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Effect of vibration therapy on physical function in critically ill adults (VTICIA trial): Protocol for a randomized controlled trial

Short running title: Vibration therapy in critically ill adults

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ABSTRACT

Introduction: Vibration therapy has been used as an additional approach in passive rehabilitation. Recently, it has been shown to be feasible and safe for critically ill patients. However, the effectiveness is not clear in this specific population. There is an urgent need for devices to support rehabilitation as muscle weakness has become a serious problem in critically ill patients. A protocol for vibration therapy in a single-center, randomized controlled trial is described herein.

Methods and analysis: This study will enroll 188 adult critically ill patients who are expected to remain in the intensive care unit (ICU) for ≥5 days. They will be randomized to vibration therapy coupled with protocolized mobilization or to protocolized mobilization alone; outcomes will be compared between the two groups. Therapy will be administered using a low-frequency vibration device (5.6–13 Hz) for 15 minutes/day from when the patient first achieves a sitting position and onward until discharge from the ICU. Primary outcome is measured using the Functional Status Score for the ICU at discharge. Secondary outcomes are identified as follows: delirium, Medical Research Council score, ICU-acquired weakness, muscle atrophy measured by ultrasound, ICU mobility scale, and ventilator- and ICU-free days (number of free days 28 days after admission) with vital sign monitoring.

Ethics and dissemination: This study was approved by the Clinical Research Ethics Committee of Tokushima University Hospital. Results will be disseminated through publication in a peer-reviewed journal and presented at conferences.

Trial registration number: UMIN-Clinical Trials Registry: 000039616

Article Summary

Strengths and limitations of this study

- This randomized controlled trial is the first to evaluate whether vibration therapy can improve physical function and delirium in critically ill patients.
- The 15-minute intervention is added to protocolized mobilization from the start of sitting position onward to discharge from the ICU.
- This trial will contribute evidence-based treatment data in using vibration therapy in critically ill patients, a population for which current data are insufficient.
- Limitations of this study are the short length of intervention and the use of vibration therapy as an addition to protocolized mobilization versus vibration therapy alone.

Keywords: vibration therapy, critically ill patients, mobilization, muscle atrophy, delirium

INTRODUCTION

The mortality rate for critically ill patients has been on a decline by 35% over a decade.[1] However, survivors often experience prolonged impairment in their quality of life. In a study, one third of septic patients were identified to have some type of psychological or physical dysfunction 6 months after discharge from the intensive care unit (ICU).[2] These conditions are referred to as *post-intensive care syndrome* (PICS), which encompasses prolonged physical, mental, and cognitive dysfunction.[3] A significant cause of PICS is muscle weakness newly acquired in the ICU, which is termed *ICU-acquired weakness* (ICU-AW). This condition is associated to prolonged physical dysfunction, which is observed in 40% of critically ill patients.[4]

Physical therapy is essential to prevent muscle weakness.[5, 6] Mobilization has been widely recognized to be important in critically ill patients; however, out-of-bed mobilization is not widely practiced.[7] In one-point prevalence study, 33% of mechanically ventilated patients were mobilized out of bed and 2% ambulated, suggesting active mobilization is still infrequent in critically ill patients.[8] The barriers to mobilization vary, such as very heavy medical staff workload, limited staffing, and insufficient equipment.[9] The heavy workload of nurses hampers their active involvement in patient mobilization,[10] and full-time physical therapists are still not common in many ICUs.[11] Because these human resources are often limited, there is an urgent need for equipment and devices to support rehabilitation in the ICU.

Since 1960, vibration therapy has been used as an additional approach in passive rehabilitation.[12] This therapy generates vertical sinusoidal vibration. The transmitted vibration stimulates muscle spindles and produce muscle contractions. Vibration therapy has improved physical function in healthy individuals and in patients with chronic disease.[13, 14] A recent report documented that vibration therapy was safe and feasible in critically ill patients.[15] The device does not require patients' active cooperation and can be used passively. Because mobilization for critically ill patients is often limited to sitting without standing or ambulating,[8] the device can contribute to maximizing passive mobilization.

The study hypothesis is that vibration therapy can improve physical function in critically ill patients. The primary objective is to examine the effect it has on physical function measured at the discharge from the ICU. Secondary objectives are to assess the effects of vibration therapy on muscle strength, atrophy, mobility level, delirium, and ventilator- and ICU-free days (number of free days 28 days after admission) with vital sign monitoring. The structure and protocol of a single-center, randomized controlled trial are reported herein.

MATERIALS AND METHODS

Study Design and Settings

In August 2020, the authors will begin the conduct of a single-blinded, randomized controlled trial at the mixed medical/surgical ICU of Tokushima University Hospital in Japan. The trial is expected to take 2 years to complete. This study was approved by the Clinical Research Ethics Committee of Tokushima University Hospital (approval number 3763). This trial was registered as a clinical trial (UMIN-Clinical Trials Registry: 000039616). This study is based on the prospective, randomized, open-label, blinded endpoint (PROBE) study model and standard protocol items: recommendations for interventional trials (SPIRIT) statement.[16, 17]

Recruitment

The study will enroll all consecutive patients who meet the inclusion and exclusion criteria described in the following text. At the time of enrollment, written informed consent will be obtained from patients or their authorized surrogate decision-makers.

Inclusion and Exclusion Criteria

The study will enroll consecutive critically ill patients age ≥18 years who are expected to remain in the ICU for ≥5 days (Figure 1). Patients will be eligible when they can achieve sitting at the edge of the bed or wheelchair with or without mechanical ventilation. The study will exclude

patients based on the consensus for early mobilization in the Japanese Society of Intensive Care Medicine (JSICM) as follows[18]: (1) no permission from the primary physician; (2) excessive agitation [Richmond agitation-sedation scale (RASS) ≥2]; (3) impaired consciousness (RASS ≤3); (4) unstable vital signs requiring circulatory support devices, such as intra-aortic balloon pump; (5) sustained low blood pressure even with the use of catecholamine; (6) dynamic blood pressure change after body position change; (7) risk for rupture in untreated aneurysms; (8) uncontrolled pain; (9) uncontrolled intracranial pressure ≥20 mmHg; (10) unstable phase in the head or cervical spine injury; (11) unstable bone fracture; (12) active bleeding; (13) insufficient stabilization or length of catheters; (14) insufficient staffing; and (15) no consent from patients or surrogates.

Withdrawal from the Study

Patients can withdraw from the study at any time, which will not affect the medical care they are receiving upon withdrawal. The research team will stop the intervention and consider withdrawal for patients based on the JSICM criteria as follows.[18]

(1) *Generalized symptoms*: unresponsive state; agonized facial expression, pale skin, or cyanosis; newly occurred impaired consciousness; agitation with risk to safety; sudden limb weakness or dependence; inability to sustain posture, and risk for fall.

(2) *Subjective symptoms*: sudden dyspnea; unbearable fatigue or suffering; and desire to withdraw.

(3) *Respiration*: respiratory rate <5/min or >40/min; oxygen saturation <88%; increased work of breathing; and asynchrony with mechanical ventilation or fighting the ventilator.

(4) *Circulation*: heart rate <40/min or >130/min; electrocardiogram, newly occurred arrhythmia, sign of cardiac ischemia; blood pressure, systolic blood pressure >180 mmHg, decreased systolic or diastolic blood pressure >20%, mean arterial pressure <65 mmHg or >110 mmHg.

(5) *Devices*: risk for unplanned extubation or removal of tube, catheter, and drain.

(6) *Other conditions*: desire to withdraw from the study; increased drainage of blood; and risk for widening a wound.

Randomization

The patients will be randomized using computer-generated randomization lists.[19] Randomization will be stratified by age (<70 years, ≥70) and sex (female or male), and the randomization list will be generated with a block size of 4 before the start of recruitment.[20] Patients will be subjected either to vibration therapy added to protocolized mobilization or to protocolized mobilization alone as the usual standard of care.

Blinding

This study is a single-blinded trial design because patients can understand the intervention or control. For the control group, the vibration device will be used as a footrest without vibration by blinded staff. All interventions will be conducted by bedside nurses. The intervention duration will be 15 minutes and will be conducted when no other staff who are involved in outcome assessments, treatments, and usual rehabilitation are present.

Interventions

A vibration device (BW-750, BodyGreen) will be used by bedside nurses once daily (Figure 2 and supplementary video file). The device will be used in sitting position for 15 minutes. A low-frequency vibration from 5.6 to 13 Hz with an amplitude of 2 mm in vertical direction can be chosen on the device. This study will use a continuous automatic course of 5.6 Hz, 7 Hz, and 8 Hz for 30 seconds each in turn. The intervention days will be recorded in compliance with the protocol. With or without intervention, protocolized mobilization will be conducted in all patients. Protocolized mobilization is based on a progressive mobilization protocol described by Morris et al.[21] in which the mobilization level is decided according to patients' consciousness

and muscle strength. Passive range of motion is conducted for unconscious patients, whereas in conscious patients, the intensity is gradually elevated to active resistance, sitting on the edge of bed, and ambulation. Mobilization level will be restricted in patients with unstable vital signs.

Outcomes

The primary outcome is physical function assessment using the Functional Status Score for the ICU (FSS-ICU) at the discharge from the ICU, measured by a blinded nurse. The FSS-ICU is a physical function score involving five functional tasks: (1) rolling, (2) transferring from resting on spine to sitting, (3) sitting at the edge of bed, (4) transferring from sit to stand, and (5) walking.[22] Each task is scored from 0 to 7, with the maximum score of 35. The research team conducted a training period for the use of FSS-ICU for 2 months before the start of this study to ensure the scoring accuracy.

Secondary outcomes are muscle strength and the incidence of ICU-AW and score on the ICU mobility scale (IMS). After patients are awake and attentive, nurses evaluate the Medical Research Council (MRC) score and the incidence of ICU-AW on daily practice. Intact level of consciousness and awareness will be assessed by patient's response to at least three of five orders: "open/close your eyes"; "look at me"; "open your mouth and put out your tongue"; "nod your head"; and "raise your eyebrows." [23] The MRC score is the sum of the manual muscle testing in six bilaterally tested muscle groups: (1) shoulder abductors, (2) elbow flexors, (3) wrist extensors, (4) hip flexors, (5) knee extensors, and (6) ankle dorsiflexors. The ICU-AW is defined as an MRC score of <48 on two separate occasions, and patients with expected preadmission MRC score of <48 will be excluded.[24] The research team will use the MRC score and the incidence of ICU-AW at discharge from the ICU for comparison. To assess mobilization level during the ICU stay, the research team will use the IMS, which is a measure of mobilization capabilities from 0 (lying in bed) to 10 (walking independently).[25] In addition to the discharge from the ICU, the research team will evaluate the maximum IMS score during the study period

because the maximum level of mobility is considered to be an important prognostic factor.[26] Blinded nurses will evaluate MRC score, ICU-AW, and IMS as conducted in clinical practice.

Muscle atrophy will be evaluated with serial ultrasound measurements on admission and at the discharge from the ICU.[27] Ultrasound has been identified as a reliable way to measure muscle mass.[28, 29] The cross-sectional area of the rectus femoris muscle will be evaluated at the midway point between the anterior superior iliac spine and the proximal end of the patella. A transducer will be placed perpendicular to the long axis of the rectus femoris muscle with patients in the supine position under passive knee extension. The rectus femoris cross-sectional area will be measured thrice, and the median value will be used for evaluation. The research team will use the change of rectus femoris cross-sectional area from ICU admission to the discharge from the ICU for comparison. All measurements will be conducted by two examiners. In the authors' previous studies, intraclass and interclass correlation coefficients were determined to be 0.99 and 0.99 for rectus femoris cross-sectional area, respectively.[30]

As another secondary outcome, the research team will assess delirium by using the confusion assessment method for the ICU (CAM-ICU), which includes acute change or a fluctuation in mental status, altered level of consciousness, disorganized thinking, and inattention.[31] To assess the level of consciousness, the RASS will be used, which ranges from −5 to 4, with lower scores indicating less arousal.[32] The research team will assess the duration of delirium and the state at discharge from the ICU. Nurses in the ICU will conduct the CAM-ICU assessment three times daily.

The *ICU-free days* are defined as the number after discharge from ICU during the 28 days after ICU admission, whereas *ventilator-free days* are defined as the number of days without mechanical ventilation during the 28 days after ICU admission.

Safety

To assess the safety of vibration therapy, vital signs will be monitored from baseline

measurements conducted before the start of vibration therapy and 5 or 15 minutes after the use of therapy. Vital signs include blood pressure (systolic, diastolic, and mean), heart rate, and oxygen saturation. Finally, follow-up will be conducted at discharge from the hospital to assess the patient's post-study health status and any harmful events. In the authors' facility, no adverse events, as described in the withdrawal criteria, were observed in 30 critically ill patients who were treated with vibration therapy (BW-750, BodyGreen) before the start of this study.

Data Collection and Management

The research director and Clinical Research Ethics Committee will oversee the study protocol and data to ensure the accuracy. All data must be presented as requested, and any missing or inconsistent data will be requested or addressed by the research director. Any adverse effects or complications will be immediately reported, and necessary compensation will be provided to any patients who experience harm from trial participation. All records will be retained for 3 years after the completion or termination of the study.

Confidentiality

All datasets will be stored by creating identification codes to anonymize study participants' information. The coding keys linking identification codes will be stored by the research director. The study participants' information will be protected when publishing the trial results or reporting results at an academic conference. This information will be used only for this research and not for exchange with other facilities.

Data Access and Dissemination

Study protocol will be available to subjects upon request. Study data will also be available unless the request hinders the protection of personal information or the quality of this study. Individuals involved in the study will have access to the final dataset and will be able to publish the study or

report the study at an academic conference.

Patient and Public Involvement

This study will not involve patients in the development of the research question and outcome measures. Patients will not be involved in the design and recruitment. Results will be disseminated to study participants upon request.

Sample Size

The sample size calculation will be based on two studies.[22, 33] The FSS-ICU at the discharge from ICU is reported to be 20 (10–30), with a minimal clinically important difference from 2.0 to 5.0. The authors hypothesize that in this study, a 3.0 difference will be observed because vibration therapy is expected to improve standing and ambulating by 2–4. The standard deviation is reported to be 5.9. These data estimate that 171 patients will be needed to observe the difference with alpha 0.05 and power of 90%. Assuming a 10% dropout rate due to complete withdrawal or death, a total of 188 patients will be needed. Study participants will be randomized either to vibration therapy coupled with protocolized mobilization (n = 94) or protocolized mobilization alone (n = 94).

Statistical Analysis

After data collection, descriptive analyses will be conducted on the obtained data. Continuous data will be presented as mean ± standard deviation or median (interquartile range), whereas categorical data will be presented as number (%). Variables will be compared using the t-test or the Mann–Whitney U-test for the comparison of the two groups. The efficacy and safety analysis will be conducted in a full-analysis set and safety analysis set following the intention-to-treat principle. The full-analysis set includes patients who received at least one intervention and had primary outcome assessment. The safety analysis set includes patients who received at least one

intervention. In addition, a subgroup analysis will be conducted by the duration of intervention. Primary outcome will be compared at the discharge from the ICU; secondary outcomes will be compared in each point as previously described. Patients with missing values will be excluded from the analysis. Safety analysis will be conducted by comparing the change in vital signs from the start of the therapy session as the baseline to 5 or 15 minutes after the intervention. Data analyses will be conducted using JMP version 13.1.0 (SAS Institute). All statistical tests will be two tailed, and $p < 0.05$ will be considered statistically significant.

DISCUSSION

This study describes an intervention protocol of vibration therapy to improve physical function in critically ill patients. Although vibration therapy has been used for decades, its effect remains unclear in the field of critical illness. To the best of these authors' knowledge, no studies to date have conducted to examine the efficacy of vibration therapy in critically ill patients.

The randomized controlled trial design is feasible because research has already proven that vibration therapy can be used safely in critically ill patients.[34] Vibration therapy is typically used for days or weeks; however, some patients in the ICU stay for a short time (<1 week). In Japan, 38.9% of patients are admitted to the ICU only for monitoring, and the median length of ICU stay is 2.5 (1.4–4.8) days in critically ill patients.[35] Therefore, the selection of patients is important, and this study will enroll the patients who are expected to require a longer stay of ≥5 days in the ICU. Vibration therapy will be used for 15 minutes/day, which is proven to be safe in critically ill patients.[15] In previous studies, vibration therapy was beneficial with the use of 6–18 minutes/day in patients with cystic fibrosis or stroke.[36, 37] In those studies, vibration therapy was used for weeks to months; however, for this current study, the intervention duration depends on the time from the first use of vibration therapy in the ICU to discharge from the ICU. Therefore, subgroup analysis by the intervention duration is necessary because it is unclear how the short-term use of vibration therapy affects physical function.

Among the different vibration devices, the frequency of vibration varies from 2 to 90 Hz. Although the vibration frequency of 2 Hz is too low to have a treatment effect,[38] the higher vibration frequencies have some effect. This study will use a relatively low-frequency vibration device (5.6–8 Hz). These frequencies of vibration are useful to improve physical function, and a 5–14 Hz vibration has been shown to significantly improve physical function, including gait speed and handgrip strength.[39] In another study, a low frequency ranging from 2 to 20 Hz improved muscle strength for the knee extensor.[40] A recent study that used the same vibration device that will be used in this study, the BW-750, BodyGreen, reported that this device was useful in improving muscle strength knee extensor in patients with post-total knee arthroplasty.[41] Moreover, low-frequency vibrations of 12–15 Hz had more beneficial effects on bone mass than vibrations of 30–90 Hz or even than walking.[42, 43]

The research team will monitor muscle atrophy because physical function is difficult to assess in some critically ill patients.[44] Muscle atrophy is a critical problem in the ICU, and in 1 week, the muscle atrophy may reach the degree of 13.2–16.9% and 18.8–20.7% in the upper and lower limbs, respectively.[45] Moreover, muscle atrophy occurs in respiratory muscles.[46] Vibration therapy has reportedly contributed to preventing limb muscle atrophy. In one study, vibration therapy contributed to preventing atrophy of quadriceps femoris muscle in healthy volunteers (−3.3% vs. −14.4% in 56 days).[47] Vibration not only serves as resistance training but also provides the stimulation that can promote the proliferation of myoblast cells and downregulates atrophy genes.[48] We will monitor muscle atrophy using ultrasound because biomarker is increased in surgical patients who will be included in this study.[49]

Delirium has been observed in 30% of critically ill patients,[50] and the length of ICU stay is associated with long-term cognitive dysfunction.[51] Delirium is another significant cause of PICS. The authors believe that vibration therapy will contribute to improving delirium based on three reasons. First, enhanced rehabilitation using vibration therapy will contribute to decreasing delirium[6] because early mobilization has been reported to reduce the days of delirium (2 vs. 4, *p*

= 0.03).[52] Second, vibration therapy improves circulation. Low cerebral perfusion is a risk factor of delirium, and 10-mmHg decrease in cerebral perfusion has an odds ratio of 2.08 (95% confidence interval, 1.02–4.24) in predicting delirium.[53] Vibration can improve circulation to vital organs, including the brain.[54] This effect has also been confirmed via a post-cardiac arrest model using pigs.[55] The mechanism is considered to be increased nitric oxide or decreased endothelial damage.[56, 57] Third, vibration therapy affects the hormone signals produced from the body.[58] The growth hormone, which is increased by vibration, has neuroprotective properties, and these effects may improve delirium.[59]

However, this study has some limitations. First, although early intervention with vibration therapy may be beneficial for patients, the therapy will not be used for this trial until patients can sit. In these authors' experience, the use of vibration therapy is stressful to patients when they are confined to the bed. Second, for this study, the muscle load may be weak, as commented on previously, because vibration therapy will be used in the sitting position without additional muscle load.[34] The authors are using this approach to avoid adding stress for critically ill patients. Third, this study will provide the results of vibration therapy added to protocolized mobilization, not vibration therapy alone. The effect may be limited in patients who can not do active mobilization because a recent study showed electrical muscle stimulation and in-bed leg cycling did not improve physical function in patients who had active mobilization.[60] Electrical muscle stimulation was effective in patients with limited mobilization.[61] Therefore, subgroup analysis may be required to determine the effect in patients for whom active mobilization is limited.

Trial status

This trial is not recruiting patients at the time of manuscript submission.

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Author Contributions

NN was involved in study concept and design and drafting of the manuscript. SD, YK, and MS took part in study concept and design. JO took part in the critical revision of the manuscript. All authors read and approved the final manuscript.

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Competing interests None declared.

Patient consent for publication Consent was obtained for the use of Figure 1 and video.

Ethics approval Ethics approval was obtained from Tokushima University Hospital (approval number: 3763).

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REFERENCES

1. Zimmerman JE, Kramer AA, Knaus WA. Changes in hospital mortality for United States intensive care unit admissions from 1988 to 2012. *Crit Care* 2013;17:R81.

2. Yende S, Austin S, Rhodes A, et al. Long-term quality of life among survivors of severe sepsis: analyses of two international trials. *Crit Care Med* 2016;44:1461-7.

3. Inoue S, Hatakeyama J, Kondo Y, et al. Post-intensive care syndrome: its pathophysiology, prevention, and future directions. *Acute Med Surg* 2019;6:233-46.

4. Van Aerde N, Meersseman P, Debaveye Y, et al. Five-year impact of ICU-acquired neuromuscular complications: a prospective, observational study. *Intensive Care Med* 2020:10.1007/s00134-020-5927-5.

5. Fuke R, Hifumi T, Kondo Y, et al. Early rehabilitation to prevent postintensive care syndrome in patients with critical illness: a systematic review and meta-analysis. *BMJ Open* 2018;8:e019998.

6. Inouye SK, Westendorp RG, Saczynski JS. Delirium in elderly people. *Lancet* 2014;383:911-22.

7. Jolley SE, Moss M, Needham DM, et al. Point prevalence study of mobilization practices for

acute respiratory failure patients in the United States. *Crit Care Med* 2017;45:205-15.

8. Sibilla A, Nydahl P, Greco N, et al. Mobilization of mechanically ventilated patients in switzerland. *J Intensive Care Med* 2020;35:55-62.

9. Wang J, Xiao Q, Zhang C, et al. Intensive care unit nurses' knowledge, attitudes, and perceived barriers regarding early mobilization of patients. *Nurs Crit Care* 2020.

10. Eakin MN, Ugbah L, Arnautovic T, et al. Implementing and sustaining an early rehabilitation program in a medical intensive care unit: A qualitative analysis. *J Crit Care* 2015;30:698-704.

11. Taito S, Sanui M, Yasuda H, et al. Current rehabilitation practices in intensive care units: a preliminary survey by the Japanese Society of Education for Physicians and Trainees in Intensive Care (JSEPTIC) Clinical Trial Group. *J Intensive Care* 2016;4:66.

12. Buckhout R. Effect of whole body vibration on human performance. *Hum Factors* 1964;6:157-63.

13. Cardim AB, Marinho PE, Nascimento JF, Jr., et al. Does whole-body vibration improve the functional exercise capacity of subjects with COPD? a meta-analysis. *Respir Care* 2016;61:1552-59.

14. Furness TP, Maschette WE, Lorenzen C, et al. Efficacy of a whole-body vibration intervention on functional performance of community-dwelling older adults. *J Altern Complement Med* 2010;16:795-7.

15. Wollersheim T, Haas K, Wolf S, et al. Whole-body vibration to prevent intensive care unit-acquired weakness: safety, feasibility, and metabolic response. *Critical Care* 2017;21:9.

16. Hansson L, Hedner T, Dahlöf B. Prospective randomized open blinded end-point (PROBE) study. A novel design for intervention trials. Prospective Randomized Open Blinded End-Point. *Blood Press* 1992;1:113-9.

17. Chan AW, Tetzlaff JM, Gøtzsche PC, et al. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. *BMJ* 2013;346:e7586.

18. Ad Hoc Committee for Early Rehabilitation TJSoICM. Evidence based expert consensus for

early rehabilitation in the intensive care unit. *J Jpn Soc Intensive Care Med* 2017;24:255-303.

19. Nagashima K. A computerized number generator through the stratified block randomization. [Internet] 2017 April 26. https://nshi.jp/contents/js/randblock/

20. Zelen M. The randomization and stratification of patients to clinical trials. *J Chronic Dis* 1974;27:365-75.

21. Morris PE, Goad A, Thompson C, et al. Early intensive care unit mobility therapy in the treatment of acute respiratory failure. *Crit Care Med* 2008;36:2238-43.

22. Huang M, Chan KS, Zanni JM, et al. Functional status score for the ICU: An international clinimetric analysis of validity, responsiveness, and minimal important difference. *Crit Care Med* 2016;44:e1155-e64.

23. De Jonghe B, Bastuji-Garin S, Durand MC, et al. Respiratory weakness is associated with limb weakness and delayed weaning in critical illness. *Crit Care Med* 2007;35:2007-15.

24. Stevens RD, Marshall SA, Cornblath DR, et al. A framework for diagnosing and classifying intensive care unit-acquired weakness. *Crit Care Med* 2009;37:S299-308.

25. Hodgson C, Needham D, Haines K, et al. Feasibility and inter-rater reliability of the ICU mobility scale. *Heart Lung* 2014;43:19-24.

26. Kim RY, Murphy TE, Doyle M, et al. Factors associated with discharge home among medical ICU patients in an early mobilization program. *Crit Care Explor* 2019;1:e0060.

27. Palakshappa JA, Bakhru RN. Bedside ultrasonography can and should be used in the ICU to evaluate muscle atrophy. *Ann Am Thorac Soc* 2019;16:1107-11.

28. Lambell KJ, Tierney AC, Wang JC, et al. Comparison of ultrasound-derived muscle thickness with computed tomography muscle cross-sectional area on admission to the Intensive Care Unit: a pilot cross-sectional study. *JPEN J Parenter Enteral Nutr* 2020.

29. Yuguchi S, Asahi R, Kamo T, et al. Gastrocnemius thickness by ultrasonography indicates the low skeletal muscle mass in Japanese elderly people. *Arch Gerontol Geriatr* 2020;90:104093.

30. Nakanishi N, Tsutsumi R, Okayama Y, et al. Monitoring of muscle mass in critically ill

patients: comparison of ultrasound and two bioelectrical impedance analysis devices. *J Intensive Care* 2019;7:61.

31. Ely EW, Inouye SK, Bernard GR, et al. Delirium in mechanically ventilated patients: validity and reliability of the confusion assessment method for the intensive care unit (CAM-ICU). *JAMA* 2001;286:2703-10.

32. Sessler CN, Gosnell MS, Grap MJ, et al. The Richmond Agitation-Sedation Scale: validity and reliability in adult intensive care unit patients. *Am J Respir Crit Care Med* 2002;166:1338-44.

33. Reid JC, Clarke F, Cook DJ, et al. Feasibility, reliability, responsiveness, and validity of the patient-reported functional scale for the intensive care unit: a pilot study. *J Intensive Care Med* 2019:885066618824534.

34. Alter P, Boeselt T, Nell C, et al. Feasibility and safety of whole-body vibration therapy in intensive care patients. *Crit Care* 2017;21:91.

35. Irie H, Okamoto H, Uchino S, et al. The Japanese Intensive care PAtient Database (JIPAD): A national intensive care unit registry in Japan. *J Crit Care* 2020;55:86-94.

36. Rietschel E, van Koningsbruggen S, Fricke O, et al. Whole body vibration: a new therapeutic approach to improve muscle function in cystic fibrosis? *Int J Rehabil Res* 2008;31:253-6.

37. Tihanyi TK, Horváth M, Fazekas G, et al. One session of whole body vibration increases voluntary muscle strength transiently in patients with stroke. *Clin Rehabil* 2007;21:782-93.

38. Jackson KJ, Merriman HL, Vanderburgh PM, et al. Acute effects of whole-body vibration on lower extremity muscle performance in persons with multiple sclerosis. *J Neurol Phys Ther* 2008;32:171-6.

39. Sá-Caputo D, Paineiras-Domingos LL, Francisca-Santos A, et al. Whole-body vibration improves the functional parameters of individuals with metabolic syndrome: an exploratory study. *BMC Endocr Disord* 2019;19:6.

40. Eftekhari E, Mostahfezian M, Etemadifar M, et al. Resistance training and vibration improve

muscle strength and functional capacity in female patients with multiple sclerosis. *Asian J Sports Med* 2012;3:279-84.

41. Hsiao YH, Chien SH, Tu HP, et al. Early post-operative intervention of whole-body vibration in patients after total knee arthroplasty: a pilot study. *J Clin Med* 2019;8.

42. Minematsu A, Nishii Y, Imagita H, et al. Whole body vibration at low-frequency can increase trabecular thickness and width in adult rats. *J Musculoskelet Neuronal Interact* 2019;19:169-77.

43. Gusi N, Raimundo A, Leal A. Low-frequency vibratory exercise reduces the risk of bone fracture more than walking: a randomized controlled trial. *BMC Musculoskelet Disord* 2006;7:92.

44. Nakanishi N, Takashima T, Oto J. Muscle atrophy in critically ill patients: a review of its cause, evaluation, and prevention. *J Med Invest* 2020;67:1-10.

45. Nakanishi N, Oto J, Tsutsumi R, et al. Upper and lower limb muscle atrophy in critically ill patients: an observational ultrasonography study. *Intensive Care Med* 2018;44:263-64.

46. Nakanishi N, Oto J, Ueno Y, et al. Change in diaphragm and intercostal muscle thickness in mechanically ventilated patients: a prospective observational ultrasonography study. *J Intensive Care* 2019;7:56.

47. Belavý DL, Miokovic T, Armbrecht G, et al. Resistive vibration exercise reduces lower limb muscle atrophy during 56-day bed-rest. *J Musculoskelet Neuronal Interact* 2009;9:225-35.

48. Ceccarelli G, Benedetti L, Galli D, et al. Low-amplitude high frequency vibration down-regulates myostatin and atrogin-1 expression, two components of the atrophy pathway in muscle cells. *J Tissue Eng Regen Med* 2014;8:396-406.

49. Nakanishi N, Tsutsumi R, Hara K, et al. Urinary titin is a novel biomarker for muscle atrophy in nonsurgical critically ill patients: a two-center, prospective observational study. *Crit Care Med* 2020.

50. Salluh JI, Wang H, Schneider EB, et al. Outcome of delirium in critically ill patients: systematic review and meta-analysis. *BMJ* 2015;350:h2538.

51. Pandharipande PP, Girard TD, Jackson JC, et al. Long-term cognitive impairment after critical illness. *N Engl J Med* 2013;369:1306-16.

52. Schweickert WD, Pohlman MC, Pohlman AS, et al. Early physical and occupational therapy in mechanically ventilated, critically ill patients: a randomised controlled trial. *Lancet* 2009;373:1874-82.

53. Smith PJ, Blumenthal JA, Hoffman BM, et al. Reduced cerebral perfusion pressure during lung transplant surgery is associated with risk, duration, and severity of postoperative delirium. *Ann Am Thorac Soc* 2016;13:180-7.

54. Adams JA, Mangino MJ, Bassuk J, et al. Regional blood flow during periodic acceleration. *Crit Care Med* 2001;29:1983-8.

55. Adams JA, Uryash A, Wu H, et al. Microcirculatory and therapeutic effects of whole body periodic acceleration (pGz) applied after cardiac arrest in pigs. *Resuscitation* 2011;82:767-75.

56. Sackner MA, Gummels E, Adams JA. Nitric oxide is released into circulation with whole-body, periodic acceleration. *Chest* 2005;127:30-9.

57. Matsumoto T, Fujita M, Tarutani Y, et al. Whole-body periodic acceleration enhances brachial endothelial function. *Circ J* 2008;72:139-43.

58. Bosco C, Iacovelli M, Tsarpela O, et al. Hormonal responses to whole-body vibration in men. *Eur J Appl Physiol* 2000;81:449-54.

59. Adamis D, Lunn M, Martin FC, et al. Cytokines and IGF-I in delirious and non-delirious acutely ill older medical inpatients. *Age Ageing* 2009;38:326-32; discussion 251.

60. Fossat G, Baudin F, Courtes L, et al. Effect of in-bed leg cycling and electrical stimulation of the quadriceps on global muscle strength in critically ill adults: a randomized clinical trial. *JAMA* 2018;320:368-78.

61. Nakanishi N, Oto J, Tsutsumi R, et al. Effect of electrical muscle stimulation on upper and lower limb muscles in critically ill patients: A two-center randomized controlled trial. *Crit Care Med* 2020.

Figure Legends

Figure 1. Flow chart of study protocol. ICU, intensive care unit.

Figure 2. Image of vibration therapy. (BW-750, BodyGreen). Consent was obtained for the use of this image.

Supplemental Data

Supplemental file. Video image of vibration therapy.

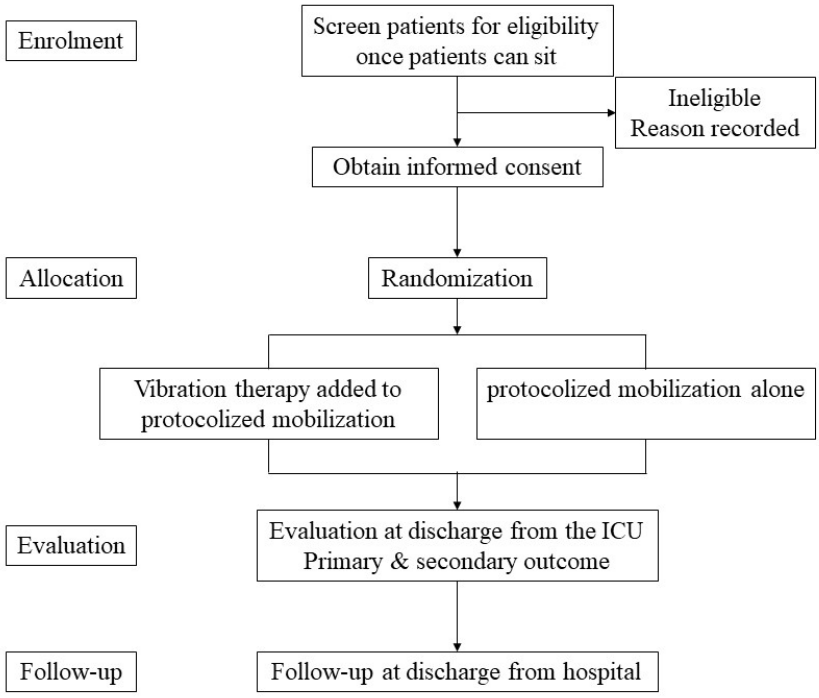

Figure 1

81x60mm (300 x 300 DPI)

Figure 2

81x60mm (300 x 300 DPI)

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

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	4
	2b	All items from the World Health Organization Trial Registration Data Set	4
Protocol version	3	Date and version identifier	4
Funding	4	Sources and types of financial, material, and other support	12
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	12
	5b	Name and contact information for the trial sponsor	None
	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	None
	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)	None

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	3
	6b	Explanation for choice of comparators	3
Objectives	7	Specific objectives or hypotheses	4
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)	4
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	4
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)	4,5
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	6
	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)	5,6
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	5
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	6,7
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	7,8
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)	4,5

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	9
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	9
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	6
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	6
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	6
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	6
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	6
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	7,8
	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	8

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	9
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	10
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	10
	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)	10
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	8
	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	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	8
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	8
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	4
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)	4

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	4
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	4
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	9
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	12
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	9
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	8
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	9
	31b	Authorship eligibility guidelines and any intended use of professional writers	12
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	9
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	No English document
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	None

*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

Effect of vibration therapy on physical function in critically ill adults (VTICIA trial): Protocol for a single-blinded randomised controlled trial

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Supplementary File-Video.mp4	

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Effect of vibration therapy on physical function in critically ill adults (VTICIA trial): Protocol for a single-blinded randomised controlled trial

Short running title: Vibration therapy in critically ill adults

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ABSTRACT

Introduction: Vibration therapy has been used as an additional approach in passive rehabilitation. Recently, it has been demonstrated to be feasible and safe for critically ill patients, in who muscle weakness and intensive care unit (ICU)-acquired weakness are serious problems. However, the effectiveness of vibration therapy in this population is unclear.

Methods and analysis: This study will enrol 188 adult critically ill patients who are expected to remain in the ICU for ≥5 days. The sample size calculation is based on a 15% improvement of Functional Status Score for the ICU. They will be randomised to vibration therapy coupled with protocolised mobilisation or to protocolised mobilisation alone; outcomes will be compared between the two groups. Therapy will be administered using a low-frequency vibration device (5.6–13 Hz) for 15 min/day from when the patient first achieves a sitting position and onward until discharge from the ICU. Outcome assessments will be blinded to the intervention. Primary outcome will be measured using the Functional Status Score for the ICU at discharge. Secondary outcomes will be identified as follows: delirium, Medical Research Council score, ICU-acquired weakness, the change of biceps brachii and rectus femoris muscle mass measured by ultrasound, ICU mobility scale and ventilator- and ICU-free days (number of free days 28 days after admission). For safety assessment, vital signs will be monitored during the intervention.

Ethics and dissemination: This study has been approved by the Clinical Research Ethics Committee of Tokushima University Hospital. Results will be disseminated through publication in a peer-reviewed journal and presented at conferences.

Trial registration number: UMIN-Clinical Trials Registry: 000039616

Article Summary

Strengths and limitations of this study

- This randomised controlled trial is the first to evaluate whether vibration therapy can improve physical function and delirium in critically ill patients.

- The 15-min intervention is added to protocolised mobilisation from the start of sitting position onward to discharge from the ICU.
- This trial will contribute evidence-based treatment data in using vibration therapy in critically ill patients, a population for which current data are insufficient.
- Limitations of this study are the short length of intervention and the use of vibration therapy added to protocolised mobilisation, not vibration therapy alone.

Keywords: vibration therapy, critically ill patients, mobilisation, muscle mass, delirium

INTRODUCTION

There has been a decline in the mortality rate for critically ill patients by 35% over a decade.[1] However, survivors often experience prolonged impairment in their quality of life. In a study, one-third of septic patients were identified to have some type of psychological or physical dysfunction 6 months after discharge from the intensive care unit (ICU).[2] These conditions are referred to as *post-intensive care syndrome* (PICS), which encompasses prolonged physical, mental and cognitive dysfunction.[3] A significant cause of PICS is muscle weakness newly acquired in the ICU, which is termed as *ICU-acquired weakness* (ICU-AW). This condition is associated with prolonged physical dysfunction, which is observed in 40% of critically ill patients.[4]

Physical therapy is essential to prevent muscle weakness.[5, 6] Mobilisation has been widely recognised to be important in critically ill patients; however, out-of-bed mobilisation is not widely practiced.[7] In a one-point prevalence study, 33% of mechanically ventilated patients were mobilised out of bed and 2% were ambulated, suggesting that active mobilisation is still infrequent in critically ill patients.[8] The barriers to mobilisation vary, such as very heavy medical staff workload, limited staffing and insufficient equipment.[9] The heavy workload of nurses hampers their active involvement in patient mobilisation,[10] and full-time physical therapists are still not common in several ICUs.[11] Because these human resources are often limited, there is an urgent need for equipment and devices to support rehabilitation in the ICU.

Since 1960, vibration therapy has been used as an additional approach in passive rehabilitation.[12] This therapy generates vertical sinusoidal vibration. The transmitted vibration stimulates muscle spindles and produces muscle contractions. Studies have reported that vibration therapy improved physical function in both healthy individuals and patients with chronic disease.[13, 14] A recent report documented that vibration therapy was safe and feasible in critically ill patients.[15] The device does not require patients' active cooperation and can be used passively. Because mobilisation for critically ill patients is often limited to sitting without

standing or ambulating,[8] the device can contribute to maximising passive mobilisation.

The study hypothesis is that vibration therapy can improve physical function in critically ill patients. The primary objective is to investigate its effect on physical function measured at discharge from the ICU. The secondary objectives are to determine the effects of vibration therapy on muscle strength, muscle mass, mobility level, delirium and ventilator- and ICU-free days (number of free days 28 days after admission). This study will allow us to objectively analyse whether vibration therapy can improve physical functions and how it impacts clinical outcomes in critically ill patients.

MATERIALS AND METHODS

Study Design and Settings

In August 2020, the authors will initiate a single-blinded, randomised controlled trial at the mixed medical/surgical ICU of Tokushima University Hospital in Japan. The trial is expected to take 2 years to complete. This study has been approved by the Clinical Research Ethics Committee of Tokushima University Hospital (approval number 3763) and registered as a clinical trial (UMIN-Clinical Trials Registry: 000039616). This study is based on the prospective, randomised, open-label, blinded endpoint (PROBE) study model and the standard protocol items: recommendations for interventional trials (SPIRIT) statement.[16, 17]

Recruitment

All consecutive patients who meet the inclusion and exclusion criteria described in the following text will be enrolled in this study. At the time of enrollment, written informed consent will be obtained from patients or their authorised surrogate decision-makers.

Inclusion and Exclusion Criteria

The study will enroll consecutive critically ill patients aged ≥18 years who are expected to

remain in the ICU for ≥5 days at the time of study enrollment (Figure 1). Patients will be eligible when they can achieve sitting at the edge of the bed or wheelchair with or without mechanical ventilation. The study will exclude patients based on the consensus for early mobilisation in the Japanese Society of Intensive Care Medicine (JSICM) as follows[18]: (1) no permission from the primary physician; (2) excessive agitation [Richmond agitation-sedation scale (RASS) ≥ 2]; (3) impaired consciousness (RASS ≤3); (4) unstable vital signs requiring circulatory support devices, such as intra-aortic balloon pump; (5) sustained low blood pressure even with the use of catecholamine; (6) dynamic blood pressure change after body position change; (7) risk for rupture in untreated aneurysms; (8) uncontrolled pain; (9) uncontrolled intracranial pressure ≥20 mmHg; (10) unstable phase in the head or cervical spine injury; (11) metal implants or unstable bone fractures in the extremities or spine; (12) active bleeding; (13) insufficient stabilisation or length of catheters; (14) insufficient staffing and (15) no consent from patients or surrogates.

Withdrawal from the Study

Patients can withdraw from the study at any time, which will not affect the medical care they are receiving upon withdrawal. The research team will stop the intervention and consider withdrawal for patients based on the JSICM criteria as follows:[18]

(1) *Generalised symptoms*: unresponsive state; agonised facial expression, pale skin or cyanosis; newly occurred impaired consciousness; agitation with risk to safety; sudden limb weakness or dependence; inability to sustain posture and risk for fall.

(2) *Subjective symptoms*: sudden dyspnoea; unbearable fatigue or suffering and desire to withdraw.

(3) *Respiration*: respiratory rate <5/min or >40/min; oxygen saturation <88%; increased work of breathing and asynchrony with mechanical ventilation or fighting the ventilator.

(4) *Circulation*: heart rate <40/min or >130/min; electrocardiogram, newly occurred arrhythmia, sign of cardiac ischaemia; blood pressure, systolic blood pressure >180 mmHg, decreased

systolic or diastolic blood pressure >20%, mean arterial pressure <65 or >110 mmHg.

(5) *Devices*: risk for unplanned extubation or removal of tube, catheter and drain.

(6) *Other conditions*: desire to withdraw from the study; increased drainage of blood and risk for widening a wound.

Randomisation

Patients will be randomised using computer-generated randomisation lists.[19] Randomisation will be stratified by age (<70 years, ≥70) and sex (female or male), and the randomisation list will be generated with a block size of 4 before the start of recruitment.[20] The list will be created by people who are not related to study recruitment and intervention. Patients will be subjected either to vibration therapy added to protocolised mobilisation or to protocolised mobilisation alone as the usual standard of care.

Blinding

This study uses a single-blinded trial design because patients can understand the intervention or control by themselves. However, to minimise subject bias, the same vibration device will be used as a footrest for 15 min without vibration by blinded staff. All interventions will be conducted by bedside nurses. The intervention duration will be 15 min and will be conducted when no other staff who are involved in outcome assessments, treatments and usual rehabilitation are present.

Interventions

Vibration therapy

A vibration device (BW-750, BodyGreen) will be used by bedside nurses once-daily (Figure 2 and supplementary video file). The device will be used on the feet in the sitting position for 15 min. A low-frequency vibration from 5.6 to 13 Hz with an amplitude of 2 mm in vertical direction can be chosen on the device. This study will use a continuous automatic course of 5.6,

7 and 8 Hz for 30 s each in turn. The number of intervention days will be recorded in compliance with the protocol.

Protocolised mobilisation

With or without intervention, protocolised mobilisation will be conducted in all patients. Protocolised mobilisation is based on a progressive mobilisation protocol described by Morris et al.[21] in which the mobilisation level is decided according to patients' consciousness and muscle strength. Passive range of motion is conducted for unconscious patients, whereas in conscious patients, the intensity is gradually elevated to active resistance, sitting on the edge of bed and ambulation. Mobilisation level will be restricted in patients with unstable vital signs.

Primary outcome

The primary outcome is physical function assessment using the Functional Status Score for the ICU (FSS-ICU) at discharge from the ICU, measured by a blinded nurse. The FSS-ICU is a physical function score involving the following five functional tasks: (1) rolling, (2) transferring from resting on spine to sitting, (3) sitting at the edge of bed, (4) transferring from sitting to standing and (5) walking.[22] Each task is scored from 0 to 7, with the maximum score of 35. The research team has conducted a training period for the use of FSS-ICU for 2 months before the start of this study to ensure scoring accuracy.

Secondary outcomes

Medical Research Council score and ICU-AW

After the patients are awake and attentive, nurses evaluate the Medical Research Council (MRC) score and the incidence of ICU-AW in daily practice. Intact level of consciousness and awareness will be evaluated based on the patient's response to at least three of the following five orders: 'open/close your eyes'; 'look at me'; 'open your mouth and put out your tongue'; 'nod

your head' and 'raise your eyebrows'.[23] The MRC score is the sum of the manual muscle testing in the following six bilaterally tested muscle groups: (1) shoulder abductors, (2) elbow flexors, (3) wrist extensors, (4) hip flexors, (5) knee extensors and (6) ankle dorsiflexors. The ICU-AW is defined as an MRC score of <48 on two separate occasions, and patients with an expected preadmission MRC score of <48 will be excluded in the assessment of the ICU-AW.[24] The research team will use the MRC score and the incidence of ICU-AW at discharge from the ICU for comparison. Blinded nurses will evaluate the MRC score and ICU-AW.

ICU mobility scale

To evaluate the mobilisation level during the ICU stay, the research team will use the ICU mobility scale (IMS), which is a measure of mobilisation capabilities from 0 (lying in bed) to 10 (walking independently).[25] In addition to discharge from the ICU, the research team will evaluate the maximum IMS score during the study period because the maximum level of mobility is considered as an important prognostic factor.[26] IMS will be evaluated by blinded nurses as conducted in clinical practice.

Muscle mass

Muscle thickness and cross-sectional area will be evaluated using serial ultrasound measurements on admission and at discharge from the ICU.[27] Muscle mass measurements will be conducted on admission when patients are expected to be enrolled in this study. Ultrasound has been identified as a reliable method to measure muscle mass.[28, 29] The biceps brachii muscle will be evaluated at two-thirds of the way between the acromion and the antecubital crease, and the thickness is between the superficial fascia of the biceps brachii muscle and the uppermost part of the humerus. The rectus femoris muscle will be evaluated at the midway point between the anterior superior iliac spine and the proximal end of the patella, and the thickness is between the superficial fascia of the rectus femoris muscle and the uppermost part of the femur. A transducer

will be placed perpendicular to the long axis of limbs with patients in the supine position under passive limb extension. The muscle mass will be measured three times, and the median value will be used for evaluation. The research team will use the change in muscle mass from ICU admission to discharge from the ICU for comparison. All measurements will be conducted by two examiners. In the authors' previous studies, the intraclass and interclass correlation coefficients were determined to be 0.96–0.99 and 0.98–0.99, respectively.[30]

Delirium

Nurses in the ICU will evaluate delirium using the confusion assessment method for the ICU (CAM-ICU), which includes an acute change or a fluctuation in mental status, altered level of consciousness, disorganised thinking and inattention.[31] CAM-ICU assessment will be performed three times daily as a clinical practice. To evaluate the level of consciousness, the RASS will be used, which ranges from −5 to 4, with lower scores indicating less arousal.[32] The research team will assess the duration of delirium and the state at discharge from the ICU.

ICU- and ventilator-free days

The *ICU-free days* are defined as the number of days after discharge from the ICU during the 28 days after ICU admission, whereas *ventilator-free days* are defined as the number of days without mechanical ventilation during the 28 days after ICU admission. Patients who die before 28 days without extubation or ICU discharge are counted as no free days, whereas patients who die before 28 days with extubation or ICU discharge are counted as days from the event to the death.

Safety

For evaluating the safety of vibration therapy, vital signs will be monitored from baseline measurements conducted before the start of vibration therapy and 5 or 15 min after the use of

therapy. Vital signs will include blood pressure (systolic, diastolic and mean), heart rate and oxygen saturation. Finally, follow-up will be conducted at discharge from the hospital to evaluate the patient's post-study health status and any harmful events. In the authors' facility, no adverse events, as described in the withdrawal criteria, were observed in 30 critically ill patients who were treated with vibration therapy (BW-750, BodyGreen) before the start of this study.

Data Collection and Management

The research director and the Clinical Research Ethics Committee will supervise the study protocol and data to ensure the accuracy. All data will be presented as requested, and any missing or inconsistent data will be requested or addressed by the research director. Any adverse effects or complications will be immediately reported, and necessary compensation will be provided to any patients who experience harm from trial participation. All records will be retained for 3 years after the completion or termination of the study.

Confidentiality

All datasets will be stored by creating identification codes to anonymise the information of study participants. The coding keys linking identification codes will be stored by the research director. The study participants' information will be protected when publishing the trial results or reporting results at an academic conference. This information will be used only for this research and not for exchange with other facilities.

Data Access and Dissemination

Study protocol will be available to subjects upon request. Study data will also be available for academic, non-commercial research purpose unless the request hinders the protection of personal information or the quality of this study. Individuals involved in this study will have access to the final dataset and will be able to publish the study or report the study at an academic conference.

Patient and Public Involvement

This study will not involve patients in the development of the research question and outcome measures. They will also not be involved in the design and recruitment. Results will be disseminated to study participants upon request.

Sample Size

The sample size calculation is based on two studies.[22, 33] The FSS-ICU at discharge from the ICU is reported to be 20 (10–30), with a minimal clinically important difference from 2.0 to 5.0. The authors hypothesise that in this study, a 3.0 difference will be observed because vibration therapy is expected to improve standing and ambulating by 2–4. The standard deviation is reported to be 5.9. These data estimate that 171 patients will be required to observe the difference with alpha 0.05 and power of 90%. Assuming a 10% dropout rate due to complete withdrawal or death, a total of 188 patients will be required. Study participants will be randomised either to vibration therapy coupled with protocolised mobilisation (n = 94) or to protocolised mobilisation alone (n = 94).

Statistical Analysis

After data collection, descriptive analyses will be conducted on the obtained data. Continuous data will be presented as mean ± standard deviation or median (interquartile range), whereas categorical data will be presented as number (%). Variables will be compared using the t-test or the Mann–Whitney U-test for comparing the two groups. Efficacy and safety analysis will be conducted in a full-analysis set and safety analysis set following the intention-to-treat principle. The full-analysis set includes patients who received at least one intervention and had primary outcome assessment. The safety analysis set includes patients who received at least one intervention. In addition, a subgroup analysis will be conducted by the duration of intervention,

mobilisation level (IMS score) and patient's severity (APACHE II score). If heterogeneity exists, a subgroup analysis will be conducted on the factors. Primary outcome will be compared at discharge from the ICU; secondary outcomes will be compared during the ICU stay or at discharge from the ICU. Patients with missing values will be excluded from the analysis. Safety analysis will be conducted by comparing the change in vital signs from the start of the therapy session as the baseline to 5 or 15 min after the intervention. Data analyses will be conducted using JMP version 13.1.0 (SAS Institute). All statistical tests will be two-tailed, and $p < 0.05$ will be considered as statistically significant.

DISCUSSION

This study describes an intervention protocol of vibration therapy to improve physical function in critically ill patients. Although vibration therapy has been used for decades, its effect remains unclear in the field of critical illness. Several studies have reported the safety of vibration therapy in critically ill patients,[15, 34] whereas no studies have been conducted till date to examine the efficacy of vibration therapy in critically ill patients.

The randomised controlled trial design is feasible because research has already confirmed that vibration therapy can be used safely in critically ill patients.[34] Vibration therapy is typically used for days or weeks; however, some patients in the ICU stay for a short time (<1 week). In Japan, 38.9% of patients are admitted to the ICU only for monitoring, and the median length of ICU stay is 2.5 (1.4–4.8) days in critically ill patients.[35] Therefore, the selection of patients is important, and this study will enroll those patients who are expected to require a longer stay of ≥5 days in the ICU. Vibration therapy will be used for 15 min/day, which has been confirmed to be safe in critically ill patients.[15] In previous studies, vibration therapy for 6–18 min/day was found to be beneficial in patients with cystic fibrosis or stroke.[36, 37] In those studies, vibration therapy was used for weeks to months; however, in the present study, the intervention duration will depend on the time from the first use of vibration therapy in the ICU to discharge

from the ICU. Therefore, a subgroup analysis by the intervention duration is necessary because it is unclear how the short-term use of vibration therapy affects physical function. Moreover, a subgroup analysis will be required in the case of disease severity because limited data are available in critically ill patients.

Among the different vibration devices, the frequency of vibration varies from 2 to 90 Hz. Although the vibration frequency of 2 Hz is too low to have a treatment effect,[38] higher vibration frequencies have some effect. This study will use a relatively low-frequency vibration device (5.6–8 Hz). These frequencies of vibration are useful to improve physical function, and a vibration of 5–14 Hz has been demonstrated to significantly improve physical function, including gait speed and handgrip strength.[39] In another study, a low frequency ranging from 2 to 20 Hz was found to improve muscle strength for the knee extensor.[40] A recent study that used the same vibration device that will be used in the present study, the BW-750, BodyGreen, reported that this device was useful in improving the muscle strength of knee extensor in patients with post-total knee arthroplasty.[41] Furthermore, low-frequency vibrations of 12–15 Hz were found to have more beneficial effects on bone mass than vibrations of 30–90 Hz or even than walking.[42, 43]

In addition to the vibration frequency, the posture is an important component for successful vibration therapy. In our study, vibration therapy will be used in patients in the sitting position, whereas the majority of vibration therapy sessions are conducted in the standing position.[41, 44] We will use vibration therapy in the sitting position because standing is conducted in only 1%–2% of critically ill patients.[8, 45] Vibration therapy in the sitting position is also beneficial because Faes et al. have reported that foot-transmitted vibration in the sitting position can improve balance and flexibility.[46] This foot-transmitted vibration in the sitting position can be equivalent to whole-body vibration, not partial-body vibration, because the vibration is transmitted to the whole body.[46] On the other hand, we will not use vibration therapy in the flat position because it may not have sufficient load in the flat supine position.[34] In addition, from the

authors' experience, vibration therapy in the flat position may cause additional stress for critically ill patients when they are confined to the bed.

In this study, we set FSS-ICU as the primary outcome of this research because it is a reliable functional score in the ICU.[33] FSS-ICU at discharge from the ICU can predict discharge home at an AUC of 0.88 (0.77–0.84), which is preferable than the IMS score of 0.73 (0.68–0.77).[47] In a study, an FSS-ICU ≥ 19 had a sensitivity of 82.9% and a specificity of 79.7% to predict discharge home.[47] We consider physical function as an important functional outcome because functions require not only muscle strength but also postural control, endurance, cognition and response to the change.[48] Therefore, we will use FSS-ICU as a primary outcome rather than MRC score.

The research team will monitor muscle mass because it is difficult to assess physical function in some critically ill patients.[49] Muscle atrophy is a critical problem in the ICU, and in 1 week, the decreased muscle mass reaches the degree of 13.2%–16.9% and 18.8%–20.7% in the upper and lower limbs, respectively.[30] Furthermore, muscle atrophy occurs in respiratory muscles.[50] Vibration therapy has reportedly contributed to preventing limb muscle atrophy. In one study, vibration therapy contributed to preventing the loss of quadriceps femoris muscle mass in healthy volunteers (−3.3% vs. −14.4% in 56 days).[51] Vibration not only serves as resistance training but also provides the stimulation that can promote the proliferation of myoblast cells and downregulate the expression of atrophy genes.[52] We will monitor muscle mass using ultrasound because biomarker level is increased in surgical patients who will be included in this study.[53]

Delirium has been observed in 30% of critically ill patients,[54] and the length of ICU stay is associated with long-term cognitive dysfunction.[55] Delirium is another significant cause of PICS. The authors believe that vibration therapy will contribute to improving delirium based on three reasons. First, enhanced rehabilitation using vibration therapy will contribute to decreasing delirium[6] because early mobilisation has been reported to reduce the number of days of delirium

(2 vs. 4, $p = 0.03$).[56] Second, vibration therapy improves circulation. Low cerebral perfusion is a risk factor for delirium, and a 10-mmHg decrease in cerebral perfusion has an odds ratio of 2.08 (95% confidence interval, 1.02–4.24) in predicting delirium.[57] Vibration can improve circulation to vital organs, including the brain.[58] This effect has also been confirmed through a post-cardiac arrest model using pigs.[59] The mechanism is considered to be increased nitric oxide or decreased endothelial damage.[60, 61] Third, vibration therapy affects the hormone signals produced from the body.[62] The growth hormone, whose levels are increased by vibration, has neuroprotective properties that may improve delirium.[63]

There are several limitations in this study. First, this study will provide the results of vibration therapy added to protocolised mobilisation, not the results of vibration therapy alone. The effects may be limited in patients who cannot perform active mobilisation, because a recent study demonstrated that electrical muscle stimulation and in-bed leg cycling did not improve physical function in patients who had active mobilisation.[64] Electrical muscle stimulation was effective in patients with limited mobilisation.[65] Therefore, a subgroup analysis is required to determine the effect in patients for whom active mobilisation is limited. Second, the intervention period is different among subjects. The intervention may be conducted for a short time period due to ICU discharge, intolerance and death. An organised intervention period is desirable but not feasible in the ICU. Therefore, we will conduct the subgroup analysis in the intervention period. Third, due to the single-centre design, heterogeneity may exist, thereby requiring a subgroup analysis on the factors. Fourth, double blinding is not feasible because patients can understand the intervention or control. Therefore, some bias may remain, although the outcome assessment is blinded. Fifth, vibration therapy will be conducted at the time when patients can achieve sitting on the edge of bed, whereas we will measure muscle mass on admission when the patients are expected to be enrolled in this study. Therefore, some missing values may exist in the ultrasound measurements.

Ethics and Dissemination

This study has been approved by the Clinical Research Ethics Committee of Tokushima University Hospital (approval number 3763). At the time of enrollment, written informed consent will be obtained from patients or their authorised surrogate decision-makers. The study participants' information will be protected at all times, and all data will be stored securely. Results will be disseminated through publication in a peer-reviewed journal and presented at conferences.

Trial status

This trial is not recruiting patients at the time of manuscript submission.

Acknowledgments

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Author Contributions

NN was involved in study concept and design and drafting of the manuscript. SD, YK, and MS took part in study concept and design. JO took part in the critical revision of the manuscript. All authors read and approved the final manuscript.

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Competing interests None declared.

Patient consent for publication Consent was obtained for the use of Figure 1 and video.

Ethics approval Ethics approval was obtained from Tokushima University Hospital (approval number: 3763).

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement Data are available upon reasonable request for academic, non-commercial research purpose, which will not breach patients' confidentiality.

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REFERENCES

1. Zimmerman JE, Kramer AA, Knaus WA. Changes in hospital mortality for United States intensive care unit admissions from 1988 to 2012. *Crit Care* 2013;17:R81.

2. Yende S, Austin S, Rhodes A, et al. Long-term quality of life among survivors of severe

sepsis: analyses of two international trials. *Crit Care Med* 2016;44:1461-7.

3. Inoue S, Hatakeyama J, Kondo Y, et al. Post-intensive care syndrome: its pathophysiology, prevention, and future directions. *Acute Med Surg* 2019;6:233-46.

4. Van Aerde N, Meersseman P, Debaveye Y, et al. Five-year impact of ICU-acquired neuromuscular complications: a prospective, observational study. *Intensive Care Med* 2020;46:1184-93.

5. Fuke R, Hifumi T, Kondo Y, et al. Early rehabilitation to prevent postintensive care syndrome in patients with critical illness: a systematic review and meta-analysis. *BMJ Open* 2018;8:e019998.

6. Inouye SK, Westendorp RG, Saczynski JS. Delirium in elderly people. *Lancet* 2014;383:911-22.

7. Jolley SE, Moss M, Needham DM, et al. Point prevalence study of mobilization practices for acute respiratory failure patients in the United States. *Crit Care Med* 2017;45:205-15.

8. Sibilla A, Nydahl P, Greco N, et al. Mobilization of mechanically ventilated patients in switzerland. *J Intensive Care Med* 2020;35:55-62.

9. Wang J, Xiao Q, Zhang C, et al. Intensive care unit nurses' knowledge, attitudes, and perceived barriers regarding early mobilization of patients. *Nurs Crit Care* 2020.

10. Eakin MN, Ugbah L, Arnautovic T, et al. Implementing and sustaining an early rehabilitation program in a medical intensive care unit: A qualitative analysis. *J Crit Care* 2015;30:698-704.

11. Taito S, Sanui M, Yasuda H, et al. Current rehabilitation practices in intensive care units: a preliminary survey by the Japanese Society of Education for Physicians and Trainees in Intensive Care (JSEPTIC) Clinical Trial Group. *J Intensive Care* 2016;4:66.

12. Buckhout R. Effect of whole body vibration on human performance. *Hum Factors* 1964;6:157-63.

13. Cardim AB, Marinho PE, Nascimento JF, Jr., et al. Does whole-body vibration improve the functional exercise capacity of subjects with COPD? a meta-analysis. *Respir Care*

2016;61:1552-59.

14. Furness TP, Maschette WE, Lorenzen C, et al. Efficacy of a whole-body vibration intervention on functional performance of community-dwelling older adults. *J Altern Complement Med* 2010;16:795-7.

15. Wollersheim T, Haas K, Wolf S, et al. Whole-body vibration to prevent intensive care unit-acquired weakness: safety, feasibility, and metabolic response. *Critical Care* 2017;21:9.

16. Hansson L, Hedner T, Dahlöf B. Prospective randomized open blinded end-point (PROBE) study. A novel design for intervention trials. Prospective Randomized Open Blinded End-Point. *Blood Press* 1992;1:113-9.

17. Chan AW, Tetzlaff JM, Gøtzsche PC, et al. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. *BMJ* 2013;346:e7586.

18. Ad Hoc Committee for Early Rehabilitation TJSoICM. Evidence based expert consensus for early rehabilitation in the intensive care unit. *J Jpn Soc Intensive Care Med* 2017;24:255-303.

19. Nagashima K. A computerized number generator through the stratified block randomization. [Internet] 2017 April 26. https://nshi.jp/contents/js/randblock/

20. Zelen M. The randomization and stratification of patients to clinical trials. *J Chronic Dis* 1974;27:365-75.

21. Morris PE, Goad A, Thompson C, et al. Early intensive care unit mobility therapy in the treatment of acute respiratory failure. *Crit Care Med* 2008;36:2238-43.

22. Huang M, Chan KS, Zanni JM, et al. Functional status score for the ICU: An international clinimetric analysis of validity, responsiveness, and minimal important difference. *Crit Care Med* 2016;44:e1155-e64.

23. De Jonghe B, Bastuji-Garin S, Durand MC, et al. Respiratory weakness is associated with limb weakness and delayed weaning in critical illness. *Crit Care Med* 2007;35:2007-15.

24. Stevens RD, Marshall SA, Cornblath DR, et al. A framework for diagnosing and classifying intensive care unit-acquired weakness. *Crit Care Med* 2009;37:S299-308.

25. Hodgson C, Needham D, Haines K, et al. Feasibility and inter-rater reliability of the ICU mobility scale. *Heart Lung* 2014;43:19-24.

26. Kim RY, Murphy TE, Doyle M, et al. Factors associated with discharge home among medical ICU patients in an early mobilization program. *Crit Care Explor* 2019;1:e0060.

27. Palakshappa JA, Bakhru RN. Bedside ultrasonography can and should be used in the ICU to evaluate muscle atrophy. *Ann Am Thorac Soc* 2019;16:1107-11.

28. Lambell KJ, Tierney AC, Wang JC, et al. Comparison of ultrasound-derived muscle thickness with computed tomography muscle cross-sectional area on admission to the Intensive Care Unit: a pilot cross-sectional study. *JPEN J Parenter Enteral Nutr* 2020.

29. Nakanishi N, Tsutsumi R, Okayama Y, et al. Monitoring of muscle mass in critically ill patients: comparison of ultrasound and two bioelectrical impedance analysis devices. *J Intensive Care* 2019;7:61.

30. Nakanishi N, Oto J, Tsutsumi R, et al. Upper and lower limb muscle atrophy in critically ill patients: an observational ultrasonography study. *Intensive Care Med* 2018;44:263-64.

31. Ely EW, Inouye SK, Bernard GR, et al. Delirium in mechanically ventilated patients: validity and reliability of the confusion assessment method for the intensive care unit (CAM-ICU). *JAMA* 2001;286:2703-10.

32. Sessler CN, Gosnell MS, Grap MJ, et al. The Richmond Agitation-Sedation Scale: validity and reliability in adult intensive care unit patients. *Am J Respir Crit Care Med* 2002;166:1338-44.

33. Reid JC, Clarke F, Cook DJ, et al. Feasibility, reliability, responsiveness, and validity of the patient-reported functional scale for the intensive care unit: a pilot study. *J Intensive Care Med* 2019:885066618824534.

34. Alter P, Boeselt T, Nell C, et al. Feasibility and safety of whole-body vibration therapy in intensive care patients. *Crit Care* 2017;21:91.

35. Irie H, Okamoto H, Uchino S, et al. The Japanese Intensive care PAtient Database (JIPAD):

A national intensive care unit registry in Japan. *J Crit Care* 2020;55:86-94.

36. Rietschel E, van Koningsbruggen S, Fricke O, et al. Whole body vibration: a new therapeutic approach to improve muscle function in cystic fibrosis? *Int J Rehabil Res* 2008;31:253-6.

37. Tihanyi TK, Horváth M, Fazekas G, et al. One session of whole body vibration increases voluntary muscle strength transiently in patients with stroke. *Clin Rehabil* 2007;21:782-93.

38. Jackson KJ, Merriman HL, Vanderburgh PM, et al. Acute effects of whole-body vibration on lower extremity muscle performance in persons with multiple sclerosis. *J Neurol Phys Ther* 2008;32:171-6.

39. Sá-Caputo D, Paineiras-Domingos LL, Francisca-Santos A, et al. Whole-body vibration improves the functional parameters of individuals with metabolic syndrome: an exploratory study. *BMC Endocr Disord* 2019;19:6.

40. Eftekhari E, Mostahfezian M, Etemadifar M, et al. Resistance training and vibration improve muscle strength and functional capacity in female patients with multiple sclerosis. *Asian J Sports Med* 2012;3:279-84.

41. Hsiao YH, Chien SH, Tu HP, et al. Early post-operative intervention of whole-body vibration in patients after total knee arthroplasty: a pilot study. *J Clin Med* 2019;8.

42. Minematsu A, Nishii Y, Imagita H, et al. Whole body vibration at low-frequency can increase trabecular thickness and width in adult rats. *J Musculoskelet Neuronal Interact* 2019;19:169-77.

43. Gusi N, Raimundo A, Leal A. Low-frequency vibratory exercise reduces the risk of bone fracture more than walking: a randomized controlled trial. *BMC Musculoskelet Disord* 2006;7:92.

44. Wong RMY, Ho WT, Tang N, et al. A study protocol for a randomized controlled trial evaluating vibration therapy as an intervention for postural training and fall prevention after distal radius fracture in elderly patients. *Trials* 2020;21:95.

45. Fontela PC, Lisboa TC, Forgiarini-Júnior LA, et al. Early mobilization practices of mechanically ventilated patients: a 1-day point-prevalence study in southern Brazil. *Clinics (Sao*

Paulo) 2018;73:e241.

46. Faes Y, Banz N, Buscher N, et al. Acute effects of partial-body vibration in sitting position. *World J Orthop* 2018;9:156-64.

47. Tymkew H, Norris T, Arroyo C, et al. The use of physical therapy ICU assessments to predict discharge home. *Crit Care Med* 2020;48:1312-18.

48. Parry SM, Denehy L, Beach LJ, et al. Functional outcomes in ICU – what should we be using? - an observational study. *Critical Care* 2015;19:127.

49. Nakanishi N, Takashima T, Oto J. Muscle atrophy in critically ill patients: a review of its cause, evaluation, and prevention. *J Med Invest* 2020;67:1-10.

50. Nakanishi N, Oto J, Ueno Y, et al. Change in diaphragm and intercostal muscle thickness in mechanically ventilated patients: a prospective observational ultrasonography study. *J Intensive Care* 2019;7:56.

51. Belavý DL, Miokovic T, Armbrecht G, et al. Resistive vibration exercise reduces lower limb muscle atrophy during 56-day bed-rest. *J Musculoskelet Neuronal Interact* 2009;9:225-35.

52. Ceccarelli G, Benedetti L, Galli D, et al. Low-amplitude high frequency vibration down-regulates myostatin and atrogin-1 expression, two components of the atrophy pathway in muscle cells. *J Tissue Eng Regen Med* 2014;8:396-406.

53. Nakanishi N, Tsutsumi R, Hara K, et al. Urinary titin is a novel biomarker for muscle atrophy in nonsurgical critically ill patients: a two-center, prospective observational study. *Crit Care Med* 2020;48:1327-33.

54. Salluh JI, Wang H, Schneider EB, et al. Outcome of delirium in critically ill patients: systematic review and meta-analysis. *BMJ* 2015;350:h2538.

55. Pandharipande PP, Girard TD, Jackson JC, et al. Long-term cognitive impairment after critical illness. *N Engl J Med* 2013;369:1306-16.

56. Schweickert WD, Pohlman MC, Pohlman AS, et al. Early physical and occupational therapy in mechanically ventilated, critically ill patients: a randomised controlled trial. *Lancet*

2009;373:1874-82.

57. Smith PJ, Blumenthal JA, Hoffman BM, et al. Reduced cerebral perfusion pressure during lung transplant surgery is associated with risk, duration, and severity of postoperative delirium. *Ann Am Thorac Soc* 2016;13:180-7.

58. Adams JA, Mangino MJ, Bassuk J, et al. Regional blood flow during periodic acceleration. *Crit Care Med* 2001;29:1983-8.

59. Adams JA, Uryash A, Wu H, et al. Microcirculatory and therapeutic effects of whole body periodic acceleration (pGz) applied after cardiac arrest in pigs. *Resuscitation* 2011;82:767-75.

60. Sackner MA, Gummels E, Adams JA. Nitric oxide is released into circulation with whole-body, periodic acceleration. *Chest* 2005;127:30-9.

61. Matsumoto T, Fujita M, Tarutani Y, et al. Whole-body periodic acceleration enhances brachial endothelial function. *Circ J* 2008;72:139-43.

62. Bosco C, Iacovelli M, Tsarpela O, et al. Hormonal responses to whole-body vibration in men. *Eur J Appl Physiol* 2000;81:449-54.

63. Adamis D, Lunn M, Martin FC, et al. Cytokines and IGF-I in delirious and non-delirious acutely ill older medical inpatients. *Age Ageing* 2009;38:326-32; discussion 251.

64. Fossat G, Baudin F, Courtes L, et al. Effect of in-bed leg cycling and electrical stimulation of the quadriceps on global muscle strength in critically ill adults: a randomized clinical trial. *JAMA* 2018;320:368-78.

65. Nakanishi N, Oto J, Tsutsumi R, et al. Effect of electrical muscle stimulation on upper and lower limb muscles in critically ill patients: a two-center randomized controlled trial. *Crit Care Med* 2020;48:e997-e1003.

Figure Legends

Figure 1. Flow chart of study protocol. ICU, intensive care unit.

Figure 2. Image of vibration therapy. (BW-750, BodyGreen). Consent was obtained for the use of this image.

Supplemental Data

Supplemental file. Video image of vibration therapy.

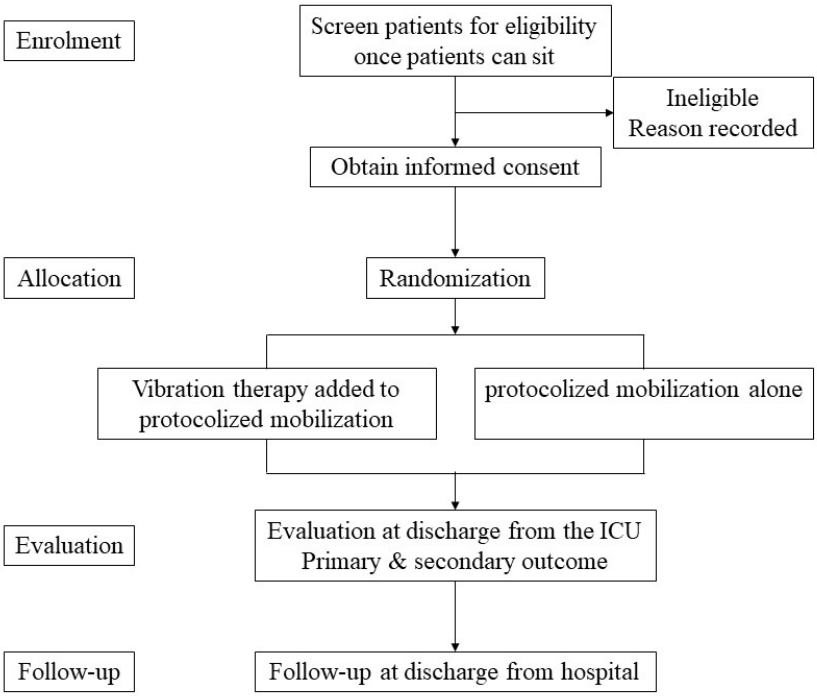

Figure 1

81x60mm (300 x 300 DPI)

Figure 2

81x60mm (300 x 300 DPI)

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

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	4
	2b	All items from the World Health Organization Trial Registration Data Set	4
Protocol version	3	Date and version identifier	4
Funding	4	Sources and types of financial, material, and other support	12
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	12
	5b	Name and contact information for the trial sponsor	None
	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	None
	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)	None

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	3
	6b	Explanation for choice of comparators	3
Objectives	7	Specific objectives or hypotheses	4
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)	4
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	4
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)	4,5
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	6
	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)	5,6
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	5
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	6,7
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	7,8
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)	4,5

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	9
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	9
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	6
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	6
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	6
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	6
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	6
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	7,8
	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	8

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	9
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	10
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	10
	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)	10
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	8
	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	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	8
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	8
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	4
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)	4

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	4
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	4
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	9
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	12
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	9
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	8
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	9
	31b	Authorship eligibility guidelines and any intended use of professional writers	12
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	9
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	No English document
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	None

*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.

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Effect of vibration therapy on physical function in critically ill adults (VTICIA trial): Protocol for a single-blinded randomised controlled trial

Short running title: Vibration therapy in critically ill adults

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ABSTRACT

Introduction: Vibration therapy has been used as an additional approach in passive rehabilitation. Recently, it has been demonstrated to be feasible and safe for critically ill patients, in who muscle weakness and intensive care unit (ICU)-acquired weakness are serious problems. However, the effectiveness of vibration therapy in this population is unclear.

Methods and analysis: This study will enrol 188 adult critically ill patients who require further ICU stay after they can achieve sitting at the edge of the bed or wheelchair. The sample size calculation is based on a 15% improvement of Functional Status Score for the ICU. They will be randomised to vibration therapy coupled with protocolised mobilisation or to protocolised mobilisation alone; outcomes will be compared between the two groups. Therapy will be administered using a low-frequency vibration device (5.6–13 Hz) for 15 min/day from when the patient first achieves a sitting position and onward until discharge from the ICU. Outcome assessments will be blinded to the intervention. Primary outcome will be measured using the Functional Status Score for the ICU at discharge. Secondary outcomes will be identified as follows: delirium, Medical Research Council score, ICU-acquired weakness, the change of biceps brachii and rectus femoris muscle mass measured by ultrasound, ICU mobility scale and ventilator- and ICU-free days (number of free days 28 days after admission). For safety assessment, vital signs will be monitored during the intervention.

Ethics and dissemination: This study has been approved by the Clinical Research Ethics Committee of Tokushima University Hospital. Results will be disseminated through publication in a peer-reviewed journal and presented at conferences.

Trial registration number: UMIN-Clinical Trials Registry: 000039616

Article Summary

Strengths and limitations of this study

- This randomised controlled trial is the first to evaluate whether vibration therapy can improve physical function and delirium in critically ill patients.
- The 15-min intervention is added to protocolised mobilisation from the start of sitting position onward to discharge from the ICU.
- This trial will contribute evidence-based treatment data in using vibration therapy in critically ill patients, a population for which current data are insufficient.
- Limitations of this study are the short length of intervention and the use of vibration therapy added to protocolised mobilisation, not vibration therapy alone.

Keywords: vibration therapy, critically ill patients, mobilisation, muscle mass, delirium

INTRODUCTION

There has been a decline in the mortality rate for critically ill patients by 35% over a decade.[1] However, survivors often experience prolonged impairment in their quality of life. In a study, one-third of septic patients were identified to have some type of psychological or physical dysfunction 6 months after discharge from the intensive care unit (ICU).[2] These conditions are referred to as *post-intensive care syndrome* (PICS), which encompasses prolonged physical, mental and cognitive dysfunction.[3] A significant cause of PICS is muscle weakness newly acquired in the ICU, which is termed as *ICU-acquired weakness* (ICU-AW). This condition is associated with prolonged physical dysfunction, which is observed in 40% of critically ill patients.[4]

Physical therapy is essential to prevent muscle weakness.[5, 6] Mobilisation has been widely recognised to be important in critically ill patients; however, out-of-bed mobilisation is not widely practiced.[7] In a one-point prevalence study, 33% of mechanically ventilated patients were mobilised out of bed and 2% were ambulated, suggesting that active mobilisation is still infrequent in critically ill patients.[8] The barriers to mobilisation vary, such as very heavy medical staff workload, limited staffing and insufficient equipment.[9] The heavy workload of nurses hampers their active involvement in patient mobilisation,[10] and full-time physical therapists are still not common in several ICUs.[11] Because these human resources are often limited, there is an urgent need for equipment and devices to support rehabilitation in the ICU.

Since 1960, vibration therapy has been used as an additional approach in passive rehabilitation.[12] This therapy generates vertical sinusoidal vibration. The transmitted vibration stimulates muscle spindles and produces muscle contractions. Studies have reported that vibration therapy improved physical function in both healthy individuals and patients with chronic disease.[13, 14] A recent report documented that vibration therapy was safe and feasible in critically ill patients.[15] The device does not require patients' active cooperation and can be used passively. Because mobilisation for critically ill patients is often limited to sitting without

standing or ambulating,[8] the device can contribute to maximising passive mobilisation.

The study hypothesis is that vibration therapy can improve physical function in critically ill patients. The primary objective is to investigate its effect on physical function measured at discharge from the ICU. The secondary objectives are to determine the effects of vibration therapy on muscle strength, muscle mass, mobility level, delirium and ventilator- and ICU-free days (number of free days 28 days after admission). This study will allow us to objectively analyse whether vibration therapy can improve physical functions and how it impacts clinical outcomes in critically ill patients.

MATERIALS AND METHODS

Study Design and Settings

In August 2020, the authors will initiate a single-blinded, randomised controlled trial at the mixed medical/surgical ICU of Tokushima University Hospital in Japan. The trial is expected to take 2 years to complete. This study has been approved by the Clinical Research Ethics Committee of Tokushima University Hospital (approval number 3763) and registered as a clinical trial (UMIN-Clinical Trials Registry: 000039616). This study is based on the prospective, randomised, open-label, blinded endpoint (PROBE) study model and the standard protocol items: recommendations for interventional trials (SPIRIT) statement.[16, 17]

Recruitment

All consecutive patients who meet the inclusion and exclusion criteria described in the following text will be enrolled in this study. At the time of enrollment, written informed consent will be obtained from patients or their authorised surrogate decision-makers. A model consent form used in this study is available in the supplemental file.

Inclusion and Exclusion Criteria

The study will enroll consecutive critically ill patients aged ≥18 years who requires further ICU stay after being eligible for study participation (Figure 1). Patients will be eligible when they can achieve sitting at the edge of the bed or wheelchair with or without mechanical ventilation. The study will exclude patients based on the consensus for early mobilisation in the Japanese Society of Intensive Care Medicine (JSICM) as follows[18]: (1) no permission from the primary physician; (2) excessive agitation [Richmond agitation-sedation scale (RASS) ≥ 2]; (3) impaired consciousness (RASS ≤3); (4) unstable vital signs requiring circulatory support devices, such as intra-aortic balloon pump; (5) sustained low blood pressure even with the use of catecholamine; (6) dynamic blood pressure change after body position change; (7) risk for rupture in untreated aneurysms; (8) uncontrolled pain; (9) uncontrolled intracranial pressure ≥20 mmHg; (10) unstable phase in the head or cervical spine injury; (11) metal implants or unstable bone fractures in the extremities or spine; (12) active bleeding; (13) insufficient stabilisation or length of catheters; (14) insufficient staffing and (15) no consent from patients or surrogates.

Withdrawal from the Study

Patients can withdraw from the study at any time, which will not affect the medical care they are receiving upon withdrawal. The research team will stop the intervention and consider withdrawal for patients based on the JSICM criteria as follows:[18]

(1) *Generalised symptoms*: unresponsive state; agonised facial expression, pale skin or cyanosis; newly occurred impaired consciousness; agitation with risk to safety; sudden limb weakness or dependence; inability to sustain posture and risk for fall.

(2) *Subjective symptoms*: sudden dyspnoea; unbearable fatigue or suffering and desire to withdraw.

(3) *Respiration*: respiratory rate <5/min or >40/min; oxygen saturation <88%; increased work of breathing and asynchrony with mechanical ventilation or fighting the ventilator.

(4) *Circulation*: heart rate <40/min or >130/min; electrocardiogram, newly occurred arrhythmia,

sign of cardiac ischaemia; blood pressure, systolic blood pressure >180 mmHg, decreased systolic or diastolic blood pressure >20%, mean arterial pressure <65 or >110 mmHg.

(5) *Devices*: risk for unplanned extubation or removal of tube, catheter and drain.

(6) *Other conditions*: desire to withdraw from the study; increased drainage of blood and risk for widening a wound.

Randomisation

Patients will be randomised using computer-generated randomisation lists.[19] Randomisation will be stratified by age (<70 years, ≥70) and sex (female or male), and the randomisation list will be generated with a block size of 4 before the start of recruitment.[20] The list will be created by an independent person outside of the research team. At the allocation, the independent person will check the list and allocate patients either to vibration therapy added to protocolised mobilisation or to protocolised mobilisation alone as the usual standard of care.

Blinding

This study uses a single-blinded trial design because patients can understand the intervention or control by themselves. However, to minimise subject bias, the same vibration device will be used as a footrest for 15 min without vibration by blinded staff. All interventions will be conducted by bedside nurses. The intervention duration will be 15 min and will be conducted when no other staff who are involved in outcome assessments, treatments and usual rehabilitation are present.

Interventions

Vibration therapy

A vibration device (BW-750, BodyGreen) will be used by bedside nurses once-daily (Figure 2 and supplementary video file). The device will be used on the feet in the sitting position for 15 min. A low-frequency vibration from 5.6 to 13 Hz with an amplitude of 2 mm in vertical

direction can be chosen on the device. This study will use a continuous automatic course of 5.6, 7 and 8 Hz for 30 s each in turn. The number of intervention days will be recorded in compliance with the protocol.

Protocolised mobilisation

With or without intervention, protocolised mobilisation will be conducted in all patients. Protocolised mobilisation is based on a progressive mobilisation protocol described by Morris et al.[21] in which the mobilisation level is decided according to patients' consciousness and muscle strength. Passive range of motion is conducted for unconscious patients, whereas in conscious patients, the intensity is gradually elevated to active resistance, sitting on the edge of bed and ambulation. Mobilisation level will be restricted in patients with unstable vital signs.

Primary outcome

The primary outcome is physical function assessment using the Functional Status Score for the ICU (FSS-ICU) at discharge from the ICU, measured by a blinded nurse. The FSS-ICU is a physical function score involving the following five functional tasks: (1) rolling, (2) transferring from resting on spine to sitting, (3) sitting at the edge of bed, (4) transferring from sitting to standing and (5) walking.[22] Each task is scored from 0 to 7, with the maximum score of 35. The research team has conducted a training period for the use of FSS-ICU for 2 months before the start of this study to ensure scoring accuracy.

Secondary outcomes

Medical Research Council score and ICU-AW

After the patients are awake and attentive, nurses evaluate the Medical Research Council (MRC) score and the incidence of ICU-AW in daily practice. Intact level of consciousness and awareness will be evaluated based on the patient's response to at least three of the following five

orders: ‘open/close your eyes’; ‘look at me’; ‘open your mouth and put out your tongue’; ‘nod your head’ and ‘raise your eyebrows’.[23] The MRC score is the sum of the manual muscle testing in the following six bilaterally tested muscle groups: (1) shoulder abductors, (2) elbow flexors, (3) wrist extensors, (4) hip flexors, (5) knee extensors and (6) ankle dorsiflexors. The ICU-AW is defined as an MRC score of <48 on two separate occasions, and patients with an expected preadmission MRC score of <48 will be excluded in the assessment of the ICU-AW.[24] The research team will use the MRC score and the incidence of ICU-AW at discharge from the ICU for comparison. Blinded nurses will evaluate the MRC score and ICU-AW.

ICU mobility scale

To evaluate the mobilisation level during the ICU stay, the research team will use the ICU mobility scale (IMS), which is a measure of mobilisation capabilities from 0 (lying in bed) to 10 (walking independently).[25] In addition to discharge from the ICU, the research team will evaluate the maximum IMS score during the study period because the maximum level of mobility is considered as an important prognostic factor.[26] IMS will be evaluated by blinded nurses as conducted in clinical practice.

Muscle mass

Muscle thickness and cross-sectional area will be evaluated using serial ultrasound measurements at the inclusion and discharge from the ICU.[27] Ultrasound has been identified as a reliable method to measure muscle mass.[28, 29] The biceps brachii muscle will be evaluated at two-thirds of the way between the acromion and the antecubital crease, and the thickness is between the superficial fascia of the biceps brachii muscle and the uppermost part of the humerus. The rectus femoris muscle will be evaluated at the midway point between the anterior superior iliac spine and the proximal end of the patella, and the thickness is between the superficial fascia of the rectus femoris muscle and the uppermost part of the femur. A transducer will be placed

perpendicular to the long axis of limbs with patients in the supine position under passive limb extension. The muscle mass will be measured three times, and the median value will be used for evaluation. The research team will use the change in muscle mass from the inclusion to discharge from the ICU for comparison. All measurements will be conducted by two examiners. In the authors' previous studies, the intraclass and interclass correlation coefficients were determined to be 0.96–0.99 and 0.98–0.99, respectively.[30]

Delirium

Nurses in the ICU will evaluate delirium using the confusion assessment method for the ICU (CAM-ICU), which includes an acute change or a fluctuation in mental status, altered level of consciousness, disorganised thinking and inattention.[31] CAM-ICU assessment will be performed three times daily as a clinical practice. To evaluate the level of consciousness, the RASS will be used, which ranges from −5 to 4, with lower scores indicating less arousal.[32] The research team will assess the duration of delirium and the state at discharge from the ICU.

ICU- and ventilator-free days

The *ICU-free days* are defined as the number of days after discharge from the ICU during the 28 days after ICU admission, whereas *ventilator-free days* are defined as the number of days without mechanical ventilation during the 28 days after ICU admission. Patients who die before 28 days without extubation or ICU discharge are counted as no free days, whereas patients who die before 28 days with extubation or ICU discharge are counted as days from the event to the death.

Safety

For evaluating the safety of vibration therapy, vital signs will be monitored from baseline measurements conducted before the start of vibration therapy and 5 or 15 min after the use of

therapy. Vital signs will include blood pressure (systolic, diastolic and mean), heart rate and oxygen saturation. Finally, follow-up will be conducted at discharge from the hospital to evaluate the patient's post-study health status and any harmful events. In the authors' facility, no adverse events, as described in the withdrawal criteria, were observed in 30 critically ill patients who were treated with vibration therapy (BW-750, BodyGreen) before the start of this study.

Data Collection and Management

The research director and the Clinical Research Ethics Committee will supervise the study protocol and data to ensure the accuracy. All data will be presented as requested, and any missing or inconsistent data will be requested or addressed by the research director. Any adverse effects or complications will be immediately reported, and necessary compensation will be provided to any patients who experience harm from trial participation. All records will be retained for 3 years after the completion or termination of the study.

Confidentiality

All datasets will be stored by creating identification codes to anonymise the information of study participants. The coding keys linking identification codes will be stored by the research director. The study participants' information will be protected when publishing the trial results or reporting results at an academic conference. This information will be used only for this research and not for exchange with other facilities.

Data Access and Dissemination

Study protocol will be available to subjects upon request. Study data will also be available for academic, non-commercial research purpose unless the request hinders the protection of personal information or the quality of this study. Individuals involved in this study will have access to the final dataset and will be able to publish the study or report the study at an academic conference.

Patient and Public Involvement

This study will not involve patients in the development of the research question and outcome measures. They will also not be involved in the design and recruitment. Results will be disseminated to study participants upon request.

Sample Size

The sample size calculation is based on two studies.[22, 33] The FSS-ICU at discharge from the ICU is reported to be 20 (10–30), with a minimal clinically important difference from 2.0 to 5.0. The authors hypothesise that in this study, a 3.0 difference will be observed because vibration therapy is expected to improve standing and ambulating by 2–4. The standard deviation is reported to be 5.9. These data estimate that 171 patients will be required to observe the difference with alpha 0.05 and power of 90%. Assuming a 10% dropout rate due to complete withdrawal or death, a total of 188 patients will be required. Study participants will be randomised either to vibration therapy coupled with protocolised mobilisation (n = 94) or to protocolised mobilisation alone (n = 94).

Statistical Analysis

After data collection, descriptive analyses will be conducted on the obtained data. Continuous data will be presented as mean ± standard deviation or median (interquartile range), whereas categorical data will be presented as number (%). Variables will be compared using the t-test or the Mann–Whitney U-test for comparing the two groups. Efficacy and safety analysis will be conducted in a full-analysis set and safety analysis set following the intention-to-treat principle. The full-analysis set includes patients who received at least one intervention and had primary outcome assessment. The safety analysis set includes patients who received at least one intervention. In addition, a multivariate and subgroup analysis will be conducted by the duration

of intervention, duration of ICU stay before the intervention, mobilisation level (IMS score) and patient's severity (Acute Physiology and Chronic Health Evaluation II score: the score to predict in-hospital mortality in patients admitted to the ICU). If heterogeneity exists, the further analysis will be conducted on the factors. Primary outcome will be compared at discharge from the ICU; secondary outcomes will be compared during the ICU stay or at discharge from the ICU. Missing values at the discharge will be imputed from the last recorded values. Safety analysis will be conducted by comparing the change in vital signs from the start of the therapy session as the baseline to 5 or 15 min after the intervention. Data analyses will be conducted using JMP version 13.1.0 (SAS Institute). All statistical tests will be two-tailed, and $p < 0.05$ will be considered as statistically significant.

DISCUSSION

This study describes an intervention protocol of vibration therapy to improve physical function in critically ill patients. Although vibration therapy has been used for decades, its effect remains unclear in the field of critical illness. Several studies have reported the safety of vibration therapy in critically ill patients,[15, 34] whereas no studies have been conducted till date to examine the efficacy of vibration therapy in critically ill patients.

The randomised controlled trial design is feasible because research has already confirmed that vibration therapy can be used safely in critically ill patients.[34] Vibration therapy is typically used for days or weeks; however, some patients in the ICU stay for a short time (<1 week). In Japan, 38.9% of patients are admitted to the ICU only for monitoring, and the median length of ICU stay is 2.5 (1.4–4.8) days in critically ill patients.[35] Therefore, the selection of patients is important, and this study will enroll those patients who are expected to require further ICU stay after the intervention. Vibration therapy will be used for 15 min/day, which has been confirmed to be safe in critically ill patients.[15] In previous studies, vibration therapy for 6–18 min/day was found to be beneficial in patients with cystic fibrosis or stroke.[36, 37] In those studies,

vibration therapy was used for weeks to months; however, in the present study, the intervention duration will depend on the time from the first use of vibration therapy in the ICU to discharge from the ICU. Therefore, a multivariate and subgroup analysis by the intervention duration is necessary because it is unclear how the short-term use of vibration therapy affects physical function. Moreover, the duration of ICU stay before the intervention needs further analysis because muscle atrophy and weakness should be more critical at the time of later intervention.

Among the different vibration devices, the frequency of vibration varies from 2 to 90 Hz. Although the vibration frequency of 2 Hz is too low to have a treatment effect,[38] higher vibration frequencies have some effect. This study will use a relatively low-frequency vibration device (5.6–8 Hz). These frequencies of vibration are useful to improve physical function, and a vibration of 5–14 Hz has been demonstrated to significantly improve physical function, including gait speed and handgrip strength.[39] In another study, a low frequency ranging from 2 to 20 Hz was found to improve muscle strength for the knee extensor.[40] A recent study that used the same vibration device that will be used in the present study, the BW-750, BodyGreen, reported that this device was useful in improving the muscle strength of knee extensor in patients with post-total knee arthroplasty.[41] Furthermore, low-frequency vibrations of 12–15 Hz were found to have more beneficial effects on bone mass than vibrations of 30–90 Hz or even than walking.[42, 43]

In addition to the vibration frequency, the posture is an important component for successful vibration therapy. In our study, vibration therapy will be used in patients in the sitting position, whereas the majority of vibration therapy sessions are conducted in the standing position.[41, 44] We will use vibration therapy in the sitting position because standing is conducted in only 1%–2% of critically ill patients.[8, 45] Vibration therapy in the sitting position is also beneficial because Faes et al. have reported that foot-transmitted vibration in the sitting position can improve balance and flexibility.[46] This foot-transmitted vibration in the sitting position can be equivalent to whole-body vibration, not partial-body vibration, because the vibration is

transmitted to the whole body.[46] On the other hand, we will not use vibration therapy in the flat position because it may not have sufficient load in the flat supine position.[34] In addition, from the authors' experience, vibration therapy in the flat position may cause additional stress for critically ill patients when they are confined to the bed.

In this study, we set FSS-ICU as the primary outcome of this research because it is a reliable functional score in the ICU.[33] FSS-ICU at discharge from the ICU can predict discharge home at an AUC of 0.88 (0.77–0.84), which is preferable than the IMS score of 0.73 (0.68–0.77).[47] In a study, an FSS-ICU ≥ 19 had a sensitivity of 82.9% and a specificity of 79.7% to predict discharge home.[47] We consider physical function as an important functional outcome because functions require not only muscle strength but also postural control, endurance, cognition and response to the change.[48] Therefore, we will use FSS-ICU as a primary outcome rather than MRC score.

The research team will monitor muscle mass because it is difficult to assess physical function in some critically ill patients.[49] Muscle atrophy is a critical problem in the ICU, and in 1 week, the decreased muscle mass reaches the degree of 13.2%–16.9% and 18.8%–20.7% in the upper and lower limbs, respectively.[30] Furthermore, muscle atrophy occurs in respiratory muscles.[50] Vibration therapy has reportedly contributed to preventing limb muscle atrophy. In one study, vibration therapy contributed to preventing the loss of quadriceps femoris muscle mass in healthy volunteers (−3.3% vs. −14.4% in 56 days).[51] Vibration not only serves as resistance training but also provides the stimulation that can promote the proliferation of myoblast cells and downregulate the expression of atrophy genes.[52] We will monitor muscle mass using ultrasound because biomarker level is increased in surgical patients who will be included in this study.[53]

Delirium has been observed in 30% of critically ill patients,[54] and the length of ICU stay is associated with long-term cognitive dysfunction.[55] Delirium is another significant cause of PICS. The authors believe that vibration therapy will contribute to improving delirium based on

three reasons. First, enhanced rehabilitation using vibration therapy will contribute to decreasing delirium[6] because early mobilisation has been reported to reduce the number of days of delirium (2 vs. 4, $p = 0.03$).[56] Second, vibration therapy improves circulation. Low cerebral perfusion is a risk factor for delirium, and a 10-mmHg decrease in cerebral perfusion has an odds ratio of 2.08 (95% confidence interval, 1.02–4.24) in predicting delirium.[57] Vibration can improve circulation to vital organs, including the brain.[58] This effect has also been confirmed through a post-cardiac arrest model using pigs.[59] The mechanism is considered to be increased nitric oxide or decreased endothelial damage.[60, 61] Third, vibration therapy affects the hormone signals produced from the body.[62] The growth hormone, whose levels are increased by vibration, has neuroprotective properties that may improve delirium.[63]

There are several limitations in this study. First, this study will provide the results of vibration therapy added to protocolised mobilisation, not the results of vibration therapy alone. The effects may be limited in patients who cannot perform active mobilisation, because a recent study demonstrated that electrical muscle stimulation and in-bed leg cycling did not improve physical function in patients who had active mobilisation.[64] Electrical muscle stimulation was effective in patients with limited mobilisation.[65] Therefore, a multivariate and subgroup analysis is required to determine the effect in patients for whom active mobilisation is limited. Second, the intervention period is different among subjects. The intervention may be conducted for a short time period due to ICU discharge, intolerance and death. An organised intervention period is desirable but not feasible in the ICU. Therefore, we will conduct a multivariate and subgroup analysis in the intervention period. Third, due to the single-centre design, heterogeneity may exist, thereby requiring further analysis on the factors. Fourth, double blinding is not feasible because patients can understand the intervention or control. Therefore, some bias may remain, although the outcome assessment is blinded.

Ethics and Dissemination

This study has been approved by the Clinical Research Ethics Committee of Tokushima University Hospital (approval number 3763). At the time of enrollment, written informed consent will be obtained from patients or their authorised surrogate decision-makers. The study participants' information will be protected at all times, and all data will be stored securely. Results will be disseminated through publication in a peer-reviewed journal and presented at conferences.

Trial status

This trial is not recruiting patients at the time of manuscript submission.

Acknowledgments

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Author Contributions

NN was involved in study concept and design and drafting of the manuscript. SD, YK, and MS took part in study concept and design. JO took part in the critical revision of the manuscript. All authors read and approved the final manuscript.

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Competing interests None declared.

Patient consent for publication Consent was obtained for the use of Figure 2 and video.

Ethics approval Ethics approval was obtained from Tokushima University Hospital (approval number: 3763).

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement Data are available upon reasonable request for academic, non-commercial research purpose, which will not breach patients' confidentiality.

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REFERENCES

1. Zimmerman JE, Kramer AA, Knaus WA. Changes in hospital mortality for United States intensive care unit admissions from 1988 to 2012. *Crit Care* 2013;17:R81.

2. Yende S, Austin S, Rhodes A, et al. Long-term quality of life among survivors of severe

sepsis: analyses of two international trials. *Crit Care Med* 2016;44:1461-7.

3. Inoue S, Hatakeyama J, Kondo Y, et al. Post-intensive care syndrome: its pathophysiology, prevention, and future directions. *Acute Med Surg* 2019;6:233-46.

4. Van Aerde N, Meersseman P, Debaveye Y, et al. Five-year impact of ICU-acquired neuromuscular complications: a prospective, observational study. *Intensive Care Med* 2020;46:1184-93.

5. Fuke R, Hifumi T, Kondo Y, et al. Early rehabilitation to prevent postintensive care syndrome in patients with critical illness: a systematic review and meta-analysis. *BMJ Open* 2018;8:e019998.

6. Inouye SK, Westendorp RG, Saczynski JS. Delirium in elderly people. *Lancet* 2014;383:911-22.

7. Jolley SE, Moss M, Needham DM, et al. Point prevalence study of mobilization practices for acute respiratory failure patients in the United States. *Crit Care Med* 2017;45:205-15.

8. Sibilla A, Nydahl P, Greco N, et al. Mobilization of mechanically ventilated patients in switzerland. *J Intensive Care Med* 2020;35:55-62.

9. Wang J, Xiao Q, Zhang C, et al. Intensive care unit nurses' knowledge, attitudes, and perceived barriers regarding early mobilization of patients. *Nurs Crit Care* 2020.

10. Eakin MN, Ugbah L, Arnautovic T, et al. Implementing and sustaining an early rehabilitation program in a medical intensive care unit: A qualitative analysis. *J Crit Care* 2015;30:698-704.

11. Taito S, Sanui M, Yasuda H, et al. Current rehabilitation practices in intensive care units: a preliminary survey by the Japanese Society of Education for Physicians and Trainees in Intensive Care (JSEPTIC) Clinical Trial Group. *J Intensive Care* 2016;4:66.

12. Buckhout R. Effect of whole body vibration on human performance. *Hum Factors* 1964;6:157-63.

13. Cardim AB, Marinho PE, Nascimento JF, Jr., et al. Does whole-body vibration improve the functional exercise capacity of subjects with COPD? a meta-analysis. *Respir Care*

2016;61:1552-59.

14. Furness TP, Maschette WE, Lorenzen C, et al. Efficacy of a whole-body vibration intervention on functional performance of community-dwelling older adults. *J Altern Complement Med* 2010;16:795-7.

15. Wollersheim T, Haas K, Wolf S, et al. Whole-body vibration to prevent intensive care unit-acquired weakness: safety, feasibility, and metabolic response. *Critical Care* 2017;21:9.

16. Hansson L, Hedner T, Dahlöf B. Prospective randomized open blinded end-point (PROBE) study. A novel design for intervention trials. Prospective Randomized Open Blinded End-Point. *Blood Press* 1992;1:113-9.

17. Chan AW, Tetzlaff JM, Gøtzsche PC, et al. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. *BMJ* 2013;346:e7586.

18. Ad Hoc Committee for Early Rehabilitation TJSoICM. Evidence based expert consensus for early rehabilitation in the intensive care unit. *J Jpn Soc Intensive Care Med* 2017;24:255-303.

19. Nagashima K. A computerized number generator through the stratified block randomization. [Internet] 2017 April 26. https://nshi.jp/contents/js/randblock/

20. Zelen M. The randomization and stratification of patients to clinical trials. *J Chronic Dis* 1974;27:365-75.

21. Morris PE, Goad A, Thompson C, et al. Early intensive care unit mobility therapy in the treatment of acute respiratory failure. *Crit Care Med* 2008;36:2238-43.

22. Huang M, Chan KS, Zanni JM, et al. Functional status score for the ICU: An international clinimetric analysis of validity, responsiveness, and minimal important difference. *Crit Care Med* 2016;44:e1155-e64.

23. De Jonghe B, Bastuji-Garin S, Durand MC, et al. Respiratory weakness is associated with limb weakness and delayed weaning in critical illness. *Crit Care Med* 2007;35:2007-15.

24. Stevens RD, Marshall SA, Cornblath DR, et al. A framework for diagnosing and classifying intensive care unit-acquired weakness. *Crit Care Med* 2009;37:S299-308.

25. Hodgson C, Needham D, Haines K, et al. Feasibility and inter-rater reliability of the ICU mobility scale. *Heart Lung* 2014;43:19-24.

26. Kim RY, Murphy TE, Doyle M, et al. Factors associated with discharge home among medical ICU patients in an early mobilization program. *Crit Care Explor* 2019;1:e0060.

27. Palakshappa JA, Bakhru RN. Bedside ultrasonography can and should be used in the ICU to evaluate muscle atrophy. *Ann Am Thorac Soc* 2019;16:1107-11.

28. Lambell KJ, Tierney AC, Wang JC, et al. Comparison of ultrasound-derived muscle thickness with computed tomography muscle cross-sectional area on admission to the Intensive Care Unit: a pilot cross-sectional study. *JPEN J Parenter Enteral Nutr* 2020.

29. Nakanishi N, Tsutsumi R, Okayama Y, et al. Monitoring of muscle mass in critically ill patients: comparison of ultrasound and two bioelectrical impedance analysis devices. *J Intensive Care* 2019;7:61.

30. Nakanishi N, Oto J, Tsutsumi R, et al. Upper and lower limb muscle atrophy in critically ill patients: an observational ultrasonography study. *Intensive Care Med* 2018;44:263-64.

31. Ely EW, Inouye SK, Bernard GR, et al. Delirium in mechanically ventilated patients: validity and reliability of the confusion assessment method for the intensive care unit (CAM-ICU). *JAMA* 2001;286:2703-10.

32. Sessler CN, Gosnell MS, Grap MJ, et al. The Richmond Agitation-Sedation Scale: validity and reliability in adult intensive care unit patients. *Am J Respir Crit Care Med* 2002;166:1338-44.

33. Reid JC, Clarke F, Cook DJ, et al. Feasibility, reliability, responsiveness, and validity of the patient-reported functional scale for the intensive care unit: a pilot study. *J Intensive Care Med* 2019:885066618824534.

34. Alter P, Boeselt T, Nell C, et al. Feasibility and safety of whole-body vibration therapy in intensive care patients. *Crit Care* 2017;21:91.

35. Irie H, Okamoto H, Uchino S, et al. The Japanese Intensive care PAtient Database (JIPAD):

A national intensive care unit registry in Japan. *J Crit Care* 2020;55:86-94.

36. Rietschel E, van Koningsbruggen S, Fricke O, et al. Whole body vibration: a new therapeutic approach to improve muscle function in cystic fibrosis? *Int J Rehabil Res* 2008;31:253-6.

37. Tihanyi TK, Horváth M, Fazekas G, et al. One session of whole body vibration increases voluntary muscle strength transiently in patients with stroke. *Clin Rehabil* 2007;21:782-93.

38. Jackson KJ, Merriman HL, Vanderburgh PM, et al. Acute effects of whole-body vibration on lower extremity muscle performance in persons with multiple sclerosis. *J Neurol Phys Ther* 2008;32:171-6.

39. Sá-Caputo D, Paineiras-Domingos LL, Francisca-Santos A, et al. Whole-body vibration improves the functional parameters of individuals with metabolic syndrome: an exploratory study. *BMC Endocr Disord* 2019;19:6.

40. Eftekhari E, Mostahfezian M, Etemadifar M, et al. Resistance training and vibration improve muscle strength and functional capacity in female patients with multiple sclerosis. *Asian J Sports Med* 2012;3:279-84.

41. Hsiao YH, Chien SH, Tu HP, et al. Early post-operative intervention of whole-body vibration in patients after total knee arthroplasty: a pilot study. *J Clin Med* 2019;8.

42. Minematsu A, Nishii Y, Imagita H, et al. Whole body vibration at low-frequency can increase trabecular thickness and width in adult rats. *J Musculoskelet Neuronal Interact* 2019;19:169-77.

43. Gusi N, Raimundo A, Leal A. Low-frequency vibratory exercise reduces the risk of bone fracture more than walking: a randomized controlled trial. *BMC Musculoskelet Disord* 2006;7:92.

44. Wong RMY, Ho WT, Tang N, et al. A study protocol for a randomized controlled trial evaluating vibration therapy as an intervention for postural training and fall prevention after distal radius fracture in elderly patients. *Trials* 2020;21:95.

45. Fontela PC, Lisboa TC, Forgiarini-Júnior LA, et al. Early mobilization practices of mechanically ventilated patients: a 1-day point-prevalence study in southern Brazil. *Clinics (Sao*

Paulo) 2018;73:e241.

46. Faes Y, Banz N, Buscher N, et al. Acute effects of partial-body vibration in sitting position. *World J Orthop* 2018;9:156-64.

47. Tymkew H, Norris T, Arroyo C, et al. The use of physical therapy ICU assessments to predict discharge home. *Crit Care Med* 2020;48:1312-18.

48. Parry SM, Denehy L, Beach LJ, et al. Functional outcomes in ICU – what should we be using? - an observational study. *Critical Care* 2015;19:127.

49. Nakanishi N, Takashima T, Oto J. Muscle atrophy in critically ill patients: a review of its cause, evaluation, and prevention. *J Med Invest* 2020;67:1-10.

50. Nakanishi N, Oto J, Ueno Y, et al. Change in diaphragm and intercostal muscle thickness in mechanically ventilated patients: a prospective observational ultrasonography study. *J Intensive Care* 2019;7:56.

51. Belavý DL, Miokovic T, Armbrecht G, et al. Resistive vibration exercise reduces lower limb muscle atrophy during 56-day bed-rest. *J Musculoskelet Neuronal Interact* 2009;9:225-35.

52. Ceccarelli G, Benedetti L, Galli D, et al. Low-amplitude high frequency vibration down-regulates myostatin and atrogin-1 expression, two components of the atrophy pathway in muscle cells. *J Tissue Eng Regen Med* 2014;8:396-406.

53. Nakanishi N, Tsutsumi R, Hara K, et al. Urinary titin is a novel biomarker for muscle atrophy in nonsurgical critically ill patients: a two-center, prospective observational study. *Crit Care Med* 2020;48:1327-33.

54. Salluh JI, Wang H, Schneider EB, et al. Outcome of delirium in critically ill patients: systematic review and meta-analysis. *BMJ* 2015;350:h2538.

55. Pandharipande PP, Girard TD, Jackson JC, et al. Long-term cognitive impairment after critical illness. *N Engl J Med* 2013;369:1306-16.

56. Schweickert WD, Pohlman MC, Pohlman AS, et al. Early physical and occupational therapy in mechanically ventilated, critically ill patients: a randomised controlled trial. *Lancet*

2009;373:1874-82.

57. Smith PJ, Blumenthal JA, Hoffman BM, et al. Reduced cerebral perfusion pressure during lung transplant surgery is associated with risk, duration, and severity of postoperative delirium. *Ann Am Thorac Soc* 2016;13:180-7.

58. Adams JA, Mangino MJ, Bassuk J, et al. Regional blood flow during periodic acceleration. *Crit Care Med* 2001;29:1983-8.

59. Adams JA, Uryash A, Wu H, et al. Microcirculatory and therapeutic effects of whole body periodic acceleration (pGz) applied after cardiac arrest in pigs. *Resuscitation* 2011;82:767-75.

60. Sackner MA, Gummels E, Adams JA. Nitric oxide is released into circulation with whole-body, periodic acceleration. *Chest* 2005;127:30-9.

61. Matsumoto T, Fujita M, Tarutani Y, et al. Whole-body periodic acceleration enhances brachial endothelial function. *Circ J* 2008;72:139-43.

62. Bosco C, Iacovelli M, Tsarpela O, et al. Hormonal responses to whole-body vibration in men. *Eur J Appl Physiol* 2000;81:449-54.

63. Adamis D, Lunn M, Martin FC, et al. Cytokines and IGF-I in delirious and non-delirious acutely ill older medical inpatients. *Age Ageing* 2009;38:326-32; discussion 251.

64. Fossat G, Baudin F, Courtes L, et al. Effect of in-bed leg cycling and electrical stimulation of the quadriceps on global muscle strength in critically ill adults: a randomized clinical trial. *JAMA* 2018;320:368-78.

65. Nakanishi N, Oto J, Tsutsumi R, et al. Effect of electrical muscle stimulation on upper and lower limb muscles in critically ill patients: a two-center randomized controlled trial. *Crit Care Med* 2020;48:e997-e1003.

Figure Legends

Figure 1. Flow chart of study protocol. ICU, intensive care unit.

Figure 2. Image of vibration therapy. (BW-750, BodyGreen). Consent was obtained for the use of this image.

Supplemental File

Supplemental file. A model consent form given to patients or their authorised surrogates

Supplementary video file. Video image of vibration therapy.

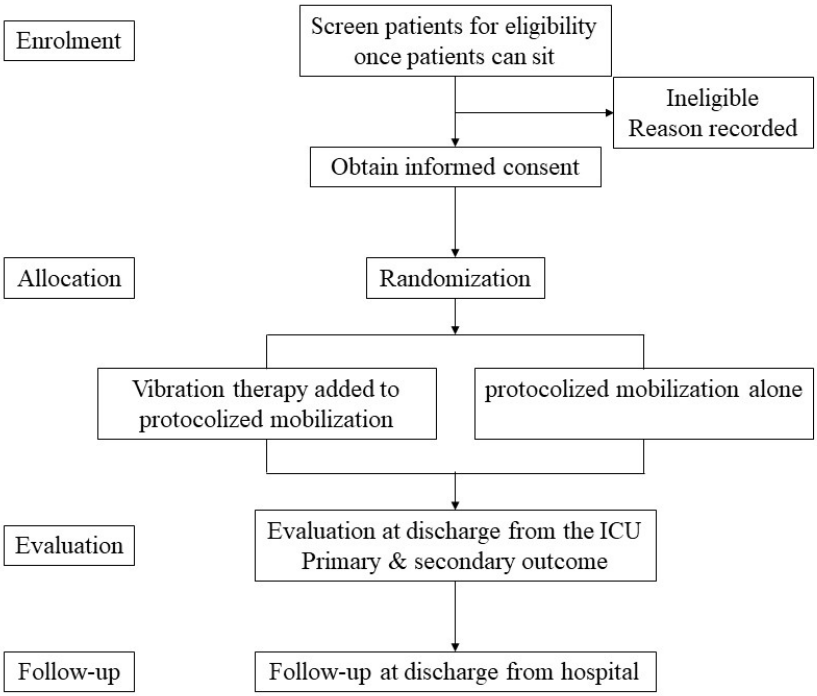

Figure 1

81x60mm (300 x 300 DPI)

Figure 2

81x60mm (300 x 300 DPI)

（西暦 2020 年 9 月 7 日 版数 2）

Supplemental File

Effect of vibration therapy on physical function in critically ill adults (VTICIA trial):

Protocol for a single-blinded randomised controlled trial

Consent form

研究の説明文書

ICU 長期入室患者に対する振動療法の有効性の検証

1. 臨床試験について

あなたに参加をお願いする研究は、「臨床試験」と呼ばれるもので、実際に診療に携わる医師・看護師が、医学的必要性や重要性を検討したうえで作成した試験計画にしたがって患者様が治療を受け、その有効性と安全性を検討すること等を目的とした試験です。当該研究の実施について研究機関の長の許可を得ております。

2. 本研究の意義及び目的について

振動療法による身体機能障害予防効果の検証を行います。集中治療室で治療を受ける患者にとって筋肉の萎縮を防ぐことは、病気を治療していくうえで大変重要です。今回の研究では通常のリハビリテーションに加えて振動療法という下肢を振動させる機材を用いてリハビリテーションを行います。ICU 在室時に身体機能を評価してリハビリテーションの効果を調査します。

3. 研究対象者として選定された理由、参加予定の本研究の対象と本学の対象例数

ICU への長期在室が予測される、ベッドの端に座ることができる 18 歳以上の患者 180 名です。

4. 研究の方法について

振動療法器材を集中治療室でのリハビリテーションに用います。1㎜ の垂直振動器がリズミカルに上下するので、ベッドの端に座り両足を器材の上に乗せることで縄跳びのような振動効果を得ることができます。

振動療法を受ける方と受けない方を無作為に振り分けて選択します。どちらに割り付けられるかは対象者には選択できません。ベッドの端に座ることができるようになれば、通常の早期リハビリテーションに加え 1 日 1 度 15 分間の振動療法を ICU 退室時まで毎日繰り返す予定となっています。振動療法の周波数は身体に負担をかけないように低周波数を選択します。振動療法開始後、5 分後、終了後に自覚症状とバイタルサイン変動の有無を確認します。経過時間に関わらず不快感を認めた際は中止

を行います。通常の診療情報からは身体機能状態や入院期間、ICU 在室期間等のデータを収集させて頂きます。研究期間は徳島大学病院医学系研究倫理審査委員会承認日より 2023 年 7 月 31 日までとします。

5. 情報・データ等の保存及び使用方法並びに保存期間

本研究では試料・情報を扱う場合には個人情報とは無関係の記号を付して管理し、その番号を使用することで個人が特定できないように匿名化します。匿名化にあたっては対応表を作成しますが、対応表は研究責任者の白石美恵が適切に管理を行い外部への提供は行いません。徳島大学病院では、個人情報管理者は研究責任者とし、収集した情報は研究責任者のみがパスワードを知るコンピューター上のファイルに記録し、試験の中止又は終了後 3 年間保管します。収集したデータは施錠可能な集学治療病棟内に設置します。尚、収集した情報は本研究以外には使用しません。保管期間終了後、データは破棄します。

6. 本研究の倫理的配慮

今回の臨床試験の実施にあたっては、徳島大学病院医学系研究倫理審査委員会の審査を経て、研究機関の長より許可を受けています。この臨床試験に参加されるかどうかはあなたの自由な意思で決めて下さい。同意されなくてもあなたの診断や治療に不利益になることは全くありません。また、いったん同意した後でもいつでも撤回できます。どちらの場合もその時の状態により責任をもって最善の治療に当たります。また、ご本人等からの求めに応じて、被験者の個人情報保護や本研究の独創性の確保に支障がない範囲内で本研究計画及び本研究の方法に関する資料を入手または閲覧できます。希望される方は連絡先までご連絡下さい。

7. 本研究に参加することによって生じる負担並びに予測されるリスク及び利益

本研究への参加を拒否した場合にも治療や診断等の評価において影響を及ぼすことは一切ありません。 タップマスター（本研究で使用する振動療法の器材）は従来の振動療法の器材と比較し、13Hz 以下の自然界に現れる低周波数で構成される整列振動であり、固有感覚(筋肉の張り具合や関節の曲げ伸ばしを感じ取る感覚)やバランスを整え、内臓刺激による便秘予防効果等の多様な効果が報告されています。対象者によっては全身的な不良反応として頭痛や気分不良、筋肉痛等も報告されていますが、これまで当院 ICU では、有害事象は発生しておらず安全に使用できています。

8. 個人情報の取扱い

研究対象者を研究対象者識別コードで特定する等，被験者のプライバシーを保護します。本研究の結果を公表する場合も同様に研究対象者のプライバシーを保護します。研究の信頼性の確保のため研究者以外の者がカルテを閲覧すること（モニタリング）があります。

9. 公表について

本研究の未発表データ等の情報及び本研究の結果の一部又は全部を学会、雑誌等外部に発表する場合には、氏名、生年月日、住所等を消去することで特定の研究対象者を識別できないようにし、研究責任者の責任のもと取り扱うこととします。

10. 研究対象者の費用負担の有無に関すること，謝礼について

集中治療室内にある器材を使用するため費用負担はありません。また、謝礼はありません。

11. 本研究に係る資金源，起こり得る利害の衝突及び研究者等の関連組織との関わり

本研究は一般財団法人厚仁会から助成金の提供を受けて行います。本研究の利害関係については，臨床研究利益相反審査委員会の審査を受け，承認を得ております。

12. 本研究の結果から生じる知的財産権について

この臨床研究の結果として特許権などの知的財産権が生じる可能性はありません。

13. 研究機関の名称及び研究責任者の氏名，職名並びに連絡先徳島大学病院 東病棟 4 階 ICU

研究責任者：白石美恵 看護部 看護師長

（西暦 2020 年 9 月 7 日 版数 2）

同　意　書

徳島大学病院長　殿

今回、ICU 長期入室患者に対する振動療法の有効性の検証に関し、下記の説明者より、試験の目的及び方法等について文書により説明を受けるとともに、いつでも中止の申し出ができることも説明を受け理解しましたので、本試験を行うことについて同意いたします。

被験者

同意年月日　西暦＿＿＿＿年＿＿＿月＿＿＿日

住　　所　＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿

氏　　名　＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿印

生年月日　大・昭・平・令＿＿＿年＿＿＿月＿＿＿日

代諾者

同意年月日　西暦＿＿＿＿年＿＿＿月＿＿＿日

住　　所　＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿

氏　　名　＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿印（続柄　　）

説明者

説明年月日　西暦＿＿＿＿年＿＿＿月＿＿＿日

所属・職名　＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿

氏　　名　＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿印

同意説明文書及び同意書（写し）の交付日（西暦　　年　　月　　日）

※ 本同意書に署名または記名･捺印した後に、同意説明文書及び同意書の写しをお受け取り下さい。

患者 ID

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

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	4
	2b	All items from the World Health Organization Trial Registration Data Set	4
Protocol version	3	Date and version identifier	4
Funding	4	Sources and types of financial, material, and other support	12
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	12
	5b	Name and contact information for the trial sponsor	None
	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	None
	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)	None

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	3
	6b	Explanation for choice of comparators	3
Objectives	7	Specific objectives or hypotheses	4
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)	4
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	4
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)	4,5
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	6
	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)	5,6
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	5
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	6,7
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	7,8
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)	4,5

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	9
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	9
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	6
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	6
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	6
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	6
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	6
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	7,8
	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	8

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	9
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	10
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	10
	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)	10
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	8
	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	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	8
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	8
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	4
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)	4

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	4
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	4
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	9
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	12
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	9
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	8
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	9
	31b	Authorship eligibility guidelines and any intended use of professional writers	12
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	9
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	No English document
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	None

*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.