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*R*elaxation for Critically ill *P*atient *O*utcomes and *S*tress-coping *E*nhancement (REPOSE): A protocol for a pilot randomized trial of an integrative intervention to improve critically ill patients' delirium and related outcomes

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Abstract

Introduction: Delirium is a common complication of critical illness, associated with negative patient outcomes. Preventive or therapeutic interventions are mostly ineffective. Although relaxation-inducing approaches may benefit critically ill patients, no well-designed studies target delirium prevention as a primary outcome. The objective of this study is to assess feasibility and treatment effect estimates of a multimodal integrative intervention incorporating relaxation, guided imagery, and moderate pressure touch-massage for prevention of critical illness delirium and for related outcomes.

Methods and analysis: Randomized, controlled, double-blinded trial with 2 parallel groups (1:1 allocation: intervention and standard care) and stratified randomization [age (18-64, ≥65), presence of trauma) with blocking, involving 104 patients with Intensive Care Delirium Screening Checklist (ICDSC): 0-3 recruited from 2 academic ICUs. Intervention group participants receive the intervention in addition to standard care for up to 5 consecutive days (or until transfer/ discharge); control group participants receive standard care and a sham intervention. We will assess pre-defined feasibility outcomes, i.e., recruitment rates, protocol adherence. The primary clinical outcome is incidence of delirium (ICDSC ≥4). Secondary outcomes include pain scores, inflammatory biomarkers, heart rate variability, stress and quality of life (6 weeks; 4 months) post-ICU discharge. Feasibility measures will be analyzed descriptively, and outcomes longitudinally. Estimates of effects will be calculated.

Ethics and dissemination: The study has received approval from the Human Research Ethics Board, University of Alberta. Results will inform the design of a future multi-center trial.

Registration: clinicaltrials.gov (NCT02905812).

Protocol date: March 3, 2018, version 5, Protocol amendment number: 07

Primary reasons for amendment: Refining feasibility of intervention and data collection.

Summary

Strengths and limitations of this study

- **We will test feasibility and measures of effect of a previously piloted relaxation-inducing intervention for the prevention of delirium and improvement of related outcomes in critically ill patients.**
- **We will employ an evidence-based, non-pharmacological multimodal integrative intervention that has shown effectiveness for reducing pain and improving a number of secondary outcomes in a previous pilot study.**
- **This pilot aims to assess estimates of effect and feasibility to inform a future trial.**
- **Although clinicians and outcome assessors will be blinded, due to the nature of the intervention, participants and nurses providing direct care to patients cannot be blinded to allocation, although they will be blinded to the study hypotheses.**
- **The mechanisms of effects of relaxation-inducing interventions in critical illness are not well understood; hence, we aim to explore effects of the intervention on parasympathetic system activation and inflammatory markers.**

Introduction

ICU delirium affects 35-55% of critically ill patients, and is independently associated with a 13-fold (adjusted odds ratio (OR):4.88-13.0) increased risk of death (1). ICU delirium carries important financial and societal burdens [(39% higher adjusted ICU (95% CI:12-72%), and 31% higher hospital costs (95% CI:1-70%)] (2). Moreover, patients identify frightening delirium experiences and pain as the most severe stressors (3,4) in critical care. Pharmacological interventions for the prevention and treatment of delirium have limited benefit and are associated with high costs and risks for side effects (5, 6). Although clinical guidelines recommend the development of non-pharmacologic interventions to prevent delirium (7), effective prevention strategies have yet to be established (8).

A prolonged and eventually aberrant stress response and depressed parasympathetic (PNS) activity have been postulated as the pathophysiological basis for the development of both ICU delirium and systemic inflammation (9-12). Frightening hallucinations and ideations during delirium may further exaggerate the stress-response and prolong critical illness with detrimental consequences. Pain may worsen matters by reciprocal incremental feed-back on inflammation and stress (3, 13). Thus, in critical illness, stress, delirium, pain and systemic inflammation may comprise a self-perpetuating syndrome. Attenuating the cascade of negative health impacts from pain and delirium has become a high clinical priority (Fig. 1) (7). Moreover, the growing recognition that delirium and other critical illness sequelae may have long term consequences in critical illness survivors (14) further highlights the need for prevention strategies.

Animal models illustrate that PNS stimulation and acetylcholine (ACh) release suppress inflammation and decrease fatality, via the cholinergic anti-inflammatory pathway (15). Devising ways to draw on the autonomic nervous systems' inflammation- and stress-regulatory properties

by non-pharmacological interventions has the potential to improve outcomes with low side-effect risk. However, stimulation of the PNS in critical care is challenging. Relaxation-inducing interventions can induce PNS activity. Such approaches have successfully been used in diverse patient populations to counter stress, but remain under-tested in critical illness (16). A recent systematic review shows favorable effects of relaxation and guided imagery intervention in reducing pain, anxiety and length of stay in critically ill patients (17) In a pilot randomized controlled trial (RCT) of the effects of a similar multi-modal intervention on the incidence of pain and on a number of secondary outcomes, we observed significant decreases in pain incidence (RR=0.56, p=0.003) and severity (p<0.0001), systolic arterial pressure, anxiety, along with improved sleep quality (18).

Hypothesis

We hypothesize that a multimodal intervention incorporating relaxation and guided imagery (RGI) and moderate pressure touch-massage is feasible within a critical care setting and can have an effect in decreasing delirium incidence and duration, and in improving physiological and psychological outcomes in randomized critically patients who will receive the intervention compared to patients receiving standard care plus a sham intervention only.

Design and Methods

Study design

Relaxation for Critically ill Patient Outcomes and Stress-coping Enhancement (REPOSE) is a pilot feasibility, randomized, controlled, double-blinded trial with 2 parallel groups (intervention and standard care). Accounting for major risk factors of delirium (13), stratified randomization

according to age (18-64, ≥65) and presence of either surgical or trauma injury with blocking and 1:1 allocation to assure balance in numbers per group will be employed.

Research Objectives

Research objectives include to:

a) Assess clinical trial feasibility with pre-defined goals (enrolment, randomization, adherence, timing of intervention, workload)

b) Calculate estimates and variance of treatment effect across outcome measures

c) Calculate Confidence Intervals (CI) of incidence proportions, means and Standard Deviation (SD) of outcome measures in study groups, and

d) Explore the feasibility of identifying underlying physiological mechanisms

Setting, recruitment and sample size:

Consecutive patients admitted to 2 academic ICUs, in Edmonton, AB, Canada, with an ICDSC score of 0-3 will be screened for study eligibility and will be recruited by research staff at each site. In cases where an ICDSC score cannot be obtained on admission, we will screen patients for up to 4 days after admission. Since delirium occurs most often within 5 days of admission, screening and enrolment will take place as soon as possible and within 96 hours after ICU admission. This pilot is not powered to determine a difference in a primary outcome, since we aim to assess estimates of effect. For a definitive trial, we would require 290 (145/arm) patients to detect a 10% difference in incidence proportion between intervention (20%) and control (30%) arm (two-sided alpha=0.05, power=80%, drop-out rate=10%). The Pan method (19), which is based on generalized estimating equations, was used to perform the sample size

calculation under the assumption of AR(1) correlation structure among 5 days repeated measurements with correlation between any two adjacent observations from the same subject of 0.5. Since this is a pilot, aiming to explore feasibility and estimates of effects, and the incidence rates used for the calculation might not be appropriate, we used 36% of the sample size of the full study to estimate the parameters accurately and get an experience for a full trial (20).

Eligibility:

Inclusion criteria: a) Age over 18 years, b) ICDSC:0-3.

Exclusion Criteria: Patients: a) Already in the ICU for more than 96 hours, b) with ICDSC>3 within 72 h of screening in case intervention has not been initiated, c) on special contact precautions (i.e., MRSA, VRE, HIV), d) with expected Intensive Care Unit (ICU) Length of stay (LOS) < 72 hours, e) with acute neurological illness/ neurological trauma, persistent deep sedation or coma [Richmond Agitation Sedation Scale (RASS = -4, -5)] f) with current history of severe mental health problems and dementia, as per history, g) with hearing impairment or conditions not permitting use of headphones, h) on neuro-muscular blockers, i) with known or suspected substance/ alcohol withdrawal, and j) enrolled in trials of sedatives, antipsychotics.

Intervention

The choice of a multimodal intervention (duration: 55min) is based on an evidence-based literature review, its superiority to unidimensional approaches (21), the recommendations of the American Holistic Nurses Association (22) and a successful pilot (18). The intervention has been developed by the research team and a group of experts based at the University of Alberta and Cyprus University of Technology. It includes: a) a brief moderate pressure massage session (massage: 15 minutes), b) relaxation and guided imagery (30 minutes, through headphones). The

30 min recorded RGI intervention involves: a) guided relaxation, b) a structured guided imagery script supported by instrumental music, and c) recorded instrumental music for 15 minutes (60 beats per min approximately). Moderate pressure (4 N, approximately or patient pressure rating 3/10) low velocity (1-5cm/second) massage consists of broad and repetitive circular movements with wide area of contact, applied sequentially for 2-3 minutes at each site: hands, forearms, lateral arms, and then over trapezius muscles, the temple, scalp, face and forehead area. Areas are to be contacted as appropriate to each participant, and the protocol may be adapted taking into account safety issues (i.e., to avoid area around intravascular catheter or injury). Moderate pressure massage is involved in PNS activation, in contrast to light pressure (23). The intervention will be administered once daily (09:00-15:00) for up to 5 consecutive days by trained research staff not involved in patient care, who will be randomly audited by the Trial Steering Committee (TSC) to ensure protocol compliance. Deviations from the intervention protocol will be recorded in detail. The intervention will be terminated upon a patient's transfer or discharge from the ICU. The intervention may be discontinued in case of adverse events related to the intervention or withdrawal of consent.

Randomization and concealment

Participants will be randomly assigned to either control or intervention (1:1 allocation) as per a computer-generated randomization schedule, generated by the Epidemiology Coordinating Research Centre (EPICORE), University of Alberta (UofA), stratified by site, age (18-64, ≥65), and presence of surgery or trauma using permuted blocks of random sizes. The block size will not be disclosed to ensure concealment. After baseline measurements, allocation will be disclosed only to the intervention staff. Codes will be generated prior to the beginning of the study by EPICORE.

Blinding

Investigators, physicians and nurses (when possible), outcome assessors, research assistants, and laboratory technicians will be blinded to group allocation during the trial and analysis. Due to the nature of the intervention, participants cannot be blinded to allocation. Also, participants' primary nurses cannot be blinded to study procedures (i.e., delivery of massage); however, they will remain blinded to study hypotheses, study design (i.e., numbers and types of participants' groups) and allocation will not be revealed to them. These along with the sham intervention will maintain an adequate level of blindness even among participants' primary nurses, in order to minimize bias.

Treatment arms

Patients randomly allocated to the intervention group will receive the intervention in addition to standard care. Patients allocated to the control group will receive standard care and a sham intervention consisting of presence of a research staff at the bedside with drawn curtains and silent headphones (Schematic of study design in Figure 2).

Concomitant care

Standard care will be continued for all participants. Type and dose of all administered sedative, psychoactive and analgesic medication will be recorded.

Duration of participation: The total duration may vary according to ICU length of stay and will be 17 weeks approximately, from enrolment until the last follow up at 4 months post-ICU discharge.

Data Collection and Instruments

Data will be collected for each participant by blinded data collectors and captured in a Research Electronic Data Capture (RedCap) database developed and monitored by EPICORE. Time points include: baseline measurements, follow-up while in the ICU for up to 5 days, follow up 48-96 hours after ICU discharge, follow-up 6 weeks and 4 months after ICU discharge. In case of participants who discontinue participation, data already collected will be retained.

All study scales are routinely used in clinical practice and have established psychometric properties. The ICDSC is one of the most reliable tools for assessment of ICU delirium advocated by recent guidelines (3, 24). Inter-observer reliability of and sensitivity (80.1, 95% CI:73.3-85.8) of ICDSC have been established and will be further assessed in this study (24). For comatose, deeply sedated patients [Richmond Agitation Sedation Scale (RASS = -4, -5)] delirium cannot be assessed. Data captured on Case Reports Forms are included in Figure 2. Baseline data captured at enrolment will include: Sociodemographic data, admission diagnosis, history of alcohol use, medications prior to admission, metabolic acidosis, ICDSC, RASS, Short Form Informant Questionnaire on Cognitive Decline in the Elderly (Short IQCODE), Pre-Deliric Delirium Risk Score, baseline IV sedation, analgesia and antipsychotic dose, disease severity at admission (Acute Physiology & Chronic Health Evaluation II (APACHE II), Sequential Organ Failure Assessment: SOFA), number of days in hospital and ICU prior to protocol enrolment.

Outcome Measures

Primary and secondary outcome, as well as feasibility, measures include (Appendix 1):

A. ***Primary clinical outcome***: a) Incidence rate of delirium (ICDSC ≥4), during 5 days of intervention. Presence of delirium will be assessed by blinded trained nurse assessors 2 times daily (8am, 8pm).

B. Secondary outcomes [Estimates, variance of effects, proportions and means, SD (where applicable) per group]:

1. ***Delirium related secondary outcomes****:* a) Incidence rate of delirium (ICDSC ≥4) during ICU stay and post-intervention, b) incidence rate of subsyndromal delirium (ICDSC: 1-3) during the intervention period and subsequent ICU stay, c) time to delirium occurrence, d) proportion of delirium-free time during up to 8 days of ICU stay (excluding periods with deep sedation, coma), e) Sedation levels (Richmond Agitation Sedation Scale (RASS) score, f) Daily sedative (benzo-equivalents and propofol), analgesic (morphine equivalents) and antipsychotic agent (type, mg/24 hours) dose.
2. ***Pain related outcomes*** (*Pre- and post-intervention)*: a) Pain intensity (self-reported (S-R) numeric rating scale (NRS), pain indicators (Critical Care Pain Observation Tool (CPOT) in patients unable to self-report, b) perceived stress level (S-R NRS).
3. ***Sleep*** (*Daily):* a) Sleep quality (S-R NRS), b) sleep duration (in minutes) (sleep monitors and nurses' log).
4. ***Disease severity*** ***(****Daily):* Sequential Organ Failure (SOFA) score
5. ***Physiological Biomarkers*** *(Pre- & post-intervention):* a) Serum Inflammation biomarkers [High-mobility-group-box 1 (HMGB-1), C-reactive protein (CRP) levels, b) High (HF) and low frequency (LF) components of heart rate variability (HRV) as measures of PNS status, c) Serum ACh levels, as a measure of PNS activation.
6. ***Psychological outcomes*** *(2-7 day after ICU discharge*): Anxiety (Hospital Anxiety and Depression Scale: HADS & State Trait Anxiety Inventory-6: STAI-6)

7. ***Clinical outcomes*** *(At discharge)*: a) length of ICU stay (ICU LOS) (or ward-ready), b) Duration of mechanical ventilation/ proportion of mechanical ventilation-free days, c) survival, d) hospital LOS and e) (*3 months post-ICU discharge)*: 90-day survival.
8. ***Quality of life outcomes*** (*6 weeks and 4 months post-ICU discharge):* EuroQol Five Dimensions Questionnaire (EQ-5DL), Short Form 36 Health Survey (SF-36)
9. ***Recollection and perception of the intervention*** *(2-7 days after ICU discharge and 6 weeks post-ICU discharge):* Qualitative open-ended questions to explore recollection of intervention, views on intervention and acceptability.

C. Feasibility

1. ***Enrolment & consent:*** a) percentage (%) of eligible patients; reasons for non-eligibility, b) time from admission to enrolment, c) recruitment rates, d) % of patients declining consent
2. ***Randomization & concealment***: a) time from enrolment to randomization, b) % of cases at which allocation was inappropriately revealed; description of incident.
3. ***Protocol adherence & intervention fidelity:*** Percentage of: a) participants completing the entire study protocol, b) sessions missed, interrupted, delayed; reasons. Adherence to intervention protocol assessed by random observation audits.
4. ***Data Collection & management:*** a) timeliness, accuracy of data collection, reliability, b) testing of trial database, c) type, % of missing values, d) qualitative data on participants' perceptions of the study.

Blood sampling: One 5 ml blood sample will be collected in pre-coded general anti-coagulated vials, through an intravascular catheter already in place, within 10 min before and 10 min after the intervention.

Biomarker quantifications

a. Serum levels of HMGB-1, ACh and CRP.

These will be quantified by commercially available sandwich enzyme-linked immunosorbent colorimetric assay (ELISA) kits (LifeSpan Biosciences, Seattle; WA, Biosource, S. Diego, CA; R & D Systems, Minneapolis, MN, respectively). Intra- and inter-assay coefficients of variation (CV) are expected to be less than 10%. All samples will be tested within the same assay run in duplicate by a specialized laboratory technician. Measurements will be carried out at the Women's Health Research Laboratory, Faculty of Nursing, University of Alberta.

b. **ANS (Autonomic Nervous System) activity: HF, LF AND LF/HF ratio**

ANS activity will be assessed through frequency domain analysis of electrocardiographic (ECG) recordings. ECG recordings will be logged using the Zephyr™ BioModule™ and data will be imported into the OmniSense™ software. Data from OmniSense™ will then be uploaded to Kubios HRV software (Kubios HRV- Hear Rate Variability Analysis Software) and HF, LF and LF/HF ratios will be computed.

Data Analysis

Statistical Methods

Demographic/ clinical characteristics of patients and all outcomes will be presented by treatment group using descriptive statistics— mean (SD), median (IQR) or proportion. Outcomes will be

analyzed longitudinally over 5 days by logistic regression model based on generalized estimating equations (GEE) with AR(1) correlation structure. ANCOVA, t-test or Mann-Whitney test, as appropriate, will be conducted for the continuous outcomes that are not longitudinal. Chi-square or exact test, as appropriate, will be used for categorical outcomes. Confidence intervals will be presented with estimated effects. Primary analysis will be based on all available data utilizing data from all assessments. Since GEE assumes missing completely at random (MCAR) mechanism, we plan to conduct a sensitivity analysis based on inverse probability weighted GEE (IPWGEE) (**22**) (25) which employs a less restrictive missing at random (MAR) mechanism. A "last observation carried forward" (LOCF) approach was not considered because analyzing all available data performs better than LOCF in GEE setting with respect to bias, Type I error rate and coverage probability under both MCAR and MAR mechanisms. Analysis will be conducted by EPICORE.

To account for noncompliance, protocol deviations and missing outcomes, intention-to-treat (ITT) analysis will be employed. ITT analysis includes every randomized subject according to treatment assignment. Additionally, per protocol analysis will also be employed. Per-protocol (PP) population is defined as a subset of the ITT population who completed the study without any major protocol violations. If ITT and PP analyses lead to similar conclusions the reliability of results will be supported.

Qualitative analyses

Interview transcriptions will be thematically analyzed by an inductive content analysis approach (26). A coding scheme will be developed based on recurrent themes of the first five interviews. Subsequently, two researchers (EP, TP) will code independently, using axial and inductive coding to formulate a final coding template by consensus. The final coding scheme will then be

used to code, compare and interpret all transcripts. Individual analyses of the team members will be discussed to achieve shared understanding and to increase reliability. The data will be analyzed via NVivo software (QSR International Doncaster, Victoria, Australia).

Quality Control and Quality Assurance

This pilot will be supervised by an independent trial steering committee (TSC), consisting of 3 clinical trial experts independent of the research team. Periodical audits of trial processes at both sites by personnel independent from investigators will be initiated by the TSC. Randomization, recruitment, intervention adherence, blinding, stability and data collection processes will be monitored. Trial Monitoring Committee (TMC) will also review relevant information from similar studies and will consider the recommendations of the Data Monitoring (DMC) and Ethics Committee. Study personnel will be trained for standardized processes. Clinical data will be retrieved from the quality-controlled clinical information system of the units. Detailed electronic data collection forms with embedded quality controls will be used and reviewed in detail. Data quality will be monitored through EPICORE before, during, and after entry. All data will be entered electronically using study forms generated through RedCap with embedded quality control processes. Study data will be collected and managed using REDCap electronic data capture tools hosted at the University of Alberta (27). A quality control system will be applied for biological measurements as per lab protocol. Day-to-day operations of the trial will be overseen by a Trial Management Group (TMG) comprising, as a minimum, the Principal Investigator, Senior Trial Manager, Trial Manager, Trial Statistician and Data Manager. TMG meetings will take place on a regular basis throughout the duration of the study. The TMG will have responsibility for ensuring the compliance and progress of the study in relation to all regulatory, administrative academic and any clinical or safety issues.

Ethics

The protocol has received approval from the Human Research Ethics Board (HREB) University of Alberta and administrative approvals from participating institutions. This study will be conducted in compliance Canadian and International Good Clinical Practice standards. No deviation from the protocol will be implemented without the prior review and approval of the HREB except where it may be necessary to eliminate an immediate hazard to a research participant. In such case, the deviation will be reported to the HREB.

Experienced research personnel not involved with the delivery of the intervention and in patient care will acquire informed consent from legal surrogates. Participant assent will be acquired when participants regain capacity. Confidentiality, anonymity and right to withdraw at any point with no questions asked and no effect on the quality of care received will be assured. After completion of the study the data and samples will remain stored at the academic institution for 5 years.

Confidentiality

Code-identified encrypted study data will be stored separately from participant information at an EPICORE database permitting code-access only. All study forms, lab specimens and data will be identified by an alphanumeric code to maintain confidentiality. Records that contain names, identifiers will be stored separately from study data identified by code. Participants' information will not be released outside the study. Participant information will be stored at an encrypted limited code-initiated access electronic file. Consent forms will be kept in a locked file cabinet at a pre-specified limited-access room, University of Alberta.

Safety

Although prior pilot data did not provide evidence of adverse effects or increased rate of complications, any physiological/ behavioural alteration during interventions will be recorded and analysed. Adverse events, irrespective of causal relationship, will be collected for all participants, during and up to half an hour after the intervention.

Patient and Public involvement

The protocol is based on a pilot study with 60 randomized patients (18), 12 of which provided feedback regarding the desirability, burden and specific components of the intervention, study procedures and preferred outcomes. Participants' feedback informed the design of the study, resulting in many significant changes. Preferred post-ICU follow-up times were informed by an informal advisory group through the Alberta Innovates Strategy for Patient Oriented Research (SPOR) network of patient representatives. Moreover, as a patient and clinician engagement strategy, an advisory group with representatives of patients, families and clinicians will act as a consultation group for the research team. Acceptance and desirability will be assessed further. Recommendations will inform future development of the intervention and research design. Canadian Institutes of Health Research (CIHR) guidelines for patient engagement will be used to establish and facilitate the advisory group. Feedback on: a) concerns on the intervention, study processes, b) desirability of intervention (massage, music choices, complexity, voice of recording, pace), c) timing within the day, d) duration/ feasibility of the intervention, e) burden of study processes, f) outcomes to be addressed in the future trial, g) interpretation of results, h) strategies for dissemination of findings will be collected.

Data Dissemination

Results will be disseminated to participants, healthcare professionals, health services authorities and the public via conference presentations and publications. Results of this study will be used to inform the design and conduct of a future multi-center trial. The results of the trial will be presented at national and international meetings and published in peer-reviewed journals. A lay summary of the results will be available to trial participants on request. An online summary of the findings will also be made available.

Conclusions: This pilot clinical trial integrates a low-risk, patient-centered strategy, translational research and psychological outcomes to allow an evaluation of non-pharmacologic delirium management with mechanistic insights. Implications of the definitive trial include the potential to reassure patients, decrease the incidence of frightening delirium experiences, and improve longitudinal outcomes.

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Authors' conflict of interest: None declared

Data Statement: Technical appendix, statistical code, and dataset will be available from EPICORE, University of Alberta.

Legends

Figure 1.

Evidence-based framework for the physiological mechanism implicated in relaxation-induced effects in critical illness. Relaxation acts early at the pathophysiological cascade through which an exaggerated stress response results in pro-inflammatory effects, suppressed PNS outflow and subsequently in systemic inflammation, multiple organ dysfunction and death. The relaxation response counterbalances the exaggerated stress response and activates PNS and cholinergic anti-inflammatory signaling, which downregulates pro-inflammatory (e.g., HMGB-1) and up-regulates anti-inflammatory cytokines; therefore attenuating systemic inflammation and its detrimental organ effects. (*α7-nAChR: alpha7- nicotinic acetylcholine receptor, HMGB-1: High Mobility Group Box-1; PNS: Parasympathetic Nervous System)*

Figure 2:

Schematic of study design. *(Ach: Acetylcholine, AE: Adverse Event, APACHE: Acute Physiology & Chronic Health Evaluation, CPOT: Critical Care Pain Observation Tool, CRP: C-Reactive Protein, EQ-5D: EuroQol Five Dimensions Questionnaire, HADS: Hospital Anxiety and Depression Scale, HF: High Frequency, HMGB: High Mobility Group Box, HRV: Heart Rate Variability, ICDSC: Intensive Care Delirium Screening Checklist, ICU: Intensive Care Unit, IQCODE: Informant Questionnaire on Cognitive Decline in the Elderly, IV: Intravenous, LF: Low Frequency, LOS : Length of Stay, NRS: Numeric Rating Scale, RASS: Richmond*

Agitation Sedation Scale, RGI: Relaxation and Guided Imagery, S-R: Self-Reported, SOFA: Sequential Organ Failure, STAI: State Trait Anxiety Inventory).

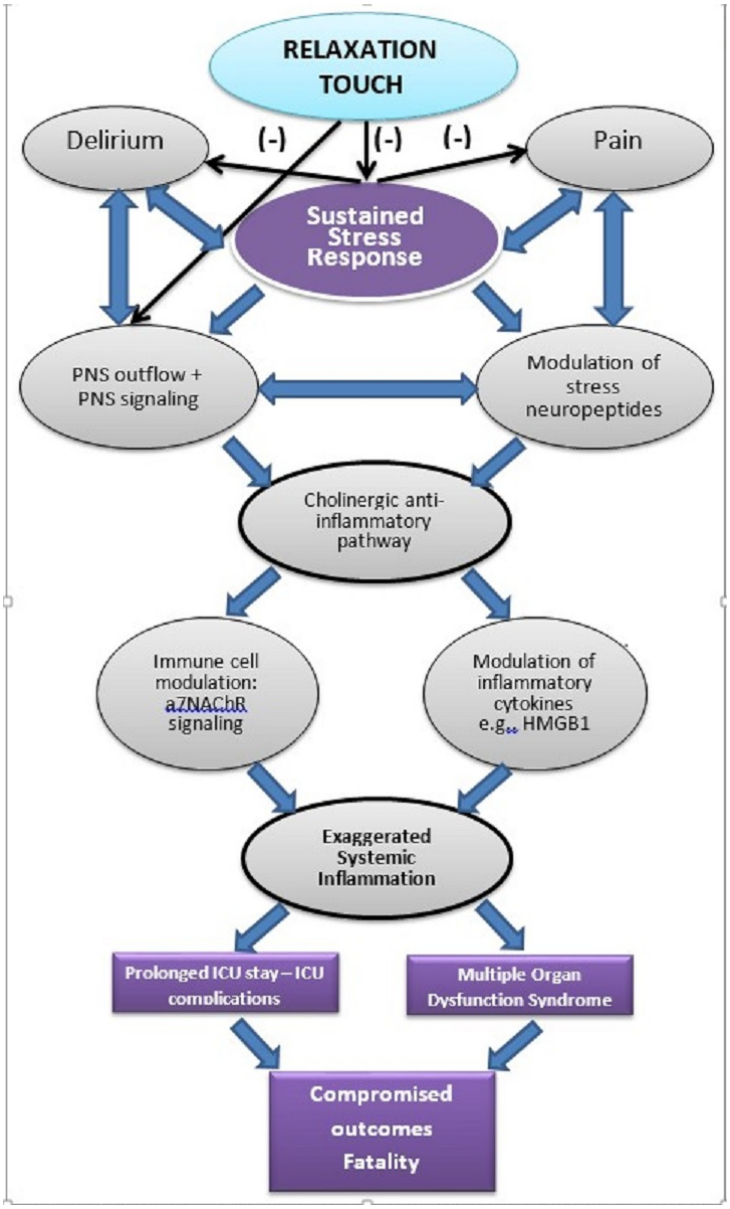
Appendix 1. Schedule of enrolment, interventions, and assessments. Adapted from (28).

	Enrolment	Allocation	Post-allocation in-ICU					Post-intervention / in-ICU (daily until discharge)	*At ICU-discharge (or ward-ready)*	Post ICU discharge (In hospital: 2-7 days)	*At hospital discharge*	Post ICU Discharge (6 weeks)	Post ICU Discharge (4 months)
TIMEPOINT	$-t_1$	0	Day_1	Day_2	Day_3	Day_4	Day_5						
ENROLMENT:													
Eligibility screen	X												
Informed consent	X												
Random Allocation		X											
INTERVENTIONS:													
[Intervention: RGI + massage]			←	—	—	—	→						
[Control: Sham Intervention]			←	—	—	—	→						
BASELINE ASSESSMENTS: ***[***demographics diagnosis, hx, short IQCODE), pre-DDRS, sedatives/ analgesics/ antipsychotics dose, Prior LOS***]***	X												
Primary Outcome:		X	X	X	X	X	X						

ICDSC≥4												
Secondary outcomes: *ICDSC, ICDSC:1-3, RASS, daily* sedatives/ analgesics/ antipsychotics dose, ***sleep NRS, sleep duration, APACHE II, SOFA***		X	X	X	X	X	X	X				
			pre-post-Intervention									
C-POT, PAIN NRS, pain distress NRS, stress NRS, HF- LF HRV		X	X2	X2	X2	X2	X2					
			pre-post-Intervention									
HMGB-1, CRP, Ach			X2	X2	X2	X2	X2					
ICU LOS, duration MV, ICU survival									X			
HADS										X		
Hospital survival, Hospital LOS											X	
6 week survival, Interview, EQ-5D, SF-36												X

4-month survival, EQ-5D, SF-36													X

Ach: Acetylcholine, CPOT: Critical Care Pain Observation Tool, CRP: C-Reactive Protein, DEMMI: de Morton Mobility Index, EQ-5D: EuroQol Five Dimensions Questionnare, HADS: Hospital Anxiety and Depression Scale, HF: High Frequency, HMGB: High Mobility Group Box, HRV: Heart Rate Variability, ICDSC: Intensive Care Delirium Screening Checklist, ICU: Intensive Care Unit, Interview: Qualitative open ended questions; IQCODE: Informant Questionnaire on Cognitive Decline in the Elderly, LF: Low Frequency, LOS : Length of Stay, MV: mechanical ventilation, NRS: Numeric Rating Scale, RASS: Richmond Agitation Sedation Scale, RGI: Relaxation and Guided Imagery, S-R: Self-Reported, SOFA: Sequential Organ Failure, STAI: State Trait Anxiety Inventory.



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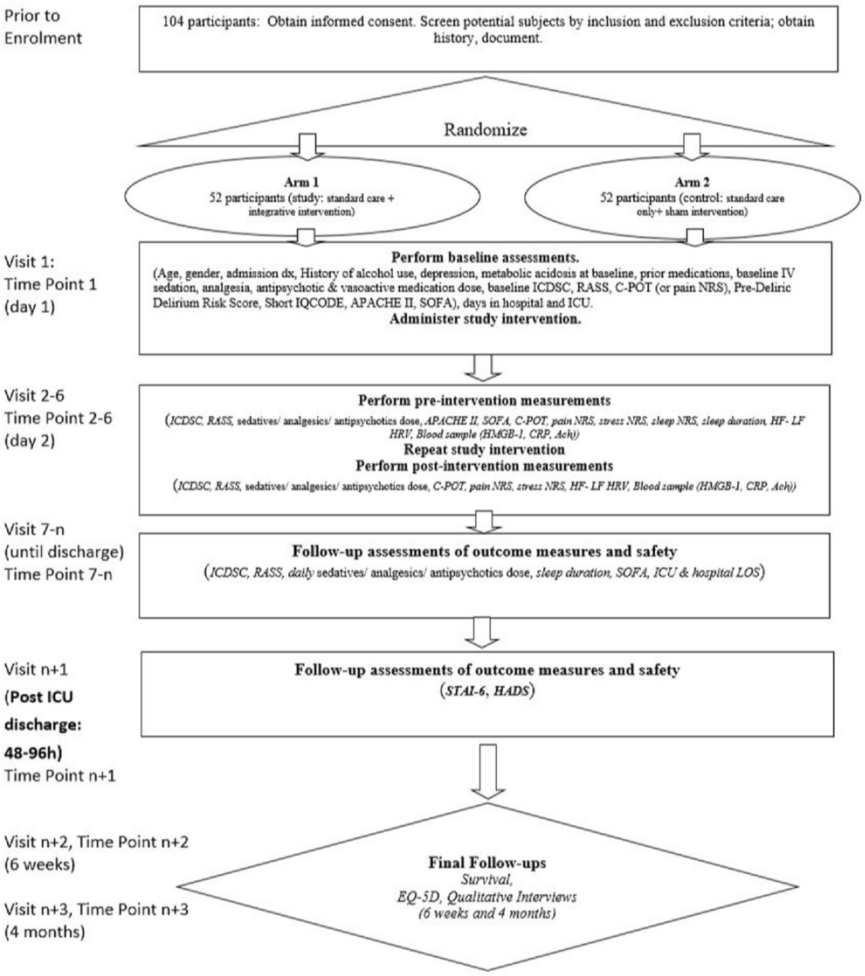

778x824mm (96 x 96 DPI)

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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		Reporting Item	Page Number
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	2
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	2
Protocol version	#3	Date and version identifier	2
Funding	#4	Sources and types of financial, material, and other support	22
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	22

Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	22
22Roles and responsibilities: sponsor and funder	#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	22
Roles and responsibilities: committees	#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)	14-15
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	4-5
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	5
Objectives	#7	Specific objectives or hypotheses	5, 6
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, non-inferiority, exploratory)	5
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	6
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and	7

		individuals who will perform the interventions (eg, surgeons, psychotherapists)	
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7-8,9
Interventions: modifications	#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)	8
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	8
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	9
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	10-12
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)	1. Appendix
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	6-7
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	6

Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of 8any 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	8
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	8
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	8
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	8-9
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	9, NA
Data collection plan	#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	9-10
Data collection plan: retention	#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	9

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	9,15
Statistics: outcomes	#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	13-14
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	13-14
Statistics: analysis population and missing data	#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)	14
Data monitoring: formal committee	#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	14-15
Data monitoring: interim analysis	#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	NA
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	16
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	8,15

Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	15,16
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)	15
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	15-16
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	16
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	16
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	22
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	NA
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	NA
Dissemination policy: trial results	#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	16

Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	NA
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	16
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	Upon request
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	12-13 & upon request

BMJ Open

Relaxation for Critically ill Patient Outcomes and Stress-coping Enhancement (REPOSE): A protocol for a pilot randomized trial of an integrative intervention to improve critically ill patients' delirium and related outcomes

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Primary Subject Heading:	Intensive care
Secondary Subject Heading:	Complementary medicine, Nursing
Keywords:	critical illness, music therapy, relaxation, guided imagery, delirium, complex intervention

*R*elaxation for Critically ill *P*atient *O*utcomes and *S*tress-coping *E*nhancement (REPOSE): A protocol for a pilot randomized trial of an integrative intervention to improve critically ill patients' delirium and related outcomes

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Key words: critical illness, music therapy, relaxation, guided imagery, autonomic nervous system, delirium, complex intervention

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Abstract

Introduction: Delirium is a common complication of critical illness, associated with negative patient outcomes. Preventive or therapeutic interventions are mostly ineffective. Although relaxation-inducing approaches may benefit critically ill patients, no well-designed studies target delirium prevention as a primary outcome. The objective of this study is to assess feasibility and treatment effect estimates of a multimodal integrative intervention incorporating relaxation, guided imagery, and moderate pressure touch-massage for prevention of critical illness delirium and for related outcomes.

Methods and analysis: Randomized, controlled, single-blinded trial with 2 parallel groups (1:1 allocation: intervention and standard care) and stratified randomization [age (18-64, ≥65), presence of trauma) with blocking, involving 104 patients with Intensive Care Delirium Screening Checklist (ICDSC): 0-3 recruited from 2 academic ICUs. Intervention group participants receive the intervention in addition to standard care for up to 5 consecutive days (or until transfer/ discharge); control group participants receive standard care and a sham intervention. We will assess pre-defined feasibility outcomes, i.e., recruitment rates, protocol adherence. The primary clinical outcome is incidence of delirium (ICDSC ≥4). Secondary outcomes include pain scores, inflammatory biomarkers, heart rate variability, stress and quality of life (6 weeks; 4 months) post-ICU discharge. Feasibility measures will be analyzed descriptively, and outcomes longitudinally. Estimates of effects will be calculated.

Ethics and dissemination: The study has received approval from the Human Research Ethics Board, University of Alberta. Results will inform the design of a future multi-center trial.

Registration: clinicaltrials.gov (NCT02905812).

Protocol date: March 3, 2018, version 5, Protocol amendment number: 07

Primary reasons for amendment: Refining feasibility of intervention and data collection.

Summary

Strengths and limitations of this study

- **We will test feasibility and measures of effect of a previously piloted relaxation-inducing intervention for the prevention of delirium and improvement of related outcomes in critically ill patients.**
- **We will employ an evidence-based, non-pharmacological multimodal integrative intervention that has shown effectiveness for reducing pain and improving a number of secondary outcomes in a previous pilot study.**
- **This pilot aims to assess estimates of effect and feasibility to inform a future trial.**
- **Although clinicians and outcome assessors will be blinded, due to the nature of the intervention, participants and nurses providing direct care to patients cannot be blinded to allocation, although they will be blinded to the study hypotheses.**
- **The mechanisms of effects of relaxation-inducing interventions in critical illness are not well understood; hence, we aim to explore effects of the intervention on parasympathetic system activation and inflammatory markers.**

Introduction

ICU delirium affects 35-55% of critically ill patients, and is independently associated with a 13-fold (adjusted odds ratio (OR):4.88-13.0) increased risk of death (1) and long-term cognitive impairment (2). ICU delirium carries important financial and societal burdens [(39% higher adjusted ICU (95% CI:12-72%), and 31% higher hospital costs (95% CI:1-70%)] (3). Moreover, patients identify frightening delirium experiences and pain as the most severe stressors (4,5) in critical care. Pharmacological interventions for the prevention and treatment of delirium have limited benefit and are associated with high costs and risks for side effects (6,7). Although clinical guidelines recommend the development of non-pharmacological interventions to prevent delirium (8), effective prevention strategies have yet to be established (9).

A prolonged and eventually aberrant stress response and depressed parasympathetic (PNS) activity have been postulated as the pathophysiological basis for the development of both ICU delirium and systemic inflammation (10-13). Frightening hallucinations and ideations during delirium may further exaggerate the stress-response and prolong critical illness with detrimental consequences. Pain may worsen matters by reciprocal incremental feed-back on inflammation and stress (4, 14). Thus, in critical illness, stress, delirium, pain and systemic inflammation may comprise a self-perpetuating syndrome. Attenuating the cascade of negative health impacts from pain and delirium has become a high clinical priority (Figure 1) (8). Moreover, the growing recognition that delirium and other critical illness sequelae may have long term consequences in critical illness survivors (15) further highlights the need for prevention strategies.

Evidence-based theoretical work postulates that the multitude of psychological stressors in critically ill individuals may contribute to the development of pathophysiologic sequelae (10).

Moreover, animal models illustrate that PNS stimulation and acetylcholine (ACh) release suppress inflammation and decrease fatality, via the cholinergic anti-inflammatory pathway (16). Devising ways to draw on the autonomic nervous systems' inflammation- and stress-regulatory properties by non-pharmacological interventions has, in theory, the potential to improve outcomes with low side-effect risk. However, stimulation of the PNS in critical care is challenging. Relaxation-inducing interventions can induce PNS activity. Such approaches have successfully been used in diverse patient populations to counter stress, but remain under-tested in critical illness (17). A recent systematic review shows favorable effects of relaxation and guided imagery intervention in reducing pain, anxiety and length of stay in critically ill patients (18); whereas, the relaxation inducing effects of music in critical care have been well supported by evidence (19). In a pilot randomized controlled trial (RCT) of the effects of a similar multi-modal intervention on the incidence of pain and on a number of secondary outcomes, we observed significant decreases in pain incidence (RR=0.56, p=0.003) and severity (p<0.0001), systolic arterial pressure, anxiety, along with improved sleep quality (20).

Hypotheses

Overall, we hypothesize that a multimodal intervention incorporating relaxation and guided imagery (RGI) and moderate pressure touch-massage is feasible within a critical care setting, and can have an effect on decreasing delirium and in improving physiological and psychological outcomes in randomized critically patients who will receive standard care and the intervention compared to patients receiving standard care plus a sham intervention only.

Primary Hypotheses:

We hypothesize that the intervention will be feasible and that it will have an effect on decreasing delirium incidence and duration.

Secondary hypotheses:

We hypothesize that the intervention will have an effect on: a) incidence rate of subsyndromal delirium, time to delirium occurrence, proportion of delirium-free time during up to 8 days of ICU stay; b) sedation levels and daily sedative, analgesic and antipsychotic agent dose; c) pain occurrence and intensity; d) perceived stress level; e) sleep duration and quality; f) anxiety; g) length of ICU stay and duration of mechanical ventilation/ proportion of mechanical ventilation-free days; h) hospital LOS, i) physiological biomarkers; and k) quality of life after ICU discharge.

Design and Methods

Study design

Relaxation for Critically ill Patient Outcomes and Stress-coping Enhancement (REPOSE) is a pilot feasibility, randomized, controlled, single-blinded trial with 2 parallel groups (intervention and standard care). Accounting for major risk factors of delirium (15), stratified randomization according to age (18-64, ≥65) and presence of either surgical or trauma injury with blocking and 1:1 allocation to assure balance in numbers per group will be employed.

Research Objectives

Research objectives include to:

a) Assess clinical trial feasibility with pre-defined goals (enrolment, randomization, adherence, timing of intervention, workload)

b) Calculate estimates and variance of treatment effect across outcome measures

c) Calculate Confidence Intervals (CI) of incidence proportions, means and Standard Deviation (SD) of outcome measures in study groups, and

d) Explore the feasibility of identifying underlying physiological mechanisms

Setting, recruitment and sample size

Consecutive patients admitted to 2 academic ICUs, in Edmonton, AB, Canada, with an ICDSC score of 0-3 will be screened for study eligibility and will be recruited by research staff at each site. In cases where an ICDSC score cannot be obtained on admission, we will screen patients for up to 4 days after admission. Since delirium occurs most often within the first 5 days of admission, screening and enrolment will take place as soon as possible and within 96 hours after ICU admission. This pilot is not powered to determine a difference in a primary outcome, since we aim to assess estimates of effect. For a definitive trial, we would require 290 (145/arm) patients to detect a 10% difference in incidence proportion between intervention (20%) and control (30%) arm (two-sided alpha=0.05, power=80%, drop-out rate=10%). The Pan method (21), which is based on generalized estimating equations, was used to perform the sample size calculation under the assumption of AR(1) correlation structure among 5 days repeated measurements with correlation between any two adjacent observations from the same subject of 0.5. Since this is a pilot, aiming to explore feasibility and estimates of effects, and the incidence rates used for the calculation might not be appropriate, we used 36% of the sample size of the full study to estimate the parameters accurately and get an experience for a full trial (22).

Eligibility

Inclusion criteria: a) Age over 18 years, b) ICDSC:0-3, c) written informed consent.

Exclusion Criteria: Patients: a) Already in the ICU for more than 96 hours, b) with ICDSC>3 within 72 h of screening in case intervention has not been initiated, c) on special contact precautions (i.e., MRSA, VRE, HIV), d) with expected Intensive Care Unit (ICU) Length of stay (LOS) < 72 hours, e) with acute neurological illness/ neurological trauma, persistent deep sedation or coma [Richmond Agitation Sedation Scale (RASS = -4, -5)] f) with current history of severe mental health problems and dementia, as per history, g) with hearing impairment or conditions not permitting use of headphones, h) on neuro-muscular blockers, i) with known or suspected substance/ alcohol withdrawal, and j) enrolled in trials of sedatives, antipsychotics.

Patient and Public involvement

The protocol is based on a pilot study with 60 randomized patients (20), 12 of which provided feedback regarding the desirability, burden and specific components of the intervention, study procedures and preferred outcomes. Participants' feedback informed the design of the study, resulting in many significant changes. Preferred post-ICU follow-up times were informed by an informal advisory group through the Alberta Innovates Strategy for Patient Oriented Research (SPOR) network of patient representatives. Moreover, as a patient and clinician engagement strategy, an advisory group with representatives of patients, families and clinicians will act as a consultation group for the research team. Acceptance and desirability will be assessed further. Recommendations will inform future development of the intervention and research design. Canadian Institutes of Health Research (CIHR) guidelines for patient engagement will be used to establish and facilitate the advisory group. Feedback on: a) concerns on the intervention, study processes, contamination of the control group by implementation of aspects of the intervention, b) desirability of intervention (massage, music choices, complexity, voice of recording, pace), c) timing within the day, d) duration/ feasibility of the intervention, e) burden of study processes, f)

outcomes to be addressed in the future trial, g) interpretation of results, h) strategies for dissemination of findings will be collected.

Intervention

The choice of a multimodal intervention (duration: 55min) was based on an evidence-based literature review, its superiority to unidimensional approaches (23), the recommendations of the American Holistic Nurses Association (24) and a successful pilot (20). According to the UK Medical Research Council (MRC) guidance for complex intervention trials (25), development of the protocol included extensive theoretical work (10), two systematic reviews (18, 26), modeling of outcomes, extensive consultations with groups of experts, one small feasibility and acceptability pilot (n=10 participants) and one larger pilot (n=60) (20) and consultation with pilot participants and patients' representatives. The intervention has been developed by the research team and a group of experts based at the University of Alberta and Cyprus University of Technology. It includes: a) a brief moderate pressure massage session (massage: 15 minutes), b) relaxation and guided imagery (30 minutes, through headphones). The 30 min recorded RGI intervention involves: a) guided relaxation, b) a structured guided imagery script supported by instrumental music, and c) recorded instrumental music for 15 minutes (Haydn concerto no 1 in C major and Bach violin concerto in D minor, 60 beats per min approximately). The same recorded RGI script will be used at all sessions. It includes positive suggestions and instructions for gradual relaxation, followed by guidance to visualize one's body being healed. Moderate pressure (4 N, approximately or patient pressure rating 3/10) low velocity (1-5cm/second) massage consists of broad and repetitive circular movements with wide area of contact, applied sequentially for 2-3 minutes at each site: hands, forearms, lateral arms, and then over trapezius muscles, the temple, scalp, face and forehead area. Areas are to be contacted as appropriate to

each participant, and the protocol may be adapted taking into account safety issues (i.e., to avoid area around intravascular catheter or injury). Moderate pressure massage is involved in PNS activation, in contrast to light pressure (27). The intervention will be administered once daily (09:00-15:00) for up to 5 consecutive days by trained research staff not involved in patient care, who will be randomly audited by the Trial Steering Committee (TSC) to ensure protocol adherence. The decision to deliver the intervention for the first 5 days after enrollment only was based on epidemiological data regarding the onset of delirium (9), data on median length of stay of the target populations in the study institutions and cost considerations. However, it will be important to study the effect of the intervention on longer stay patients in future trials. The decision to deliver only one intervention daily was based on a small acceptability/ feasibility pilot, and pragmatic considerations for knowledge translation and future implementation of this approach, as well as cost considerations and burden to participants and units. The durations of guided imagery, music therapy and touch intervention were based on the acceptability pilot, expert opinions on the minimum duration to achieve a relaxation effect and on published evidence (18). Despite evidence on the importance of providing choice to patients regarding music therapy (19), we will use standardized music for intervention stability purposes. It will be important to look at the effect of patient-directed music in future trials of this intervention.

Interruptions and deviations from the intervention protocol will be recorded in detail. The intervention will be terminated upon a patient's transfer or discharge from the ICU. The intervention may be discontinued in case of adverse events related to the intervention or withdrawal of consent. If we observe ICDSC scores above 3 once the intervention has been commenced, the intervention will be continued, unless otherwise indicated by a participant's condition. Although, contamination of the control group by spontaneously mimicking aspects of

the intervention by health care personnel cannot be excluded, health care providers in the units are very familiar with clinical trials and have been instructed on the need to abstain from mimicking the intervention. Additionally, the touch component of the intervention requires specific training and it is unlikely to be successfully replicated.

Randomization and allocation concealment

Participants will be randomly assigned to either control or intervention group (1:1 allocation) as per a computer-generated randomization schedule, generated by the Epidemiology Coordinating Research Centre (EPICORE), University of Alberta (UofA), stratified by site, age (18-64, ≥65), and presence of surgery or trauma using permuted blocks of random sizes. The block size will not be disclosed to ensure concealment. After baseline measurements, allocation will be disclosed only to the intervention staff. Codes will be generated prior to the beginning of the study by EPICORE.

Blinding

Investigators, physicians and nurses (when possible), data collectors, research assistants, and laboratory technicians will be blinded to group allocation during the trial and analysis. Due to the nature of the intervention, participants cannot be blinded to allocation. Also, participants' primary nurses cannot be blinded to study procedures (i.e., delivery of massage); however, they will remain blinded to study hypotheses, study design (i.e., study outcomes, numbers and types of participants' groups) and allocation. We believe that these procedures along with the sham intervention will maintain an adequate level of concealment even among participants' primary nurses, to minimize bias. The same intervention personnel will be involved in the delivery of the intervention and sham intervention. Intervention personnel are not involved in assessment of

patient outcomes, and have been trained on the importance of preserving blinding, therefore minimizing the risk for potential bias.

Treatment arms

Patients randomly allocated to the intervention group will receive the intervention in addition to standard care (standard care + multimodal intervention group). Patients allocated to the control group will receive standard care and a sham intervention consisting of presence of a research staff at the bedside with drawn curtains and silent headphones (standard care + sham intervention group; Schematic of study design in Figure 2).

Concomitant care

Standard care will be continued for all participants. Type and dose of all administered sedative, psychoactive and analgesic medication will be recorded.

Duration of participation

The total duration may vary according to ICU length of stay and will be 17 weeks approximately, from enrolment until the last follow up at 4 months post-ICU discharge.

Data Collection and Instruments

Data will be collected for each participant by blinded data collectors and captured in a Research Electronic Data Capture (RedCap®) database developed and monitored by EPICORE. Time points include: baseline measurements, follow-up while in the ICU for up to 5 days, follow up 48-96 hours after ICU discharge, follow-up 6 weeks and 4 months after ICU discharge. In case of participants who discontinue participation, data already collected will be retained.

All study scales are routinely used in clinical practice and have established psychometric properties. The ICDSC is one of the most reliable tools for assessment of ICU delirium advocated by recent guidelines (4, 28). Inter-observer reliability of and sensitivity (80.1, 95% CI:73.3-85.8) of ICDSC have been established and will be further assessed in this study (28). For comatose, deeply sedated patients [Richmond Agitation Sedation Scale (RASS = -4, -5)] delirium cannot be assessed. Data captured on Case Reports Forms are included in Figure 2. Baseline data captured at enrolment will include: Sociodemographic data, admission diagnosis, history of alcohol use, medications prior to admission, metabolic acidosis, ICDSC, RASS, Short Form Informant Questionnaire on Cognitive Decline in the Elderly (Short IQCODE), Pre-Deliric Delirium Risk Score, baseline IV sedation, analgesia and antipsychotic dose, disease severity at admission (Acute Physiology & Chronic Health Evaluation II (APACHE II), Sequential Organ Failure Assessment: SOFA), number of days in hospital and ICU prior to protocol enrolment. For pain, scores obtained at the first pre-intervention measurement will be considered as baseline.

Outcome Measures

Primary and secondary outcome, as well as feasibility, measures include (Appendix 1):

A. *Primary clinical outcome*: a) Incidence rate of delirium (ICDSC ≥4), during 5 days of intervention (first 5 days of enrolment). Presence of delirium will be assessed by blinded trained nurse assessors 2 times daily (8am, 8pm).

B. *Secondary outcomes [Estimates, variance of effects, proportions and means, SD (where applicable) per group]:*

1. *Delirium related secondary outcomes:* a) Incidence rate of delirium (ICDSC ≥4) during ICU stay and post-intervention, b) incidence rate of subsyndromal delirium (ICDSC: 1-

3) during the intervention period and subsequent ICU stay, c) time to delirium occurrence, d) proportion of delirium-free time during up to 8 days of ICU stay (excluding periods with deep sedation, coma), e) Sedation levels (Richmond Agitation Sedation Scale (RASS) score, f) Daily sedative (benzo-equivalents and propofol), analgesic (morphine equivalents) and antipsychotic agent (type, mg/24 hours) dose.

2. *Pain related outcomes* (*Pre- and post-intervention)*: a) Pain intensity (self-reported (S-R) numeric rating scale (NRS) for patients able to self-report, pain indicators (Critical Care Pain Observation Tool (CPOT) in patients unable to self-report, b) perceived stress level (S-R NRS).
3. *Sleep* (*Daily):* a) Sleep quality (S-R NRS), b) sleep duration (in minutes) (sleep monitors and nurses' log). Although more reliable, due to considerations around burden to the unit and cost, we do not use polysomnography in this pilot.
4. *Disease severity* ***(****Daily):* Sequential Organ Failure (SOFA) score
5. *Physiological Biomarkers (Pre- & post-intervention):* a) Serum Inflammation biomarkers [High-mobility-group-box 1 (HMGB-1), C-reactive protein (CRP) levels, b) High (HF) and low frequency (LF) components of heart rate variability (HRV) as measures of PNS status, c) Serum ACh levels, as a measure of PNS activation. The choice of biomarkers was based on the theoretical framework guiding this work (triggering of a relaxation parasympathetic response and attenuation of the inflammatory response; Figure 1), and results of the pilot study (20, 29), which showed alterations in biomarkers immediately post-intervention and over-time, despite great variability in biomarker levels. The results will help us generate more informed hypotheses for a subsequent trial.

6. *Psychological outcomes (2-7 day after ICU discharge*): Anxiety (Hospital Anxiety and Depression Scale: HADS & State Trait Anxiety Inventory-6: STAI-6)
7. *Clinical outcomes (At discharge)*: a) length of ICU stay (ICU LOS) (or ward-ready), b) Duration of mechanical ventilation/ proportion of mechanical ventilation-free days, c) survival, d) hospital LOS and e) (*3 months post-ICU discharge)*: 90-day survival.
8. *Quality of life outcomes* (*6 weeks and 4 months post-ICU discharge):* EuroQol Five Dimensions Questionnaire (EQ-5DL), Short Form 36 Health Survey (SF-36)
9. *Recollection and perception of the intervention (2-7 days after ICU discharge and 6 weeks post-ICU discharge):* Qualitative open-ended questions to explore recollection of intervention, views on intervention and acceptability (**Appendix 2**).

C. Feasibility

1. *Acceptability*: Number of patients refusing or wishing to discontinue a session. Acceptability will be further assessed with the patients and clinicians advisory group.
2. *Enrolment & consent:* a) percentage (%) of eligible patients; reasons for non-eligibility, b) time from admission to enrolment, c) recruitment rates, d) % of patients declining consent
3. *Randomization & concealment*: a) time from enrolment to randomization, b) % of cases at which allocation was inappropriately revealed; description of incident.
4. *Protocol adherence & intervention fidelity:* Percentage of: a) participants completing the entire study protocol, b) sessions missed, interrupted, delayed; reasons. Adherence to intervention protocol assessed by random observation audits.

5. *Data Collection & management:* a) timeliness, accuracy of data collection, reliability, b) testing of trial database, c) type, % of missing values, d) qualitative data on participants' perceptions of the study, e) time required for all study procedures and intervention (to be used in future economic assessment and assessment of burden of the trial).

Primary Feasibility criteria:

The study design will be considered feasible if the following 5 criteria are met:

a) Eligible patients declining consent<60%
b) Cases at which allocation was inappropriately revealed< 3%
c) Participants withdrawing from study protocol while still in the ICU<10%
d) Average sessions missed per patient< 40%
e) Average sessions interrupted per patient<50%

Biomarker quantifications

Blood sampling

One 5 ml blood sample will be collected in pre-coded general anti-coagulated vials, through an intravascular catheter already in place, within 10 min before and 10 min after the intervention.

Biomarker analyses

a. *Serum levels of HMGB-1, ACh and CRP.*

These will be quantified by commercially available sandwich enzyme-linked immunosorbent colorimetric assay (ELISA) kits (LifeSpan Biosciences, Seattle; WA, Biosource, S. Diego, CA; R & D Systems, Minneapolis, MN, respectively). Intra- and inter-assay coefficients of variation

(CV) are expected to be less than 10%. All samples will be tested within the same assay run in duplicate by a specialized laboratory technician. Measurements will be carried out at the Women's Health Research Laboratory, Faculty of Nursing, University of Alberta.

b. ANS (Autonomic Nervous System) activity: HF, LF AND LF/HF ratio

ANS activity will be assessed through frequency domain analysis of electrocardiographic (ECG) recordings. ECG recordings will be logged using the Zephyr™ BioModule™ and data will be imported into the OmniSense™ software. Data from OmniSense™ will then be uploaded to Kubios HRV software (Kubios HRV- Hear Rate Variability Analysis Software) and HF, LF and LF/HF ratios will be computed. HRV data will be analyzed for 5 minutes before the intervention, 5 minutes after the intervention and several times during the intervention based on the timing of its various components. Specifically, HRV components will be analyzed on the 8th and 15th minute of massage (half-way and conclusion of massage), 3rd and 15th minute of RGI (induction and conclusion of RGI), and end of music therapy.

Data Analysis

Statistical Methods

Demographic/ clinical characteristics of patients and all outcomes will be presented by treatment group using descriptive statistics— mean (SD), median (IQR) or proportion. Outcomes will be analyzed longitudinally over 5 days by logistic regression model based on generalized estimating equations (GEE) with AR(1) correlation structure. ANCOVA, t-test or Mann-Whitney test, as appropriate, will be conducted for the continuous outcomes that are not longitudinal. Models will be adjusted for co-variates including pre-deliric score, administration of medication (sedatives, analgesics, vasoactives and antipsychotics) and severity score (SOFA, APACHE). Chi-square or

exact test, as appropriate, will be used for categorical outcomes. We will treat pain outcomes as both categorical (presence or absence of pain) and continuous variables (pain score). Confidence intervals will be presented with estimated effects. Primary analysis will be based on all available data utilizing data from all assessments. Since GEE assumes missing completely at random (MCAR) mechanism, we plan to conduct a sensitivity analysis based on inverse probability weighted GEE (IPWGEE) (30) which employs a less restrictive missing at random (MAR) mechanism. A "last observation carried forward" (LOCF) approach was not considered because analyzing all available data performs better than LOCF in GEE setting with respect to bias, Type I error rate and coverage probability under both MCAR and MAR mechanisms. Analysis will be conducted by EPICORE.

To account for noncompliance, protocol deviations and missing outcomes, intention-to-treat (ITT) analysis will be employed. ITT analysis includes every randomized subject according to treatment assignment. Additionally, per protocol analysis will also be employed. Per-protocol (PP) population is defined as a subset of the ITT population who completed the study without any major protocol violations. If ITT and PP analyses lead to similar conclusions the reliability of results will be supported. Although, this is a pilot trial, ITT will help reduce potential effects of selection bias. PP analysis will assess whether the ITT result is too conservative. This will provide important data regarding the effect size for the subsequent trial. Both analyses will assist us in revising the protocol for the larger trial.

Qualitative analyses

Interview transcriptions will be thematically analyzed by an inductive content analysis approach (31). A coding scheme will be developed based on recurrent themes of the first five interviews. Subsequently, two researchers (EP, TP) will code independently, using axial and inductive

coding to formulate a final coding template by consensus. The final coding scheme will then be used to code, compare and interpret all transcripts. Individual analyses of the team members will be discussed to achieve shared understanding and to increase reliability. The data will be analyzed via NVivo software (QSR International Doncaster, Victoria, Australia).

Quality Control and Quality Assurance

This pilot will be supervised by an independent trial steering committee (TSC), consisting of 3 clinical trial experts independent of the research team. Periodical audits of the intervention and trial processes at both sites by personnel independent from investigators will be initiated by the TSC. Randomization, recruitment, intervention adherence, blinding, stability and data collection processes will be monitored. Trial Monitoring Committee (TMC) will also review relevant information from similar studies and will consider the recommendations of the Data Monitoring (DMC) and Ethics Committee. Study personnel have been trained to standardize processes. We have developed two training videos including detailed demonstration of the intervention. Moreover, research personnel involved with the intervention has received 18-21 hours of hands-on training, including detailed auditing, and several hours of self-paced training to standardize the process, communication and timing of intervention. Study personnel will meticulously record any deviations from the intervention protocol to assess feasibility and effect on outcomes. Clinical data will be retrieved from the quality-controlled clinical information system of the units. Detailed electronic data collection forms with embedded quality controls will be used and reviewed in detail. Data quality will be monitored through EPICORE before, during, and after entry. All data will be entered electronically using study forms generated through RedCap® with embedded quality control processes. Study data will be collected and managed using REDCap® electronic data capture tools hosted at the University of Alberta (32). A quality control system

will be applied for biological measurements as per lab protocol. Day-to-day operations of the trial will be overseen by a Trial Management Group (TMG) comprising, as a minimum, the Principal Investigator, Senior Trial Manager, Trial Manager, Trial Statistician and Data Manager. TMG meetings will take place on a regular basis throughout the duration of the study. The TMG will have responsibility for ensuring the adherence and progress of the study in relation to all regulatory, administrative academic and any clinical or safety issues.

Ethics

The protocol has received approval from the Human Research Ethics Board (HREB) University of Alberta and administrative approvals from participating institutions. This study will be conducted in compliance Canadian and International Good Clinical Practice standards. No deviation from the protocol will be implemented without the prior review and approval of the HREB except where it may be necessary to eliminate an immediate hazard to a research participant. In such case, the deviation will be reported to the HREB.

Experienced research personnel not involved with the delivery of the intervention and in patient care will acquire informed consent from legal surrogates or participants if competent to consent. Participant assent will be acquired when participants regain capacity. Confidentiality, anonymity and right to withdraw at any point with no questions asked and no effect on the quality of care received will be assured. After completion of the study the data and samples will remain stored at the academic institution for 5 years.

Confidentiality

Code-identified encrypted study data will be stored separately from participant information at an EPICORE database permitting code-access only. All study forms, lab specimens and data will be

identified by an alphanumeric code to maintain confidentiality. Records that contain names, identifiers will be stored separately from study data identified by code. Participants' information will not be released outside the study. Participant information will be stored at an encrypted limited code-initiated access electronic file. Consent forms will be kept in a locked file cabinet at a pre-specified limited-access room, University of Alberta.

Safety

Although prior pilot data did not provide evidence of adverse effects or increased rate of complications, any physiological/ behavioural alteration during interventions will be recorded and analysed. Adverse events, irrespective of causal relationship, will be collected for all participants, during and up to half an hour after the intervention.

Data Dissemination

Results will be disseminated to participants, healthcare professionals, health services authorities and the public via conference presentations and publications. Results of this study will be used to inform the design and conduct of a future multi-center trial. The results of the trial will be presented at national and international meetings and published in peer-reviewed journals. A lay summary of the results will be available to trial participants on request. An online summary of the findings will also be made available.

Conclusions: This pilot clinical trial integrates a low-risk, patient-centered strategy, translational research and psychological outcomes to allow an evaluation of non-pharmacological delirium management with mechanistic insights. Implications of the definitive trial include the potential to

reassure patients, decrease the incidence of frightening delirium experiences, and improve longitudinal outcomes.

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Authors' conflict of interest: None declared

Data Statement: Technical appendix, statistical code, and dataset will be available from EPICORE, University of Alberta.

Legends

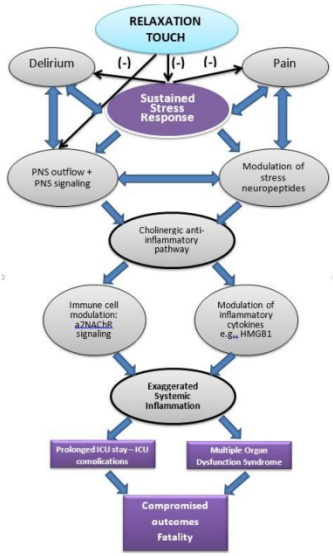
Figure 1.

Evidence-based framework for the physiological mechanism implicated in relaxation-induced effects in critical illness. Relaxation acts early at the pathophysiological cascade through which an exaggerated stress response results in pro-inflammatory effects, suppressed PNS outflow and subsequently in systemic inflammation, multiple organ dysfunction and death. The relaxation response counterbalances the exaggerated stress response and activates PNS and cholinergic anti-inflammatory signaling, which downregulates pro-inflammatory (e.g., HMGB-1) and up-regulates anti-inflammatory cytokines; therefore attenuating systemic inflammation and its detrimental organ effects. (*α7-nAChR: alpha7- nicotinic acetylcholine receptor, HMGB-1: High Mobility Group Box-1; PNS: Parasympathetic Nervous System)*

Figure 2:

Schematic of study design. *(Ach: Acetylcholine, AE: Adverse Event, APACHE: Acute Physiology & Chronic Health Evaluation, CPOT: Critical Care Pain Observation Tool, CRP: C-Reactive Protein, EQ-5D: EuroQol Five Dimensions Questionnaire, HADS: Hospital Anxiety and Depression Scale, HF: High Frequency, HMGB: High Mobility Group Box, HRV: Heart Rate Variability, ICDSC: Intensive Care Delirium Screening Checklist, ICU: Intensive Care Unit, IQCODE: Informant Questionnaire on Cognitive Decline in the Elderly, IV: Intravenous,*

LF: Low Frequency, LOS : Length of Stay, NRS: Numeric Rating Scale, RASS: Richmond Agitation Sedation Scale, RGI: Relaxation and Guided Imagery, S-R: Self-Reported, SOFA: Sequential Organ Failure, STAI: State Trait Anxiety Inventory).



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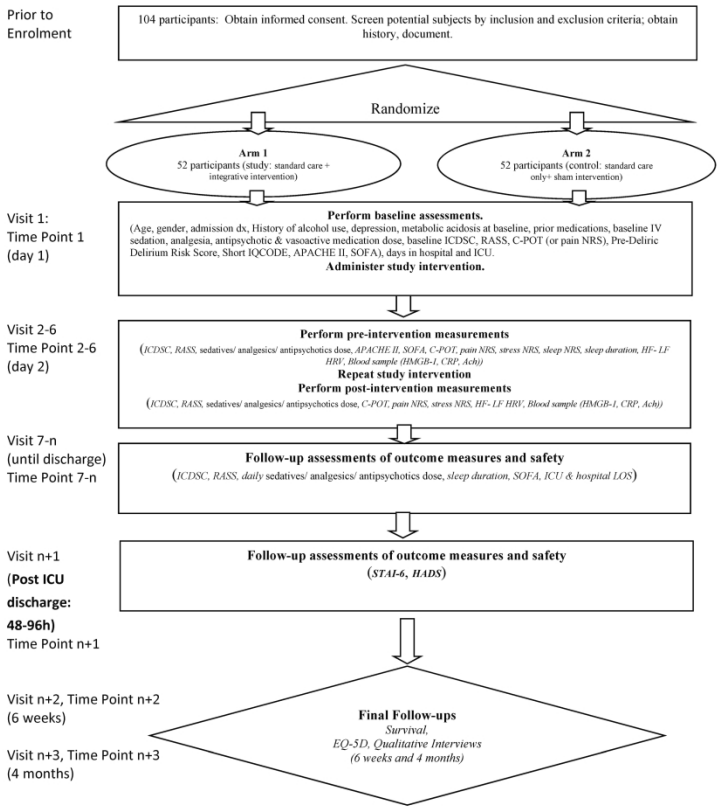

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Appendix 1. Schedule of enrolment, interventions, and assessments.

	Enrolment	**Allocation**	**Post-allocation in-ICU**					**Post-intervention / in-ICU** (daily until discharge)	*At ICU-discharge (or ward-ready)*	**Post ICU discharge (In hospital: 2-7 days)**	*At hospital discharge*	**Post ICU Discharge (6 weeks)**	**Post ICU Discharge (4 months)**
TIMEPOINT	$-t_1$	**0**	***Day*$_1$**	***Day*$_2$**	***Day*$_3$**	***Day*$_4$**	***Day*$_5$**						
ENROLMENT:													
Eligibility screen	X												
Informed consent	X												
Random Allocation		X											
INTERVENTIONS:													
[Intervention: RGI + massage]			←	—	—	—	→						
[Control: Sham Intervention]			←	—	—	—	→						
BASELINE ASSESSMENTS: ***[***demographics diagnosis, hx, short IQCODE), pre-DDRS, sedatives/ analgesics/ antipsychotics dose, Prior LOS***]***	X												
		X	X	X	X	X	X						

Primary Outcome: ICDSC≥4												
Secondary outcomes: *ICDSC, ICDSC:1-3, RASS, daily* sedatives/ analgesics/ antipsychotics dose, ***sleep NRS, sleep duration, APACHE II, SOFA***		X	X	X	X	X	X	X				
			pre-post-Intervention									
C-POT, PAIN NRS, pain distress NRS, stress NRS, HF- LF HRV		X	X2	X2	X2	X2	X2					
			pre-post-Intervention									
HMGB-1, CRP, Ach			X2	X2	X2	X2	X2					
ICU LOS, duration MV, ICU survival									X			
HADS										X		
Hospital survival, Hospital LOS											X	
											X	

6 week survival, Interview, EQ-5D, SF-36													
4-month survival, EQ-5D, SF-36													X

Ach: Acetylcholine, CPOT: Critical Care Pain Observation Tool, CRP: C-Reactive Protein, DEMMI: de Morton Mobility Index, EQ-5D: EuroQol Five Dimensions Questionnare, HADS: Hospital Anxiety and Depression Scale, HF: High Frequency, HMGB: High Mobility Group Box, HRV: Heart Rate Variability, ICDSC: Intensive Care Delirium Screening Checklist, ICU: Intensive Care Unit, Interview: Qualitative open ended questions; IQCODE: Informant Questionnaire on Cognitive Decline in the Elderly, LF: Low Frequency, LOS : Length of Stay, MV: mechanical ventilation, NRS: Numeric Rating Scale, RASS: Richmond Agitation Sedation Scale, RGI: Relaxation and Guided Imagery, S-R: Self-Reported, SOFA: Sequential Organ Failure, STAI: State Trait Anxiety Inventory.

Appendix 2. Telephone interview guide (Qualitative open-ended questions)

1. Do you remember listening to music while in the ICU? Can you describe what you remember?
2. Do you remember listening to a voice through the headphones? Can you describe what you remember?
3. If yes, how did this make you feel? Were you able to follow the instructions with your mind/ imagination? Please describe
4. Do you remember somebody giving you a massage? Can you describe what you remember?
5. If yes, how did this make you feel?
6. Would you wish to receive this intervention again? Why?
7. Would you recommend this intervention for other patients? Why?

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRIT reporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. Ann Intern Med. 2013;158(3):200-207

		Reporting Item	Page Number
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	2
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	2
Protocol version	#3	Date and version identifier	2
Funding	#4	Sources and types of financial, material, and other support	22
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	22
Roles and	#5b	Name and contact information for the trial sponsor	22

responsibilities: sponsor contact information			
22Roles and responsibilities: sponsor and funder	#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	22
Roles and responsibilities: committees	#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)	14-15
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	4-5
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	5
Objectives	#7	Specific objectives or hypotheses	5, 6
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, non-inferiority, exploratory)	5
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	6
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and	7

		individuals who will perform the interventions (eg, surgeons, psychotherapists)	
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7-8,9
Interventions: modifications	#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)	8
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	8
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	9
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	10-12
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)	1. Appendix
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	6-7
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	6
Allocation:	#16a	Method of generating the allocation sequence (eg,	8

sequence generation		computer-generated random numbers), and list of 8any 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	
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	8
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	8
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	8-9
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	9, NA
Data collection plan	#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	9-10
Data collection plan: retention	#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	9
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data	9,15

		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	
Statistics: outcomes	#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	13-14
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	13-14
Statistics: analysis population and missing data	#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)	14
Data monitoring: formal committee	#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	14-15
Data monitoring: interim analysis	#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	NA
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	16
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	8,15
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	15,16
Protocol	#25	Plans for communicating important protocol	15

amendments		modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	15-16
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	16
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	16
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	22
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	NA
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	NA
Dissemination policy: trial results	#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	16
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	NA
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	16

Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	Upon request
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	12-13 & upon request

BMJ Open

Relaxation for Critically ill Patient Outcomes and Stress-coping Enhancement (REPOSE): A protocol for a pilot randomized trial of an integrative intervention to improve critically ill patients' delirium and related outcomes

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Secondary Subject Heading:	Complementary medicine, Nursing
Keywords:	critical illness, music therapy, relaxation, guided imagery, delirium, complex intervention

*R*elaxation for Critically ill *P*atient *O*utcomes and *S*tress-coping *E*nhancement (REPOSE): A protocol for a pilot randomized trial of an integrative intervention to improve critically ill patients' delirium and related outcomes

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Key words: critical illness, music therapy, relaxation, guided imagery, autonomic nervous system, delirium, complex intervention

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Abstract

Introduction: Delirium is a common complication of critical illness, associated with negative patient outcomes. Preventive or therapeutic interventions are mostly ineffective. Although relaxation-inducing approaches may benefit critically ill patients, no well-designed studies target delirium prevention as a primary outcome. The objective of this study is to assess feasibility and treatment effect estimates of a multimodal integrative intervention incorporating relaxation, guided imagery, and moderate pressure touch-massage for prevention of critical illness delirium and for related outcomes.

Methods and analysis: Randomized, controlled, single-blinded trial with 2 parallel groups (1:1 allocation: intervention and standard care) and stratified randomization [age (18-64, ≥65), presence of trauma) with blocking, involving 104 patients with Intensive Care Delirium Screening Checklist (ICDSC): 0-3 recruited from 2 academic ICUs. Intervention group participants receive the intervention in addition to standard care for up to 5 consecutive days (or until transfer/ discharge); control group participants receive standard care and a sham intervention. We will assess pre-defined feasibility outcomes, i.e., recruitment rates, protocol adherence. The primary clinical outcome is incidence of delirium (ICDSC ≥4). Secondary outcomes include pain scores, inflammatory biomarkers, heart rate variability, stress and quality of life (6 weeks; 4 months) post-ICU discharge. Feasibility measures will be analyzed descriptively, and outcomes longitudinally. Estimates of effects will be calculated.

Ethics and dissemination: The study has received approval from the Human Research Ethics Board, University of Alberta. Results will inform the design of a future multi-center trial.

Registration: clinicaltrials.gov (NCT02905812).

Protocol date: March 3, 2018, version 5, Protocol amendment number: 07

Primary reasons for amendment: Refining feasibility of intervention and data collection.

Summary

Strengths and limitations of this study

- **We will test feasibility and measures of effect of a previously piloted relaxation-inducing intervention for the prevention of delirium and improvement of related outcomes in critically ill patients.**
- **We will employ an evidence-based, non-pharmacological multimodal integrative intervention that has shown effectiveness for reducing pain and improving a number of secondary outcomes in a previous pilot study.**
- **This pilot aims to assess estimates of effect and feasibility to inform a future trial.**
- **Although clinicians and outcome assessors will be blinded, due to the nature of the intervention, participants and nurses providing direct care to patients cannot be blinded to allocation, although they will be blinded to the study hypotheses.**
- **The mechanisms of effects of relaxation-inducing interventions in critical illness are not well understood; hence, we aim to explore effects of the intervention on parasympathetic system activation and inflammatory markers.**

Introduction

ICU delirium affects 35-55% of critically ill patients, and is independently associated with a 13-fold (adjusted odds ratio (OR):4.88-13.0) increased risk of death (1) and long-term cognitive impairment (2). ICU delirium carries important financial and societal burdens [(39% higher adjusted ICU (95% CI:12-72%), and 31% higher hospital costs (95% CI:1-70%)] (3). Moreover, patients identify frightening delirium experiences and pain as the most severe stressors (4,5) in critical care. Pharmacological interventions for the prevention and treatment of delirium have limited benefit and are associated with high costs and risks for side effects (6,7). Although clinical guidelines recommend the development of non-pharmacological interventions to prevent delirium (8), effective prevention strategies have yet to be established (9).

A prolonged and eventually aberrant stress response and depressed parasympathetic (PNS) activity have been postulated as the pathophysiological basis for the development of both ICU delirium and systemic inflammation (10-13). Frightening hallucinations and ideations during delirium may further exaggerate the stress-response and prolong critical illness with detrimental consequences. Pain may worsen matters by reciprocal incremental feed-back on inflammation and stress (4, 14). Thus, in critical illness, stress, delirium, pain and systemic inflammation may comprise a self-perpetuating syndrome. Attenuating the cascade of negative health impacts from pain and delirium has become a high clinical priority (Figure 1) (8).

Moreover, the growing recognition that delirium and other critical illness sequelae may have long term consequences in critical illness survivors (15) further highlights the need for prevention strategies.

Evidence-based theoretical work postulates that the multitude of psychological stressors in critically ill individuals may contribute to the development of pathophysiologic sequelae (10). Moreover, animal models illustrate that PNS stimulation and acetylcholine (ACh) release suppress inflammation and decrease fatality, via the cholinergic anti-inflammatory pathway (16). Devising ways to draw on the autonomic nervous systems' inflammation- and stress-regulatory properties by non-pharmacological interventions has, in theory, the potential to improve outcomes with low side-effect risk. However, stimulation of the PNS in critical care is challenging. Relaxation-inducing interventions can induce PNS activity. Such approaches have successfully been used in diverse patient populations to counter stress, but remain under-tested in critical illness (17). A recent systematic review shows favorable effects of relaxation and guided imagery intervention in reducing pain, anxiety and length of stay in critically ill patients (18); whereas, the relaxation inducing effects of music in critical care have been well supported by evidence (19). In a pilot randomized controlled trial (RCT) of the effects of a similar multi-modal intervention on the incidence of pain and on a number of secondary outcomes, we observed significant decreases in pain incidence (RR=0.56, p=0.003) and severity (p<0.0001), systolic arterial pressure, anxiety, along with improved sleep quality (20).

Hypotheses

Overall, we hypothesize that a multimodal intervention incorporating relaxation and guided imagery (RGI) and moderate pressure touch-massage is feasible within a critical care setting, and can have an effect on decreasing delirium and in improving physiological and psychological outcomes in randomized critically patients who will receive standard care and the intervention compared to patients receiving standard care plus a sham intervention only.

Primary Hypotheses:

We hypothesize that the intervention will be feasible and that it will have an effect on decreasing delirium incidence and duration.

Secondary hypotheses:

We hypothesize that the intervention will have an effect on: a) incidence rate of subsyndromal delirium, time to delirium occurrence, proportion of delirium-free time during up to 8 days of ICU stay; b) sedation levels and daily sedative, analgesic and antipsychotic agent dose; c) pain occurrence and intensity; d) perceived stress level; e) sleep duration and quality; f) anxiety; g) length of ICU stay and duration of mechanical ventilation/ proportion of mechanical ventilation-free days; h) hospital LOS, i) physiological biomarkers; and k) quality of life after ICU discharge.

Design and Methods

Study design

Relaxation for Critically ill Patient Outcomes and Stress-coping Enhancement (REPOSE) is a pilot feasibility, randomized, controlled, single-blinded trial with 2 parallel groups (intervention and standard care). Accounting for major risk factors of delirium (15), stratified randomization according to age (18-64, ≥65) and presence of either surgical or trauma injury with blocking and 1:1 allocation to assure balance in numbers per group will be employed.

Research Objectives

Research objectives include to:

a) Assess clinical trial feasibility with pre-defined goals (enrolment, randomization, adherence, timing of intervention, workload)

b) Calculate estimates and variance of treatment effect across outcome measures

c) Calculate Confidence Intervals (CI) of incidence proportions, means and Standard Deviation (SD) of outcome measures in study groups, and

d) Explore the feasibility of identifying underlying physiological mechanisms

Setting, recruitment and sample size

Consecutive patients admitted to 2 academic ICUs, in Edmonton, AB, Canada, with an ICDSC score of 0-3 will be screened for study eligibility and will be recruited by research staff at each site. In cases where an ICDSC score cannot be obtained on admission, we will screen patients for up to 4 days after admission. Since delirium occurs most often within the first 5 days of admission, screening and enrolment will take place as soon as possible and within 96 hours after ICU admission. This pilot is not powered to determine a difference in a primary outcome, since we aim to assess estimates of effect. For a definitive trial, we would require 290 (145/arm) patients to detect a 10% difference in incidence proportion between intervention (20%) and control (30%) arm (two-sided alpha=0.05, power=80%, drop-out rate=10%). The Pan method (21), which is based on generalized estimating equations, was used to perform the sample size calculation under the assumption of AR(1) correlation structure among 5 days repeated measurements with correlation between any two adjacent observations from the same subject of 0.5. Since this is a pilot, aiming to explore feasibility and estimates of effects, and the incidence rates used for the calculation might not be appropriate, we used 36% of the sample

size of the full study to estimate the parameters accurately and get an experience for a full trial (22).

Eligibility

Inclusion criteria: a) Age over 18 years, b) ICDSC:0-3, c) written informed consent, by participant or by family member/ surrogate in case participant not capable.

Exclusion Criteria: Patients: a) Already in the ICU for more than 96 hours, b) with ICDSC>3 within 72 h of screening in case intervention has not been initiated, c) on special contact precautions (i.e., MRSA, VRE, HIV), d) with expected Intensive Care Unit (ICU) Length of stay (LOS) < 72 hours, e) with acute neurological illness/ neurological trauma, persistent deep sedation or coma [Richmond Agitation Sedation Scale (RASS = -4, -5)] f) with current history of severe mental health problems and dementia, as per history, g) with hearing impairment or conditions not permitting use of headphones, h) on neuro-muscular blockers, i) with known or suspected substance/ alcohol withdrawal, and j) enrolled in trials of sedatives, antipsychotics.

Patient and Public involvement

The protocol is based on a pilot study with 60 randomized patients (20), 12 of which provided feedback regarding the desirability, burden and specific components of the intervention, study procedures and preferred outcomes. Participants' feedback informed the design of the study, resulting in many significant changes. Preferred post-ICU follow-up times were informed by an informal advisory group through the Alberta Innovates Strategy for Patient Oriented Research

(SPOR) network of patient representatives. Moreover, as a patient and clinician engagement strategy, an advisory group with representatives of patients, families and clinicians will act as a consultation group for the research team. Acceptance and desirability of the protocol by clinicians and patients/ families will be assessed further by focus group discussions. Recommendations will inform future development of the intervention and research design. Canadian Institutes of Health Research (CIHR) guidelines for patient engagement will be used to establish and facilitate the advisory group. Feedback on: a) concerns on the intervention, study processes, contamination of the control group by implementation of aspects of the intervention, b) desirability of intervention (massage, music choices, complexity, voice of recording, pace), c) timing within the day, d) duration/ feasibility of the intervention, e) burden of study processes, f) outcomes to be addressed in the future trial, g) interpretation of results, h) strategies for dissemination of findings will be collected.

Intervention

The choice of a multimodal intervention (duration: 55min) was based on an evidence-based literature review, its superiority to unidimensional approaches (23), the recommendations of the

American Holistic Nurses Association (24) and a successful pilot (20). According to the UK Medical Research Council (MRC) guidance for complex intervention trials (25), development of the protocol included extensive theoretical work (10), two systematic reviews (18, 26), modeling of outcomes, extensive consultations with groups of experts, one small feasibility and acceptability pilot (n=10 participants) and one larger pilot (n=60) (20) and consultation with pilot participants and patients' representatives. The intervention has been developed by the research team and a group of experts based at the University of Alberta and Cyprus University of Technology. It includes: a) a brief moderate pressure massage session (massage: 15 minutes), b) relaxation and guided imagery (30 minutes, through headphones). The 30 min recorded RGI intervention involves: a) guided relaxation, b) a structured guided imagery script supported by instrumental music, and c) recorded instrumental music for 15 minutes (Haydn concerto no 1 in C major and Bach violin concerto in D minor, 60 beats per min approximately). The same recorded RGI script will be used at all sessions. It includes positive suggestions and instructions for gradual relaxation, followed by guidance to visualize one's body being healed. Moderate pressure (4 N, approximately or patient pressure rating 3/10) low velocity (1-5cm/second) massage consists of broad and repetitive circular movements with wide area of contact, applied sequentially for 2-3 minutes at each site: hands, forearms, lateral arms, and then over trapezius muscles, the temple, scalp, face and forehead area. Areas are to be contacted as appropriate to each participant, and the protocol may be adapted taking into account safety issues (i.e., to avoid area around intravascular catheter or injury). Moderate pressure massage is involved in PNS activation, in contrast to light pressure (27). The intervention will be administered once daily (09:00-15:00) for up to 5 consecutive days by trained research staff not involved in patient care, who will be randomly audited by the Trial Steering Committee (TSC) to ensure protocol

adherence. The decision to deliver the intervention for the first 5 days after enrollment only was based on epidemiological data regarding the onset of delirium (9), data on median length of stay of the target populations in the study institutions and cost considerations. However, it will be important to study the effect of the intervention on longer stay patients in future trials. The decision to deliver only one intervention daily was based on a small acceptability/ feasibility pilot, and pragmatic considerations for knowledge translation and future implementation of this approach, as well as cost considerations and burden to participants and units. The durations of guided imagery, music listening and touch intervention were based on the acceptability pilot, expert opinions on the minimum duration to achieve a relaxation effect and on published evidence (18). Despite evidence on the importance of providing choice to patients regarding music listening (19), we will use standardized music for intervention stability purposes. It will be important to look at the effect of patient-directed music in future trials of this intervention.

Interruptions and deviations from the intervention protocol will be recorded in detail. The intervention will be terminated upon a patient's transfer or discharge from the ICU. The intervention may be discontinued in case of adverse events related to the intervention or withdrawal of consent. If we observe ICDSC scores above 3 once the intervention has been commenced, the intervention will be continued, unless otherwise indicated by a participant's condition. Although, contamination of the control group by spontaneously mimicking aspects of the intervention by health care personnel cannot be excluded, health care providers in the units are very familiar with clinical trials and have been instructed on the need to abstain from mimicking the intervention. Additionally, the touch component of the intervention requires specific training and it is unlikely to be successfully replicated.

Randomization and allocation concealment

Participants will be randomly assigned to either control or intervention group (1:1 allocation) as per a computer-generated randomization schedule, generated by the Epidemiology Coordinating Research Centre (EPICORE), University of Alberta (UofA), stratified by site, age (18-64, ≥65), and presence of surgery or trauma using permuted blocks of random sizes. The block size will not be disclosed to ensure concealment. After baseline measurements, allocation will be disclosed only to the intervention staff. Codes will be generated prior to the beginning of the study by EPICORE.

Blinding

Investigators, physicians and nurses (when possible), data collectors, research assistants, and laboratory technicians will be blinded to group allocation during the trial and analysis. Due to the nature of the intervention, participants cannot be blinded to allocation. Also, participants' primary nurses cannot be blinded to study procedures (i.e., delivery of massage); however, they will remain blinded to study hypotheses, study design (i.e., study outcomes, numbers and types of participants' groups), to minimize performance bias. We believe that these procedures along with the sham intervention will maintain an adequate level of concealment even among participants' primary nurses, to minimize bias. The same intervention personnel will be involved in the delivery of the intervention and sham intervention. Intervention personnel are not involved in assessment of patient outcomes, and have been trained on the importance of preserving blinding, therefore minimizing the risk for potential bias.

Treatment arms

Patients randomly allocated to the intervention group will receive the intervention in addition to standard care (standard care + multimodal intervention group). Patients allocated to the control group will receive standard care and a sham intervention consisting of presence of a research staff at the bedside with drawn curtains and silent headphones (standard care + sham intervention group; Schematic of study design in Figure 2).

Concomitant care

Standard care will be continued for all participants. Type and dose of all administered sedative, psychoactive and analgesic medication will be recorded.

Duration of participation

The total duration may vary according to ICU length of stay and will be 17 weeks approximately, from enrolment until the last follow up at 4 months post-ICU discharge.

Data Collection and Instruments

Data will be collected for each participant by blinded data collectors and captured in a Research Electronic Data Capture (RedCap®) database developed and monitored by EPICORE. Time points include: baseline measurements, follow-up while in the ICU for up to 5 days, follow up 48-96 hours after ICU discharge, follow-up 6 weeks and 4 months after ICU discharge. In case of participants who discontinue participation, data already collected will be retained.

All study scales are routinely used in clinical practice and have established psychometric properties. The ICDSC is one of the most reliable tools for assessment of ICU delirium advocated by recent guidelines (4, 28). Inter-observer reliability of and sensitivity (80.1, 95% CI:73.3-85.8) of ICDSC have been established and will be further assessed in this study (28). For

comatose, deeply sedated patients [Richmond Agitation Sedation Scale (RASS = -4, -5)] delirium cannot be assessed. Data captured on Case Reports Forms are included in Figure 2. Baseline data captured at enrolment will include: Sociodemographic data, admission diagnosis, history of alcohol use, medications prior to admission, metabolic acidosis, ICDSC, RASS, Short Form Informant Questionnaire on Cognitive Decline in the Elderly (Short IQCODE), Pre-Deliric Delirium Risk Score, baseline IV sedation, analgesia and antipsychotic dose, disease severity at admission (Acute Physiology & Chronic Health Evaluation II (APACHE II), Sequential Organ Failure Assessment: SOFA), number of days in hospital and ICU prior to protocol enrolment. For pain, scores obtained at the first pre-intervention measurement will be considered as baseline.

Outcome Measures

Primary and secondary outcome, as well as feasibility, measures include (Appendix 1):

A. *Primary clinical outcome*: a) Incidence rate of delirium (ICDSC ≥4), during 5 days of intervention (first 5 days of enrolment). Presence of delirium will be assessed by blinded trained nurse assessors 2 times daily (8am, 8pm).

B. *Secondary outcomes [Estimates, variance of effects, proportions and means, SD (where applicable) per group]:*

1. *Delirium related secondary outcomes:* a) Incidence rate of delirium (ICDSC ≥4) during ICU stay and post-intervention, b) incidence rate of subsyndromal delirium (ICDSC: 1-3) during the intervention period and subsequent ICU stay, c) time to delirium occurrence, d) proportion of delirium-free time during up to 8 days of ICU stay (excluding periods with deep sedation, coma), e) Sedation levels (Richmond Agitation

Sedation Scale (RASS) score, f) Daily sedative (benzo-equivalents and propofol), analgesic (morphine equivalents) and antipsychotic agent (type, mg/24 hours) dose.

2. *Pain related outcomes* (*Pre- and post-intervention)*: a) Pain intensity (self-reported (S-R) numeric rating scale (NRS) for patients able to self-report, pain indicators (Critical Care Pain Observation Tool (CPOT) in patients unable to self-report, b) perceived stress level (S-R NRS).
3. *Sleep* (*Daily):* a) Sleep quality (S-R NRS), b) sleep duration (in minutes) [(sleep monitors (Fitbit Alta HR: daily sleep cycle) and nurses' log (duration of sleep between 7pm-7 am)]. Although more reliable, due to considerations around burden to the unit and cost, we do not use polysomnography in this pilot.
4. *Disease severity* ***(****Daily):* Sequential Organ Failure (SOFA) score
5. *Physiological Biomarkers (Pre- & post-intervention):* a) Serum Inflammation biomarkers [High-mobility-group-box 1 (HMGB-1), C-reactive protein (CRP) levels, b) High (HF) and low frequency (LF) components of heart rate variability (HRV) as measures of PNS status, c) Serum ACh levels, as a measure of PNS activation. The choice of biomarkers was based on the theoretical framework guiding this work (triggering of a relaxation parasympathetic response and attenuation of the inflammatory response; Figure 1), and results of the pilot study (20, 29), which showed alterations in biomarkers immediately post-intervention and over-time, despite great variability in biomarker levels. The results will help us generate more informed hypotheses for a subsequent trial.
6. *Psychological outcomes (2-7 day after ICU discharge*): Anxiety (Hospital Anxiety and Depression Scale: HADS & State Trait Anxiety Inventory-6: STAI-6)

7. *Clinical outcomes (At discharge)*: a) length of ICU stay (ICU LOS) (or ward-ready), b) Duration of mechanical ventilation/ proportion of mechanical ventilation-free days, c) survival, d) hospital LOS and e) (*3 months post-ICU discharge)*: 90-day survival.
8. *Quality of life outcomes* (*6 weeks and 4 months post-ICU discharge):* EuroQol Five Dimensions Questionnaire (EQ-5DL), Short Form 36 Health Survey (SF-36)
9. *Recollection and perception of the intervention (2-7 days after ICU discharge and 6 weeks post-ICU discharge):* Qualitative open-ended questions to explore recollection of intervention, views on intervention and acceptability (**Appendix 2**).

C. Feasibility

1. *Acceptability*: Number of patients refusing or wishing to discontinue a session. Acceptability will be further assessed with the patients and clinicians advisory group.
2. *Enrolment & consent:* a) percentage (%) of eligible patients; reasons for non-eligibility, b) time from admission to enrolment, c) recruitment rates, d) % of patients declining consent
3. *Randomization & concealment*: a) time from enrolment to randomization, b) % of cases at which allocation was inappropriately revealed; description of incident.
4. *Protocol adherence & intervention fidelity:* Percentage of: a) participants completing the entire study protocol, b) sessions missed, interrupted, delayed; reasons. Adherence to intervention protocol assessed by random observation audits, and by intervener's detailed reports of any deviations from protocol and related reasons.
5. *Data Collection & management:* a) timeliness, accuracy of data collection, reliability, b) testing of trial database, c) type, % of missing values, d) qualitative data on

participants' perceptions of the study, e) time required for all study procedures and intervention (to be used in future economic assessment and assessment of burden of the trial).

Primary Feasibility criteria:

The study will be considered feasible for the specific population and ICU context if the following 5 criteria are met:

a) Eligible patients declining consent<60%

b) Cases at which allocation was inappropriately revealed< 3%

c) Participants withdrawing from study protocol while still in the ICU<10%

d) Average sessions missed per patient< 40%

e) Average sessions interrupted per patient<50%

Biomarker quantifications

Blood sampling

One 5 ml blood sample will be collected in pre-coded general anti-coagulated vials, through an intravascular catheter already in place, within 10 min before and 10 min after the intervention.

Biomarker analyses

a. *Serum levels of HMGB-1, ACh and CRP.*

These will be quantified by commercially available sandwich enzyme-linked immunosorbent colorimetric assay (ELISA) kits (LifeSpan Biosciences, Seattle; WA, Biosource, S. Diego, CA; R & D Systems, Minneapolis, MN, respectively). Intra- and inter-assay coefficients of variation (CV) are expected to be less than 10%. All samples will be tested within the same assay run in duplicate

by a specialized laboratory technician. Measurements will be carried out at the Women's Health Research Laboratory, Faculty of Nursing, University of Alberta.

b. ANS (Autonomic Nervous System) activity: HF, LF AND LF/HF ratio

ANS activity will be assessed through frequency domain analysis of electrocardiographic (ECG) recordings. ECG recordings will be logged using the Zephyr™ BioModule™ and data will be imported into the OmniSense™ software. Data from OmniSense™ will then be uploaded to Kubios HRV software (Kubios HRV- Hear Rate Variability Analysis Software) and HF, LF and LF/HF ratios will be computed. HRV data will be recorded continuously starting from 5 min before, during and 5 min after the intervention. For ease of incorporation into statistical models, HRV components will be analyzed at 5 minutes before the intervention, 5 minutes after the intervention and several times during the intervention based on the timing of its various components. Specifically, HRV components will be will be analyzed on the 8th and 15th minute of massage (half-way and conclusion of massage), 3rd and 15th minute of RGI (induction and conclusion of RGI), and end of music therapy.

Data Analysis

Statistical Methods

Demographic/ clinical characteristics of patients and all outcomes will be presented by treatment group using descriptive statistics— mean (SD), median (IQR) or proportion. Outcomes will be analyzed longitudinally over 5 days by logistic regression model based on generalized estimating equations (GEE) with AR(1) correlation structure. ANCOVA, t-test or Mann-Whitney test, as appropriate, will be conducted for the continuous outcomes that are not longitudinal. Models will be adjusted for co-variates including pre-deliric score, administration of medication (sedatives,

analgesics, vasoactives and antipsychotics) and severity score (SOFA, APACHE). Chi-square or exact test, as appropriate, will be used for categorical outcomes. We will treat pain outcomes as both categorical (presence or absence of pain) and continuous variables (pain score). Confidence intervals will be presented with estimated effects. Primary analysis will be based on all available data utilizing data from all assessments. Since GEE assumes missing completely at random (MCAR) mechanism, we plan to conduct a sensitivity analysis based on inverse probability weighted GEE (IPWGEE) (30) which employs a less restrictive missing at random (MAR) mechanism. A "last observation carried forward" (LOCF) approach was not considered because analyzing all available data performs better than LOCF in GEE setting with respect to bias, Type I error rate and coverage probability under both MCAR and MAR mechanisms. Although we are not able to formally assess potential effects of the sham intervention with the current 2-group design, GEE models will provide indications of such potential effects that will be taken into account at a future trial. Analysis will be conducted by EPICORE.

To account for noncompliance, protocol deviations and missing outcomes, intention-to-treat (ITT) analysis will be employed. ITT analysis includes every randomized subject according to treatment assignment. Additionally, per protocol analysis will also be employed. Per-protocol (PP) population is defined as a subset of the ITT population who completed the study without any major protocol violations. If ITT and PP analyses lead to similar conclusions the reliability of results will be supported. Although, this is a pilot trial, ITT will help reduce potential effects of selection bias. PP analysis will assess whether the ITT result is too conservative. This will provide important data regarding the effect size for the subsequent trial. Both analyses will assist us in revising the protocol for the larger trial.

Qualitative analyses

Interview transcriptions will be thematically analyzed by an inductive content analysis approach (31). A coding scheme will be developed based on recurrent themes of the first five interviews. Subsequently, two researchers (EP, TP) will code independently, using axial and inductive coding to formulate a final coding template by consensus. The final coding scheme will then be used to code, compare and interpret all transcripts. Individual analyses of the team members will be discussed to achieve shared understanding and to increase reliability. The data will be analyzed via NVivo software (QSR International Doncaster, Victoria, Australia).

Quality Control and Quality Assurance

This pilot will be supervised by an independent trial steering committee (TSC), consisting of 3 clinical trial experts independent of the research team. Periodical audits of the intervention and trial processes at both sites by personnel independent from investigators will be initiated by the TSC. Randomization, recruitment, intervention adherence, blinding, stability and data collection processes will be monitored. Trial Monitoring Committee (TMC) will also review relevant information from similar studies and will consider the recommendations of the Data Monitoring (DMC) and Ethics Committee. Study personnel have been trained to standardize processes. We have developed two training videos including detailed demonstration of the intervention. Moreover, research personnel involved with the intervention has received 18-21 hours of hands-on training, including detailed auditing, and several hours of self-paced training to standardize the process, communication and timing of intervention. Study personnel will meticulously record any deviations from the intervention protocol to assess feasibility and effect on outcomes. Clinical data will be retrieved from the quality-controlled clinical information system of the units. Detailed electronic data collection forms with embedded quality controls will be used and reviewed in detail. Data quality will be monitored through EPICORE before, during, and after entry. All data

will be entered electronically using study forms generated through RedCap® with embedded quality control processes. Study data will be collected and managed using REDCap® electronic data capture tools hosted at the University of Alberta (32). A quality control system will be applied for biological measurements as per lab protocol. Day-to-day operations of the trial will be overseen by a Trial Management Group (TMG) comprising, as a minimum, the Principal Investigator, Senior Trial Manager, Trial Manager, Trial Statistician and Data Manager. TMG meetings will take place on a regular basis throughout the duration of the study. The TMG will have responsibility for ensuring the adherence and progress of the study in relation to all regulatory, administrative academic and any clinical or safety issues.

Ethics

The protocol has received approval from the Human Research Ethics Board (HREB) University of Alberta and administrative approvals from participating institutions. This study will be conducted in compliance Canadian and International Good Clinical Practice standards. No deviation from the protocol will be implemented without the prior review and approval of the HREB except where it may be necessary to eliminate an immediate hazard to a research participant. In such case, the deviation will be reported to the HREB.

Experienced research personnel not involved with the delivery of the intervention and in patient care will acquire informed consent from legal surrogates or participants if competent to consent. Participant assent will be acquired when participants regain capacity. Confidentiality, anonymity and right to withdraw at any point with no questions asked and no effect on the quality of care received will be assured. After completion of the study the data and samples will remain stored at the academic institution for 5 years.

Confidentiality

Code-identified encrypted study data will be stored separately from participant information at an EPICORE database permitting code-access only. All study forms, lab specimens and data will be identified by an alphanumeric code to maintain confidentiality. Records that contain names, identifiers will be stored separately from study data identified by code. Participants' information will not be released outside the study. Participant information will be stored at an encrypted limited code-initiated access electronic file. Consent forms will be kept in a locked file cabinet at a pre-specified limited-access room, University of Alberta.

Safety

Although prior pilot data did not provide evidence of adverse effects or increased rate of complications, any physiological/ behavioural alteration during interventions will be recorded and analysed. Adverse events, irrespective of causal relationship, will be collected for all participants, during and up to half an hour after the intervention.

Data Dissemination

Results will be disseminated to participants, healthcare professionals, health services authorities and the public via conference presentations and publications. Results of this study will be used to inform the design and conduct of a future multi-center trial. The results of the trial will be presented at national and international meetings and published in peer-reviewed journals. A lay summary of the results will be available to trial participants on request. An online summary of the findings will also be made available.

Conclusions: This pilot clinical trial integrates a low-risk, patient-centered strategy, translational research and psychological outcomes to allow an evaluation of non-pharmacological delirium management with mechanistic insights. Implications of the definitive trial include the potential to reassure patients, decrease the incidence of frightening delirium experiences, and improve longitudinal outcomes.

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Authors' conflict of interest: None declared

Data Statement: Technical appendix, statistical code, and dataset will be available from EPICORE, University of Alberta.

Legends

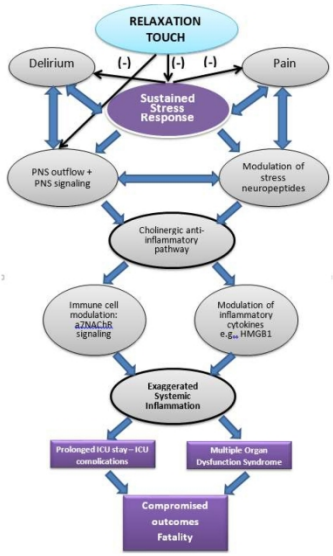
Figure 1.

Evidence-based framework for the physiological mechanism implicated in relaxation-induced effects in critical illness. Relaxation acts early at the pathophysiological cascade through which an exaggerated stress response results in pro-inflammatory effects, suppressed PNS outflow and subsequently in systemic inflammation, multiple organ dysfunction and death. The relaxation response counterbalances the exaggerated stress response and activates PNS and cholinergic anti-inflammatory signaling, which downregulates pro-inflammatory (e.g., HMGB-1) and up-regulates anti-inflammatory cytokines; therefore attenuating systemic inflammation and its detrimental organ effects. (*α7-nAChR: alpha7- nicotinic acetylcholine receptor, HMGB-1: High Mobility Group Box-1; PNS: Parasympathetic Nervous System)*

Figure 2:

Schematic of study design. *(Ach: Acetylcholine, AE: Adverse Event, APACHE: Acute Physiology & Chronic Health Evaluation, CPOT: Critical Care Pain Observation Tool, CRP: C-Reactive Protein, EQ-5D: EuroQol Five Dimensions Questionnaire, HADS: Hospital Anxiety*

and Depression Scale, HF: High Frequency, HMGB: High Mobility Group Box, HRV: Heart Rate Variability, ICDSC: Intensive Care Delirium Screening Checklist, ICU: Intensive Care Unit, IQCODE: Informant Questionnaire on Cognitive Decline in the Elderly, IV: Intravenous, LF: Low Frequency, LOS : Length of Stay, NRS: Numeric Rating Scale, RASS: Richmond Agitation Sedation Scale, RGI: Relaxation and Guided Imagery, S-R: Self-Reported, SOFA: Sequential Organ Failure, STAI: State Trait Anxiety Inventory).



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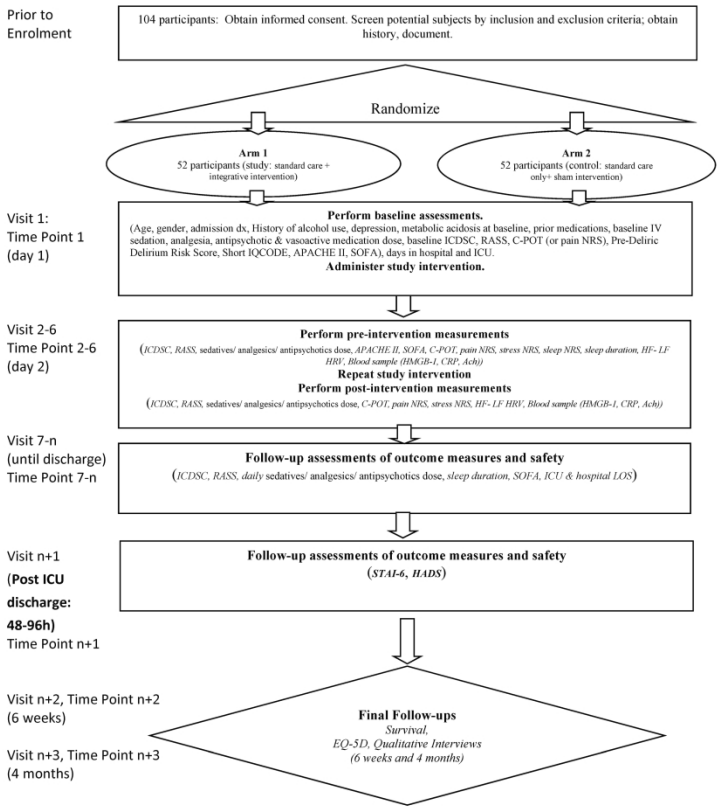

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Appendix 1. Schedule of enrolment, interventions, and assessments.

	Enrolment	**Allocation**	**Post-allocation in-ICU**					**Post-intervention / in-ICU** (daily until discharge)	*At ICU-discharge (or ward-ready)*	**Post ICU discharge (In hospital: 2-7 days)**	*At hospital discharge*	**Post ICU Discharge (6 weeks)**	**Post ICU Discharge (4 months)**
TIMEPOINT	$-t_1$	**0**	Day_1	Day_2	Day_3	Day_4	Day_5						
ENROLMENT:													
Eligibility screen	X												
Informed consent	X												
Random Allocation		X											
INTERVENTIONS:													
[Intervention: RGI + massage]			←	—	—	—	→						
[Control: Sham Intervention]			←	—	—	—	→						
BASELINE ASSESSMENTS: ***[***demographics diagnosis, hx, short IQCODE), pre-DDRS, sedatives/ analgesics/ antipsychotics dose, Prior LOS***]***	X												
		X	X	X	X	X	X						

Primary Outcome: ICDSC≥4												
Secondary outcomes: *ICDSC, ICDSC:1-3, RASS, daily* sedatives/ analgesics/ antipsychotics dose, ***sleep NRS, sleep duration, APACHE II, SOFA***		X	X	X	X	X	X	X				
			pre-post-Intervention									
C-POT, PAIN NRS, pain distress NRS, stress NRS, HF- LF HRV		X	X2	X2	X2	X2	X2					
			pre-post-Intervention									
HMGB-1, CRP, Ach			X2	X2	X2	X2	X2					
ICU LOS, duration MV, ICU survival									X			
HADS										X		
Hospital survival, Hospital LOS											X	
											X	

6 week survival, Interview, EQ-5D, SF-36													
4-month survival, EQ-5D, SF-36													X

Ach: Acetylcholine, CPOT: Critical Care Pain Observation Tool, CRP: C-Reactive Protein, DEMMI: de Morton Mobility Index, EQ-5D: EuroQol Five Dimensions Questionnare, HADS: Hospital Anxiety and Depression Scale, HF: High Frequency, HMGB: High Mobility Group Box, HRV: Heart Rate Variability, ICDSC: Intensive Care Delirium Screening Checklist, ICU: Intensive Care Unit, Interview: Qualitative open ended questions; IQCODE: Informant Questionnaire on Cognitive Decline in the Elderly, LF: Low Frequency, LOS : Length of Stay, MV: mechanical ventilation, NRS: Numeric Rating Scale, RASS: Richmond Agitation Sedation Scale, RGI: Relaxation and Guided Imagery, S-R: Self-Reported, SOFA: Sequential Organ Failure, STAI: State Trait Anxiety Inventory.

Appendix 2. Telephone interview guide (Qualitative open-ended questions)

1. Do you remember listening to music while in the ICU? Can you describe what you remember?
2. Do you remember listening to a voice through the headphones? Can you describe what you remember?
3. If yes, how did this make you feel? Were you able to follow the instructions with your mind/ imagination? Please describe
4. Do you remember somebody giving you a massage? Can you describe what you remember?
5. If yes, how did this make you feel?
6. Would you wish to receive this intervention again? Why?
7. Would you recommend this intervention for other patients? Why?

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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		Reporting Item	Page Number
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	2
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	2
Protocol version	#3	Date and version identifier	2
Funding	#4	Sources and types of financial, material, and other support	22
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	22
Roles and	#5b	Name and contact information for the trial sponsor	22

responsibilities: sponsor contact information			
22Roles and responsibilities: sponsor and funder	#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	22
Roles and responsibilities: committees	#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)	14-15
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	4-5
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	5
Objectives	#7	Specific objectives or hypotheses	5, 6
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, non-inferiority, exploratory)	5
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	6
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and	7

		individuals who will perform the interventions (eg, surgeons, psychotherapists)	
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7-8,9
Interventions: modifications	#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)	8
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	8
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	9
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	10-12
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)	1. Appendix
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	6-7
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	6
Allocation:	#16a	Method of generating the allocation sequence (eg,	8

sequence generation		computer-generated random numbers), and list of 8any 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	
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	8
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	8
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	8-9
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	9, NA
Data collection plan	#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	9-10
Data collection plan: retention	#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	9
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data	9,15

		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	
Statistics: outcomes	#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	13-14
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	13-14
Statistics: analysis population and missing data	#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)	14
Data monitoring: formal committee	#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	14-15
Data monitoring: interim analysis	#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	NA
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	16
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	8,15
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	15,16
Protocol	#25	Plans for communicating important protocol	15

amendments		modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	15-16
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	16
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	16
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	22
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	NA
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	NA
Dissemination policy: trial results	#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	16
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	NA
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	16

Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	Upon request
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	12-13 & upon request