that at least half of patients discharged from ICU, regardless of their age, are unable to return to their previous level of physical activity because of muscle weakness and lack of endurance (2,3,15, 16).
The neuromuscular damage and the related muscle weakness result from a combination of inflammation, metabolic disorders such as hyperglycemia and forced muscular rest (bed-ridden patient, sedation, mechanical ventilation) (17-20). Several pathological entities have been described: critical illness polyneuropathy, critical illness myopathy, and damage of the neuromuscular junction. Differential diagnosis between these entities, which can also be intricate, requires making additional tests (21), sometimes including muscle biopsy. In practice they are often included under the generic term "ICU-acquired neuromyopathy", or “ICU-acquired weakness” (ICUAW), and cared for in similar ways.

The causes of ICUAW are complex and include the consequences of forced muscle rest, high levels of cytokines seen in acute inflammatory and infectious diseases, the combined action of drugs such as muscle relaxants and corticosteroids (22), protein-energy malnutrition, electrolyte disturbances and glutamine deficiency (23,24).

Forced muscle rest triggers a cascade of metabolic effects including slowdown of protein synthesis, accelerated proteolysis and myocytes apoptosis that modify the relative proportions of the different types of muscle fibers, alter their contractile properties and reduce their aerobic capacity. The combination of these phenomena induces muscle catabolism, atrophy and weakness (25-30).

The main risk factors for marked ICUAW are severe sepsis, multiple organ failure, hyperglycemia, the need for renal replacement therapy, administration of catecholamines, corticosteroids, muscle relaxants, duration of mechanical ventilation and the female sex (12).

Clinically ICUAW results in a marked decrease in muscle mass, quadri-paresis/plegia with tendon hypo-or areflexia, and frequently in a decrease in respiratory muscle strength (22,30). The forced rest of the respiratory muscles may result in diaphragmatic atrophy, which may be detected as soon as within the first 24 hours of mechanical ventilation (14,31).

Consequently, ICUAW may result in difficult/prolonged weaning from ventilator, thus increasing the time spent under mechanical ventilation, in the ICU and in hospital. This prolongs the time period during which the patient is exposed to potentially lethal complications (nosocomial infections especially ventilator-associated pneumonia, aggravation of muscle atrophy further extending the duration of mechanical ventilation, etc.) (11, 13). Peripheral and respiratory muscle damages derive from the same pathophysiological mechanisms. Indeed, difficult weaning from the ventilator and the frequency of re-intubation related to insufficient cough strength seem correlated to impaired peripheral muscle function (13) assessed by the MRC (32) Score (Medical Research Council of the United Kingdom 1978, *see Appendix 1*).

Ways to prevent ICUAW are few. Until recently, only intensive insulin therapy seemed to be beneficial (24). Unfortunately, this intervention brings side effects including profound hypoglycemia, which can result in increased mortality (33).

While the benefits of physical activity on survival time, cognitive and physical performances are well established in patients outside the ICU (34-37), it is only recently that the mobilization of the musculoskeletal system, passive and / or active, known to prevent muscle deconditioning, has emerged as a way to prevent ICUAW and long-term cognitive dysfunction (9,18,38-43). The fear of side effects during mobilization of unstable ICU patients expressed by some teams is unfounded since many studies have demonstrated the feasibility and the safety of early mobilization programs (37,44-47).

In a clinical trial conducted in 330 patients receiving mechanical ventilation for acute respiratory failure, Morris et al (40) showed that passive and active mobilization (adapted to the patient's arousal/responsiveness) of all limb segments at least once a day, transfer to chair and standing position as soon as technically possible shortened ICU and hospital stay, without inducing additional costs. Early mobilization seemed to protect from death or re-hospitalization in the year following ICU discharge (48).
Burtin et al (49) compared daily bedside bicycling on a cycle ergometer added to early mobilization versus early mobilization alone in 90 patients. At hospital discharge, quadriceps strength, distance walked in 6 minutes and the proportion of patients returning home were significantly greater in patients who cycled than in those who did not. Overall patients of the bicycling group felt better and had better quality of life at hospital discharge.
Schweickert et al (41), in a randomized trial in 104 mechanically ventilated patients, also showed that the application of mobilization made as early as possible by daily interruption of sedation resulted in more frequent return to functional autonomy at hospital discharge, lower incidence of delirium during ICU stay, shorter period of mechanical ventilation, and more frequent return to home.
The above trials and some observational studies allow to state that the early mobilization of ICU patients, even when they are still treated by mechanical ventilation is feasible and safe (38,40,41,50).

In 2013, an expert panel of the French Intensive Care Society (Société de Reanimation de Langue Française – SRLF) professional recommendations, edited guidelines regarding the indications of all mobilization techniques used in the ICU (51). The experts strongly agreed on the need for early mobilization in ICU patients. Their key recommendations were:
• Unconscious patients without voluntary motor activity should be mobilized early to prevent tendon contractures and maintain range of motion.
• Active mobilization should be proposed to conscious and cooperative patients
• Patients should be sit in bed as soon as possible, even if treated by mechanical ventilation
• Patients should be put in a standing position as soon as their recover sufficient muscle strength and if technically possible, even if treated by mechanical ventilation
• Early mobilization programs should be progressive and adapted to the patient's tolerance and cooperation

Other recommendations are based on weaker scientific evidence (their impact on important patient's outcomes such as length of stay, duration of mechanical ventilation or quality of life has been insufficiently studied) and are therefore more nuanced (51):
• Early standing on a tilt table should probably be proposed
• Early passive, passive/active and then active bicycling on cycle ergometer (pedaling in bed) should probably be proposed
• Early passive, passive/active and then active transfer to chair, even if treated by mechanical ventilation, should probably be proposed
• If the patient can not participate in an active program early, electrical muscle stimulation should probably be proposed.

Pedaling on a cycle ergometer can increase endurance during exercise by reconditioning the cardiovascular system. When combined with other rehabilitation techniques, observational studies and randomized trials have shown that it can improve muscle metabolic conditions, the strength of contraction of the quadriceps and the quality of life in the midterm (49,52). This bicycling exercise has no reported adverse side effect and can be safely applied even to patients still under inotrope or vasopressor therapy (53). Despite these encouraging results, bed or chair bicycling have been insufficiently studied in ICU patients. In the few studies available, pedaling was associated with other rehabilitation techniques. This explains why experts strongly recommend that additional studies be conducted (51).

Electrical muscle stimulation can cause involuntary muscle contractions through low voltage electrical pulses issued via transcutaneous electrodes stuck to the skin (54). It has proven effective against muscle atrophy in healthy subjects (55), and increases muscle strength and endurance in patients with chronic obstructive pulmonary disease (56). No studies have yet demonstrated the benefit of adding an electrical muscle stimulation program to early mobilization in critically ill patients. Conflicting results have been reported (57-62) regarding the beneficial effects in the short and mid-term, but studies are consistent on one point, the lack of significant adverse side effect of electrical stimulation. Of note, electrical stimulation does not result in significant cardiovascular changes if conventional contraindications such as the presence of a pacemaker/implantable defibrillator are taken into account (62).

1.2 Objectives

1.2.1 Main Hypothesis

Early electrical stimulation of the quadriceps, and early work on a cycle ergometer associated with a standard early rehabilitation program (i.e., early passive, then passive/active and as soon as possible fully active mobilization while in the intensive care unit) can improve muscle function and thus reduce the duration of mechanical ventilation, length of ICU stay, readmissions and improve quality of life in the midterm in critically ill patients, as compared with a standard early rehabilitation program alone.

1.2.2 Main objective

The main objective of the study is to show that the combination of early electrical stimulation of the quadriceps and early work on a cycle ergometer improves the effects of early mobilization in ICU patients, in terms of global muscle strength assessed at ICU discharge time.

1.2.3 Secondary Objectives

Secondary objectives are to compare the duration of mechanical ventilation, the frequency of delirium, functional autonomy, and quality of life at ICU discharge and six months after, between the two groups of patients: those treated with electrical muscle stimulation (ES) and work on a cycle ergometer (CE) in addition to standard early rehabilitation program (SERP) ("intervention" group), and those treated with SERP alone ("usual care" group).

2. Endpoints

2.1 Primary endpoint

Global muscle strength assessed by the MRC score (on the day of ICU discharge (+/- 1 day)). ***A physiotherapist blinded to the randomization group will conduct this assessment.***

2.2 Secondary endpoints:

- Functional autonomy at ICU discharge (+/- 1 day) assessed by the *ICU Mobility Scale* (63) (blinded assessment)
- Frequency of delirium in ICU. Delirium is defined by the CAM-ICU scale (**Appendix 2**) (64,65).
- Modification of functional autonomy, as compared to the period before ICU admission, assessed by the Katz scale (**Appendix 3**) (66) and by the Barthel Index (**Appendix 4**) (67) at ICU discharge (+/- 1 day) and at six months after ICU discharge.
- Duration of invasive mechanical ventilation.
- Ventilator-free days from inclusion through Day 28.
- Proportion of patients who needed re-intubation in the ICU
- ICU, hospital and Day 28 mortality rates
- Functional status and perceived quality of life assessed by the SF-36 questionnaire by regular mail or by telephone interview with the patient him/herself at 6 months. ***Clinical research assistants blinded to the group of randomization will conduct telephone interviews.***
- Change in the thickness of the *rectus femoris* muscle of each thigh, measured by ultrasound (68,69) between inclusion date and ICU discharge date (+/- 1 day) .
- **Safety:** Adverse events during interventions
- Analysis of subgroups: the study will be sized to assess the effect of the intervention on the primary endpoint in patients discharged alive from the ICU, who were mechanically ventilated, and among

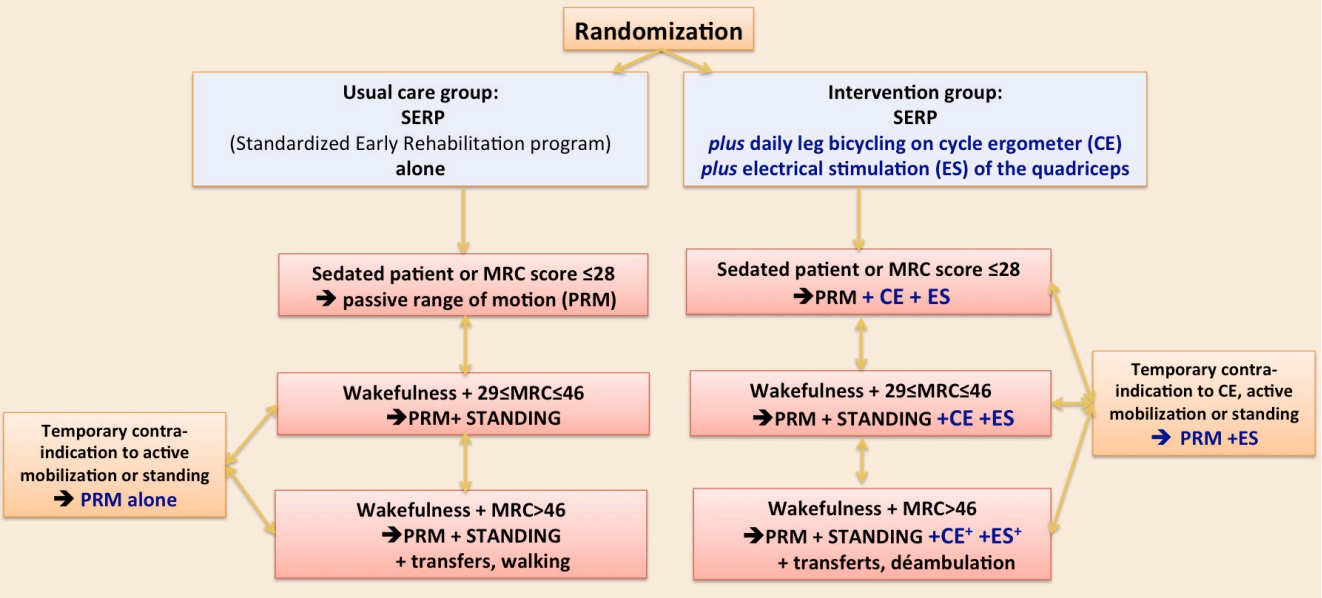
them in the subset of patients who were admitted in the ICU on weekdays other than Thursday or Friday (see below: "Mitigation of bias" chapter).

3. Interventions

One group of patients (usual care group) will receive SERP 5 days/week as part of routine care.
One group of patients (intervention group) will be applied Early Electrical muscle stimulation (of the quadriceps) and Early bedside leg bicycling on a cycle ergometer added to SERP

In both arms of the study, the SERP will be a progressive multistep program beginning with 10 passive range of motion of each limb joint applied once every weekday by physiotherapists to comatose/sedated patients, followed by passive/active muscle exercises, transfer to the edge of the bed or to chair, standing and walking, depending on the patient's cardio-respiratory status, level of wakefulness, cooperation and muscle strength. Global muscle strength will be assessed each weekday by physiotherapists.

3.1 Programs of rehabilitation used in both groups are exposed in the following figure and detailed below



3.2 Description of the modalities of daily adaptation of the rehabilitation programs to the patient's level of cardio-vascular impairment, consciousness, cooperation, muscle strength and tolerance:

3.2.1 Usual care group (Standardized Early Rehabilitation Program: SERP)

- *Sedated patient (Ramsay score> 3 (70) and Richmond Agitation-Sedation Scale (RASS) <0 (71)) or MRC≤28:*
  Passive motion of all limb joints repeated 10 times in all degrees of freedom (except extension of hips and shoulders), every weekday (not possible on Saturday and Sunday)

- *Patient in the awakening phase and 29≤MRC≤46:*
  Every weekday (not possible on Saturday and Sunday)
  Assisted active mobilization: 5 contractions in all degrees of freedom of all limb joints (except extension of hips and shoulders).
  Raising on tilt table ("standing")

- *Patient in the awakening phase and 47≤MRC:*
  Every weekday (not possible on Saturday and Sunday)
  Assisted active mobilization: 5 contractions in all degrees of freedom of all joints (except extension of hips and shoulders).
  Raising on tilt table ("standing")

- *Awake and 29≤MRC≤46:*
  Every weekday (not possible on Saturday and Sunday)
  Assisted active mobilization: 5 contractions in all degrees of freedom of all joints (except extension of hips and shoulders).
  Multistep transfer program beginning by sitting on the edge of the bed. The good tolerance of each exercise allows trying the next step on the next day:
  - Sitting on the edge of the bed
  - Transfer to chair
  - Standing on a tilt table or in front of the chair
  - Active work of the lower limbs (flexion/extension of the knees; stand on tiptoe) while standing beside the chair with upper limb support and support from at least one physiotherapist.
  - Assisted walking by two caregivers, with or without technical assistance (walker, crutches)

- *Awake and* 47≤MRC:
  Every weekday (not possible on Saturday and Sunday)
  Active mobilization: 5 contractions in all degrees of freedom of all joints (except extension of hips and shoulders).
  Multistep transfer program beginning by sitting on the edge of the bed. The good tolerance of each exercise allows trying the next step on the next day:
  - Sitting on the edge of the bed
  - Transfer to chair
  - Standing on a tilt table or in front of the chair
  - Active work of the lower limbs (flexion/extension of the knees; stand on tiptoe) while standing beside the chair with upper limb support and support from at least one physiotherapist.
  - Assisted walking by two caregivers, with or without technical assistance (walker, crutches)

3.2.2 Intervention group: SERP *plus* Electrical Muscle Stimulation (ES) of the quadriceps *plus* bedside leg bicycling on a cycle ergometer (CE)

Same protocol as above (SERP), *plus*:

- *Sedated patient (Ramsay score> 3 and RASS <0) or in awaking phase and MRC≤28:*
  Passive leg bicycling on a cycle ergometer (MOTOmed letto2, RECK-Technik, Betzenweiler, Germany), each weekday for 15 minutes (protocol in **Appendix 7**)
  Electrical stimulation of the quadriceps following the 54-min "atrophy prevention program" of the manufacturer of the 4-chanel electrical stimulator (Rehab 400, CefarCompex, DJO France, Mouguerre, France) (**Appendix 8**), once a day, each weekday

- *Patient in the awakening phase and 29≤MRC≤46:*
  Active/passive leg bicycling on cycle ergometer, each weekday for 15 minutes (protocol in Appendix 9)
  Electrical stimulation of the quadriceps following the 54-min "atrophy prevention program" (Appendix 8), once a day, each weekday.

- *Awake patient and 29≤MRC≤46:*
  Active/passive leg bicycling on cycle ergometer, for 15 minutes each weekday (protocol in Appendix 9).
  Electrical stimulation of the quadriceps following the 54-min "atrophy prevention" program (Appendix 8), once a day, each weekday.

- *Awake and* 47≤MRC:
  Active leg bicycling on cycle ergometer (30-second working phase and 1-min recovery), in bed or in chair, for 15 minutes each weekday (protocol in **Appendix 11**) (protocol referred as CE+ in figure above).
  Electrical stimulation of the quadriceps following the 20-min "muscle building" program of the manufacturer (referred as ES+ in the figure above) (**Appendix 10**) once a day, each weekday.

3.3 Criteria for temporarily delaying the mobilization program

3.3.1 Cases where electrical muscle stimulation it is still possible

In both groups, the following pathological conditions should lead to temporary interruption of all mobilization actions, except electrical muscle stimulation. The presence or absence of these conditions will be reassessed 2 times a day in order to resume the mobilization program as soon as possible (The existence of one of these conditions is not a criterion for non-inclusion in the study):

- Cardio-vascular system
  - Mean arterial pressure <65 mmHg
  - Systolic arterial pressure > 180 mmHg
  - Heart rate> 135 or <45 b./min
  - Acute arrhythmia
  - Need of vasopressor therapy (continuous iv norepinephrine + epinephrine dosage > 0.5 µg/kg/min
  - Suspected or confirmed acute myocardial ischemia
  - Extra-Corporeal Membrane Oxygenation
  - Intra-aortic balloon counter pulsation triggered by blood pressure signal
- Respiratory system
  - Respiratory rate <8 or > 36/min
  - SpO2 <90% (or <88% in COPD patient)
  - Presence of a chest tube with persistent air leak
- Anemia (Hemoglobin level <7 g/dL)
- Hemodialysis or hemodiafiltration ongoing
- Agitation (RASS score> 1) (**Appendix 2**)

3.3.2 Cases in which electrical stimulation is temporarily contraindicated:

- Intra-aortic balloon counter pulsation triggered by ECG signal
- QRS-inhibited temporary cardiac pacing

3.4 Criteria that should lead to the temporary interruption of the ongoing mobilization action

- Cardio-vascular system
  - Mean arterial pressure <65 mmHg
  - Systolic arterial pressure > 180 mmHg
  - Heart rate> 135 or <45 b./min
  - Acute arrhythmia
  - Need of vasopressor therapy (continuous iv norepinephrine + epinephrine dosage > 0.5 µg/kg/min
  - Suspected or confirmed acute myocardial ischemia
  - Extra-Corporeal Membrane Oxygenation
  - Intra-aortic balloon counter pulsation triggered by blood pressure signal
- Respiratory system
  - Respiratory rate <8 or > 36/min
  - SpO2 <90% (or <88% in COPD patient) despite increased oxygen flow or increased FiO2
  - Presence of a chest tube with persistent air leak
- Agitation (RASS score> 1) (**Appendix 2**)
- Muscle fatigue or poor tolerance expressed by the patient (major dizziness, shortness of breath, pain, etc.)
- Any other event or condition that requires stopping the current mobilization action according to the physiotherapist, nurse or physician in charge.

In the event where a mobilization session has been interrupted for one or several of the above reasons, the patient's clinical condition will be reassessed as soon as possible and the mobilization action resumed if possible.

4. General design of the study

The study will be a single-center, pragmatic, add-on, open-label, assessor-blinded, controlled, randomized trial comparing two parallel groups of patients with 1:1 allocation ratio. Analysis will follow a *modified* intention-to-treat (mITT) principle (instead of full ITT approach) since the primary endpoint will not be assessable in nonsurvivors at ICU discharge.

4.1 Rationale for the chosen study design

Blinding of patients and caregivers is not technically possible.
The primary endpoint, the MRC score, may be fraught with some degree of subjectivity.
Randomization and assessment of the MRC score by a person blinded to the treatment group should minimize selection and information bias.

4.2 Randomization

We will use a randomized block design, stratified by
1) sex,
2) respiratory status of the patient on the day of inclusion (invasive mechanical ventilation or not),
3) day of ICU admission (Thursday/Friday versus other days).

Each randomization block in each stratification group will be designated to randomly assign the patients, in a 1:1 ratio, to either the usual care or the intervention group.

Randomization lists will be created by a Clinical Research Assistant (CRA), using the StatsDirect software (version 2.7.9, StatsDirect, Altrincham, UK), in blocks of 4 or 6 patients. Investigators will not be aware of the size of the randomization blocks.

Allocation concealment:
The CRA will prepare eight groups of sealed and opaque envelopes:

- "Thursday/Friday, woman, non-ventilated" group
- "Thursday or Friday, woman ventilated" group
- "Other Day, woman, non-ventilated" group
- "Other Day, woman, ventilated" group
- "Thursday/Friday, man, non-ventilated" group
- "Thursday or Friday, man ventilated" group
- "Other Day, man, non-ventilated" group
- "Other Day, man, ventilated" group

The envelopes will contain for each enrolled patient, the assigned treatment (“SERP” or “SERP+CE+ES”) on a printed sheet that the investigator will date, sign and store it in the patient record. Each envelope will contain, printed on the outside, an alphanumeric identifier: 4 letters identifying the stratification group, and a 3-digit number (order number in a given stratification group).
The 8 randomization lists will be retained by a CRA (not involved in the conduct of the study) to verify at the end of the study that the random allocation of treatment has not been violated.

At each inclusion of a patient, the investigator, or a person delegated by him, will open the envelope containing the smallest item number in the appropriate group of stratification. The investigator will write in the patient's record the assigned treatment group (“SERP” or “SERP+CE+ES”), and will transmit it to the physiotherapists’ team.
The patient will be identified by the alphanumeric code of the envelope and its rank of randomization.
For example: if it is the ninth patient included in the study, and the third of the "Thursday or Friday ventilated Man" group, its identification number will be "JVHV003009." If this is the 105th patient in the study group and the 27th "Another Day, Woman, Not Ventilated ", her ID number will be “AJFN027105”. (*in theses alphanumeric numbers J and V stand for “jeudi” and “vendredi” (Thursday and Friday), AJ stands for “autre jour” (other day), H stands for “homme” (man), F for “femme” (woman), V for “ventilated” and N for “not ventilated”*).

5. Subject selection

5.1 Inclusion criteria:

- Age ≥ 18 years
- Admitted to the ICU less than 72 hours before screening and randomization
- Patient deemed to need more than 48 additional hours of care in the ICU at time of screening
- Sufficient functional autonomy: Barthel's score > 55 within 15 days before ICU admission, assessed by interview of the patient or his/her family/caregivers.

5.2 Non-inclusion criteria:

- Consent refusal (by patient, family members of legal representative)
- Pregnant Woman
- Cardiac arrest as the cause of ICU admission or cardiac arrest between admission and screening
- Presence of a pacemaker or an implantable defibrillator
- Acute cerebral disease requiring deep sedation for at least 72 hours to prevent secondary brain insult (severe traumatic brain injury, *status epilepticus*, stroke, and others causes of intracranial hypertension)
- Acute polyradiculoneuropathy (Guillain-Barre syndrome)
- Myasthenia
- Advanced Dementia
- Deep venous thrombosis or pulmonary embolism treated for less than 48 hours
- Contraindication to electrical muscle stimulation and/or leg bicycling, for musculoskeletal and/or dermatological and/or surgical reasons.
- Contraindication to standing and/or transfer to chair
- Amputation of a lower limb

NB: This research is qualified as a study investigating routine care strategies, so that, according to French Law, patients under guardianship can be enrolled.

6. Mitigation of bias

Logistically and technically, sham electrical muscle stimulation and sham bicycling are not possible so that patients, investigators, charge nurses and auxiliary nurses will not be blinded to the assigned treatment group.

Measures taken to minimize selection, attrition, and information biases:

Recruitment

To minimize selection and attrition biases, the investigators will seek to include all eligible patients during the study period. To verify that patients are not selected and that the enrolled sample is representative of the general population of eligible patients, a prospective screening will be performed by CRA and research nurses on a daily basis.

Randomization and blinded assessment of the primary outcome measure

These measures should minimize or avoid information bias.

Stratification

- Stratification by sex and respiratory status on the day of inclusion should increase the comparability of the groups.
- Stratification on sex is justified by the fact that female sex has been identified as a risk factor for ICUAW in some studies.
- Until now randomized trials investigating the effect of early rehabilitation in the ICU have been limited to mechanically ventilated patients, and their main objective was to determine if early rehabilitation could speed up the withdrawal of respiratory support. In our study, since the primary endpoint is the patient's global muscle strength at ICU discharge, there is no conceptual reason not to also study not ventilated patients. At the end of study, stratification on the respiratory status will make interventions to be well balanced between groups and will allow to study the effect of the intervention in both not ventilated and ventilated groups separately.

- Like in most studies of early rehabilitation in the ICU, it will not be possible, for reasons of availability of staff including physiotherapists, to apply the different interventions on Saturday and Sunday. Thus, patients admitted and included on Thursday or Friday will not benefit of at least 2 days of mobilization exercises within the 3 calendar days following admission. In these cases, early rehabilitation will not be, strictly speaking, actually early. Those patients should represent about 29% of the study population. Assessing the effect of the tested interventions in the subgroup of patients with full application of the assigned intervention will need well-balanced allocation of treatment in this subgroup. This is why we chose to stratify on the day of the week ("Thursday or Friday" *versus* "Another Day").

Standardization of sedation-analgesia and ventilator weaning process

This is very important because the ways to manage sedation and ventilator weaning greatly affect the duration of ventilation, the length of stay and the occurrence of delirium in the ICU, which constitute secondary endpoints of the study. Moreover, the duration of sedation determines the time at which the patient's wakefulness will allow active mobilization, which may directly influence changes in muscle mass and strength, i.e. the primary endpoint chosen for the study.

Withdrawal of sedation-analgesia

In our ICU we follow a Standardized Operational Procedure to daily interrupt sedation-analgesia, jointly managed by nurses, residents and senior physicians. It will be applied as usual, by the morning of the second day of hospitalization in patients receiving continuous intravenous sedation-analgesia. The procedure is to discontinue treatment with iv benzodiazepine (or propofol) every morning and to halve the dose of intravenous opioid analgesia (fentanyl) every morning, and to adjust the dosages of these drugs according to the state of agitation and pain reported by the patient (agitation is assessed by the RASS and pain is assessed by the Behavioral Pain Scale in non communicant patients). It aims to prevent overdoses and accumulation of analgesic and sedative drugs, ensure patient comfort, prevent ICUAW, and to avoid undue prolongation of the period of invasive mechanical ventilation.
Reasons for not applying this usual procedure will be notified in the patient's record.

Respirator weaning

A Standardized Operational Procedure to assess whether a patient is "weanable" and to conduct the weaning process, jointly managed by therapists, residents and senior physicians will be applied as usual, by the morning of the second day in mechanically ventilated patients. This procedure should aim to avoid undue prolongation of the period of invasive mechanical ventilation. It involves placing the patient under Pressure Support mode set to 10 cm H2O and end-expiratory pressure set at 5 cm H2O) as soon as the patient is sufficiently alert (Ramsay score ≤3 [Appendix 6]). If the strength of cough, oxygenation and Pressure Support tolerance are judged sufficient or sufficiently improved, then a spontaneous breathing trial (SBT) through endotracheal tube is performed at least 2 times a day. When tolerance of SBT is judged good or sufficient, the patient is extubated (including at night).
In order to verify the proper application of this procedure, the source file and the case report form will include the daily recording, throughout the period of invasive mechanical ventilation, of:

- Use midazolam, propofol, fentanyl, remifentanil intravenous: Yes or no
- Change to Pressure Support mode: Yes or no
- Switch to Pressure Support mode with pressure support of 10cmH2O and PEEP 5cmH2O: Yes or no
- SBT performed: Yes or no
- Good tolerance of SBT: Yes or no
- Extubation: Yes or no, if yes, time
- In cases where the patient would not be extubated despite well tolerated SBT, the reason(s) should be notified in the patient's record.

7. Sample size

Our primary endpoint, the MRC score, is often expressed in the literature as median and interquartile (IQR) because of its non-normal distribution in most cases.
In the Schweickert et al's study (41), the MRC score was 52 in the intervention group and 48 in the control group.
We hypothesize that we will also observe such a difference and that for 70% of the ordered pairs, the MRC score will be higher in the SERP+CE+ES group (intervention group) than in the SERP group (usual care group). This will be assessed by the nonparametric Wilcoxon-Mann-Whitney test. To show that this difference is

statistically significant with an alpha risk set at 5% and power set at 90%, it is necessary to include at least 45 patients per group.
The primary outcome will be assessable only in patients discharged alive from the ICU.
In addition, we plan to examine 1) the effect of the intervention on the primary outcome in the subgroup of ICU survivors who have been ventilated invasively during ICU stay and 2) in mechanically ventilated survivors who have been admitted in the ICU another day than Thursday or Friday. Considering that 65% of patients will be ventilated, that the mortality rate in these patients will be about 30% and that 71% of patients will be admitted another day than Thursday or Friday, this will need to randomize a minimum of 141 patients per group to obtain 45 patients per group in the smallest subgroup to analyze.
Assuming that 10% of patients will not be analyzable (assessment of MRC at discharge not possible, or consent withdrawal), we plan to include 157 patients per group, i.e. a total of 314 patients.

8. Expected duration of participation of subjects involved in research

8.1 Duration of Study

If case of acceptance of the request made to the Ethical Committee (*Comité de Protection des Personnes, Ouest-1, Tours, France*) to allow the "in emergency" inclusion of patients unable to consent themselves and to waive the need of family (or legal representative) consent if family members are not present nor reachable by phone on the day of admission, the enrolment of 314 patients is feasible in a 12-mo period, which we extend to 24 months.
The anticipated duration of the study is approximately 30 months, from the day of enrollment of the first patient to the end of the 6-mo follow-up of the last study patient discharged (not including the time needed for data analysis).
For a given patient, the duration of study extends from the date of his/her inclusion to 6 months after his/her discharge from the ICU.

8.2 Rules for stopping the research

The sponsor (Centre Hospitalier Régional d'Orléans) can decide to stop the study without justification.
At the request of a member or of an investigator, the scientific committee can decide to stop the study in case of unforeseen events jeopardizing patients' safety or the feasibility of the study. In this case, the principal investigator must inform the sponsor immediately.

8.3 Exclusion rules for a given patient

Patients secondarily expressing their opposition to participation in the study will be excluded and their data collected for the purpose of the study will be destroyed. These patients will be excluded from the analysis.
If after being included it turns out that the patient has a permanent contraindication to active muscular work or electrical stimulation, the study procedures will be stopped. The data collected will be stored and assessment of primary endpoint performed if possible. These patients will be included in the main analysis (modified intention-to-treat analysis").
The following events or circumstances may constitute reasons for exclusion and to stop the study procedures after consultation between investigators, physicians, physiotherapists, and nurses:

- Unplanned placement of a pacemaker or implantable defibrillator after inclusion
- Unplanned veno-venous or veno-arterial ECMO initiation
- Post-inclusion onset of acute cerebral disease requiring deep sedation for at least 72 hours to prevent secondary brain insult (severe traumatic brain injury, *status epilepticus*, stroke, and others causes of intracranial hypertension)
- New contraindication to electrical muscle stimulation and/or leg bicycling, for musculoskeletal and/or dermatological and/or surgical reasons, that would prevent the application of bicycling exercise and/or electrical stimulation and/or standing and/or transfer to chair for at least 3 consecutive days.
- Limb amputation after inclusion

In any case these events should be reported in the patient's medical record.

9. Matrix of scheduled procedures and visits

	Inclusion Visit 1	Nth visits	ICU discharge visit	Last visit at 6 months after ICU discharge
DAYS :	Day 1 (calendar day of inclusion)	D2, D3, etc. (calendar days)	Discharge day	*D180*
Screening visit	X			
Information of patient and/or family, obtain informed consent (or « in emergency inclusion as allowed by the Ethical Committee)	X	X	X	X
Randomization : Investigator opens the randomization envelope with the smallest number in the stratification group to which the patient belongs	X			
Additional lab tests or radiographies	none	none	none	
Application of the assigned intervention	If possible	**Every weekday**		
Clinical exam including delirium (CAM-ICU) assessment, respiratory status, ventilator weaning attempts, extubation, sedation…	X	**Every day**		
Measurement by ultrasound of the thickness of the muscle *rectus femoris* of both tights	X (within first 48 hours)		X (+/- 1 day)	
« ICU mobility scale » blinded assessment			X	
Primary endpoint assessment (patient's global musle strength assessed by the MRC score blinded measurement)			**X (+/- 1 day)**	
Blinded assessment of ▪ Barthel score ▪ Katz index ▪ SF-36 questionnaire	 X X -		 X X -	 X X X

Patients will be followed daily during their ICU stay.
Their survival status will be collected at ICU discharge, hospital discharge, and day180.

10. Risks and benefits

10.1 Risks

The risks associated with the practice of early mobilization are minimal. Indeed, adverse events reported in the literature are very infrequent and/or of very low severity (43). In the Bailey et al's study (38), among 1449 mobilization procedures (passive or active in bed, sitting on the edge of the bed, passive standing, or transfer to chair) applied to 103 ventilated patients, less than 1% of adverse events were recorded, and in all cases without consequences for the patient. No unplanned extubation was recorded. The events were essentially changes in pulsed oxygen saturation (SpO2), heart rate, blood pressure, which exceeded predetermined safety boundaries. The frequency and severity of adverse events were similar in the study by Bourdin et al (72). Pohlman et al (42) reported no unplanned extubation in 49 mechanically ventilated patients but a rather high frequency (16%) of adverse events that was due to very stringent predetermined cardiovascular and respiratory safety limits. These events needed interruption of the ongoing mobilization action in only 4% of the cases, with no adverse consequences for the patients. In a group of surgical ICU patients, carrying various drainage tubes, external fixation materials or complex dressings, early mobilization caused no adverse reaction (73). Even in the most severe patients treated with mechanical ventilation and ECMO, adverse events are extremely rare (43, 73-77).
Pedaling on a bedside cycle ergometer, even in patients still exhibiting a certain degree of cardiovascular impairment, seems to cause no significant adverse events (53).
Provided that contraindications are respected, the use of electrical muscle stimulation in critically ill patients does not cause side effects, including no cardiovascular effect (62). Furthermore, since we began to hold

regular morbidity and mortality rounds in 2008 in our ICU (78,79), no critical adverse events related to any mobilization or physiotherapy action has been reported.
These data allow us to confidently state that the early mobilization procedures planned in the present study (including bicycling and electrical muscle stimulation), which we consider as routine care procedures, bring very minimal risk.

10.2 Benefits

Evidences are now accumulating for the beneficial effect of early mobilization on the duration of mechanical ventilation, muscular strength and endurance, and quality of life in the mid term (43,51,80,81). This explains why early mobilization is now part of routine care in the ICU. The addition of bicycling exercises on a cycle ergometer (49,52) and of electrical muscle stimulation (56), which may further improve endurance and muscle performance, might logically strengthen the beneficial effect of standard early mobilization.

10.3 Benefits to risk ratio

The patients enrolled in the present study will all undergo an early mobilization program. Therefore, there is no benefit associated with this procedure in one group compared to the other. Because of the randomized 1:1 allocation of interventions, half of the patients will also undergo daily working sessions on a cycle ergometer and electrical muscular stimulation added to standardized early mobilization. In these patients we expected at least an improvement in global muscle strength at the end of the ICU stay.
Because risks related to the tested interventions are minimal, we consider that the benefits/risk ratio is favorable.

11. Safety evaluation criteria

We will ask the Ethic Committee to qualify the research as a « research on routine care » (within the meaning of the French Law) that brings minimal risks to patients. In this case, the French Law does not require specific procedures concerning adverse events.
However, any suspected unexpected adverse event or reaction (SUSAR) must be reported to the investigator and the sponsor: SUSAR could be new safety information which could lead to re-evaluation of the benefits/risk ratio of the study, or which may be sufficient to envisage modifications to documents concerning the study, to the way the study is conducted, or, if necessary, to the way studied strategies are applied.
All suspected unexpected serious adverse reaction and any serious adverse events possibly related to the research will be reported by the sponsor to the competent authorities and the Ethic Committee.
The investigators of the research must be informed of any unexpected serious adverse reaction.

11.1 Terms and duration of monitoring after the occurrence of unexpected adverse events.

All these events must be monitored until they are completely resolved or stabilized.

12. Data Management

The study data will be collected in a single hand-written report form for each patient. Investigators, nurses, research nurses and physiotherapists involved in the study will be responsible of the prospective data collection.
The data collected in the case report form will be recorded by CRAs in a computerized spreadsheet with frequent storage of back-up copies on hard disks.

13. Strategy of data analysis - Statistics

The analysis will include descriptive statistics for each quantitative variable (arithmetic mean and standard deviation or median and quartiles depending on the normal or not normal distribution of values; range, number of missing values). Categorical variables will be expressed by their frequency and 95% confidence interval.

Groups will be compared using
- Wilcoxon-Mann-Whitney test for the primary endpoint
- Fisher's exact test or chi^2 for categorical secondary endpoints
- Student's t test or nonparametric tests as appropriate for quantitative secondary endpoints.

The primary analysis of the primary endpoint will follow a planned *modified* intention-to-treat (mITT) principle: all included patients discharged alive from the ICU and who did not withdraw consent will be analyzed according to the treatment group to which they were originally assigned (Note that in the present study we anticipate non contamination bias). This is justified by the fact that the MRC score, the primary endpoint, will not be assessable at ICU discharge in non-survivors. We deliberately planned not to impute missing data related to non-surviving patients and not to study imputed data sets corresponding to plausible or extreme scenarios because we anticipate too much (on a statistical point of view) ICU deaths (around 20-35%) to allow confident interpretation of results drawn from imputed data sets analyses.

Missing data concerning the primary endpoint will not be replaced.
A two-tail p-value less than 0.05 will be retained as significant.

Several per-protocol analyses will be performed:
In the study population restricted to patients who actually received the allocated intervention at least 2 days during the first three days of the study.
In the study population restricted to patients who actually received the allocated intervention at least 80% of the week days days spent in ICU.

Several subgroup analyses will be performed:
The mITT and per-protocol analyses will be repeated 1) in patients who received invasive mechanical ventilation during the ICU stay and in those who did not, 2) in male and female patients separately, 3) in patients admitted on Thursday or Friday and those admitted on another day separately.

Despite most subgroups of patients will be sufficiently sized to detect a between-group difference in primary endpoint at the $p<0.05$ level and power of 80%, we plan no adjustment for multiple testing, so that subgroup analyses will be considered exploratory. For the same reason, the analyses of the secondary endpoints will also be considered exploratory.

Like the study design, statistical analysis and reporting will conform to the CONSORT Statement (82-84).

14. Feasibility of the study

The feasibility of the proposed study is based on 1) the ability of investigators of the involved ICU to recruit patients, and 2) their experience regarding inclusion and conduct of interventional randomized studies in the field of critical care.

Recruitment

The involved ICU admits more than 900 patients per year,. About 65% of ICU patients are mechanically ventilated. 25 to 35% of them die in the ICU.
The number of patients with pacemakers or implantable defibrillator is estimated around 5% and the number of patients with other non-inclusion criteria is estimated to be around 20%.
It is reasonable to foresee the inclusion of 314 patients during a period of 12-18 months.

Experience in clinical research

The involved ICU has included more than 500 patients in multicenter randomized trials (industrial and academic) since 2008, and has been actively involved in major trials performed in French ICUs.

15. Committees of the study

15.1 Scientific Committee

Members of the scientific committee have designed the research protocol. The Committee may decide the temporary or permanent discontinuation of the study.

15.2 Independent Monitoring Board

There is no provision for the establishment of an independent monitoring committee for this research investigating routine care strategies and carrying minimal risk.

16. Legal and Ethical Considerations

16.1 Ethical Committee

In accordance with the French law, this interventional study investigating routine care will be subject to the prior authorization of the competent *Comité de Protection des Personnes (CPP Ouest 1, Tours, France).*

16.2 Rationale for the qualification of the research as "investigating routine care" (in the meaning of the French law)

Below are the reasons why we consider the study as "investigating routine care" according to the definition given by Law No. 2004-806 of 9 August 2004 of the Public Health Law and its implementing decree (No. 2006-477) of 26 April 2006 (Articles L.1121-1, 2nd paragraph and R1121-3 of the Code of Public Health).

All eligible patients are ICU patients for whom early mobilization is usually proposed in the context of routine care.
No additional lab test or radiography is needed for the purpose of the study.
Early mobilization is performed regularly by physiotherapists in the involved ICU and also commonly performed in many ICUs in France and worldwide (51,85). Electrical muscle stimulation is also practiced for several years in our ICU. This is a technique of care practiced in many ICUs (86), although the benefits it can bring to patients warrant further investigations (51), which is the purpose the present study. The work of bedside bicycling on a cycle ergometer is now part of routine care in many ICUs in France. In Canadian ICUs (87) or in Holland (88), bedside bicycling on a cycle ergometer is common or even has become routine practice.
The recent recommendations of the SRLF (51) state that early mobilization should be routine care and that work on a cycle ergometer and electrical stimulation may be added.
Finally, the medical literature describes no serious adverse events related to the different interventions tested in the present study, provided that contraindications, such as those outlined in the present protocol, are respected.

16.3 Request made to the CPP (Ethics Committee) to approve a "modified in-emergency inclusion" procedure

Early mobilization of ICU patients must be applied as soon as possible, preferably within the first few days. However, in the context of critically illness, often a patient will not be able to understand and to give or refuse consent. Moreover, it is also frequent that family members or legal representative are neither present during the first day of admission nor reachable by phone within the first 12 hours.
Considering that the interventions under study are routine care practice and that they bring only minimal risk, we ask for the authorization of "in-emergency" inclusion and randomization based solely on the investigator's opinion in case where the eligible patient is not able to give or refuse consent and if family members or legal representative could not be interviewed or reached by phone.
In the event that the legal representative or family members can be reached by phone during the first 12 hours, the investigator will inform them of his/her intention to include the patient and will seek for their consent (or refusal). In case of consent, the study information notes will be hand-delivered directly to the family or to the legal representative as soon as possible.
In case of inclusion in the sole opinion of the investigator, the legal representative or family members will be notified verbally as soon as possible and the information notes will be supplied to them.
In any case, as soon as he/she regains capacity, the enrolled patient will be notified verbally, the information notes will be supplied to him/her, and his/her refusal or consent will be collected and notified in medical record.

16.4 *Commission Nationale Informatique et Libertés (CNIL)* (i.e. French equivalent of the US Federal trade Commission)

To comply with French regulations, the sponsor will declare the establishment of a computerized file of private data collected for the purpose of a scientific research to the CNIL.

16.5 Information Notes

See Appendix 13.

16.6 Right of access to source data and documentation

In accordance with laws and regulations (articles L.1121-3 and R.5121-13 of the French Public Health Code), people with direct access to source data will take all necessary precautions to ensure the confidentiality of

information related to the study and people taking part in them, particularly as regard their identity and the results obtained. These people, like the investigators themselves, are subject to professional secrecy.
During the study or when it is over, the information collected on the people taking part in it and forwarded to the sponsor by the investigators (or any other specialized staff member involved) will be made anonymous. Under no circumstances may the names or addresses of the people concerned appear in it.
For coding subjects the first letter of the first name and first letter of the last name of the subject will be recorded, accompanied by a code showing the order of inclusion of the subject.
The sponsor will ensure that each person taking part in the study has given his agreement in writing for access to only the individual data that are strictly necessary for quality control of the study.

16.7 Control and Quality Assurance

The research will be framed according to the standard operating procedures of the sponsor.
The conduct of research and management issues will be consistent with the Declaration of Helsinki and Good Clinical Practices recommendations.

Monitoring procedures

The research being a study investigating routine care procedures, monitoring will be simplified:
CRAs delegated by the sponsor, in accordance with Good Clinical Practices, will review the following: traceability of information given to patients and their relatives; no violation of protocol regarding the treatment group assigned by randomization; actual implementation of the program of mobilization assigned by randomization; identity of the person assessing the primary endpoint; concordance between the primary endpoint reported in the Clinical Report Form and source documents; reporting of adverse events.

16.8 Confidentiality

To ensure confidentiality, patients will be identified only by their study identification number in all study files and documents.

16.9 Data storage

In accordance with current regulations, data will be stored for a minimum of 15 years after the end of the study.

17. Costs and insurance

17.1 Financial support:

There will be no additional costs to subjects as part of this study. Subjects and their insurers will not be billed for research related services. The additional study costs above what is considered to be standard hospital care will be related to monitoring and study management and will be paid for by the sponsor. Research subjects will receive no payments or other remuneration for their participation in the study.

17.2 Insurance:

As the present research investigates routine care, the sponsor will not take out a specific insurance.

18. Rules for publication

The study will be registered on the clinicaltrials.gov international registry before enrollment of the first patient.
- The first author will be Guillaume Fossat, physiotherapist (chair of the Scientific committee)
- The senior (last) author will be the principal investigator
- The principal investigator will be responsible for correspondence with scientific journals
- Ancillary studies: each person who took an active part in the conduct of the study will have the possibility to use the database for the purpose of ancillary studies. The scientific committee should endorse these studies.

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APPENDIX 1

MRC SUM SCALE (Medical Research Council 1978)

Assessed Functions (6 in the right side and 6 on the left side)	Each muscle group is rated from 0 to 5
Shoulder Abduction Elbow Flexion Wrist Extension Hip Flexion Knee Extension Ankle Dorsiflexion	0 = No visible contraction 1= Muscle contraction without movement 2= Movement insufficient to defeat gravity 3= Movement that allow to defeat gravity 4= Movement against gravity and against a small resistance 5= Normal muscle strenght

Total sum scale is rated from 0 (complete tetraplegia) to 60 (normal muscle strength)

APPENDIX 2

CAM-ICU scale to evaluate delirium in ICU patients (Ely CCM 2001, Ely JAMA 2001)

Patient awakening must be first evaluated by the RASS scale (The Richmond Agitation-Sedation Scale) (Sessler CCM 2002)

LEVEL	LABEL	DESCRIPTION
+4	COMBATIVE	Combative, violent, immediate danger to staff
+3	VERY AGITATED	Pulls to remove tubes or catheters; aggressive
+2	AGITATED	Frequent non-purposeful movement, fights ventilator
+1	RESTLESS	Anxious, apprehensive, movements not aggressive
0	ALERT & CALM	Spontaneously pays attention to caregiver
-1	DROWSY	Not fully alert, but has sustained awakening to voice (eye opening & contact >10 sec)
-2	LIGHT SEDATION	Briefly awakens to voice (eyes open & contact <10 sec)
-3	MODERATE SEDATION	Movement or eye opening to voice (no eye contact) or any stimulating touching
-4	DEEP SEDATION	SEDATION No response to voice, but movement or eye opening to physical stimulation
-5	UNAROUSABLE	No response to voice or physical stimulation

Searching for the delirium by CAM-ICU scale must be done only if the RASS is between -3 and +4.

CAM ICU is positive if the following feature is encountered: **Feature 1 + Feature 2 + (Feature 3 or 4)**

CAM-ICU Worksheet

Feature 1: Acute Onset or Fluctuating Course	**Score**	**Check here if Present**
Is the patient different than his/her baseline mental status? OR Has the patient had any fluctuation in mental status in the past 24 hours as evidenced by fluctuation on a sedation/level of consciousness scale (i.e., RASS/SAS), GCS, or previous delirium assessment?	Either question Yes →	☐
Feature 2: Inattention		
Letters Attention Test (See training manual for alternate Pictures) Directions: Say to the patient, *"I am going to read you a series of 10 letters. Whenever you hear the letter 'A,' indicate by squeezing my hand."* Read letters from the following letter list in a normal tone 3 seconds apart. **S A V E A H A A R T** or **C A S A B L A N C A** or **A B A D B A D A A Y** **Errors are counted when patient fails to squeeze on the letter "A" and when the patient squeezes on any letter other than "A."**	Number of Errors >2 →	☐
Feature 3: Altered Level of Consciousness		
Present if the Actual RASS score is anything other than alert and calm (zero)	RASS anything other than zero →	☐
Feature 4:Disorganized Thinking		
Yes/No Questions (See training manual for alternate set of questions) 1. Will a stone float on water? 2. Are there fish in the sea? 3. Does one pound weigh more than two pounds? 4. Can you use a hammer to pound a nail? **Errors are counted when the patient incorrectly answers a question.** Command Say to patient: "Hold up this many fingers" (Hold 2 fingers in front of patient) "Now do the same thing with the other hand" (Do not repeat number of fingers) *If the patient is unable to move both arms, for 2nd part of command ask patient to "Add one more finger" **An error is counted if patient is unable to complete the entire command.**	Combined number of errors >1→	☐

Overall CAM-ICU **Feature 1 plus 2 and either 3 or 4 present = CAM-ICU positive**	Criteria Met →	☐ CAM-ICU Positive (Delirium Present)
	Criteria Not Met →	☐ CAM-ICU Negative (No Delirium)

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APPENDIX 3: Index of independence in activities of daily living (KATZ Index of ADL) (Katz, JAMA 1963

Activities	Description	Points
Bathing	Receives No Assistance	1
	Assistance for one part of the body	0,5
	Assistance for more than one part of the body (or not bathed)	0
Dressing	Gets clothes and gets completely dressed without assistance	1
	Gets clothes and gets completely dressed without assitance except for assistance in tying shoes	0,5
	Receives assistance in getting clothes or in getting dressed, or stays partly or completely undressed	0
Toileting	Goes to « toilet room », cleans self and arranges clothes without assistance	1
	Receives assistance in going to toilet room, or in cleaning self or in arranging clothes after elimination	0,5
	Doesn't go to room termed toilet for the elimination process	0
Transfer	Moves in and out of bed as in and out of chair without assistance	1
	Moves in and out of bed or chair with assistance	0,5
	Doesn't get out of bed	0
Continence	Control urination and bowel movement completely by self	1
	Has occasional « accidents »	0,5
	Supervision helps keep urine or bowel control, catheter is used, or is incontinent	0
Feeding	Feeds self without assistance	1
	Feeds self except for getting assistance in cutting meat or buttering bread	0,5
	Receives assistance in feeding or is fed partly or completely by using tubes or intravenous fluids	0

TOTAL:

APPENDIX 4: BARTHEL INDEX (Mahoney & Barthel Md State Med J 1965)

BARTHEL INDEX

		With Help	*Independent*
1.	Feeding (if food needs to be cut up = help)	5	10
2.	Moving from wheelchair to bed and return (includes sitting up in bed)	5-10	15
3.	Personal toilet (wash face, comb hair, shave, clean teeth)	0	5
4.	Getting on and off toilet (handling clothes, wipe, flush)	5	10
5.	Bathing self	0	5
6.	Walking on level surface (or if unable to walk, propel wheelchair) *score only if unable to walk	0*	5*
7.	Ascend and descend stairs	5	10
8.	Dressing (includes tying shoes, fastening fasteners)	5	10
9.	Controlling bowels	5	10
10.	Controlling bladder	5	10

A patient scoring 100 BI is continent, feeds himself, dresses himself, gets up out of bed and chairs, bathes himself, walks at least a block, and can ascend and descend stairs. This does not mean that he is able to live alone: he may not be able to cook, keep house, and meet the public, but he is able to get along without attendant care.

DEFINITION AND DISCUSSION OF SCORING

1. Feeding

10 = Independent. The patient can feed himself a meal from a tray or table when someone puts the food within his reach. He must put on an assistive device if this is needed, cut up the food, use salt and pepper, spread butter, etc. He must accomplish this in a reasonable time.

5 = Some help is necessary (with cutting up food, etc., as listed above).

2. Moving from wheelchair to bed and return

15 = Independent in all phases of this activity. Patient can safely approach the bed in his wheelchair, lock brakes, lift footrests, move safely to bed, lie down, come to a sitting position on the side of the bed, change the position of the wheelchair, if necessary, to transfer back into it safely, and return to the wheelchair.

10 = Either some minimal help is needed in some step of this activity or the patient needs to be reminded or supervised for safety of one or more parts of this activity.

5 = Patient can come to a sitting position without the help of a second person but needs to be lifted out of bed, or if he transfers with a great deal of help.

Mahoney FI, Barthel D. "Functional evaluation: The Barthel Index." *Maryland State Medical Journal* 1965;14:56-61. Used with permission.

3. Doing personal toilet

5 = Patient can wash hands and face, comb hair, clean teeth, and shave. He may use any kind of razor but must put in blade or plug in razor without help as well as get it from drawer or cabinet. Female patients must put on own makeup, if used, but need not braid or style hair.

4. Getting on and off toilet

10 = Patient is able to get on and off toilet, fasten and unfasten clothes, prevent soiling of clothes, and use toilet paper without help. He may use a wall bar or other stable object for support if needed. If it is necessary to use a bed pan instead of a toilet, he must be able to place it on a chair, empty it, and clean it. Patient needs help because of imbalance or in handling clothes or in using toilet paper.

5. Bathing self

5 = Patient may use a bath tub, a shower, or take a complete sponge bath. He must be able to do all the steps involved in whichever method is employed without another person being present.

6. Walking on a level surface

15 = Patient can walk at least 50 yards without help or supervision. He may wear braces or prostheses and use crutches, canes, or a walkerette but not a rolling walker. He must be able to lock and unlock braces if used, assume the standing position and sit down, get the necessary mechanical aides into position for use, and dispose of them when he sits. (Putting on and taking off braces is scored under dressing.)

10 = Patient needs help or supervision in any of the above but can walk at least 50 yards with a little help.

6a. Propelling a wheelchair

5 = If a patient cannot ambulate but can propel a wheelchair independently. He must be able to go around corners, turn around, maneuver the chair to a table, bed, toilet, etc. He must be able to push a chair at least 50 yards. Do not score this item if the patient gets score for walking.

7. Ascending and descending stairs

10 = Patient is able to go up and down a flight of stairs safely without help or supervision. He may and should use handrails, canes, or crutches when needed. He must be able to carry canes or crutches as he ascends or descends stairs.

5 = Patient needs help with or supervision of any one of the above items.

8. Dressing and undressing

10 = Patient is able to put on and remove and fasten all clothing, and tie shoe laces (unless it is necessary to use adaptations for this). The activity includes putting on and removing and fastening corset or braces when these are prescribed. Such special clothing as suspenders, loafer shoes, dresses that open down the front may be used when necessary.

5 = Patient needs help in putting on and removing or fastening any clothing. He must do at least half the work himself. He must accomplish this in a reasonable time.
Women need not be scored on use of a brassiere or girdle unless these are prescribed garments.

9. Continence of bowels

10 = Patient is able to control his bowels and have no accidents. He can use a suppository or take an enema when necessary (as for spinal cord injury patients who have had bowel training).

5 = Patient needs help in using a suppository or taking an enema or has occasional accidents.

10. Controlling bladder

10 = Patient is able to control his bladder day and night. Spinal cord injury patients who wear an external device and leg bag must put them on independently, clean and empty bag, and stay dry day and night.

5 = Patient has occasional accidents or can not wait for the bed pan or get to the toilet in time or needs help with an external device.

Mahoney FI, Barthel D. "Functional evaluation: The Barthel Index." *Maryland State Medical Journal* 1965;14:56-61. Used with permission.

APPENDIX 5: The Short Form (36) Health Survey (Weinberger J Am Geriatr Soc 1991)
(French validated version)

1.- En général, diriez-vous que votre santé est : (cocher ce que vous ressentez)

Excellente __ Très bonne __ Bonne __ Satisfaisante __ Mauvaise __

2.- Par comparaison avec** il y a un an**, que diriez-vous sur votre santé aujourd'hui ?

Bien meilleure qu'il y a un an __ *Un peu meilleure qu'il y a un an __*
A peu près comme il y a un an __ *Un peu moins bonne qu'il y a un an __*
Pire qu'il y a un an __

3.- vous pourriez vous livrer aux activités suivantes le même jour. Est-ce que votre état de santé vous impose des limites dans ces activités ? Si oui, dans quelle mesure ? (entourez la flèche).

a.Activités intenses : courir, soulever des objets lourds, faire du sport.
Oui, très limité — oui, plutôt limité — pas limité du tout

b.Activités modérées :déplacer une table, passer l'aspirateur.
Oui, très limité — oui, plutôt limité — pas limité du tout

c.Soulever et transporter les achats d'alimentation.
Oui, très limité — oui, plutôt limité — pas limité du tout

d.Monter plusieurs étages à la suite.
Oui, très limité — oui, plutôt limité — pas limité du tout

e.Monter un seul étage.
Oui, très limité — oui, plutôt limité — pas limité du tout

f.Vous agenouiller, vous accroupir ou vous pencher très bas.
Oui, très limité — oui, plutôt limité — pas limité du tout

g.Marcher plus d'un kilomètre et demi.
Oui, très limité — oui, plutôt limité — pas limité du tout

h.Marcher plus de 500 mètres
Oui, très limité — oui, plutôt limité — pas limité du tout

i.Marcher seulement 100 mètres.
Oui, très limité — oui, plutôt limité — pas limité du tout

j.Prendre un bain, une douche ou vous habiller.
Oui, très limité — oui, plutôt limité — pas limité du tout

4.- Au cours des 4 dernières semaines, avez-vous eu l'une des difficultés suivantes au travail ou lors des activités courantes, du fait de votre santé ? (réponse : oui ou non à chaque ligne)

	oui	non
Limiter le temps passé au travail, ou à d'autres activités ?		
Faire moins de choses que vous ne l'espériez ?		
Trouver des limites au type de travail ou d'activités possibles ?		
Arriver à tout faire, mais au prix d'un effort		

5.- Au cours des 4 dernières semaines, avez-vous eu des difficultés suivantes au travail ou lors des activités courantes parce que vous étiez déprimé ou anxieux ? (réponse : oui ou non à chaque ligne).

	oui	non
Limiter le temps passé au travail, ou à d'autres activités ?		
Faire moins de choses que vous n'espériez ?		
Ces activités n'ont pas été accomplies aussi soigneusement que d'habitude ?		

6.- Au cours des 4 dernières semaines, dans quelle mesure est-ce que votre état physique ou mental ont perturbé vos relations avec la famille, les amis, les voisins ou d'autres groupes ?
Pas du tout — très peu — assez fortement — énormément

7.- Avez-vous enduré des souffrances physiques au cours des 4 dernières semaines ?
Pas du tout — très peu — assez fortement — énormément

8.- Au cours des 4 dernières semaines la douleur a-t-elle gêné votre travail ou vos activités usuelles ?
Pas du tout — un peu — modérément — assez fortement — énormément

9.- Ces 9 questions concernent ce qui s'est passé au cours de ces dernières 4 semaines. Pour chaque question, donnez la réponse qui se rapproche le plus de ce que vous avez ressenti. Comment vous sentiez-vous au cours de ces 4 semaines :

a. vous sentiez-vous très enthousiaste ?
Tout le temps — très souvent — parfois — peu souvent — jamais

b. étiez-vous très nerveux ?
Tout le temps — très souvent — parfois — peu souvent — jamais

c. étiez-vous si triste que rien ne pouvait vous égayer ?
Tout le temps — très souvent — parfois — peu souvent — jamais

d. vous sentiez-vous au calme, en paix ?
Tout le temps — très souvent — parfois — peu souvent — jamais

e. aviez-vous beaucoup d'énergie ?
Tout le temps — très souvent — parfois — peu souvent — jamais

f. étiez-vous triste et maussade ?
Tout le temps — très souvent — parfois — peu souvent — jamais

g. aviez-vous l'impression d'être épuisé(e) ?
Tout le temps — très souvent — parfois — peu souvent — jamais

h. étiez-vous quelqu'un d'heureux ?
Tout le temps — très souvent — parfois — peu souvent — jamais

i. vous êtes-vous senti fatigué(e) ?
Tout le temps — très souvent — parfois — peu souvent — jamais

10.- Au cours des 4 dernières semaines, votre état physique ou mental a-t-il gêné vos activités sociales comme des visites aux amis, à la famille, etc ?
Tout le temps — très souvent — parfois — peu souvent — jamais

11.- Ces affirmations sont-elles vraies ou fausses dans votre cas ?

a. il me semble que je tombe malade plus facilement que d'autres.
Tout à fait vrai — assez vrai — ne sais pas — plutôt faux — faux

b. ma santé est aussi bonne que celle des gens que je connais.
Tout à fait vrai — assez vrai — ne sais pas — plutôt faux — faux

c. je m'attends à ce que mon état de santé s'aggrave.
Tout à fait vrai — assez vrai — ne sais pas — plutôt faux — faux

d. mon état de santé est excellent.
Tout à fait vrai — assez vrai — ne sais pas — plutôt faux — faux

APPENDIX 6: Screening log

Last Name First Name*	AGE	GENDER	ICU admission date	Screening date	Mechanical ventilation beetween Hour 0 and time of the screening YES/NO	ENROLLED ? (YES/NO)	If YES Identification Number and enrollement date If NO, explain why **

* This column will be deleted when documents will be archived at the end of the study

** List the number of the non-inclusion criterion (see next page) that are applied and/or:

A: Non-opposition by the confident person or family

B: Patient non-opposition

C: Deceased between H0 and H72

D: Discharge from the ICU before the 72th hour.

Non-inclusion criteria:

1. Consent refusal (by patient, family members of legal representative)
2. Pregnant Woman
3. Cardiac arrest as the cause of ICU admission or cardiac arrest between admission and screening
4. Presence of a pacemaker or an implantable defibrillator
5. Acute cerebral disease requiring deep sedation for at least 72 hours to prevent secondary brain insult (severe traumatic brain injury, *status epilepticus*, stroke, and others causes of intracranial hypertension)
6. Acute polyradiculoneuropathy (Guillain-Barre syndrome)
7. Myasthenia
8. Advanced Dementia
9. Deep venous thrombosis or pulmonary embolism treated for less than 48 hours
10. Contraindication to electrical muscle stimulation and/or leg bicycling, for musculoskeletal and/or dermatological and/or surgical reasons.
11. Contraindication to standing and/or transfer to chair
12. Amputation of a lower limb

APPENDIX 7: Passive range of motion of the lower limb using a bed-cycloergometer.

Equipment: Bed cycloergometer (Motomed, Letto, Mobile society, France)

Staff requirement: 2 staff members to put the leg on the device

Session launch:

1. Be sure of the leg position:
    a. Calf support
    b. Uncomplete leg extension
2. Start the device with a passive speed of 15 rotations by minute

During the 15 minutes session, a physiotherapist or student physiotherapist is supervising any adverse event. If one of them occurs, make a 2 minutes break and restart the device until the 15 minutes is reached.

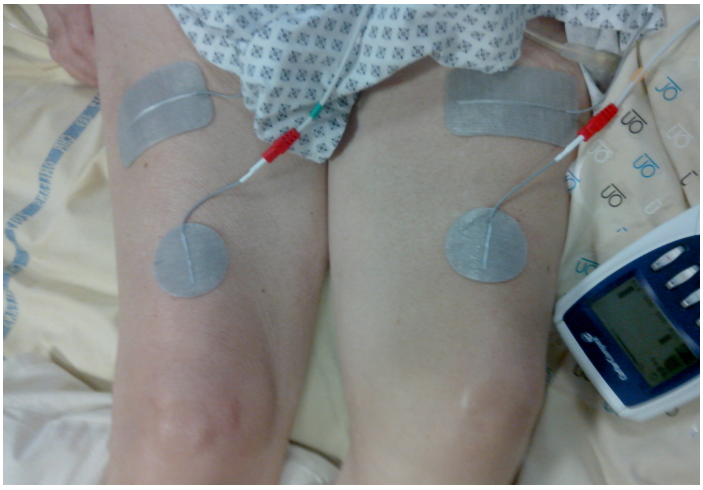
APPENDIX 8: Quadriceps electrical muscle stimulation (EMS) using the “prevention of diffuse atrophy” program.

Equipment: CefarCompex Rehab 400

Staff requirement: A physiotherapist or a physiotherapist student

Setting up:

Put the electrodes on the anterior side of the thigh along the rectus femoris muscle (see image bellow)



Session launch:

1. Press the power button
2. Select “Common treatment” mode
3. Select “Rehabilitation” mode
4. Select “Prevention of diffuse atrophy” mode
5. Choose the tigh area then press “START”
6. Rise the intensity level until observing muscle shake
7. Wait for the end of the “warm-up” phase

Treatment:

Duration = 54 minutes
Automatic ending

NMES description:

PREVENTION OF DISUSE ATROPHY, LEVEL 1 (54 MIN)				
	Warm-up	Contraction	Active rest	Final recovery phase
Frequency	6 Hz	30 Hz	4 Hz	3 Hz
Duration of ramp-up	1.5 s	3 s	1.5 s	1.5 s
Duration of phase	2 min	5 s	14 s	3 min
Duration of ramp-down	2 s	1.5 s	1.5 s	3 s

APPENDIX 9: PASSIVE/ACTIVE RANGE OF MOTION OF THE LOWER LIMBS USING A BED CYCLOERGOMETER

Equipment: Bed cycloergometer (Motomed, Letto, Mobile society, France)

Staff requirement: 2 staff members to put the leg on the device

Session launch:

1. Be sure of the leg position:
    a. Calf support
    b. Uncomplete leg extension
2. Start the device with a passive speed of 15 rotations by minute

Exercise Session

- Passive range of motion at 15 turns by minute for 1 minute
- Active cycling in the forward side without any resistance for 30 seconds
- Exercice session length: 15 minutes

Monitoring:

- Muscular spasm during the active phase
- Percentage of active work
- Total distance

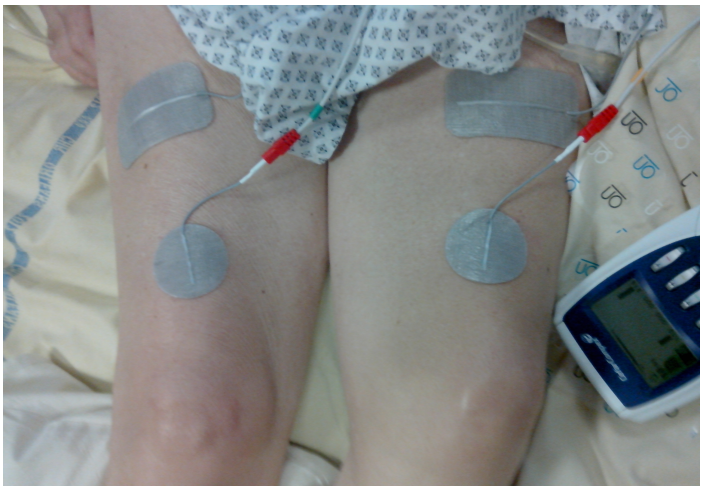
APPENDIX 10: Quadriceps electrical muscle stimulation (EMS) using the “Reinforcement” program.

Equipment: CefarCompex Rehab 400

Staff requirement: A physiotherapist or a physiotherapist student

Setting up:

Put the electrodes on the anterior side of the thigh along the rectus femoris muscle (see image bellow)



Session launch:

1. Press the power button
2. Select “Common treatment” mode
3. Select “Rehabilitation” mode
4. Select “Reinforcement” mode
5. Choose the thigh area then press “START”
6. Rise the intensity level until observing muscle shake
7. Wait for the end of the “warm-up” phase
8. Rise again the intensity until observing muscle contraction

Treatment:

Duration = 20 minutes
Automatic ending

NMES description:

REINFORCEMENT, LEVEL 1 (20 MIN)				
	Warm-up	Contraction	Active rest	Final recovery phase
Frequency	6 Hz	75 Hz	4 Hz	3 Hz
Duration of ramp-up	1.5 s	1.5 s	0.5 s	1.5 s
Duration of phase	2 min	4 s	10 s	3 min
Duration of ramp-down	2 s	0.75 s	0.5 s	3 s

APPENDIX 11: Chair or bed cycloergometer, active mode strictly

Equipment: Bed cycloergometer (Motomed, Letto, Mobile society, France) or chair cycloergometer (Motomed, Viva2, Mobile Society, France)

Staff requirement: 2 staff member to put the leg on the device for bed device or 1 staff member for the chair device

Session launch:

1. Be sure of the leg position for bed session:
    a. Calf support
    b. Uncomplete leg extension
2. Be sure of the leg position for chair session:
    a. Patient must be sit right into the bottom of the chair
    b. Uncomplete leg extension during the device rotation
3. Start the device with a passive speed of 15 rotations by minute

Exercise Session: Without resistance

- Active cycling in the forward side at 10/15 turns by minute for 1 minute
- Active cycling in the forward side at least 20/25 turns by minute for 30 seconds
- Exercise session length: 15 minutes

Monitoring:

- Muscular spasm during the active phase
- Pourcentage of active work
- Total distance
- If any tiredness criterion occurs, the patient can take 1 minute to rest in the passive mode. Then the physiotherapist must check for the active session to start again.

APPENDIX 12: Range of motion description

PASSIVE RANGE OF MOTION:

Patient in semi recumbent position in the bed
Once a day
10 times in every direction of each joint (except hip and shoulder extension)

ACTIVE HELPED RANGE OF MOTION

Patient in semi recumbent position in the bed
Once a day
5 helped contractions (maximum) in every direction of each joint (except hip and shoulder extension)

ACTIVE RANGE OF MOTION

Patient in semi recumbent position in the bed
Once a day
5 actives contractions (maximum) in every direction of each joint (except hip and shoulder extension)

APPENDIX 13: SEQUENTIAL ORGAN FAILURE ASSESSMENT (SOFA) SCORE (Vincent CCM 1998)

SOFA score	1	2	3	4
Respiration PaO2/FiO2	<400	<300	<200	<100
Coagulation Platelets $x10^3/mm^3$	<150	<100	<50	<20
Liver Bilirubin, µmol/l (mg/dl)	20-32 (1.2-1.9)	33-101 (2.0-5.9)	102-204 (6.0-11.9)	>204 (>12.0)
Cardiovascular Hypotension	MAP<70 mm Hg	Dopa ≤5 mcg/kg/min or Dobutamine (any dose)	Dopa >5 or epinephrine or norepinephrine ≤0.1	Dopa >15 or epinephrine or norepinephrine >0.1
Neurologic Glasgow	13-14	10-12	6-9	>6
Renal Creatinine µmol/l mg/dl or urine output	110-170 (1.2-1.9)	171-299 (2.0-3.4)	300-440 (3.5-4.9) or < 500 ml/day	>440 (>5.0) or <200 ml/day

APPENDIX 14: Simplified Acute Physiology Score (SAPS II)

Variable Points:	26	13	12	11	9	7	6	5	4	3	2	0
Age, y												<40
Heart rate, beats/min				<40							40-69	70-119
Systolic BP, mm Hg		<70						70-99				100-199
Body temperature, °C (°F)												<39° (<102.2°)
Only if ventilated or continuous pulmonary artery pressure PaO_2, mm Hg/FiO_2				<100	100-199		≥200					
PaO_2, kPa/FiO_2				<13.3	13.3-26.5		≥26.6					
Urinary output, L/d				<0.500					0.500-0.999			≥1.000
Serum urea level, mmol/L (g/L) or serum urea nitrogen level, mg/dL												<10.0 (<0.60) <28
WBC count (10^3/cu mm)			<1.0									1.0-19.9
Serum potassium, mmol/d										<3.0		3.0-4.9
Serum sodium level, mmol/L								<125				125-144
Serum bicarbonate level, mEq/L							<15			15-19		≥20
Bilirubin level, µmol/L (mg/dL)												<68.4 (<4.0)
Glasgow Coma Score	<6	6-8				9-10		11-13				14-15
Chronic diseases												
Type of admission												Scheduled surgical
Sum of points												