BMJ Open

Early mobilization using a mobile patient lift in the intensive care unit: Protocol for a randomized controlled trial

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-057942
Article Type:	Protocol
Date Submitted by the Author:	03-Oct-2021
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Keywords:	REHABILITATION MEDICINE, Adult intensive & critical care < ANAESTHETICS, Adult intensive & critical care < INTENSIVE & CRITICAL CARE, INTENSIVE & CRITICAL CARE

Article type: Protocol

Title: Early mobilization using a mobile patient lift in the intensive care unit: Protocol for a randomized controlled trial

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ABSTRACT

Introduction: It is important to prevent the deterioration of activities of daily living to improve the long-term prognoses of patients in the intensive care unit (ICU). Patients' conditions and human and technical resources often become barriers to achieving early mobilization after ventilation. We plan to verify the usefulness of a mobile patient lift for early mobilization.

Methods and analysis: We will conduct a single-center, open-label, randomized controlled trial. The inclusion criteria are as follows: age >18 years, independent walking before admission, and expected mechanical ventilation for at least 48 hours. The participants will be randomly divided into groups with (intervention group) or without (control group) a mobile lift protocol. A mobile lift will be actively used in the intervention group. The primary endpoint will be the number of days required to achieve an ICU mobility scale of ≥4 (standing position). The results of the two groups will be analyzed using the Student's t-test.

Ethics and dissemination: This study will be conducted in accordance with the Declaration of Helsinki and with the approval of the Toho University Omori Medical Center Ethics Committee (approval number M20259). The results of this study will be presented internationally at academic conferences and published in the literature.

Trial registration number: UMIN000044965.

STRENGTHS AND LIMITATIONS OF THE STUDY

・This study will be the first randomized controlled trial to evaluate the effectiveness of using a mobile patient lift during early mobilization in intensive care unit (ICU) patients.

・The results of this study may help promote mobilization programs for ICU patients and prevent a decline in activities of daily living.

・It is not possible to blind this study owing to the nature of the intervention.

・The relationship between early mobilization using a patient lift and muscle strength requires future prospective studies.

INTRODUCTION

In recent years, the concepts of intensive care unit-acquired weakness (ICU-AW) and post-intensive care syndrome (PICS) have been proposed in ICU patients [1,2]. Weakness during ICU stay and physical and cognitive weakness after ICU discharge have become problems among ICU patients [3,4]. Since a decline in activities of daily living (ADL) is associated with worsened long-term prognoses [3], attempts have been made during the ICU stay to prevent ICU-AW or PICS. Early mobilization during ICU stays is recommended for this purpose [5]. It remains unclear whether early mobilization prevents muscle weakness

[6] but is said to have an ADL-improving effect after ICU or hospital discharge [7-10]. On the other hand, the patients' condition and resources such as staff and equipment can be barriers to early mobilization [11-13].

The Golvo 9000 lowBase (Hillrom BV, Amsterdam, The Netherlands) is a mobile patient lift. Medical staff carry the device to the patient's bed, attach a dedicated sling to the patient, and lift the patient with a motor. The device can also be used for conversion to a sitting position, standing assistance, and walking training. We will introduce this lift and utilize it for rehabilitation in the ICU. In the United States, there are facilities with ceiling lifts permanently installed, and it is reported that the lifts can reduce the burden on medical staff [14,15]. However, it has not been verified whether the use of lifts promotes early mobilization.

Therefore, we will investigate the hypothesis that early mobilization could be promoted using a mobile patient lift. This study will be the first randomized controlled trial to evaluate the effectiveness of a mobile patient lift during early mobilization in ICU patients.

METHODS AND ANALYSIS

A single-center, open-label, randomized controlled trial will be conducted at the Toho University Omori Medical Center in accordance with the Declaration of Helsinki with the approval of the Toho University Omori Medical Center Ethics Committee (approval number M20259). All participants will provide written informed consent. If a patient cannot provide consent, a consent form will be obtained from the patient's family (an adult family member living with the patient or a relative within the third degree of kinship). This study will be reported following the Consolidated Standards of Reporting Trials statement [16]. The research protocol was registered (protocol number UMIN000044695).

Participants

We began enrolling patients on August 1, 2021. The study period is planned to be 3 years. The inclusion criteria are as follows: age >18 years, ability to walk independently before ICU admission, and expected to be ventilated for at least 48 hours. Exclusion criteria are contraindications for load exercise, neuromuscular disease, weight >200 kg, post-cardiac arrest, intracranial disease, status epilepticus, transfer after mechanical ventilation for >48 hours, and coronavirus disease 2019 diagnosis.

Rehabilitation protocol

The rehabilitation protocol is shown in Figure 1. Rehabilitation and mobilization will be performed according to the criteria proposed by the Japanese Society of Intensive Care Medicine [17]. This criterion was proposed with reference to past literature [5,18]. In addition, rehabilitation will not be performed without the permission of the attending physician.

The mobilization program is illustrated in Figure 2. The level at which rehabilitation should be initiated

will be decided on consultation with the attending physician, nurse, and physiotherapist. If the patient does not meet the discontinuation criteria and the initial rehabilitation level is achieved, the patient will step up to the next level. If the patient meets the discontinuation criteria, the rehabilitation level will be lowered by one level and resumed. Physiotherapists work only on weekdays. On Saturdays and Sundays, the nurses will rehabilitate as much as possible.

Interventions

In the control group, patients will be treated according to the above-mentioned protocol. In the intervention group, a mobile patient lift, Golvo 9000 lowBase (Hillrom BV, Amsterdam, The Netherlands) will be used to assist during the standing position. In addition, it will also be used for posture change and sitting position. After ICU discharge, nurses will not actively participate in the rehabilitation of patients; therefore, the lift will not be used in the general ward.

Randomization

Among patients admitted to the ICU with mechanical ventilation, a consent form will be obtained when mechanical ventilation is predicted to continue for at least 48 hours. We will randomize the patients after obtaining consent. The block method will be used for randomization. In addition, because physiotherapists work only on weekdays, admission on Thursday or Friday may cause a difference in the timing of physiotherapist intervention. Therefore, stratified randomization will be performed between admission on Thursdays or Fridays and other days. That is, patients admitted on Thursday or Friday and those admitted on other days of the week will be divided and randomized in each group.

Sample size estimation

There is no suitable pilot data, but a similar study using tilt beds [19] had a recruitment sample size of 80. Although this study is an observational study and the method is different, we calculated the sample size using G*Power (Ver. 3.1, Kiel, Germany) based on that study's data. The effect size was 0.81, the required sample size was 40 in total, calculated with an α error of 0.05, and a power of 80%. Considering the possibility that the severity of illness is high, and the number of dropouts will increase due to death, the sample size of this proposed study was set to 80, as in the previous study.

Outcome

The primary endpoint will be the number of days from meeting the rehabilitation initiation criteria to achieving an ICU mobility scale (IMS) ≥4 (standing position) [20]. The secondary endpoints will be the Sequential Organ Failure Assessment score at first achieving IMS ≥4, Functional Status Score (FSS)-ICU, and Medical Research Council (MRC) score at the start of mobilization, IMS/FSS-ICU/MRC, at ICU discharge, Barthel index/MRC at hospital discharge, length of ICU stay, 28 ventilator-free days, ICU death,

and hospital death.

Statistical analysis

Baseline factors related to demographics, condition severity, and prognosis will be collected. We will perform chi-square tests for categorical variables and Student's t-test for continuous variables.

The results will be analyzed by intention-to-treat analysis. In other words, even if an intervention different from the protocol is performed for grouping, the outcomes will be accumulated and analyzed according to the grouping. However, if the patient is transferred to another hospital, leaves the ICU, or dies before standing, they will be excluded from the analysis.

Statistical analyses will be performed using StatFlex® version 7 (Artec, Osaka, Japan). Differences will be considered statistically significant when the p-value <0.05.

Ethics and dissemination

All participants will provide written informed consent. However, the consent withdrawal form will also be simultaneously given to participants so that consent can be withdrawn at any time. The data set will be anonymized on a desktop computer in the ICU and stored in a password-protected file. The correspondence table will be managed using a password. The results of the study will be presented internationally in academic conferences and literature and will be presented in a form that does not include personally identifiable information.

Patient and public involvement

No patient involved.

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Authors' contributions

G.S. performed the statistical analyses and drafted the manuscript. G. S., H. K., R. I., Y. A., Y. I., Y. M., S.Y., H.S., Y.N., M.W., M.H., and S.E. contributed to the acquisition of data. H.K. participated in the design of the study design and study coordination. M.H. conceived the study, participated in the study design and coordination, and contributed to manuscript writing. All authors read and approved the final manuscript.

Funding Statement

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Competing interest statement.

Authors have no competing interests to declare.

Word Count

1458

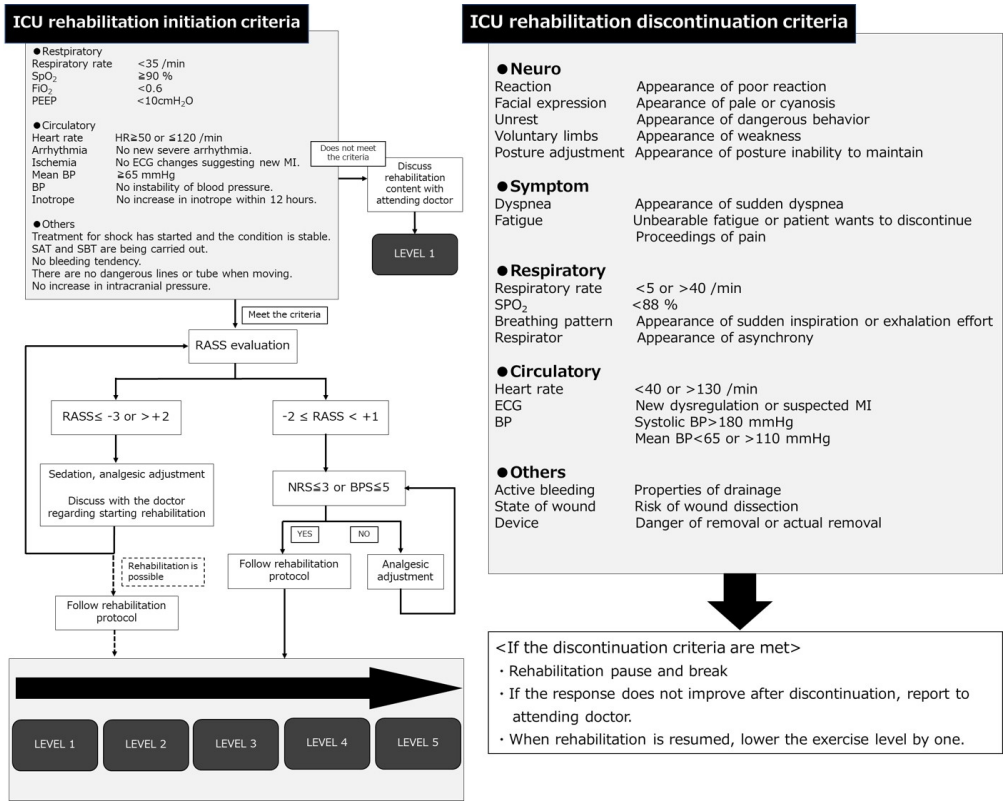
Legends

Figure 1. Rehabilitation initiation and discontinuation criteria

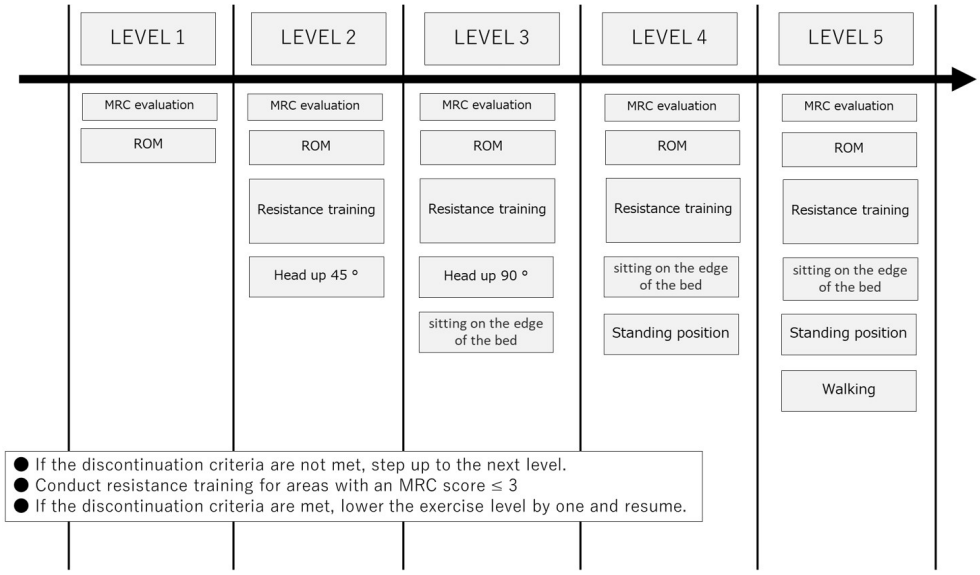
ECG,electrocardiogram; MI, myocardial infarction; BP, blood pressure; SAT, spontaneous awaking trial; SBT, spontaneous breathing trial; RASS, Richmond Agitation-Sedation Scale; NRS, numerical rating scale; BPS, behavioral pain scale.

Figure 2. Rehabilitation program

The level at which rehabilitation should be initiated will be decided on consultation with the attending physician, nurse, and physiotherapist. MRC, Medical Research Council; ROM, range of motion



238x190mm (149 x 149 DPI)



252x143mm (149 x 149 DPI)

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	2
	2b	Specific objectives or hypotheses	3
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	3
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	
Participants	4a	Eligibility criteria for participants	3
	4b	Settings and locations where the data were collected	4
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	4
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	4
	6b	Any changes to trial outcomes after the trial commenced, with reasons	
Sample size	7a	How sample size was determined	4
	7b	When applicable, explanation of any interim analyses and stopping guidelines	
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	4
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	4
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	4
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	4
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	5
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	
	13b	For each group, losses and exclusions after randomisation, together with reasons	
Recruitment	14a	Dates defining the periods of recruitment and follow-up	
	14b	Why the trial ended or was stopped	
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	
Other information			
Registration	23	Registration number and name of trial registry	2
Protocol	24	Where the full trial protocol can be accessed, if available	
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	7

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

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Primary Subject Heading:	Intensive care
Secondary Subject Heading:	Rehabilitation medicine
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ABSTRACT

Introduction: It is important to prevent the deterioration of activities of daily living to improve the long-term prognoses of patients in the intensive care unit (ICU). The patients' conditions, along with the lack of human and technical resources, often become barriers to achieving early mobilization after the introduction of mechanical ventilation. We plan to verify the usefulness of a mobile patient lift for early mobilization.

Methods and analysis: We will conduct a single-center, open-label, randomized controlled trial. The inclusion criteria are as follows: age ≥ 18 years, independent walking before admission, and expected mechanical ventilation for at least 48 hours. The participants will be randomly divided into groups with (intervention group) or without (control group) a mobile lift protocol. A mobile lift will be used in the intervention group. The primary endpoint will be the number of days required to achieve an ICU mobility scale of ≥4 (standing position). The results of the two groups will be analyzed using the Student's t-test.

Ethics and dissemination: This study will be conducted in accordance with the Declaration of Helsinki and with the approval of the Toho University Omori Medical Center Ethics Committee (approval number M20259). The results of this study will be presented internationally at academic conferences and published in the literature.

Trial registration number: UMIN000044965

STRENGTHS AND LIMITATIONS OF THE STUDY

- This will be a randomized controlled trial to evaluate the effectiveness of using a mobile patient lift during early mobilization in intensive care unit (ICU) patients.
- The results of this study may help promote mobilization programs for ICU patients and prevent a decline in activities of daily living.
- It is not possible to blind this study owing to the nature of the intervention.
- The relationship between early mobilization using a patient lift and muscle strength requires future prospective studies.

INTRODUCTION

In recent years, the concepts of intensive care unit-acquired weakness (ICU-AW) and post-intensive care syndrome (PICS) have been proposed in ICU patients. [1,2] Weakness during ICU stay and physical and

cognitive weakness after ICU discharge have become common problems among ICU patients. [3,4] Since a decline in activities of daily living (ADL) is associated with worsened long-term prognoses, [3] attempts have been made during the ICU stay to prevent ICU-AW or PICS. Early mobilization during the ICU stay is recommended for this purpose. [5] Early mobilization has been reported to be effective in preventing ICU-AW and improving physical function and ADL after ICU discharge. [6-12] On the other hand, the patients' condition and resources such as staff and equipment can be barriers to early mobilization. [13-15] The Golvo 9000 lowBase (Hillrom BV, Amsterdam, The Netherlands) is a mobile patient lift. Medical staff carry the device to the patient's bed, attach a dedicated sling to the patient, and lift the patient with a motor. The device can also be used for conversion to a sitting position, standing assistance, and walking training. We aim to introduce this lift and utilize it for rehabilitation in the ICU. In the United States, there are facilities with ceiling lifts permanently installed, and it is reported that the lifts can reduce the burden on medical staff. [16,17] However, it has not been verified whether the use of lifts promotes early mobilization.

Therefore, we will investigate the hypothesis that early mobilization could be promoted using a mobile patient lift. This study will be the first randomized controlled trial to evaluate the effectiveness of a mobile patient lift during early mobilization in ICU patients.

METHODS AND ANALYSIS

A single-center, open-label, randomized controlled trial will be conducted at the Toho University Omori Medical Center in accordance with the Declaration of Helsinki with the approval of the Toho University Omori Medical Center Ethics Committee (approval number M20259). All participants will provide written informed consent. If a patient cannot provide consent, a consent form will be obtained from the patient's family (an adult family member living with the patient or a relative within the third degree of kinship). This study will be reported following the Standard Protocol Items: Recommendations for Interventional Trials statement. [18] The research protocol has been registered (protocol number UMIN000044965).

Participants

We began enrolling patients on August 1, 2021. The study period is planned to be 3 years. The inclusion criteria are as follows: age ≥ 18 years, ability to walk independently (clinical frailty scale ≤ 4 [19]) before ICU admission, and expected to be ventilated for at least 48 hours. In detail,patients receiving extracorporeal membrane oxygenation will also be included. We will complete the screening within 24 hours of the start of mechanical ventilation. The exclusion criteria are contraindications for load exercise, neuromuscular disease, weight >200 kg, post-cardiac arrest, intracranial disease, status epilepticus, transfer after mechanical ventilation for >48 hours, and coronavirus disease (COVID-19) diagnosis. In our ICU, when medical instruments are used for COVID-19 patients, they are cleaned with alcohol and UV radiation;

therefore, we excluded COVID-19 patients because we thought it was impossible to disinfect deep into the boa of the sling due to the boa fabric attached to the load surface of the sling.

Rehabilitation protocol

The rehabilitation protocol is shown in Figure 1. Rehabilitation and mobilization will be performed according to the criteria proposed by the Japanese Society of Intensive Care Medicine. [20] This criterion was proposed with reference to past literature. [5,21] In addition, rehabilitation will not be performed without the permission of the attending physician. The mobilization will be done by the usual care team. In this ICU, early mobilization is part of the usual care. Mobilization is performed daily according to the patient's condition. The nurses are also trained to support the patient in standing position as they work closely with the physiotherapists.

The mobilization program is illustrated in Figure 2. This program is based on a previous report. [22] The level at which rehabilitation should be initiated will be decided on consultation with the attending physician, nurse, and physiotherapist. If the patient does not meet the discontinuation criteria and the initial rehabilitation level is achieved, the patient will step up to the next level. If the patient meets the discontinuation criteria, the rehabilitation level will be lowered by one level and resumed. Physiotherapists work only on weekdays. On Saturdays and Sundays, the nurses will rehabilitate as much as possible. Mobilization will be performed twice a day and, if possible, thrice a day. The physicians and nurses discuss the number of mobilizations and add more as needed. If refusal to rehabilitation is due to pain or fever, we will provide symptomatic treatment with medication; if refusal is due to fatigue, we will delay the timing of mobilization. If refusal is due to depression, we will listen to the patient and not force mobilization. However, after a while, we will try to speak to the patient again; if the patient agrees, we will perform the mobilization.

Other protocols

Daily sedation control and spontaneous breathing management will be performed according to the ABCDE bundle. When the respiratory and circulatory status become calm, continuous sedation will be discontinued and delirium and sleep will be controlled to maintain wakefulness during the day. Discontinuation of continuous sedation will be reviewed during daily morning rounds. Whenever possible, delirium will be treated by relieving pain and establishing a diurnal rhythm rather than by medication. If the patient still becomes agitated, we will consider medication. If the patient complains of insomnia, we will administer suvorexant. If the patient is awake during the day, we will try to perform a spontaneous breathing trial. If extubation is not possible due to fluid balance or other problems, we will try weaning.

Interventions

In the control group, patients will be treated according to the above-mentioned protocol. In the intervention

group, a mobile patient lift, Golvo 9000 lowBase (Hillrom BV, Amsterdam, The Netherlands) will be used to assist during the standing position. In addition, it will also be used for posture change and sitting position. Although our ICU has 15 beds and only one lift, rehabilitation is fully feasible. The physiotherapist was originally familiar with handling the lift, but the nurses received training from the physiotherapist to use the lift in a month's period. Often, the nurse alone would perform the standing position, although the physiotherapist was more likely to perform the higher stages of mobilization. Both physiotherapists and nurses will routinely follow the protocol shown in Figures 1 and 2, and the endotracheal tube and ventilator will not interfere with the standing position. Even in such a situation, if the patient's condition permits, mobilization to the standing position and sometimes beyond will be performed. If the patient's mobility is high and a lift is not necessary, the patient can be placed in a standing position without using a lift. After ICU discharge, nurses will not actively participate in the rehabilitation of patients; therefore, the lift will not be used in the general ward.

Randomization

Among patients admitted to the ICU with mechanical ventilation, a consent form will be obtained when mechanical ventilation is predicted to continue for at least 48 hours. We will randomize the patients after obtaining consent. The block method will be used for randomization. In addition, because physiotherapists work only on weekdays, admission on Thursday or Friday may cause a difference in the timing of physiotherapist intervention. Therefore, stratified randomization will be performed between admission on Thursdays or Fridays and other days. That is, patients admitted on Thursday or Friday and those admitted on other days of the week will be divided and randomized in each group.

Sample size estimation

There is no suitable pilot data, but a similar study using tilt beds [23] had a recruitment sample size of 80. Although this study is an observational study and the method is different, we calculated the sample size using G*Power (Ver. 3.1, Kiel, Germany) based on that study's data. The effect size was 0.56, and the required sample size was 80 in total, calculated with an α error of 0.05, and a power of 80%. Considering the possibility that the severity of illness is high and the number of dropouts will increase due to death, the sample size of this proposed study was set to 92.

Outcome

The primary endpoint will be the number of days from meeting the rehabilitation initiation criteria to achieving an ICU mobility scale (IMS) ≥4 (standing position). [24] As indicated in the rehabilitation protocols section, IMS is an assessment method that has not been incorporated into our protocol. We adopted IMS as a measure of mobilization to evaluate the effect of adding a lift to an existing protocol, and since the standing section of IMS clearly states that it includes the use of a lift, we adopted IMS as the

measure of mobilization in this study. The secondary endpoints will be time of preparation and postprocessing of mobilization, mobilization time, the Sequential Organ Failure Assessment score at first achieving IMS ≥4, Functional Status Score (FSS)-ICU, and Medical Research Council (MRC) score at the start of mobilization, IMS/FSS-ICU/MRC at ICU discharge, Barthel index/MRC at hospital discharge, presence and duration of delirium (CAM-ICU), length of ICU stay, 28 ventilator-free days, ICU mortality, and hospital mortality. Other unexpected adverse events will be recorded in the data set as appropriate.

Statistical analyses

Data on baseline factors related to demographics, condition severity, and prognosis will be collected. We will perform chi-square tests for categorical variables. If the variables are continuous or ordinal, the Student's t-test (for normal distribution) or the Man-Whitney U test (for non-normal distribution) will be used.

The results will be analyzed by intention-to-treat analysis. In other words, even if an intervention different from the protocol is performed for grouping, the outcomes will be accumulated and analyzed according to the grouping. However, if the patient is transferred to another hospital, leaves the ICU, or dies before meeting the rehabilitation initiation criteria, they will be excluded from the analysis. We will not perform interim analysis.

Statistical analyses will be performed using StatFlex® version 7 (Artec, Osaka, Japan). Differences will be considered statistically significant when the p-value <0.05. Statistical analyses will be performed by a different individual and not the clinicians involved in the study to eliminate bias.

Ethics and dissemination

All participants will provide written informed consent. However, the consent withdrawal form will also be simultaneously given to participants so that consent can be withdrawn at any time. The data set will be pseudonymized on a desktop computer in the ICU and stored in a password-protected file. The correspondence table will be managed using a password. The results of the study will be presented internationally in academic conferences and literature and will be presented in a form that does not include personally identifiable information.

Trial status

This protocol was finalized on June 30, 2021. Patient inclusion will begin on August 1, 2021, with a three-year implementation period.

Patient and public involvement

No patient involved.

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Authors' contributions

G.S. performed the statistical analyses and drafted the manuscript. G. S., H. K., R. I., Y. A., Y. I., Y. M., S.Y., H.S., Y.N., M.W., M.H., and S.E. contributed to the acquisition of data. H.K. participated in the design of the study design and study coordination. M.H. conceived the study, participated in the study design and coordination, and contributed to manuscript writing. All authors read and approved the final manuscript.

Funding Statement

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Competing interest statement.

Thde authors have no competing interests to declare.

Word Count

1837

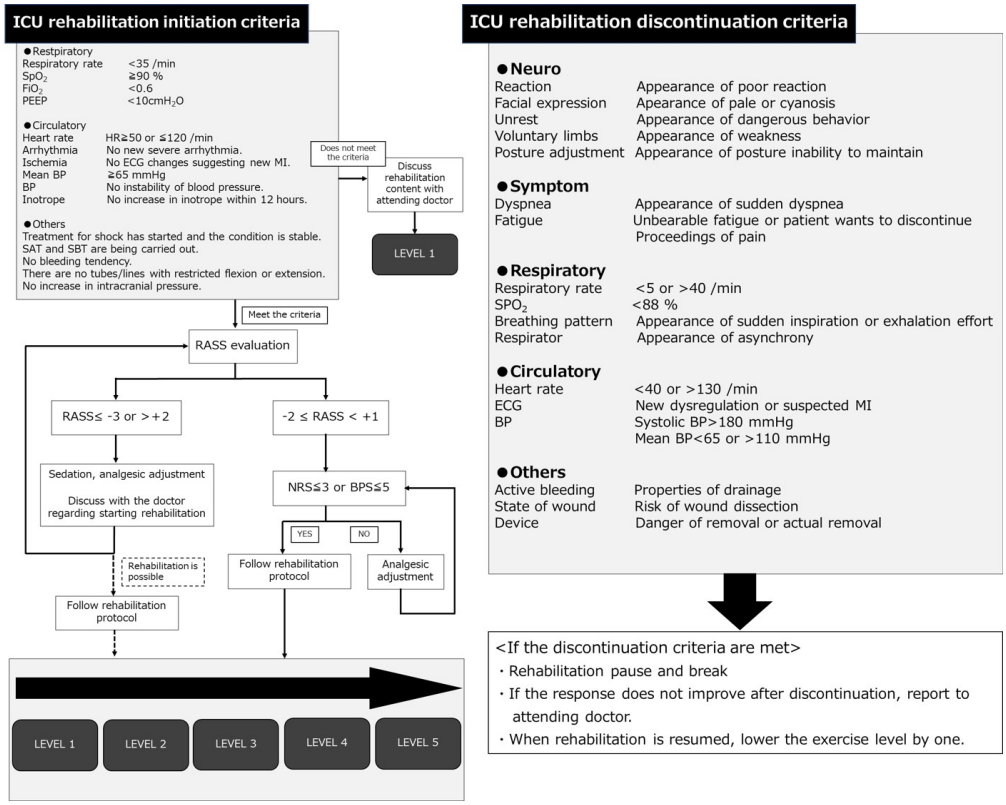
Legends

Figure 1. Rehabilitation initiation and discontinuation criteria

ECG,electrocardiogram; MI, myocardial infarction; BP, blood pressure; SAT, spontaneous awaking trial; SBT, spontaneous breathing trial; RASS, Richmond Agitation-Sedation Scale; NRS, numerical rating scale; BPS, behavioral pain scale.

Figure 2. Rehabilitation program

The level at which rehabilitation should be initiated will be decided on consultation with the attending physician, nurse, and physiotherapist. MRC, Medical Research Council; ROM, range of motion



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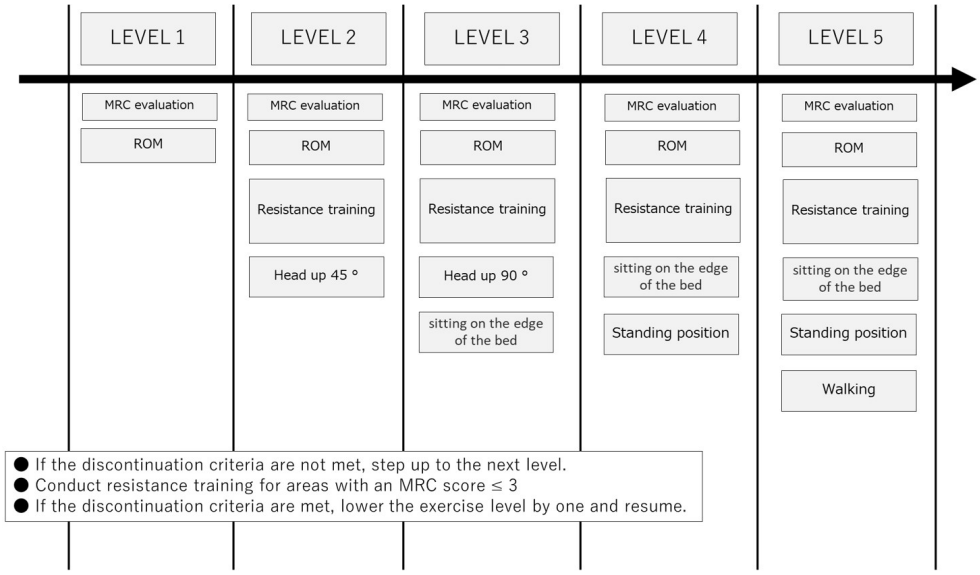

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SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	ItemNo	Description	Page / Line
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	P1 / L3-4
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	P2 / L16
	2b	All items from the World Health Organization Trial Registration Data Set	Throuout the paper.
Protocol version	3	Date and version identifier	P6 / L20-22
Funding	4	Sources and types of financial, material, and other support	P8 / L22-24
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	P1 / L6-21
	5b	Name and contact information for the trial sponsor	P1 / L10-15
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	P8 / L22-24
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	P8 / 15-19
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	P2 / L29 – P3 / L10
	6b	Explanation for choice of comparators	P2 / L29 – P3 / L10
Objectives	7	Specific objectives or hypotheses	P2 / L29 – P3 / L10

Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	P3 / 13-14
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	P3 / 13-14
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	P3 / L22-24
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	P4 / L27 – P5 / L4
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	P4 / L27 – P5 / L4
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	P4 / L27 – P5 / L4
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	P4 / L27 – P5 / L4
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	P5 / L23-34
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	P3 / L22- 32
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	P5 / 15-21
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	P3 / L22- 32
Methods: Assignment of interventions (for controlled trials)			
Allocation:			

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	P5 / L6-13
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	P5 / L6-13
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	P5 / L6-13
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	P2 / L24
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	Not blinded
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	P4 / L31 – P5 / L4
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	P4 / L 12-15
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	P5 / L14-15
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	P5 / L36 – P6 / L11
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	P5 / L36 – P6 / L11
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	P5 / L36 – P6 / L11

Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	P8 / L27-28
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	P6 / L7-8
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	P5 / L34
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	P8 / L27-28
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	P6 / L13-19
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	P6 / L13-19
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	P6 / L13-19
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	Not applicable.
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	P6 / L13-19
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	P8 / L27-28
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	P6 / L13-19
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	Not applicable.

Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	P6 / L13-19
	31b	Authorship eligibility guidelines and any intended use of professional writers	P6 / L13-19
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	P6 / L13-19
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Supplement file
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	Not applicable.

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Early mobilization using a mobile patient lift in the intensive care unit: Protocol for a randomized controlled trial

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-057942.R2
Article Type:	Protocol
Date Submitted by the Author:	21-Jan-2022
Complete List of Authors:	Suzuki, Ginga; Toho University Omori Medical Center, Kanayama, Hiromi; Toho University Omori Medical Center Ichibayashi, Ryo; Toho University Omori Medical Center Arai, Yoshiaki; Toho University Omori Medical Center Iwanami, Yuji; Toho University Omori Medical Center Masuyama, Yuka; Toho University Omori Medical Center Yamamoto, Saki; Toho University Omori Medical Center Serizawa, Hibiki; Toho University Omori Medical Center Nakamichi, Yoshimi; Toho University Omori Medical Center Watanabe, Masayuki; Toho University Omori Medical Center Honda, Mitsuru; Toho University Omori Medical Center Ebihara, Satoru; Toho University Omori Medical Center
Primary Subject Heading:	Intensive care
Secondary Subject Heading:	Rehabilitation medicine
Keywords:	REHABILITATION MEDICINE, Adult intensive & critical care < ANAESTHETICS, Adult intensive & critical care < INTENSIVE & CRITICAL CARE, INTENSIVE & CRITICAL CARE

Article type: Protocol

Title: Early mobilization using a mobile patient lift in the intensive care unit: Protocol for a randomized controlled trial

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ABSTRACT

Introduction: It is important to prevent the deterioration of activities of daily living to improve the long-term prognoses of patients in the intensive care unit (ICU). The patients' conditions, along with the lack of human and technical resources, often become barriers to achieving early mobilization after the introduction of mechanical ventilation. We plan to verify the usefulness of a mobile patient lift for early mobilization.

Methods and analysis: We will conduct a single-center, open-label, randomized controlled trial. The inclusion criteria are as follows: age ≥ 18 years, independent walking before admission, and expected mechanical ventilation for at least 48 hours. The participants will be randomly divided into groups with (intervention group) or without (control group) a mobile lift protocol. A mobile lift will be used in the intervention group. The primary endpoint will be the number of days required to achieve an ICU mobility scale of ≥4 (standing position). The results of the two groups will be analyzed using the Student's t-test.

Ethics and dissemination: This study will be conducted in accordance with the Declaration of Helsinki and with the approval of the Toho University Omori Medical Center Ethics Committee (approval number M20259). The results of this study will be presented internationally at academic conferences and published in the literature.

Trial registration number: UMIN000044965

STRENGTHS AND LIMITATIONS OF THE STUDY

- This will be a randomized controlled trial to evaluate the effectiveness of using a mobile patient lift during early mobilization in intensive care unit (ICU) patients.
- It is not possible to blind this study owing to the nature of the intervention.
- The relationship between early mobilization using a patient lift and muscle strength requires future prospective studies.

INTRODUCTION

In recent years, the concepts of intensive care unit-acquired weakness (ICU-AW) and post-intensive care syndrome (PICS) have been proposed in ICU patients. [1,2] Weakness during ICU stay and physical and cognitive weakness after ICU discharge have become common problems among ICU patients. [3,4] Since a decline in activities of daily living (ADL) is associated with worsened long-term prognoses, [3] attempts have been made during the ICU stay to prevent ICU-AW or PICS. Early mobilization during the ICU stay

is recommended for this purpose. [5] Early mobilization has been reported to be effective in preventing ICU-AW and improving physical function and ADL after ICU discharge. [6-12] On the other hand, the patients' condition and resources such as staff and equipment can be barriers to early mobilization. [13-15] The Golvo 9000 lowBase (Hillrom BV, Amsterdam, The Netherlands) is a mobile patient lift. Medical staff carry the device to the patient's bed, attach a dedicated sling to the patient, and lift the patient with a motor. The device can also be used for conversion to a sitting position, standing assistance, and walking training. We aim to introduce this lift and utilize it for rehabilitation in the ICU. In the United States, there are facilities with ceiling lifts permanently installed, and it is reported that the lifts can reduce the burden on medical staff. [16,17] However, it has not been verified whether the use of lifts promotes early mobilization.

Therefore, we will investigate the hypothesis that early mobilization could be promoted using a mobile patient lift. This study will be the first randomized controlled trial to evaluate the effectiveness of a mobile patient lift during early mobilization in ICU patients.

METHODS AND ANALYSIS

A single-center, open-label, randomized controlled trial will be conducted at the Toho University Omori Medical Center in accordance with the Declaration of Helsinki with the approval of the Toho University Omori Medical Center Ethics Committee (approval number M20259). All participants will provide written informed consent. If a patient cannot provide consent, a consent form will be obtained from the patient's family (an adult family member living with the patient or a relative within the third degree of kinship). This study will be reported following the Standard Protocol Items: Recommendations for Interventional Trials statement. [18] The research protocol has been registered (protocol number UMIN000044965).

Participants

We began enrolling patients on August 1, 2021. The study period is planned to be 3 years. The inclusion criteria are as follows: age ≥ 18 years, ability to walk independently (clinical frailty scale ≤ 4 [19]) before ICU admission, and expected to be ventilated for at least 48 hours. In detail,patients receiving extracorporeal membrane oxygenation will also be included. We will complete the screening within 24 hours of the start of mechanical ventilation. The exclusion criteria are contraindications for load exercise, neuromuscular disease, weight >200 kg, post-cardiac arrest, intracranial disease, status epilepticus, transfer after mechanical ventilation for >48 hours, and coronavirus disease (COVID-19) diagnosis. In our ICU, when medical instruments are used for COVID-19 patients, they are cleaned with alcohol and UV radiation; therefore, we excluded COVID-19 patients because we thought it was impossible to disinfect deep into the boa of the sling due to the boa fabric attached to the load surface of the sling.

Rehabilitation protocol

The rehabilitation protocol is shown in Figure 1. Rehabilitation and mobilization will be performed according to the criteria proposed by the Japanese Society of Intensive Care Medicine. [20] This criterion was proposed with reference to past literature. [5,21] In addition, rehabilitation will not be performed without the permission of the attending physician. The mobilization will be done by the usual care team. In this ICU, early mobilization is part of the usual care. Mobilization is performed daily according to the patient's condition. The nurses are also trained to support the patient in standing position as they work closely with the physiotherapists.

The mobilization program is illustrated in Figure 2. This program is based on a previous report. [22] The level at which rehabilitation should be initiated will be decided on consultation with the attending physician, nurse, and physiotherapist. If the patient does not meet the discontinuation criteria and the initial rehabilitation level is achieved, the patient will step up to the next level. If the patient meets the discontinuation criteria, the rehabilitation level will be lowered by one level and resumed. Physiotherapists work only on weekdays. On Saturdays and Sundays, the nurses will rehabilitate as much as possible. Mobilization will be performed twice a day and, if possible, thrice a day. The physicians and nurses discuss the number of mobilizations and add more as needed. If refusal to rehabilitation is due to pain or fever, we will provide symptomatic treatment with medication; if refusal is due to fatigue, we will delay the timing of mobilization. If refusal is due to depression, we will listen to the patient and not force mobilization. However, after a while, we will try to speak to the patient again; if the patient agrees, we will perform the mobilization.

Other protocols

Daily sedation control and spontaneous breathing management will be performed according to the ABCDE bundle. When the respiratory and circulatory status become calm, continuous sedation will be discontinued and delirium and sleep will be controlled to maintain wakefulness during the day. Discontinuation of continuous sedation will be reviewed during daily morning rounds. Whenever possible, delirium will be treated by relieving pain and establishing a diurnal rhythm rather than by medication. If the patient still becomes agitated, we will consider medication. If the patient complains of insomnia, we will administer suvorexant. If the patient is awake during the day, we will try to perform a spontaneous breathing trial. If extubation is not possible due to fluid balance or other problems, we will try weaning.

Interventions

In the control group, patients will be treated according to the above-mentioned protocol. In the intervention group, a mobile patient lift, Golvo 9000 lowBase (Hillrom BV, Amsterdam, The Netherlands) will be used to assist during the standing position. In addition, it will also be used for posture change and sitting position. Although our ICU has 15 beds and only one lift, rehabilitation is fully feasible. The physiotherapist

was originally familiar with handling the lift, but the nurses received training from the physiotherapist to use the lift in a month's period. Often, the nurse alone would perform the standing position, although the physiotherapist was more likely to perform the higher stages of mobilization. Both physiotherapists and nurses will routinely follow the protocol shown in Figures 1 and 2, and the endotracheal tube and ventilator will not interfere with the standing position. Even in such a situation, if the patient's condition permits, mobilization to the standing position and sometimes beyond will be performed. If the patient's mobility is high and a lift is not necessary, the patient can be placed in a standing position without using a lift. After ICU discharge, nurses will not actively participate in the rehabilitation of patients; therefore, the lift will not be used in the general ward.

Randomization

Among patients admitted to the ICU with mechanical ventilation, a consent form will be obtained when mechanical ventilation is predicted to continue for at least 48 hours. We will randomize the patients after obtaining consent. The block method will be used for randomization. In addition, because physiotherapists work only on weekdays, admission on Thursday or Friday may cause a difference in the timing of physiotherapist intervention. Therefore, stratified randomization will be performed between admission on Thursdays or Fridays and other days. That is, patients admitted on Thursday or Friday and those admitted on other days of the week will be divided and randomized in each group.

Sample size estimation

There is no suitable pilot data, but a similar study using tilt beds [23] had a recruitment sample size of 80. Although this study is an observational study and the method is different, we calculated the sample size using G*Power (Ver. 3.1, Kiel, Germany) based on that study's data. The effect size was 0.56, and the required sample size was 80 in total, calculated with an α error of 0.05, and a power of 80%. Considering the possibility that the severity of illness is high and the number of dropouts will increase due to death, the sample size of this proposed study was set to 92.

Outcome

The primary endpoint will be the number of days from meeting the rehabilitation initiation criteria to achieving an ICU mobility scale (IMS) ≥4 (standing position). [24] As indicated in the rehabilitation protocols section, IMS is an assessment method that has not been incorporated into our protocol. We adopted IMS as a measure of mobilization to evaluate the effect of adding a lift to an existing protocol, and since the standing section of IMS clearly states that it includes the use of a lift, we adopted IMS as the measure of mobilization in this study. The secondary endpoints will be time of preparation and postprocessing of mobilization, mobilization time, the Sequential Organ Failure Assessment score at first achieving IMS ≥4, Functional Status Score (FSS)-ICU, and Medical Research Council (MRC) score at the

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Statistical analyses

Data on baseline factors related to demographics, condition severity, and prognosis will be collected. We will perform chi-square tests for categorical variables. If the variables are continuous or ordinal, the Student's t-test (for normal distribution) or the Man-Whitney U test (for non-normal distribution) will be used.

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Statistical analyses will be performed using StatFlex® version 7 (Artec, Osaka, Japan). Differences will be considered statistically significant when the p-value <0.05. Statistical analyses will be performed by a different individual and not the clinicians involved in the study to eliminate bias.

Ethics and dissemination

All participants will provide written informed consent. However, the consent withdrawal form will also be simultaneously given to participants so that consent can be withdrawn at any time. The data set will be pseudonymized on a desktop computer in the ICU and stored in a password-protected file. The correspondence table will be managed using a password. The results of the study will be presented internationally in academic conferences and literature and will be presented in a form that does not include personally identifiable information.

Trial status

This protocol was finalized on June 30, 2021. Patient inclusion will begin on August 1, 2021, with a three-year implementation period.

Patient and public involvement

No patient involved.

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Authors' contributions

G.S. performed the statistical analyses and drafted the manuscript. G. S., H. K., R. I., Y. A., Y. I., Y. M., S.Y., H.S., Y.N., M.W., M.H., and S.E. contributed to the acquisition of data. H.K. participated in the design of the study design and study coordination. M.H. conceived the study, participated in the study design and coordination, and contributed to manuscript writing. All authors read and approved the final manuscript.

Funding Statement

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Competing interest statement.

Thde authors have no competing interests to declare.

Word Count

1837

Legends

Figure 1. Rehabilitation initiation and discontinuation criteria

ECG,electrocardiogram; MI, myocardial infarction; BP, blood pressure; SAT, spontaneous awaking trial; SBT, spontaneous breathing trial; RASS, Richmond Agitation-Sedation Scale; NRS, numerical rating scale; BPS, behavioral pain scale.

Figure 2. Rehabilitation program

The level at which rehabilitation should be initiated will be decided on consultation with the attending physician, nurse, and physiotherapist. MRC, Medical Research Council; ROM, range of motion

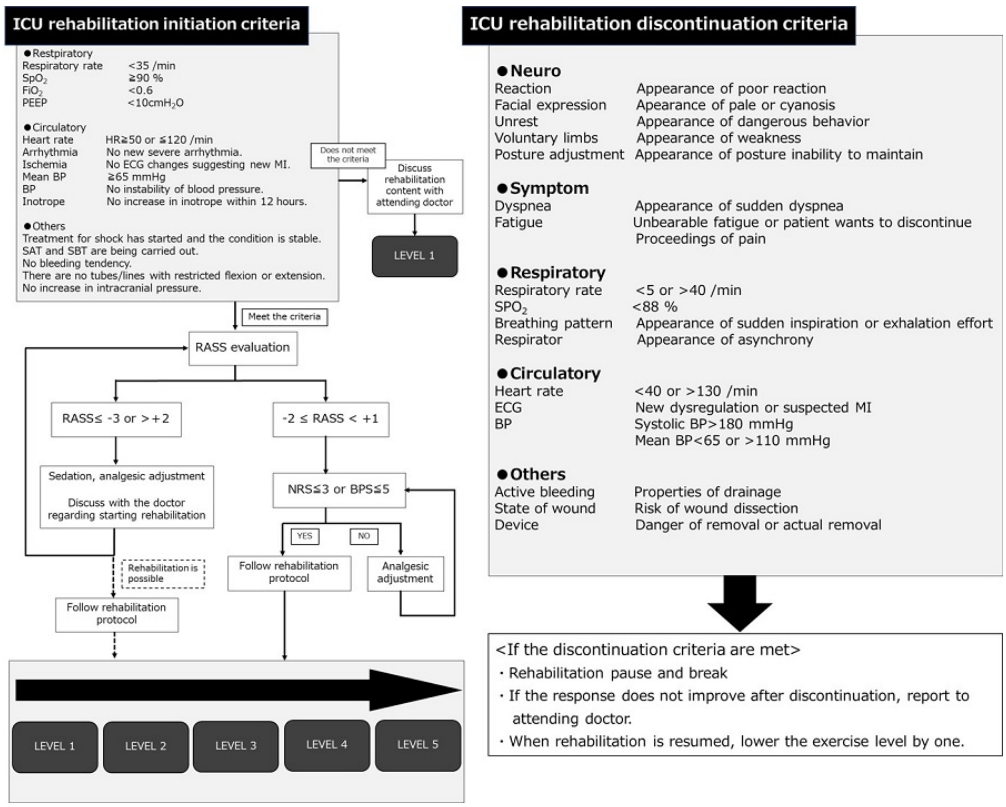

Figure 1. Rehabilitation initiation and discontinuation criteria
ECG,electrocardiogram; MI, myocardial infarction; BP, blood pressure; SAT, spontaneous awaking trial; SBT, spontaneous breathing trial; RASS, Richmond Agitation-Sedation Scale; NRS, numerical rating scale; BPS, behavioral pain scale.

153x122mm (149 x 149 DPI)

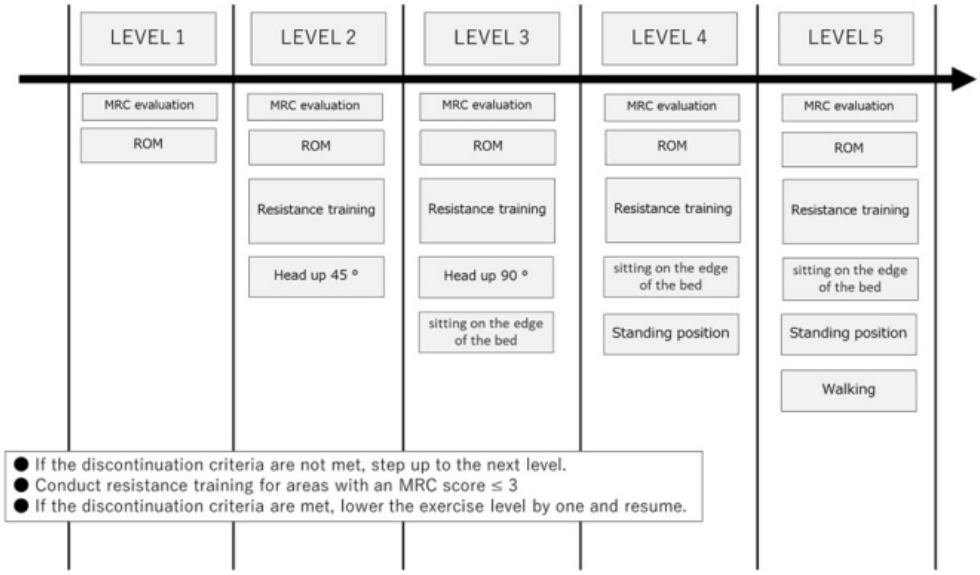

Figure 2. Rehabilitation program
The level at which rehabilitation should be initiated will be decided on consultation with the attending physician, nurse, and physiotherapist. MRC, Medical Research Council; ROM, range of motion

57x32mm (300 x 300 DPI)

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	ItemNo	Description	Page / Line
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	P1 / L3-4
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	P2 / L16
	2b	All items from the World Health Organization Trial Registration Data Set	Throuout the paper.
Protocol version	3	Date and version identifier	P6 / L20-22
Funding	4	Sources and types of financial, material, and other support	P8 / L22-24
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	P1 / L6-21
	5b	Name and contact information for the trial sponsor	P1 / L10-15
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	P8 / L22-24
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	P8 / 15-19
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	P2 / L29 – P3 / L10
	6b	Explanation for choice of comparators	P2 / L29 – P3 / L10
Objectives	7	Specific objectives or hypotheses	P2 / L29 – P3 / L10

Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	P3 / 13-14
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	P3 / 13-14
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	P3 / L22-24
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	P4 / L27 – P5 / L4
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	P4 / L27 – P5 / L4
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	P4 / L27 – P5 / L4
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	P4 / L27 – P5 / L4
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	P5 / L23-34
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	P3 / L22- 32
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	P5 / 15-21
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	P3 / L22- 32
Methods: Assignment of interventions (for controlled trials)			
Allocation:			

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	P5 / L6-13
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	P5 / L6-13
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	P5 / L6-13
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	P2 / L24
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	Not blinded
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	P4 / L31 – P5 / L4
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	P4 / L 12-15
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	P5 / L14-15
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	P5 / L36 – P6 / L11
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	P5 / L36 – P6 / L11
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	P5 / L36 – P6 / L11

Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	P8 / L27-28
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	P6 / L7-8
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	P5 / L34
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	P8 / L27-28
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	P6 / L13-19
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	P6 / L13-19
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	P6 / L13-19
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	Not applicable.
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	P6 / L13-19
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	P8 / L27-28
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	P6 / L13-19
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	Not applicable.

Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	P6 / L13-19
	31b	Authorship eligibility guidelines and any intended use of professional writers	P6 / L13-19
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	P6 / L13-19
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Supplement file
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	Not applicable.

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.