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Optimal VAsopressor TitraTION in patients 65 years and older (OVATION-65) – protocol and statistical analysis plan for a randomized clinical trial

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Optimal VAsopressor TitraTION in patients 65 years and older (OVATION-65) – protocol and statistical analysis plan for a randomized clinical trial

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OVATION-65 team members, including research personnel at clinical sites active at the time of submission of this manuscript, are listed in online supplementary file S1.

Abstract

Introduction: Vasodilatory hypotension is common among intensive care unit (ICU) patients, and vasopressors are considered standard of care. However, optimal mean arterial pressure [MAP] targets for vasopressor titration are unknown. The objective of OVATION-65 (**O**ptimal **VA**sopressor Titra**TION-65**) is to ascertain the effect of permissive hypotension (vasopressor titration to achieve MAP 60-65 mmHg) vs. usual care in hypotensive patients ≥65 years old.

Methods and analysis: OVATION-65 is an allocation-concealed randomized trial in ICUs in 7 Canadian hospitals. Eligible patients are ≥65 years old, in an ICU with vasodilatory hypotension, receiving vasopressors for ≤12 hours to maintain MAP ≥65 mmHg during or after adequate fluid resuscitation, and expected to receive vasopressors for ≥6 additional hours. Patients are excluded for any of the following: active treatment for spinal cord or acute brain injury; vasopressors given solely for bleeding, ventricular failure or post-cardiopulmonary bypass vasoplegia; withdrawal of life-sustaining treatments expected within 48 hours; death perceived as imminent; previous enrolment in OVATION-65; organ transplant within the last year; receiving extracorporeal life support; or lack of physician equipoise. Patients are randomized to permissive hypotension vs. usual care for up to 28 days. The primary outcome is high-sensitivity troponin T, a biomarker of cardiac injury. Secondary outcomes include biomarkers of injury to other organs (brain, liver, intestine, and skeletal muscle); lactate (a biomarker of global tissue dysoxia); resource utilization; adverse events; mortality (90 days and 6 months); and cognitive function (6 months). Assessors of biomarkers, mortality, and cognitive function are blinded to allocation.

Ethics and dissemination: This protocol has been approved at all participating sites. Consent is obtained from the eligible patient, the substitute decision-maker if the patient is incapable, or in a deferred fashion where permitted. Plans for end-of-grant dissemination include

conference presentations, journal publications, and social media platforms and discussion forums.

Trial registration: clinicaltrials.gov, NCT03431181

Keywords

vasopressors; shock; critical care; biomarkers; randomized controlled trial

Article summary

Strengths and limitations of this study

- OVATION-65 is an allocation-concealed randomized clinical trial of permissive hypotension vs. usual care in patients 65 years and older with hypotension from a vasodilatory cause, a population that may be more vulnerable to adverse effects of vasopressors
- Vasopressor titration is understudied in critically ill patients, compared to other interventions such as mechanical ventilation
- The primary and many secondary outcomes, selected with input from a patient representative, focus on biomarkers of organ injury; although these are not patient-centred outcomes, results will complement clinical outcome data from larger trials
- Because of the nature of the intervention, blinding is not feasible; however, outcome assessors are blinded
- The modest sample size implies that the trial is underpowered for clinical outcomes

Introduction

Shock, a clinical syndrome of which hypotension is a cardinal feature, is common and associated with high mortality. Vasopressors are used to treat hypotension that is potentially life-threatening because they raise blood pressure by inducing vasoconstriction.[1] However, these medications are associated with adverse effects,[2-4] some of which are direct consequences of vasoconstriction-induced reduction in blood flow to vital organs. Therefore, titrating vasopressors implies balancing the risks of end-organ failure caused by hypotension and potential vasopressor-induced harm, including myocardial injury and arrhythmia, excessive vasoconstriction, hyperglycemia, and immunosuppression.[2-5] Permissive hypotension is a strategy of targeting a lower blood pressure when prescribing vasopressors, compared to usual care. Benefits have been associated with other 'permissive' therapies in critically ill patients, including hypoxia,[6] underfeeding,[7] hypercapnia,[8] red blood cell transfusion,[9] and hypotension in thoracic penetrating trauma.[10]

Clinicians in the intensive care unit (ICU) use mean arterial pressure (MAP) targets to determine the intensity of vasopressor therapy. Current international practice guidelines recommend titrating vasopressors to a MAP of 65 mmHg or more.[11] Because the target lacks an upper boundary, clinicians commonly put more emphasis on preventing hypotension than on minimizing vasopressor exposure. This under-appreciation of the risks associated with vasopressor overuse was apparent in a multicentre observational study[12] that reported an average MAP of 75 (standard deviation [SD] 6) mmHg in patients receiving vasopressors, approximately 10 mmHg above the recommended MAP and self-reported practice.[13] Given the relative lack of studies about vasopressor dosing, in contrast to other common ICU treatments such as mechanical ventilation, editorialists have advocated for better characterization of the lowest acceptable blood pressure target to avoid vasopressor-induced harm.[3]

Existing evidence

Observational studies have described independent associations between dose and duration of vasopressor therapy and poor outcomes, such as adverse cardiac events and increased mortality.[14 15] However, these studies are limited by indication bias, as patients who are sicker have a greater risk of unfavourable outcomes and are therefore more likely to be exposed to higher doses of vasopressor therapy.

Two randomized clinical trials (RCTs; combined n=894) published prior to the initiation of this study compared blood pressure targets in patients receiving vasopresors.[16 17] The SEPSISPAM trial compared a MAP target of 65-70 mmHg vs. 80-85 mmHg for 5 days in 776 patients with septic shock from 29 French ICUs. This study reported no difference in 28-day mortality (lower MAP 34.0% vs. higher MAP 36.6%, p=0.57), but a greater risk of atrial fibrillation in the higher MAP arm (6.7% versus 2.8%, p=0.02).[16] However, actual MAP values were 74-76 mmHg in the lower MAP arm, precluding conclusions regarding permissive hypotension. The OVATION pilot feasibility trial randomly assigned 118 patients from 1 US and 10 Canadian ICUs to a lower (60-65 mmHg) or higher (75-80 mmHg) MAP target [17]. This trial was not powered to detect differences in mortality. A subsequent individual patient data meta-analysis (IPDMA)[18] included data from both RCTs and found that higher MAP targets (75-85 mmHg) may be associated with an increased risk of 28-day mortality in older patients (p=0.1 for interaction between age and MAP).

Based on these RCTs, guidelines state that no evidence supports the use of MAP targets >65 mmHg for patients receiving vasopressors.[19] Subsequently, the 65 trial randomized 2600 patients ≥65 years old in the United Kingdom to permissive hypotension vs. usual care using the same protocol as OVATION-65.[20 21] Patients in the permissive hypotension arm had a

lower exposure to vasopressors and a lower 90-day mortality (41.0% vs. 43.8%, p=0.15), but the difference was not statistically significant. However, the analysis adjusting for baseline covariates found lower mortality with permissive hypotension (OR 0.82, 95%CI 0.68-0.98).[22] The 65 trial collected no biological samples, precluding exploration of mechanisms underlying the clinical effect of vasopressor dosing.

Goal and Objectives

The goal of OVATION-65 is to determine whether permissive hypotension (MAP 60-65 mmHg) in patients ≥65 years old (n=200) with a vasodilatory cause of hypotension and receiving vasopressors, compared to usual MAP targets, reduces harm. Specific objectives are to ascertain the effect of permissive hypotension vs. usual care on: 1) biomarkers of organ injury (heart [primary outcome], brain, liver, intestine, skeletal muscle); 2) biomarker of global tissue dysoxia (lactate); 3) organ function (assessed by Sequential Organ Failure Assessment [SOFA] score[23]); 4) resource utilization, 5) prespecified adverse events, 6) mortality at 90 days and 6 months; 7) cognitive impairment in survivors at 6 months (Table 1).

The primary outcome and several secondary outcomes are focused on biomarkers because of well-documented limitations of mortality in critical care trials[24] and the challenges of developing valid surrogate endpoints.[25] OVATION-65 was designed to be complementary to the 65 trial.[22] A larger version of OVATION-65 (n=800) was abandoned in 2018 after repeated funding applications to the Canadian Institutes for Health Research and the Canadian Frailty Network were rejected.

Methods and analysis

OVATION-65 is a multicentre, parallel-group, allocation-concealed, superiority RCT. We developed OVATION-65 on behalf of the Canadian Critical Care Trials Group (CCCTG), a 350-member organization of clinicians and researchers, incorporating feedback received since January 2012 at each of its thrice yearly scientific meetings. Table 2 shows a timeline of trial activities. The SPIRIT checklist is available in online supplementary file S2.

Study setting and management

OVATION-65 is conducted in adult ICUs in 7 sites in Canada. The procedures in place for OVATION-65 were piloted during the OVATION pilot RCT.[17] The Unité de Recherche Clinique et Épidémiologique (URCE) is coordinating this trial and is responsible for construction and maintenance of the randomization system and the REDCap[26 27] electronic data capture (EDC) system. The URCE also oversees the activities of the OVATION-65 core laboratory (i.e. storage and analysis of blood and urine samples).

Inclusion criteria

Patients are included if they meet all the following criteria: 1) age ≥65 years; 2) diagnosis of vasodilatory hypotension as assessed by the treating team; 3) vasopressors started ≤12 hours (after/during adequate fluid resuscitation, as assessed by treating physician); and 4) vasopressors expected for ≥6 additional hours as assessed by the treating team.

Exclusion criteria

Patients are excluded if they meet any of the following criteria: 1) actively treated for spinal cord injury or acute brain injury; 2) vasopressors given solely for bleeding, acute ventricular failure or post-cardiopulmonary bypass vasoplegia; 3) lacking commitment to life-

sustaining therapies (expected withdrawal of life-sustaining treatments within the next 48 hours); 4) death perceived as imminent; 5) previously enrolled in OVATION-65; 6) organ transplant within the last year; 7) receiving extracorporeal life support at baseline; and 8) lack of treating physician equipoise regarding the overall effects of permissive hypotension vs. usual care on patient important outcomes.

Rationale for eligibility criteria

The inclusion criteria strive to identify patients most likely to benefit from permissive hypotension, namely elderly patients not already exposed to a prolonged duration of higher MAP but expected to require an additional period of vasopressor therapy. The exclusion criteria are designed to exclude patients for whom clinicians commonly apply different MAP targets (criterion 1) or whose prognosis may be dominated by factors other than the MAP target (criteria 2, 3, 4, 6, 7).

Study intervention

Treatment allocation

Using a web randomization service available 24 hours/7 days per week, patients are randomized immediately after confirming eligibility following a 1:1 sequence to permissive hypotension or usual care. We use permuted blocks of variable and undisclosed size (4, 6 and 8) and stratify randomization by site. Stratifying by site ensures equal distribution of patients between arms at each site and decreases the probability that site-specific practices confounds treatment effects.

Permissive hypotension arm

The intervention minimizes dose and duration of vasopressors. Treating teams adjust vasopressors to a target MAP range of 60 to 65 mmHg. A MAP of 60 mmHg was selected as lowest tolerable limit because it corresponds to the threshold at which Canadian intensivists usually initiate vasopressors.[13] Accordingly, it is not uncommon for patients to have MAP as low as 60 mmHg before vasopressors are instituted under usual care. Moreover, coronary perfusion pressure and glomerular filtration rate are both believed to be stable above 60 mmHg. Lastly, the same MAP range was used in the OVATION pilot RCT[17]

The duration of the trial intervention is determined, as it was in the pilot RCT, by the duration of the hypotensive episode, up to a maximum of 28 days. For trial purposes, the episode of hypotension ends when vasopressors are discontinued for 24 consecutive hours. As soon as patients are able to maintain the target MAP without vasopressors, the infusions are stopped. If MAP drops below 60 mmHg after this 24-hour period, and if the treating team determines that vasopressors should be reinstituted, they are titrated to the allocated target of 60 to 65 mmHg. If patients are discharged and then readmitted to the ICU, vasopressor therapy is left at the discretion of the treating team.

Usual care arm

Patients in the control arm receive usual care, as per local practice. This constitutes an improvement to the protocol of the OVATION pilot trial, which imposed a higher target MAP range of 75 to 80 mmHg. Given preliminary evidence suggesting that this higher MAP target may increase risk of death in older patients, we believe that mandating a higher MAP would be ethically questionable. By comparing permissive hypotension to usual care, we improve acceptance from clinicians and reduce the risk that the control group will diverge widely from usual care.[28] Risks of contamination are negligible given observational data showing that MAP values of patients treated with vasopressors are much higher than the currently

recommended target of 65 mmHg. Moreover, changing the behaviour of physicians and nurses is challenging even when there is consensus on the benefit of a new intervention,[29] and such a consensus does not exist for permissive hypotension.[30] To further decrease the risk of contamination (i.e. lack of separation of MAP between arms), we monitor separation of actual MAP between study arms and communicate regularly with sites.

Selection of vasopressors

We do not mandate the use of any specific vasopressor or combination of vasopressors. In OVATION-65, the term 'vasopressor' refers to the following medications given by infusion: norepinephrine, epinephrine, dopamine, phenylephrine, and vasopressin. In patients receiving multiple vasopressors, we calculate the total vasopressor dose as norepinephrine equivalent as previously reported.[31] In addition, we collect information on orally administered catecholaminergic medications (i.e., midodrine and ephedrine).

Other interventions

As per usual care of patients receiving vasopressors, central venous catheters (to avoid extravasation) and arterial catheters (for close MAP monitoring) are in place. Exceptions do not constitute deviations, consistent with a pragmatic study design. Use of pure inotropes, intravenous fluids, and corticosteroids are recorded but left to the discretion of the treating team.

Outcomes

Primary outcome

The primary outcome of OVATION-65 is high-sensitivity cardiac troponin T (hsTnT) at day 3; baseline samples (day 1) are collected before assignment to the intervention but after

vasopressors have started. Cardiac troponins are consistently associated with worse outcomes in critical illness[32-36], and cardiac biomarkers may be modifiable by administration of albumin[33] and medications.[34] Given that coronary perfusion autoregulation is maintained when MAP is at least 60 mmHg, we hypothesize that increasing vasopressors to achieve a higher MAP offers no advantage but increases the severity of demand-related myocardial ischemia via increased heart rate (i.e. reduced coronary perfusion time) and transmural pressure (i.e. afterload). If OVATION-65 shows that permissive hypotension prevents or limits hsTnT elevation, then patients at increased risk of secondary myocardial ischemia, possibly identified by baseline hsTnT, may benefit the most from this strategy. Similarly, this biomarker could be used to identify vasopressor-induced harm earlier and modify vasopressor use accordingly.

Secondary outcomes

Secondary outcomes include high-sensitivity cardiac troponin T (hs TnT) at day 7; biomarkers associated with cardiac wall stress (plasma N-terminal pro-B-type natriuretic peptide [NT-proBNP][33]); tissue injury to the brain[37] (glial fibrillary acidic protein [GFAP][38], ubiquitin C-terminal hydrolase L1 [UCHL1][39], myelin basic protein [MBP][40], neuron-specific enolase [NSE][41]), liver (serum alanine aminotransferase [ALT][42]), intestine (plasma intestinal-type fatty acid binding protein [FABP2][43]), skeletal muscle (plasma creatine kinase, muscular [CKM][44]); and global tissue dysoxia (plasma lactate). As for hsTnT, all biomarker outcomes are measured at baseline, day 3 and 7.

We measure secondary clinical outcomes, including organ function using SOFA score (on days 1, 2, 3, 4, 7, 10, 14 and 28 while in the ICU). We describe healthcare utilization in terms of duration of mechanical ventilation, renal replacement therapy, vasopressor therapy, ICU and hospital stay. We report the incidence of the prespecified adverse events of stroke,

acute kidney injury (KDIGO stage 3),[45] clinically detected supraventricular arrhythmia,[5 46] and limb or intestinal ischemia as defined in the OVATION pilot trial.[17] Investigators will adjudicate these adverse events using medical records, if necessary. We ascertain mortality at 90 days and 6 months. For 6-month survivors, we assess cognition using the Telephone Interview for Cognitive Status (TICS), a validated questionnaire used in ICU cohorts.[47]

Adverse events

OVATION-65 is testing a common intervention to treat a common problem in critically ill patients. All eligible patients are at risk of adverse events due to their underlying critical illness. Following Canadian guidelines for serious adverse event (SAE) reporting in academic drug trials in critical care,[48] expected SAEs (stroke, KDIGO stage 3 acute kidney injury, clinically detected supraventricular arrhythmia, limb or intestinal ischemia, death) are already incorporated as trial outcomes, defined *a priori*. SAEs are limited to events not already labelled as trial outcomes and that might reasonably occur as a consequence of the trial interventions. SAEs must be reported in the participant's medical notes, on the OVATION-65 dedicated case report form and to the coordinating centre within 24 hours of observing or learning of the event. Such events are promptly discussed with the Data and Safety Monitoring Committee (DSMC).

Data collection

We collect the following data: 1) Baseline data (day 1) – demographics, admitting diagnosis, etiology of hypotension, severity of illness (APACHE II score[49]), organ dysfunction (SOFA score[23]), comorbidities (including chronic hypertension, coronary, cerebral, or peripheral vascular disease, congestive heart failure, chronic kidney disease, severe cognitive impairment, Clinical Frailty Scale[50], co-enrolment in other prospective

observational studies or RCTs; 2) relevant co-interventions (fluid balance, inotropes, and corticosteroids); 3) protocol adherence (MAP while receiving vasopressors and corresponding vasopressor dose modification); and 4) primary and secondary outcomes.

Study Samples

To minimize the treating teams' workload, study samples (blood and urine) coincide as much as possible with clinical sampling on day 1 (baseline) and on day 3 and 7 (or the day of ICU discharge or before anticipated death or withdrawal of life-sustaining therapies, whichever comes first).

To ensure consistent measurement of biomarkers, the study samples are processed on site and shipped to URCE, where they are stored at -80°C and batched for analyses at the end of the trial. Clinical teams are blinded to the results of the biomarker assays but are free to measure any desired biomarker via local hospital laboratory. Participants are also approached for participation in a parallel Acute Care Biobank, via a separate consent form, which allows samples remaining following completion of OVATION-65 specified analyses to be stored for future projects.

Reducing bias

Risk of bias is reduced by concealed randomization using variable and undisclosed blocks. Assessors of biomarkers, pre-specified adverse events, mortality, and TICS are blinded to treatment allocation. Specimen processing and analysis are standardized as described. Finally, we record co-interventions to detect performance bias.

Protocol adherence in the permissive hypotension arm

Adherence is defined as appropriately reducing vasopressor doses (or discontinuing vasopressors) when the MAP is above 65 mm Hg. Protocol deviations are defined as a failure to reduce (or discontinue) vasopressors while the MAP is above 65 mm Hg for three consecutive hours. Investigators will adjudicate at least 10% of deviations using source data if required.

For each day on protocol, we record the MAP value recorded nearest to each hour. In the intervention arm, clinical teams are reminded to consider discontinuing vasopressor therapy if the patients are able to maintain MAP values of at least 60 mmHg. Every participating site receives on-site training, to which all ICU bedside staff are invited. We distribute standard operating procedures and protocol adherence reports generated from MAP and vasopressor data entered in the electronic case report form. Regular newsletters and trial website updates (https://www.ccctg.ca/Programs/OVATION65.aspx) keep participating sites informed of study progress, overall adherence, and answers to frequently asked questions. Research staff are available 24/7.

We report the number of protocol deviations and the number of patients with any protocol deviation in the permissive hypotension arm.

Follow-up

Participants are followed to hospital discharge by local research teams. Either the coordinating centre or the enrolling site ascertains 90-day and 6-month mortality and 6-month cognitive status in survivors by telephone. Prior verification of known vital status with local research teams and calibrated telephone scripts mitigate the risk of emotional distress in the event that the patients have died since hospital discharge. We selected TICS to measure cognitive function in survivors because telephone administration reduces risk of bias, improves measurement consistency, reduces patient burden, and enhances feasibility.

Patient and public involvement

The protocol was developed with input from ICU survivors, who advised on the selection of outcomes.

Statistical analysis

Sample size

OVATION-65 is supported by several modest operating grants, each of which required a distinct objective, sample size calculation and analysis plan. By combining funds from multiple sources, we had planned to enrol 200 participants, which provides 80% power to detect an effect size of 0.4 in the difference between day 3 hsTnT in the permissive hypotension group compared to usual care, where 0.5 is considered to be medium.[51] However, the OVATION-65 Executive Committee forwarded the 65 trial publication[22] to the DSMC, which requested a meeting to discuss the results. The DSMC subsequently issued a letter on 21 February 2020 recommending termination of enrolment in OVATION-65. The DSMC 'reasoned that in light of the accumulated evidence, mostly from the 65 trial[22] but also with some consideration of SEPSISPAM,[16] the posterior probability of lower MAP targets now being better was sufficiently high that there is no longer equipoise between the interventions being compared in OVATION-65. As of 21 February 2020, 159 patients had been randomized.

We lack resources to measure every outcome in each participant. Outcomes not measured on every participant and those that were planned originally but that remain unfunded are described in online supplementary file S4 and will be reported separately.

Patient flow

A sample CONSORT diagram is presented in Figure 1.

Data analysis

Analyses will be performed after all follow-up is completed, data queries are resolved, and the database is locked. We will adhere to the intention-to-treat principle, and data from participants will be analyzed by allocated group, regardless of protocol adherence. All participant data will be analysed unless consent to retain data is withdrawn. Statistical testing will use a superiority framework, with $p<0.05$ interpreted as statistically significant. Estimates of effect will be reported with 95% confidence intervals. No adjustments for multiplicity will be made. All analyses will use SAS 9.4 (Cary, USA). Given the modest sample size and focus on biomarkers of organ injury, no interim analysis is planned. Continuous data will be summarised as means (SD) if normally distributed and as medians (Q1, Q3) otherwise. Categorical data will be summarised as frequencies and proportions. Baseline data will be summarised as shown in Table 3.

The primary outcome of day 3 hsTnT will be analysed, adjusting for the day 1 value. We will use the original scale and analysis of covariance if the data are not skewed; if skewed we will log-transform and use robust regression to obtain more interpretable estimates. We will use pooled logistic regression to estimate the probabilities of missing values due to either death or live discharge from the ICU. Based on these models, we will compute the inverse-probability of attrition weights for each observation and use generalized estimating equation models to test the differences in hs TnT between the permissive hypotension and usual care arm,[52] adjusting for centre using fixed effects. As a sensitivity analysis, for patients that die before day 3, we will impute the worst (highest) value and for patients discharged alive before day 3, we will impute the best (lowest) value.

For the secondary outcome of day 7 hsTnT, we will use the same approach. For patients who die before day 7, we will impute the worst (highest) value. For patients discharged alive before day 7, we will impute based on data available for other patients alive at day 7. The approach for all other biomarkers will be the same as for hsTnT.

For SOFA over the first 7 days, we will use a linear mixed effects model to account for repeated measures within patients as well as the centre effect. For patients who die before day 7, we will impute the worst (highest) value. For patients discharged alive before day 7, we will impute based on data available for patients in the same group alive at day 7. We will look for interaction between time and group as well as time trends. For TICS, we will use ordinal logistic regression with fixed effect for centre to compare the distribution of patients at 6 months in 4 categories (death and 3 cognitive status categories [non-impaired, mild impairment, and moderate-severe impairment]). If proportional odds assumption does not hold, we will use multinomial regression to compare the two groups. If there is >5% loss to follow-up for TICS, we will conduct sensitivity analyses using multiple imputation techniques for the missing values. We will also report the proportion of patients in each category by arm and test for differences in separate categories of mortality and cognitive impairment. For mortality, we will use a generalized linear mixed effect model with logit link for 90 and 365 days separately. For prespecified adverse events, we will report the proportion of patients in each arm with the outcome and test for differences using chi-square test or Fisher's exact test, as appropriate.

In sensitivity analyses, we will also adjust for prespecified baseline covariates: APACHE II, total dose of vasopressor administration before randomization (in norepinephrine equivalents),[53] and history of hypertension, or coronary artery disease (angina, myocardial infarction [MI], or coronary revascularisation).

No subgroup analyses are prespecified due to the small sample size.

Registration

The trial was registered on www.clinicaltrials.gov on 13 February 2018 (NCT03431181).

Data management

The paper or electronic case report forms (CRFs) are the primary data collection tool for the study. All data requested on the CRF are recorded on paper CRFs or on the electronic CRFs within the secure REDCap EDC system. If the data are first collected on paper CRFs, site research personnel subsequently transfer all data into REDCap by direct entry.

Monitoring

Quality control measures include 1) site training of research and clinical personnel on eligibility assessment, trial procedures, and data collection; 2) standard operating procedures to guide processing, storage, and shipping of blood and urine samples; 3) ongoing assessment of trial management metrics (monthly screening logs, monthly reports (site enrolment, protocol adherence in the permissive hypotension arm and regarding study samples), and periodic feedback to the clinical sites on performance (recruitment, protocol adherence), with benchmarking from other sites; 4) ongoing review of missing data and outliers; and 5) rapid dissemination of responses to frequently asked questions via our study website and monthly newsletter. For one site, we also conducted monitoring visits for 2 of the first 5 participants and 10% of the subsequent participants. Coordinating Centre staff and the Principal Investigators were available at all times to answer study-related questions.

Trial oversight

Executive Committee

The Executive Committee is comprised of Neill KJ Adhikari, M Elizabeth Wilcox, and François Lamontagne (co-principal investigators), Marie-Claude Battista (core laboratory), and Marie-Hélène Masse (project leader). The Executive Committee is responsible for day-to-day management.

Data Safety Monitoring Committee

The DSMC is independent of the study investigators and responsible for safeguarding the interests of study participants, assessing the safety and efficacy of study procedures, and monitoring the overall conduct of the study. DSMC members have extensive trial experience and include a senior methodologist who has served as Chair on numerous DSMCs for international RCTs, a senior biostatistician, and a clinician scientist in intensive care (online supplementary file S1). The DSMC meets on an *ad hoc* basis to review reports of unanticipated serious adverse events (SAEs) not predefined as study outcomes. In accordance with a prespecified DSMC Charter, the DSMC advises the Executive Committee of any concerns related to participant safety and trial conduct. After each meeting, the DSMC makes a recommendation for study continuation as designed, continuation with major or minor modifications, temporary suspension of enrolment until some uncertainty is resolved, or termination.

Ethics and Dissemination

This protocol has been approved by the Comité d'éthique de la recherche du Centre intégré universitaire de santé et de services sociaux de l'Estrie – Centre hospitalier universitaire de Sherbrooke (MP-31-2018-1789). All participating clinical sites receive local

research ethics board (REB) approval prior to commencing participant enrolment. Before initiating the trial, each clinical site provides the Coordinating Centre with a copy of their local REB approval letter and approved informed consent form (sample in online supplementary file S4). Any required protocol amendments are submitted to each REB and disseminated to all investigators.

Informed consent is obtained by local research personnel, who approach eligible patients directly if they are able to consent. If the eligible patient is not capable, research personnel approach the substitute decision-maker (SDM) to obtain consent in person, or by telephone if the SDM is unavailable. Alternatively, the patient is randomized and consent is obtained subsequently under a deferred consent model, where permitted by the site REB. Consent is requested for future laboratory analyses that may arise from this protocol.

All personal health information collected during the study remains strictly confidential in a secure database. Participants are identified by an alphanumeric code, and the linkage from the alphanumeric code to identifying information is kept in secure storage under the supervision of the local principal investigator.

There is no compensation for harm suffered from trial participation; details on data collection for adverse events are given above. Patients enrolled in this trial are critically ill and all care is provided by intensive care clinicians. There is no provision for post-trial care other than usual clinical care for ICU patients.

Plans for end-of-grant dissemination include presentations at international critical care conferences and journal publications. In addition, building on the experience with social media during the OVATION pilot trial, we will disseminate our results via social media platforms and discussion forums managed by partner organizations.

Data statement

The OVATION-65 protocol is freely accessible via this publication. The principal investigators, project leader, and study statisticians will have access to the full trial dataset; there are no contractual limitations to such access. Requests for access to the participant-level dataset and statistical code will be considered by the Executive Committee after publication of primary results and planned secondary studies by co-investigators.

Trial status

The current protocol is version 6, dated 29 November 2019. Participant recruitment began on 17 February 2018 and was scheduled to continue until approximately June 2020. As noted, the DSMC recommended termination of enrollment on 21 February 2020. The database will be locked after the last enrolled patient completes the 6-month follow-up in August 2020, and 6 additional months will be required to address remaining data queries and to finalize the analyses.

Authors' contributions
NA and FLam drafted the protocol for the OVATION-65 trial and drafted the manuscript; they contributed equally and co-senior authors. MHM, MCB, MEW, RPi, NM, FD'A, CS-A, MM, M-AL, HQM, BGB, YP, ECa, AJES, IW, RPo, MC, ML, FLau, AT, DB, SM, ECh, EB-C, EB, and DC contributed to protocol development and revised the manuscript. MHM, MCB, MEW, FLam, and NA on the Executive Committee. All authors read and approved the final manuscript.

Competing interests
The authors declare that they have no competing interests.

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Online supplementary files

S1 (.pdf format)
OVATION-65 contributors.

S2 (.pdf format)
SPIRIT checklist.

S3 (.pdf format)
Ancillary studies.

S4 (.pdf format)
Model informed consent form.

Figure legend

Figure 1. Progress of patients through the trial. 'Co-enrolled in another study' refers to a study for which the principal investigators of OVATION-65 or the other study had prespecified that co-enrolment would not be allowed.

Table 1 Summary of objectives and outcomes

Objectives	Outcomes
Biomarkers of organ injury	
Heart	High-sensitivity cardiac troponin T (hsTnT)
	N-terminal pro-B-type natriuretic peptide (NT-proBNP)
Brain	Glial fibrillary acidic protein (GFAP)
	Ubiquitin C-terminal hydrolase L1 (UCHL1)
	Myelin Basic Protein (MBP)
	Neuron-specific enolase (NSE)
Liver	Alanine aminotransferase (ALT)
Intestine	Intestinal-type fatty acid binding protein (FABP2)
Skeletal muscle	Creatinine kinase, muscular (CKM)
Global tissue dysoxia	Lactate
Organ function	Sequential Organ Failure Assessment (SOFA) score on days 1, 2, 3, 4, 7, 10, 14, and 28 while in the ICU
Resource utilization	Incidence and duration of mechanical ventilation
	Incidence and duration of renal replacement therapy
	Duration of vasopressor therapy
	Duration of ICU stay
	Duration of hospital stay
Adverse events	Supraventricular arrhythmia
	Stroke
	Acute kidney injury (KDIGO stage 3)
	Limb ischemia
	Intestinal ischemia
Mortality	90 days
	6 months
Cognitive impairment	Telephone Interview for Cognitive Status (TICS) at 6 months

KDIGO, Kidney Disease: Improving Global Outcomes.

All biomarkers are measured in plasma.

Table 2 OVATION-65 Trial Timeline

	Study Period												
	Days	Days											Months
	Enrolment/ Allocation	Post-Allocation											
TIME POINTS	**1**	**2**	**3**	**4**	**5-6**	**7**	**8-9**	**10**	**11-13**	**14**	**15-27**	**28**	**6 months**
ENROLMENT:													
Eligibility screen	x												
Informed consent	x												
Allocation	x												
INTERVENTION:													
Permissive hypotension (MAP 60-65 mmHg) vs. usual care[a]	→	→	→	→	→	→	→	→	→	→	→	▶	
ASSESSMENTS:													
Baseline variables													
Diagnosis of admission	x												
Severity of illness (APACHE II score)	x												
Pre-existing comorbidities (Clinical Frailty Score)	x												
Outcomes													
Troponin hs TnT[b]	x		x			x							
Biomarkers of organ injury[c]	x		x			x							
Global tissue dysoxia (lactate)	x		x			x							
Organ function including renal function (SOFA score)	x	x	x	x		x		x		x		x	
Resource utilization[d]										x			
Mortality at 90 days and 6 months	→	→	→	→	→	→	→	→	→	→	→	▶	x
Cognitive impairment (TICS) at 6 months													x
Stroke	→	→	→	→	→	→	→	→	→	→	→	▶	
Supraventricular arrhythmia	→	→	→	→	→	→	→	→	→	→	→	▶	
Limb or intestinal ischemia	→	→	→	→	→	→	→	→	→	→	→	▶	
Occurrence of stage 3 acute kidney injury[e]	→	→	→	→	→	→	→	→	→	→	→	▶	
Other variables													
Protocol adherence[f]	→	→	→	→	→	→	→	→	→	→	→	▶	
Co-interventions[g]	→	→	→	→	→	→	→	→	→	→	→	▶	

[a] Mean arterial pressure target while receiving vasopressor therapy up to day 28, or discontinuation for more than 24 hours.
[b] hs TnT at day 3 is the primary outcome and at day 7 is a secondary outcome

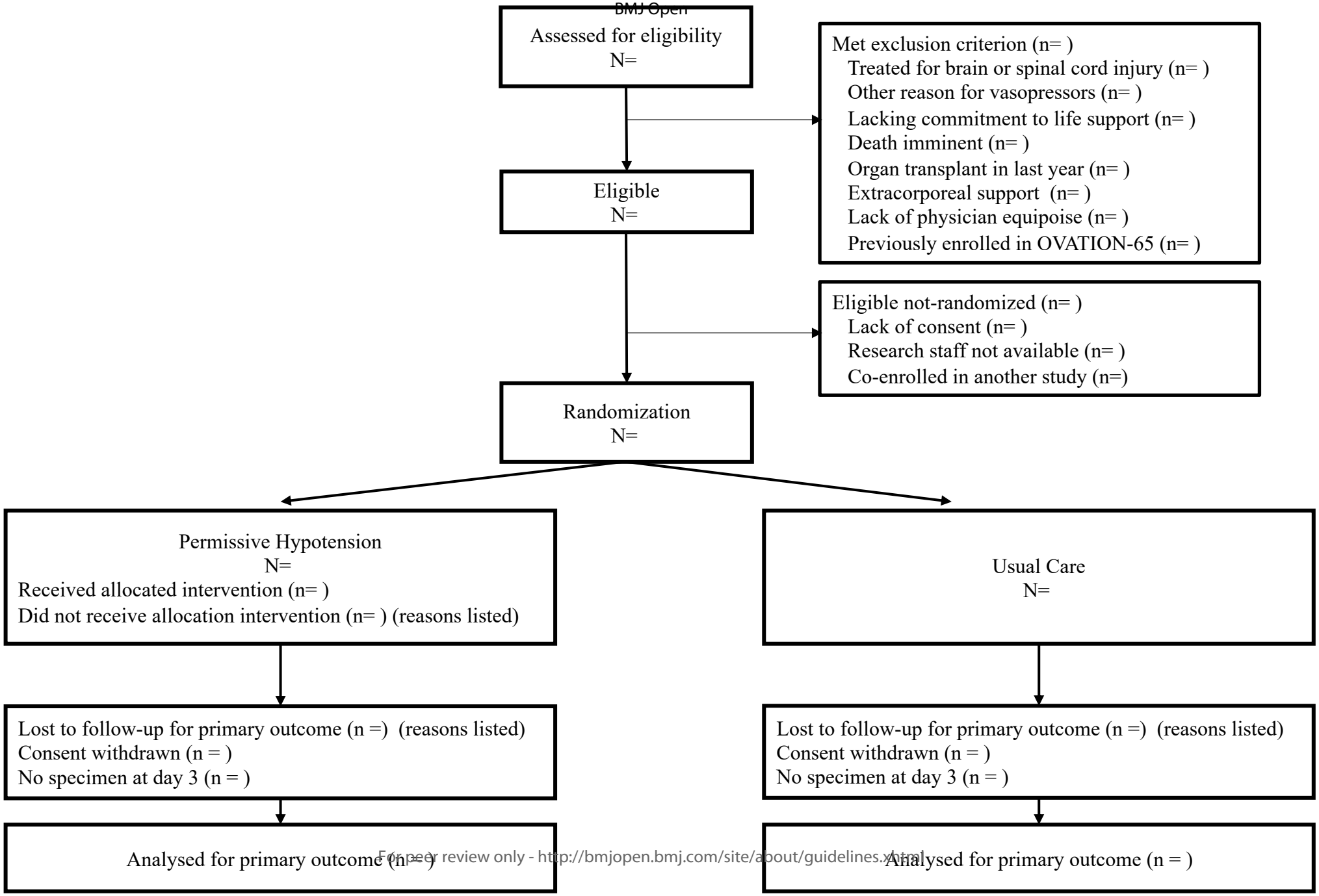
[c] NT-proBNP, GFAP, UCHL1, Myelin Basic Protein, NSE, ALT, intestinal-fatty acid binding protein, CK
[d] Mechanical ventilation, renal replacement therapy, vasopressor therapy, ICU and hospital stay
[e] As defined by KDIGO (Kidney Disease: Improving Global Outcomes) criteria
[f] Mean arterial pressure reached while on vasopressor therapy and samples collected per protocol instructions
[g] Inotropes, corticosteroids, benzodiazepines, opioids, propofol, epidural anesthesia

Table 3 Baseline characteristics

Characteristic	Permissive hypotension (n=)	Usual care (n=)
Demographics		
Age, years, mean (SD)		
Female sex, n (%)		
Weight, kg; mean (SD)		
Clinical Frailty Scale[a] >4, n (%)		
APACHE II[b], mean (SD)		
Comorbidities		
Cardiac, n (%) Supraventricular arrhythmia Ventricular arrhythmia Coronary artery disease[c] CHF class 1-3 CHF class 4 LVEF, % (mean, SD)		
Vascular, n (%) Known hypertension Peripheral vascular disease or claudication Cerebrovascular disease		
Diabetes (type 1 or 2), n (%)		
Renal, n (%) Receiving chronic dialysis Baseline creatinine[d]; mean (SD)		
Child's B or C cirrhosis, n (%)		
Chronic lung disease, n (%)		
Immunosuppression, n (%)		
Cognitive impairment or dementia, n (%)		
ICU admission data		
Primary ICU diagnosis, n (%) Medical Surgical		
Transfer from another hospital, n (%)		
Time from ICU admission to randomization, hours; mean (SD)		
Vasopressor dose, mean norepinephrine equivalents (mean µg/kg/min, [SD])		
Vasopressors, n (%) Norepinephrine Epinephrine Dopamine Phenylephrine Vasopressin		
Inotropes, n (%) Dobutamine Milrinone		
Mean arterial pressure, mmHg; mean (SD)		

APACHE II, acute physiology and chronic health evaluation II, CABG, coronary artery bypass grafting; CHF, congestive heart failure; MI, myocardial infarction; PCI, percutaneous coronary intervention

[a]The Clinical Frailty Scale [50] ranges from 1 to 7, with scores of 5-7 denoting frailty.
Scores on the APACHE II [49] range from 0 to 71, with higher scores indicating more severe disease and a higher risk of death.
[b]Scores on the SOFA [23] range from 0 to 24, with higher scores indicating more severe disease and a higher risk of death.
[c]Coronary artery disease included angina and previous MI, PCI, or CABG.
[d]The baseline creatine was determined from the outpatient creatinine within the last 12 months and closest to admission (n=) or, if not available, then the lowest inpatient creatinine before ICU admission (n=).



Online supplementary file S1 OVATION-65 team members

Executive Committee
Neill KJ Adhikari (PI, co-chair), François Lamontagne (PI, co-chair), M. Elizabeth Wilcox, (PI) Marie-Claude Battista (co-I), Marie-Hélène Masse (PL)

Data Safety Monitoring Committee
Andreas Laupacis (chair), Lauren Griffith, Scott Halpern

Coordinating Centre Personnel
Marie-Claude Battista, Marie-Hélène Masse, Louise Robert-Petit, Marie-Ève Thibault

Contributors to ancillary studies
François-Michel Boisvert, Lee Hwa Tai, Jean-Luc Parent, Xavier Roucou

Participating Clinical Site Personnel
CIUSSS de l'Estrie – Centre Hospitalier Universitaire de Sherbrooke
François Lamontagne (PI), Frédérick D'Aragon (Co-I), Marc-André Leclair (Co-I), Michaël Mayette (Co-I), Yannick Poulin (Co-I), Hector Quiroz-Martinez (Co-I), Charles St-Arnaud (Co-I), Élaine Carbonneau (RC), Line Côté (RC), Marilène Ladouceur (RC), Joannie Marchand (RA), Marie-Hélène Masse (RC), Noémie Turcotte (RA)

Centre Hospitalier de l'Université de Montréal
Michaël Chassé (PI), Martine Lebrasseur (RC), Fatna Benettaib (RC), Dounia Boumahni (RC), Marie-Ève Cantin (RA), Ali Ghamraoui (RC), Maya Salame (RC)

The Ottawa Hospital (General Campus and Civic Campus)
Andrew Seely (PI), Irene Watpool (RC), Rebecca Porteous (RC), Sydney Miezitis (RA)

Sunnybrook Health Sciences Centre
Neill KJ Adhikari (PI), Andre Carlos Amaral (Co-I), Brian Cuthbertson (Co-I), Robert Fowler (Co-I), Damon Scales (Co-I), Nicole Marinoff (RC), Navjot Kaur (RC), Wael Mohammed (RC)

Centre Hospitalier Universitaire de Québec-Université Laval
Francois Lauzier (PI), Alexis Turgeon (Co-I), Charles Francoeur (Co-I), Guillaume Leblanc (Co-I), David Bellemare (RC), Olivier Costerousse (RC), Stéphanie Grenier (RA), Gabrielle Guilbault (RA), Marjorie Daigle (RA), Ève Cloutier (RA), Isabelle St-Hilaire (RA).

Mount Sinai Hospital
Sangeeta Mehta (PI), Laveena Munshi (Co-I), Sumesh Shah (RC)

Toronto Western Hospital
Elizabeth Wilcox (PI), Jeffrey Singh (Co-I), Karolina Walczak (RC)

Juravinski Hospital (activation in progress and no patients enrolled at the time of manuscript submission)
Bram Rochwerg (PI), Tina Millen (RC)

Abbreviations:
Co-I – co-investigator; PI – principal investigator; PL – project leader; RA – research assistant; RC – research coordinator

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3, 18
	2b	All items from the World Health Organization Trial Registration Data Set	3, 18
Protocol version	3	Date and version identifier	22
Funding	4	Sources and types of financial, material, and other support	23
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1, 23
	5b	Name and contact information for the trial sponsor	23
	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	23
	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)	8,19

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	2, 5,6,7
	6b	Explanation for choice of comparators	10,11
Objectives	7	Specific objectives or hypotheses	2, 7
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	7,8
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	8
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	8,9
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9,10,11
	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)	10
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	14,15
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	11, 28
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	11,12,13
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)	16, 30

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	16
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	16,19
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	9
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	9
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	9, 10
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	2, 4, 14
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	2, 4, 14
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	12, 13, 14, 15
	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	15

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	19, 21
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	16, 17, 18
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	18
	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)	17, 18
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	20
	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	20
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	13
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	19
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	20, 21
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)	20, 21

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	21
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	21
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	21
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	21
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	21
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	21
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	2, 3, 20, 21
	31b	Authorship eligibility guidelines and any intended use of professional writers	23
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	21
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	S4
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	14

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated.

Online supplementary file S3 OVATION-65 ancillary studies

Study title	Investigators	Primary objective	Secondary objective	Funding
Measuring baseline ascorbic acid levels in the OVATION-65 trial	MC Battista NK Adhikari F Lamontagne	Measure the association between baseline plasma ascorbic acid and markers of organ injury	Measure the association between baseline ascorbic acid and 1) hourly MAP to vasopressor dose ratio; 2) biomarkers of inflammation (IL-1ß, TNF-α, C-reactive protein) 3) biomarkers of endothelial injury (thrombomodulin, angiopoietin-2)	Lotte and John Hecht Memorial Foundation
Urinary biomarkers of renal injury in the OVATION-65 trial: a Nested analysis of the urinary proteome	FM Boisvert MC Battista NK Adhikari F Lamontagne	Identify peptides and proteins expressed in the urine of OVATION-65 participants using a discovery proteomic approach	Measure the association between protein clusters and renal function	Université de Sherbrooke/ Merck Sharp and Dohme
Effects of catecholamine therapy on the immune system: unsuspected consequences of routine medical interventions and opportunities for individualized care	FM Boisvert LH Tai JL Parent X Roucou MC Battista NK Adhikari F Lamontagne	Evaluate the effects of exogenous catecholamines on plasma Th1/Th2 profiles (plasma cytokines and flow cytometry)	Evaluate the effects of exogenous catecholamines on 1) Expression and activation of peripheral blood mononuclear cell adrenergic receptors; 2) Distinct proteomic signatures	Université de Sherbrooke/ Merck Sharp and Dohme

CENTRE DE RECHERCHE | CHUS

RESEARCH INFORMATION AND CONSENT FORM

Study Title: The OVATION-65- Impact of permissive hypotension on end-organ damage in the elderly

Study Number and Date: MP-31-2018-1789

Funding Agencies: Centre de recherche du CHUS
Université de Sherbrooke

Principal Investigator: Dr. François Lamontagne, Intensivist

Co-Investigators: Dr. Frédérick D'Aragon, Intensivist,
Dr. Charles St-Arnaud, Intensivist
Dr. Michaël Mayette, Intensivist,

FOR INFORMATION

Monday through Friday, from 8 am and 4 pm, you can reach:

Dr. François Lamontagne, Intensivist	Tel.: 819-346-1110, ext. 74974
Élaine Carbonneau, Research Coordinator	Tel.: 819-346-1110, ext. 16208
Marie-Hélène Masse, Research Coordinator	Tel.: 819-346-1110, ext. 14173
Marilène Ladouceur, Research Assistant	Tel.: 819-346-1110, ext. 14169

or dial "0" and ask the operator to call them on pager # 7125.

We are seeking your participation (or that of your family member) in a research study because you (or your family member) have been admitted to an intensive care unit and will need medication administered into your veins to raise your blood pressure. However, before you agree to participate, please take the time to read, understand and carefully consider the following information. If you agree to take part in this research study, you will be asked to sign the consent form at the end of this document and we will give you a signed copy for your own records.

This Information and Consent Form explains the goals, procedures, risks and inconveniences, and benefits of the study as well as providing the names of the people to reach if needed. This document may contain information or words that you do not understand. Please ask the study investigator or members of the study staff to answer your questions and explain any word or information you do not understand.

NATURE AND GOALS OF THE RESEARCH STUDY

This study aims to determine whether the target blood pressure used to adjust the dosage of the blood-pressure-increasing medication changes the evolution of participants treated in the Intensive Care Unit (ICU). Vasopressors are drugs that are given intravenously to increase the blood pressure of patients with diseases causing dangerous pressure drops that can be harmful to the organs of the body. When a doctor

prescribes a vasopressor, he asks that the dose be adjusted to achieve a specific blood pressure. However, although vasopressors have been used for nearly a century, we still do not know whether it is preferable to try and normalize the blood pressure of our patients (which requires high doses of vasopressors) or tolerate a lower pressure (which is not normal, but requires smaller doses of drugs). The current practice is quite variable, some doctors preferring to increase the blood pressure, others preferring to restrict doses of these powerful drugs and tolerate a lower blood pressure (hypotension).

The goal of this study is to determine if tolerating a lower mean blood pressure (permissive hypotension) vs. usual blood pressure targets in hypotensive patients over 65 years of age can reduce the risk of harm associated with more aggressive vasopressor therapy. The specific objectives are to evaluate: the effect of permissive hypotension on your health status after 6 months , the effects on markers of organ injury, including the heart, brain, kidneys, liver, intestine, and skeletal muscles as well as the effects on your immune system. We wish to recruit around 100 participants at the *CIUSSS de l'Estrie - CHUS* to be among the 200 participants needed for this study that will be carried out in several hospitals.

Your physician has determined that you are eligible to participate in our study and you have been selected as a participant because you are being (or will soon be) treated in the ICU and because you were prescribed vasopressor drugs.

RESEARCH STUDY PROCEDURES

If you agree to participate in this study, you (or your family member) will be assigned to one of the following two groups: The first group includes participants who are being given vasopressors for an average blood pressure of 60-65 mmHg (limiting the amount of vasopressors given); the second group includes participants who are receiving vasopressors following usual care. Your assignment to one of these two groups was determined randomly by a computer that will not retain information about you. The odds of being assigned to either group were 50% (1 in 2 chances or half-and-half). The treating team will be aware of which group you have been assigned to.

As a study participant, you will receive vasopressors to maintain your average blood pressure at the level of your assigned group. These pressure targets will remain the same throughout your treatment with this type of medication (vasopressors) until you are discharged from hospital or up to 28 days from the beginning of your participation, whichever event comes first. Also, on days 1, 3 and 7 of participation (or when you are discharged from the intensive care unit), your nurse will collect 30 ml of blood (6 teaspoons) as well as urine samples while taking the blood samples required for your medical follow-up. We will collect a little more volume than what is needed in order to compensate for unexpected losses that may arise during laboratory testing. These samples will enable us to measure certain biomarkers in your blood and in your urine that help assess the function of your heart, kidneys, muscles, brain and liver as well as your immune system. These biomarkers are already known to be useful in clinical studies and are not genetic biomarkers. During your hospital stay, we will monitor your progress to see if your organs are functioning well, if you develop other health problems and how long you will stay in the ICU and hospital. Your medical chart will be reviewed, by the investigator and the research team as long as you remain in the study. Blood test results and procedures present in your medical record will be collected for the study.

After you are discharged from the hospital, you will be contacted by phone 6 monthss after the start of your participation in the study. Your contact information will be provided to the coordinating research team.

FUTURE ANALYSES

Once the biomarker analyses have been performed as part of this study, it is possible that part of your samples may be unused. We wish to use the remainder of your samples (blood and urine) in order to answer additional questions concerning the impact of vasopressors on blood pressure targets that may arise in future. For example, we could measure a new, as yet undefined, biomarker. Only the remainder of your samples will be used and no other additional sample will be collected. At the end of the study, if some of the samples remain unused, they will be destroyed unless you agree to biobanking. A separate consent form will be presented for biobanking.

RISKS ASSOCIATED WITH PARTICIPATION IN THIS RESEARCH STUDY

Vasopressors used in this study and that you have received or may still be receiving, are approved in Canada and commonly used in the ICUs of all hospitals. The blood pressure targets we aim for in this study are also part of current medical practices.

Since your health condition required treatment with vasopressors, and continues to require treatment at this time, to our knowledge, you are exposed to the same risks, whether or not you participate in this study.

INCONVENIENCES ASSOCIATED WITH PARTICIPATION IN THE STUDY

Other than the risks described above, you (or your family member) shouldn't experience any other inconveniences.

BENEFITS ASSOCIATED WITH YOUR PARTICIPATION IN THE RESEARCH STUDY

You (or your family member) will not personally benefit from your participation in this research study. However, the findings from this study may help increase our knowledge of pressure targets, vasopressors and biomarkers. The information obtained through this study could be useful to other patients in the future.

ALTERNATIVES TO YOUR PARTICIPATION IN THIS RESEARCH STUDY

You (or to your family member) do not have to participate in this research study to be treated for your disease.

VOLUNTARY PARTICIPATION AND THE RIGHT TO WITHDRAW

Your participation in this research study is voluntary. Therefore, you may refuse to participate. You can also withdraw from the study at any time, without providing a reason, by informing the study investigator or one of his assistants.

Your decision not to participate in the study or to withdraw from it, will have no impact on the quality of care and services you (or your family member) are entitled to or on your relationship with the investigator and other stakeholders.

The study investigator, the funding agency or the Research Ethics Board may put an end your participation in the study without your consent. This may happen if new scientific developments show that participation is no longer in your interest; if the study investigator believes it is in your best interest; or if there are administrative reasons to terminate the study.

If you withdraw or are withdrawn from the study, the information and material already collected during the course of the study will be stored, analyzed or used to ensure the integrity of the study.

Any new study findings that could influence your decision to remain in the research study will be shared with you as soon as possible.

CONFIDENTIALITY

While you take part in this research study, the study investigator and study staff will collect and record information about you in a study file. Only the information needed to meet the scientific goals of the study will be collected.

This information could include data taken from your medical record concerning your past and present medical history, your lifestyle and the test results, exams and procedures you will undergo during the study.

All the information collected during the study will remain strictly confidential to the extent provided by law. To protect your identity and privacy, you will be identified by an alphanumeric code. The key linking your identity and your research file will be kept in a safe place by the study investigator.

To ensure your safety, a mention of your participation in this research project will be included in your medical file. Therefore, any person or company to whom you will give access to your medical file will have access to this information.

Your full name and your phone number will be transmitted to a qualified person of the coordinating center of the study in order to allow this person to contact you in 6 months by phone. This personal information will allow a direct identification. This information will be kept in security and confidentiality will be preserved by the qualified person and destroyed at the end of the follow-up.

Study results will be stored by the study investigator for 25 years.

Study results may be published in medical journals or discussed at scientific meetings, but it will be impossible to identify participants.

For monitoring and control purposes, your study file and medical records may be examined by a representative of the Research Ethics Board or of the institution or by a person mandated by a regulatory authority. All of these individuals and organizations adhere to confidentiality policies.

You have the right to consult your study file at any time in order to verify the information gathered and to have it corrected, if necessary, for as long as this information is available to the study investigator or the institution. However, some of this information may be made available to you only once the study has ended, in order to protect the scientific integrity of the study.

COMPENSATION

You (or your family member) will not receive any compensation for expenses and inconveniences incurred due to your participation in this research study.

SHOULD YOU SUFFER ANY HARM

Should you suffer any harm due to your participation in this research study, you will be provided with all the necessary care and services, at no cost to you.

By agreeing to take part in this study, you are not waiving any of your legal rights nor discharging the study investigators, the sponsor or the institution where this research study is being conducted of their civil liability and professional responsibilities.

FUNDING OF THE RESEARCH STUDY

The study investigator has received funding from the grant agency to carry out this study.

CONTACT PERSONS

If you have any questions regarding your participation in this research study, please refer to the box on page 1.

If you have any questions regarding your rights as a participant in this study, if you have any comments or you wish to file a complaint, you may contact the *Bureau des plaintes et de la qualité des services of the CIUSSS de l'Estrie-CHUS* at the following number: 1-866-917-7903.

MONITORING OF ETHICAL ASPECTS OF THE STUDY

The *Comité d'éthique de la recherche du CIUSSS de l'Estrie - CHUS* has approved this study and is responsible for monitoring it at all participating institutions throughout Québec's health and social service network.

If you wish to reach a member of the Research Ethics Board (REB), please contact the *Service de soutien à l'éthique de la recherche du CIUSSS de l'Estrie - CHUS* at the following number: 819-346-1110, ext. 12856.

CONSENT

I declare that I have read this Information and Consent Form. I declare that the research study has been explained to me, that my questions were answered to my satisfaction and that I was given sufficient time for consideration and to make a decision. Upon reflection, I agree to participate in this research study under the conditions stated therein.

I agree that the remainder of the samples may be used for additional analyses that may arise during the study (future analyses). ☐ YES ☐ NO

Name of participant *(please print)*	Signature of participant	Date

I have explained the research study and this Information and Consent Form and I have answered all of his/her questions.

Name of person obtaining consent *(please print)*	Signature of person obtaining consent	Date

CONSENT FROM LEGAL REPRESENTATIVE (SUDDEN INCAPACITY)

Because Mr./Mrs. _____ has suddenly become incapable of giving consent for the hereinafter mentioned reason, the Civil Code of Québec allows you to give consent for him/her as his/her _____ (indicate your relationship with the participant).

As soon as Mr./Mrs. _____has sufficiently recovered, he/she will be asked to sign his/her own consent form to indicate whether he/she wants to continue taking part in this study.

REASON FOR THE PARTICIPANT NOT BEING ABLE TO GIVE CONSENT

By signing this page, I confirm that I have read the information in this Consent Form. I acknowledge that the study has been explained to me, that all of my questions have been answered and that I was given enough time to make a decision. I voluntarily give my consent so that Mr./Mrs. _____ can participate in this study.

I also agree that the remainder of the samples may be used for additional analyses that may arise during the study (future analyses). ☐ YES ☐ NO

Name of legal representative *(please print)* | Signature of legal representative | Date

I have explained the research study and this Consent Form to the participant's legal representative. I have answered all of his/her questions.

Name of person obtaining consent *(please print)* | Signature of person obtaining consent | Date

CONSENT FROM THE LEGAL REPRESENTATIVE OR CAREGIVER SUPPORTING THE PARTICIPATION OF THE PERMANENTLY INCAPABLE PARTICIPANT (PERMANENT INCAPACITY)

I declare that I have read this Information and Consent Form. I declare that the research study has been explained to me, that my questions were answered to my satisfaction and that I was given sufficient time for consideration and to make a decision.

I agree that _____ can participate in this research study under the conditions stated therein. I will receive a signed and dated copy of this Information and Consent Form.

I also agree that the remainder of the samples may be used for additional analyses that may arise during the study (future analyses). ☐ YES ☐ NO

If the incapacitated participant is represented:

Name and signature of the legal representative (representative, curator or mandatary)	Date

If the incapacitated participant is not represented by a legal representative:

Name and signature of the spouse, failing which, name of next-of-kin or name of a significant person	Date

I have explained the research study and this Consent Form to the participant's legal representative. I have answered all his/her questions.

Name of person obtaining consent *(please print)*	Signature of person obtaining consent	Date

PHONE CONSENT
(For the participant who is suddenly or permanently incapacitated)

Because Mr./Mrs. _____ is incapable of giving consent for the hereinafter mentioned reason,

REASON FOR THE PARTICIPANT NOT BEING ABLE TO GIVE CONSENT

_____

I have explained the research study and this Consent Form to the participant's legal representative. I have answered all his/her questions.

The representative, Mr./Mrs._____
Name of the legal representative (representative, curator or mandatary)
Name of the spouse or next-of-kin or
Name of the significant person

has given consent by phone on _____ at _____
Date Hour

The representative also agrees that the remainder of the samples may be used for additional analyses that may arise during the study (future analyses).☐ YES ☐ NO

Name of person obtaining consent *(please print)*	Signature of person obtaining consent	Date

APPENDIX 1: GENETIC PHASE

(PLEASE NOTE: This part of the consent should not appear in the patient's medical file)

We invite you to participate in the genetic component of this study. This phase is optional. You may refuse this proposal and still participate in the main phase of the project.

Please note that all sections of the main consent form apply to this appendix as well.

Genetics focuses on cells in the human body that contain a type of molecule called deoxyribonucleic acid commonly referred to as "DNA". Your DNA is contained in the inherited genes that control your entire body's growth, development and functions. For instance, some genes determine the colour of your eyes or hair. DNA presents a wide array of differences or variations from one person to another. These variations may affect the risk of contracting a disease (or not) or the way individuals respond differently to a drug. The OVATION-65 project also includes a genetic sub-study focusing on the analysis of certain genes (genetics) and certain phenomena present in your environment that modify your DNA (epigenetics). These tests can be performed on the cells in your blood.

The markers of the heart, brain, kidneys, liver, intestine and skeletal muscles that we are interested in measuring as part of the OVATION-65 study as well as the molecules (receptors) that enable the vasopressors to act (beta-adrenergic receptors) on the cells of different organs are determined in part by genes. Thus, in order to better understand how to reduce organ damage related to medication (vasopressors) received during intensive care unit admissions, we propose to study the DNA as well as the variations around this DNA (called epigenetic variations) of patients included in OVATION-65. Our goal is to demonstrate that modifications in the DNA of studied markers are associated with the levels of these same blood or urine markers, which inform us on the function/involvement of the targeted organ.

If you agree to participate, we will use a portion of the samples already collected as part of the main project and an additional sample (approximately 2 teaspoons) to conduct our genetic analyses.

FUTURE ANALYSIS

Once the genetic analyses have been conducted, it is possible that a portion of the samples will remain unused. We would like to use the remainder of your samples to answer additional research questions that might arise during the course of the study. Only the remainder of your samples will be used and no other additional samples will be taken. At the end of the study, if some samples remain unused, they will be destroyed unless you agree to biobanking. Another consent form will be presented for biobanking.

SOCIO-ECONOMIC RISKS ASSOCIATED WITH PARTICIPATION IN THIS PHASE OF THE STUDY

One of the risks associated with genetic analyses is related to the disclosure of results or of your participation to third parties. Protection against genetic discrimination is not currently well defined in Canadian and Québec legislation. Thus, we cannot fully guarantee that your participation in a genetics research project will not have an impact on your chances of getting certain jobs, or of getting insurance coverage (life insurance, disability or health) for you or for members of your family.

However, as researchers, we are committed not to disclose information related to genetic results to any third party. Your results will not be made available to third parties such as an employer, a government agency, an insurer or an educational institution. This also applies to your spouse, other members of your family and your doctor. Furthermore, rest assured that no data related to any genetic results will be included in your hospital record.

VOLUNTARY PARTICIPATION AND THE RIGHT TO WITHDRAW FROM THE GENETIC PHASE OF THE PROJECT

Your participation in the genetic phase of the project is voluntary. Therefore, you may refuse to participate. You may also withdraw your consent from the genetic phase of this research project at any time. Just call the ICU research team at 346-1110 ext. 14171.

Your decision to refuse to participate in this sub-study of the project will have no impact on the quality of the care that will be provided to you or on your relationship with the healthcare team.

If you decide to terminate your participation in the genetic sub-study after providing a sample, you must notify the research team that will then destroy your sample. If your sample has already been tested and the results are already included in an analysis or publication, it will not be possible to remove this information. However, the rest of your sample will be destroyed and no further analysis will be done on your sample.

CONFIDENTIALITY

Identification:

In order to protect your identity, your samples will be identified by a unique code. Your name and your file number will not appear on the samples. The study investigator will keep a list of patients with the code numbers to identify them. This list is kept under lock and key in the research nurse's office and will not be disclosed under any circumstances.

Storage and destruction of samples:

Your samples will be kept in the principal investigator's freezers until the end of the study, unless you agree to biobanking. Another consent form will be presented to this end. The principal investigator is responsible for the destruction of samples.

COMMUNICATION OF RESULTS

Your participation and the results of the genetic analysis conducted on your samples will not be disclosed to you or to your doctor.

MARKETING POSSIBILITIES / WAIVER

Your participation in the genetic phase of this project could lead to the creation of commercial or other products that could potentially be protected by patents or other intellectual property rights. However, you will not receive any financial benefits.

CONSENT (GENETIC SUB-STUDY)

I declare that I have read this Appendix (genetic sub-study). I acknowledge that this sub-study of the project was explained to me, that all my questions were answered and that I was given the necessary time to make a decision.

I freely and willingly consent to participate in the **genetic sub-study** of this project:

I also accept that the remainder of my samples may be used for **additional genetic analyses** that may arise during the course of this study (future analysis):

☐ YES ☐ NO

Name of participant name (please print)	Signature of participant	Date

I have explained the genetic sub-study and this Consent Form to the participant, and I answered all his/her questions.

Name of person obtaining consent *(please print)*	Signature of person obtaining consent	Date

CONSENT (GENETIC SUB-STUDY)
FROM THE LEGAL REPRESENTATIVE (SUDDEN INCAPACITY)

Because Mr./Mrs. _____ has suddenly become incapable of giving consent for the hereinafter mentioned reason, the Civil Code of Québec allows you to give consent for him/her as his/her _____ (indicate your relationship with the participant) to participate in the **genetic sub-study** of the project.

As soon as Mr./Mrs. _____has sufficiently recovered, he/she will be asked to sign his/her own consent form to indicate whether he/she wants to continue taking part in this sub-study of the study.

REASON FOR THE PARTICIPANT NOT BEING ABLE TO GIVE CONSENT

By signing this page, I confirm that I have read the information in this Consent Form. I acknowledge that the **genetic sub-study** of the project has been explained to me, that all of my questions have been answered and that I was given enough time to make a decision.

I voluntarily give my consent so that Mr./Mrs. _____ can participate in the genetic sub study.

I also agree that the remainder of the samples may be used for **additional genetic analyses** that may arise during the study (future analyses). ☐ YES ☐ NO

Name of legal representative *(please print)*	Signature of legal representative	Date

I have explained all relevant aspects of the genetic sub-study of this project to the participant's legal representative and I have answered all his/her questions.

Name of person obtaining consent *(please print)*	Signature of person obtaining consent	Date

CONSENT (GENETIC SUB-STUDY)
FROM LEGAL REPRESENTATIVE OR CAREGIVER (PERMANENT INCAPACITY)

I confirm that I have read the information in this Consent Form. I acknowledge that the genetic sub-study of the project has been explained to me, that all of my questions have been answered and that I was given enough time to make a decision.

I agree that _____ can participate in this **genetic sub study** under the conditions stated therein. I will receive a signed and dated copy of this Information and Consent Form.

I also agree that the remainder of the samples may be used for **additional genetic analyses** that may arise during the study (future analyses). ☐ YES ☐ NO

If the participant is represented:

Name and signature of the legal representative (representative, curator or mandatary)	Date

If the incapacitated participant is not represented by a legal representative:

Name and signature of the spouse, failing which, name of the next-of-kin or name of the significant person	Date

I have explained the research study and this Consent Form to the participant's legal representative. I have answered all his/her questions.

Name of person obtaining consent *(please print)*	Signature of person obtaining consent	Date

PHONE CONSENT (GENETIC SUB-STUDY)
(For the participant who is suddenly or permanently incapacitated)

Because Mr./Mrs. _____ is incapable of giving consent for the hereinafter mentioned reason.

REASON FOR THE PARTICIPANT NOT BEING ABLE TO GIVE CONSENT

_____

I have explained the genetic sub study and this Consent Form to the legal representative using the phone script and I have answered all his/her questions.

The representative, Mr./Mrs._____
Name of the legal representative (representative, curator or mandatary)
Name of the spouse or of the next-of-kin or
Name of the significant person

has given consent by phone on_____ at_____
Date Time

The representative also agrees that the remainder of the samples may be used for **additional genetic analyses** that might arise during the study (future analyses). ☐ **YES** ☐ **NO**

Name of person obtaining consent *(please print)*	Signature of person obtaining consent	Date and time

BMJ Open

Optimal VAsopressor TitraTION in patients 65 years and older (OVATION-65) – protocol and statistical analysis plan for a randomized clinical trial

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Optimal VAsopressor TitraTION in patients 65 years and older (OVATION-65) – protocol and statistical analysis plan for a randomized clinical trial

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Abstract

Introduction: Vasodilatory hypotension is common among intensive care unit (ICU) patients; vasopressors are considered standard of care. However, optimal mean arterial pressure [MAP] targets for vasopressor titration are unknown. The objective of OVATION-65 (**O**ptimal **VA**sopressor Titra**TION-65**) is to ascertain the effect of permissive hypotension (vasopressor titration to achieve MAP 60-65 mmHg) vs. usual care on biomarkers of organ injury in hypotensive patients ≥65 years old.

Methods and analysis: OVATION-65 is an allocation-concealed randomized trial in 7 Canadian hospitals. Eligible patients are ≥65 years old, in an ICU with vasodilatory hypotension, receiving vasopressors for ≤12 hours to maintain MAP ≥65 mmHg during or after adequate fluid resuscitation, and expected to receive vasopressors for ≥6 additional hours. Patients are excluded for any of the following: active treatment for spinal cord or acute brain injury; vasopressors given solely for bleeding, ventricular failure or post-cardiopulmonary bypass vasoplegia; withdrawal of life-sustaining treatments expected within 48 hours; death perceived as imminent; previous enrolment in OVATION-65; organ transplant within the last year; receiving extracorporeal life support; or lack of physician equipoise. Patients are randomized to permissive hypotension vs. usual care for up to 28 days. The primary outcome is high-sensitivity troponin T, a biomarker of cardiac injury, on day 3. Secondary outcomes include biomarkers of injury to other organs (brain, liver, intestine, skeletal muscle); lactate (a biomarker of global tissue dysoxia); resource utilization; adverse events; mortality (90 days and 6 months); and cognitive function (6 months). Assessors of biomarkers, mortality, and cognitive function are blinded to allocation.

Ethics and dissemination: This protocol has been approved at all sites. Consent is obtained from the eligible patient, the substitute decision-maker if the patient is incapable, or in a

deferred fashion where permitted. End-of-grant dissemination plans include presentations, publications, and social media platforms and discussion forums.

Trial registration: clinicaltrials.gov, NCT03431181

Keywords

vasopressors; shock; critical care; biomarkers; randomized controlled trial

Article summary

Strengths and limitations of this study

- OVATION-65 is an allocation-concealed randomized clinical trial of permissive hypotension vs. usual care in patients 65 years and older with hypotension from a vasodilatory cause, a population that may be more vulnerable to adverse effects of vasopressors
- Vasopressor titration is understudied in critically ill patients, compared to other interventions such as mechanical ventilation
- The primary and many secondary outcomes, selected with input from a patient representative, focus on biomarkers of organ injury; although these are not patient-centred outcomes, results will complement clinical outcome data from larger trials
- Because of the nature of the intervention, clinician blinding is not feasible; however, outcome assessors are blinded
- The modest sample size implies that the trial is underpowered for clinical outcomes

Introduction

Shock, a clinical syndrome of which hypotension is a cardinal feature, is common and associated with high mortality. Vasopressors are used to treat hypotension that is potentially life-threatening because they raise blood pressure by inducing vasoconstriction.[1] However, these medications are associated with adverse effects,[2-4] some of which are direct consequences of vasoconstriction-induced reduction in blood flow to vital organs. Therefore, titrating vasopressors implies balancing the risks of end-organ failure caused by hypotension and potential vasopressor-induced harm, including myocardial injury and arrhythmia, excessive vasoconstriction, hyperglycemia, and immunosuppression.[2-5] Permissive hypotension is a strategy of targeting a lower blood pressure when prescribing vasopressors, compared to usual care. Benefits have been associated with other 'permissive' therapies in critically ill patients, including hypoxia,[6] underfeeding,[7] hypercapnia,[8] red blood cell transfusion,[9] and hypotension in thoracic penetrating trauma.[10]

Clinicians in the intensive care unit (ICU) use mean arterial pressure (MAP) targets to determine the intensity of vasopressor therapy. Current international practice guidelines recommend titrating vasopressors to a MAP of 65 mmHg,[11] but because the target lacks an upper boundary, clinicians commonly put more emphasis on preventing hypotension than on minimizing vasopressor exposure. This under-appreciation of the risks associated with vasopressor overuse was apparent in a multicentre observational study[12] that reported an average MAP of 75 (standard deviation [SD] 6) mmHg in patients receiving vasopressors, approximately 10 mmHg above the recommended MAP and self-reported practice.[13] Given the relative lack of studies about vasopressor dosing, in contrast to other common ICU treatments such as mechanical ventilation, editorialists have advocated for better characterization of the lowest acceptable blood pressure target to avoid vasopressor-induced harm.[3]

Existing evidence

Observational studies have described independent associations between dose and duration of vasopressor therapy and poor outcomes, such as adverse cardiac events and increased mortality.[14 15] However, these studies are limited by indication bias, as patients who are sicker have a greater risk of unfavourable outcomes and are therefore more likely to be exposed to higher doses of vasopressor therapy.

Two randomized clinical trials (RCTs; combined n=894) published prior to the initiation of this study compared blood pressure targets in patients receiving vasopresors.[16 17] The SEPSISPAM trial compared a MAP target of 65-70 mmHg vs. 80-85 mmHg for 5 days in 776 patients with septic shock from 29 French ICUs. This study reported no difference in 28-day mortality (lower MAP 34.0% vs. higher MAP 36.6%, p=0.57), but a greater risk of atrial fibrillation in the higher MAP arm (6.7% versus 2.8%, p=0.02).[16] However, actual MAP values were 74-76 mmHg in the lower MAP arm, precluding conclusions regarding permissive hypotension. The OVATION pilot feasibility trial randomly assigned 118 patients from 1 US and 10 Canadian ICUs to a lower (60-65 mmHg) or higher (75-80 mmHg) MAP target [17]. This trial was not powered to detect differences in mortality. A subsequent individual patient data meta-analysis (IPDMA)[18] included data from both RCTs and found that higher MAP targets (75-85 mmHg) may be associated with an increased risk of 28-day mortality in older patients (p=0.1 for interaction between age and MAP).

Based on these RCTs, guidelines state that no evidence supports the use of vasopressors to achieve MAP values >65 mmHg for patients receiving vasopressors.[19] Subsequently, the 65 trial randomized 2600 patients ≥65 years old in the United Kingdom to permissive hypotension vs. usual care using a similar protocol as OVATION-65.[20 21] Patients in the permissive hypotension arm had a lower exposure to vasopressors and a lower 90-day

mortality (41.0% vs. 43.8%, p=0.15), but the difference was not statistically significant. However, an analysis adjusting for baseline covariates found lower mortality with permissive hypotension (OR 0.82, 95%CI 0.68-0.98).[22] The 65 trial collected no biological samples, precluding exploration of mechanisms underlying the effect of vasopressor dosing in that trial.

Objective and Specific Aims

The main objective of OVATION-65 is to determine whether permissive hypotension (MAP 60-65 mmHg) in patients ≥65 years old with a vasodilatory cause of hypotension and receiving vasopressors, compared to usual MAP targets, reduces organ injury as measured by biomarkers. Specific aims are to ascertain the effect of permissive hypotension vs. usual care on: 1) biomarkers of organ injury (heart [primary outcome], brain, liver, intestine, skeletal muscle); 2) biomarker of global tissue dysoxia (lactate); 3) organ function (assessed by Sequential Organ Failure Assessment [SOFA] score[23]); 4) resource utilization, 5) prespecified adverse events, 6) mortality at 90 days and 6 months; 7) cognitive impairment in survivors at 6 months (Table 1).

The primary outcome and several secondary outcomes are focused on biomarkers because of well-documented limitations of mortality in critical care trials[24] and the challenges of developing valid surrogate endpoints.[25] OVATION-65 was designed to be complementary to the 65 trial.[22] A larger version of OVATION-65 (n=800) was abandoned in 2018 after funding applications to the Canadian Institutes for Health Research and the Canadian Frailty Network were rejected. As discussed in the *Statistical Analysis* section, the Data and Safety Monitoring Committee (DSMC) recommended termination of enrollment in the current smaller version of OVATION-65 on 21 February 2020; patient follow-up is ongoing.

Methods and analysis

OVATION-65 is a multicentre, parallel-group, allocation-concealed, superiority RCT. We developed OVATION-65 on behalf of the Canadian Critical Care Trials Group (CCCTG), a 350-member organization of clinicians and researchers, incorporating feedback received since January 2012 at each of its thrice yearly scientific meetings. Table 2 shows a timeline of trial activities. The SPIRIT checklist is available in online supplementary file S1.

Study setting and management

OVATION-65 is conducted in adult ICUs in 7 sites in Canada. OVATION-65 team members, including research personnel at clinical sites active at the time of submission of this manuscript, are listed in online supplementary file S2. The procedures in place for OVATION-65 were piloted during the OVATION pilot RCT.[17] The Unité de Recherche Clinique et Épidémiologique (URCE) is coordinating this trial and is responsible for construction and maintenance of the randomization system and the REDCap[26 27] electronic data capture (EDC) system. The URCE also oversees the activities of the OVATION-65 core laboratory (i.e. storage and analysis of blood and urine samples).

Inclusion criteria

Patients are included if they meet all the following criteria: 1) age ≥65 years; 2) diagnosis of vasodilatory hypotension as assessed by the treating team; 3) vasopressors started ≤12 hours ago (after or during adequate fluid resuscitation, as assessed by treating physician); and 4) vasopressors expected for ≥6 additional hours, as assessed by the treating team. Aligned with the 65 trial,[22] we do not specify a minimum volume of fluid or specific

examinations for volume status prior to the clinical (pre-randomization) decision to commence a vasopressor.

Exclusion criteria

Patients are excluded if they meet any of the following criteria: 1) actively treated for spinal cord injury or acute brain injury; 2) vasopressors given solely for bleeding, acute ventricular failure or post-cardiopulmonary bypass vasoplegia; 3) lacking commitment to life-sustaining therapies (expected withdrawal of life-sustaining treatments within the next 48 hours); 4) death perceived as imminent; 5) previously enrolled in OVATION-65; 6) organ transplant within the last year; 7) receiving extracorporeal life support at baseline; and 8) lack of treating physician equipoise regarding the overall effects of permissive hypotension vs. usual care on patient important outcomes.

Rationale for eligibility criteria

The inclusion criteria strive to identify patients most likely to benefit from permissive hypotension, namely elderly patients not already exposed to a prolonged duration of higher MAP but expected to require an additional period of vasopressor therapy. The exclusion criteria are designed to exclude patients for whom clinicians commonly apply different MAP targets (criterion 1) or whose prognosis may be dominated by factors other than the MAP target (criteria 2, 3, 4, 6, 7).

Study intervention

Treatment allocation

Using a web randomization service available 24 hours/7 days per week, patients are randomized immediately after confirming eligibility following a 1:1 sequence to permissive

hypotension or usual care. We use permuted blocks of variable and undisclosed size (4, 6 and 8) and stratify randomization by site. Stratifying by site ensures equal distribution of patients between arms at each site and decreases the probability that site-specific practices confound treatment effects.

Permissive hypotension arm

The intervention minimizes dose and duration of vasopressors. Treating teams adjust vasopressors to a target MAP range of 60 to 65 mmHg. A MAP of 60 mmHg was selected as lowest tolerable limit because it corresponds to the threshold at which Canadian intensivists usually initiate vasopressors.[13] Accordingly, it is not uncommon for patients to have MAP as low as 60 mmHg before vasopressors are instituted under usual care. The same MAP range was used in the OVATION pilot RCT.[17]

The duration of the trial intervention is determined, as it was in the pilot RCT, by the duration of the hypotensive episode, up to a maximum of 28 days. For trial purposes, the episode of hypotension ends when vasopressors are discontinued for 24 consecutive hours. As soon as patients are able to maintain the target MAP without vasopressors, the infusions are stopped. If MAP drops below 60 mmHg after this 24-hour period, and if the treating team determines that vasopressors should be reinstituted, they are titrated to the allocated target of 60 to 65 mmHg. If patients are discharged and then readmitted to the ICU, vasopressor therapy is left at the discretion of the treating team. We do not mandate resumption of the permissive hypotension strategy to enhance trial feasibility, and we anticipate relatively few readmissions overall and rare readmissions before ascertainment of our primary outcome on day 3.

Usual care arm

Patients in the control arm receive usual care, as per local practice. This constitutes an improvement to the protocol of the OVATION pilot trial, which imposed a higher target MAP range of 75 to 80 mmHg. Given preliminary evidence suggesting that this higher MAP target may increase risk of death in older patients, we believe that mandating a higher MAP would be ethically questionable. By comparing permissive hypotension to usual care, we improve acceptance from clinicians and reduce the risk that the control group will diverge widely from usual care.[28] Risks of contamination are negligible given observational data showing that MAP values of patients treated with vasopressors are much higher than the currently recommended target of 65 mmHg. Moreover, changing the behaviour of physicians and nurses is challenging even when there is consensus on the benefit of a new intervention,[29] and such a consensus does not exist for permissive hypotension.[30] To further decrease the risk of contamination (i.e. lack of separation of MAP between arms), we monitor separation of actual MAP between study arms and communicate regularly with sites.

Selection of vasopressors

We do not mandate the use of any specific vasopressor or combination of vasopressors. In OVATION-65, the term 'vasopressor' refers to the following medications given by infusion: norepinephrine, epinephrine, dopamine, phenylephrine, and vasopressin. In patients receiving multiple vasopressors, we calculate the total vasopressor dose as norepinephrine equivalent as previously reported.[31] In addition, we collect information on orally administered catecholaminergic medications (i.e., midodrine and ephedrine).

Other interventions

As per usual care of patients receiving vasopressors, we expect central venous catheters (to avoid extravasation) and arterial catheters (for close MAP monitoring) to be in

place for most patients. MAP is measured by an arterial line if present or by a non-invasive blood pressure cuff otherwise; values are taken from the nursing vital signs flowsheet. Peripheral venous lines to deliver vasopressors or non-invasive blood pressure measurements do not constitute protocol deviations, consistent with a pragmatic study design. Use of pure inotropes, intravenous fluids, and corticosteroids are recorded but left to the discretion of the treating team.

Outcomes

Primary outcome

The primary outcome of OVATION-65 is high-sensitivity cardiac troponin T (hsTnT) at day 3, or before anticipated death or withdrawal of life-sustaining therapies, whichever comes first. A baseline sample (day 1) is collected before assignment to the intervention but after vasopressors have started. Cardiac troponins are consistently associated with worse outcomes in critical illness[32-36], and cardiac biomarkers may be modifiable by administration of albumin[33] and medications.[34] Given that coronary blood flow is maintained over a broad range of coronary perfusion pressures under most circumstances,[37] we hypothesize that increasing vasopressors to achieve a higher MAP will have little effect on coronary perfusion but may increase the severity of demand-related myocardial ischemia via increased heart rate (i.e. reduced coronary perfusion time) and transmural pressure (i.e. afterload). If OVATION-65 shows that permissive hypotension prevents or limits hsTnT elevation, then patients at increased risk of secondary myocardial ischemia, possibly identified by baseline hsTnT, may benefit the most from this strategy. Similarly, this biomarker could be used to identify vasopressor-induced harm earlier and modify vasopressor use accordingly.

Secondary outcomes

Secondary outcomes include high-sensitivity cardiac troponin T (hs TnT) at day 7; biomarkers associated with cardiac wall stress (plasma N-terminal pro-B-type natriuretic peptide [NT-proBNP][33]); tissue injury to the brain[38] (glial fibrillary acidic protein [GFAP][39], myelin basic protein [MBP][40], neuron-specific enolase [NSE][41]), liver (serum alanine aminotransferase [ALT][42]), intestine (plasma intestinal-type fatty acid binding protein [FABP2][43]), skeletal muscle (plasma creatine kinase, muscular [CKM][44]); and global tissue dysoxia (plasma lactate). As for hsTnT, all biomarker outcomes are measured at day 3 and 7, along with a baseline sample. We selected lactate as a reasonable measure of tissue hypoxia in critically ill patients but recognize that hyperlactatemia may result from other factors, including aerobic glycolysis, reduced oxidative phosphorylation, and decreased clearance.[45]

We measure secondary clinical outcomes, including organ function using SOFA score (on days 1, 2, 3, 4, 7, 10, 14 and 28 while in the ICU). We describe healthcare utilization in terms of duration of mechanical ventilation, renal replacement therapy, vasopressor therapy, and ICU and hospital stay. We report the incidence of the pre-specified adverse events of stroke, acute kidney injury (KDIGO stage 3),[46] clinically detected supraventricular arrhythmia,[5 47] and limb or intestinal ischemia as defined in the OVATION pilot trial.[17] Investigators will adjudicate these adverse events using medical records, if necessary. We ascertain mortality at 90 days and 6 months. For 6-month survivors, we assess cognition using the Telephone Interview for Cognitive Status (TICS), a validated questionnaire used in ICU cohorts.[48]

We had originally planned to measure additional secondary outcomes but lack resources to do so for each participant. We have described these as planned ancillary studies in online supplementary file S3.

Adverse events

OVATION-65 is testing a common intervention to treat a common problem in critically ill patients. All eligible patients are at risk of adverse events due to their underlying critical illness. Following Canadian guidelines for serious adverse event (SAE) reporting in academic drug trials in critical care,[49] expected SAEs (stroke, KDIGO stage 3 acute kidney injury, clinically detected supraventricular arrhythmia, limb or intestinal ischemia, death) are already incorporated as trial outcomes, defined *a priori*. SAEs are limited to events not already labelled as trial outcomes and that might reasonably occur as a consequence of the trial interventions. SAEs must be reported in the participant's medical notes, on the OVATION-65 dedicated case report form and to the coordinating centre within 24 hours of observing or learning of the event. Such events are promptly discussed with the DSMC.

Data collection

We collect the following data: 1) baseline data (day 1) – demographics, admitting diagnosis, etiology of hypotension, severity of illness (APACHE II score[50]), vasopressor name, dose and start time, organ dysfunction (SOFA score[23]), comorbidities (including chronic hypertension, coronary, cerebral, or peripheral vascular disease, congestive heart failure, chronic kidney disease, severe cognitive impairment, Clinical Frailty Scale,[51] co-enrolment in other prospective observational studies or RCTs; 2) daily data – protocol adherence (hourly MAP while receiving vasopressors and corresponding vasopressor names, doses, and modifications) and relevant co-interventions (fluid balance, inotropes, corticosteroids, life-support interventions, sedation); and 3) primary and secondary outcomes.

Study Samples

To minimize the treating teams' workload, study samples (blood and urine) coincide as much as possible with clinical sampling on day 1 (baseline) and on day 3 and 7 (or the day of

ICU discharge or before anticipated death or withdrawal of life-sustaining therapies, whichever comes first).

To ensure consistent measurement of biomarkers, the study samples are processed on site and shipped to URCE, where they are stored at -80°C and batched for analyses at the end of the trial. Clinical teams are blinded to the results of the biomarker assays but are free to measure any desired biomarker via local hospital laboratory. Participants are also approached for participation in a parallel Acute Care Biobank, via a separate consent form, which allows samples remaining following completion of OVATION-65 specified analyses to be stored for future projects.

Risk of bias

Risk of bias is reduced by concealed randomization using variable and undisclosed blocks. Although clinical teams are not blinded to treatment arms, assessors of biomarkers, pre-specified adverse events, mortality, and TICS are blinded to treatment allocation. Specimen processing and analysis are standardized as described. Finally, we record co-interventions to detect performance bias.

A risk of bias related to the biomarker outcomes is that early death or live discharge from the ICU, which may be related to treatment allocation, are competing risks for ongoing treatment in the ICU and ascertainment of these outcomes. Our analysis plan (see *Statistical analysis* below) accounts for this possibility.

Vasopressor management and protocol adherence

In the permissive hypotension arm, a protocol deviation is defined as a failure to reduce the dose of (or discontinue) vasopressors while the MAP is >65 mm Hg for three consecutive hours. Sites report protocol deviations on study forms and are asked to specify a

reason for the deviation, which may include a physician's decision to target a higher MAP because of particular clinical circumstances. Investigators will adjudicate protocol deviations using source data.

For each day on protocol, we record the MAP value recorded nearest to each hour. In the permissive hypotension arm, clinical teams are reminded to consider discontinuing vasopressor therapy if the patients are able to maintain MAP values of at least 60 mmHg. Every participating site receives on-site training, to which all ICU bedside staff are invited. We distribute standard operating procedures and protocol adherence reports generated from MAP and vasopressor data entered in the electronic case report form. Regular newsletters and trial website updates (https://www.ccctg.ca/Programs/OVATION65.aspx) keep participating sites informed of study progress, overall adherence, and answers to frequently asked questions. Research staff are available 24/7.

We will report vasopressor management in each arm in terms of duration and total dose of vasopressor therapy received, hourly MAP values and corresponding vasopressor infusion rates, and the number of episodes of vasopressor therapy. In the permissive hypotension arm, we will report the number and proportion of patients with any protocol deviation. As in the 65 trial,[22] patient-level adherence will be defined as not having experienced a protocol deviation. We will also report total time on vasopressors with recorded MAP within target range; total time on vasopressors with recorded MAP above target range; total time on vasopressors with recorded MAP >5 mmHg above upper limit of target; and total time on vasopressors with recorded MAP below target range. These measures will be summarized with descriptive statistics.

Follow-up

Participants are followed to hospital discharge by local research teams. Either the coordinating centre or the enrolling site ascertains 90-day and 6-month mortality and 6-month cognitive status in survivors by telephone. Prior verification of known vital status with local research teams and calibrated telephone scripts mitigate the risk of emotional distress in the event that a patient has died since hospital discharge. We selected TICS to measure cognitive function in survivors because telephone administration reduces risk of bias, improves measurement consistency, reduces patient burden, and enhances feasibility.

Patient and public involvement

The protocol was developed with input from 2 ICU survivors (EB and DC), who participated in protocol development meetings, contributed to the selection of 6-month cognitive function as a secondary outcome, and are co-authors of this manuscript.

Statistical analysis

Sample size

OVATION-65 is supported by several modest operating grants, each of which required a distinct objective, sample size calculation and analysis plan. By combining funds from multiple sources, we had planned to enrol 200 participants, which provides 80% power to detect an effect size of 0.4 in the difference between day 3 hsTnT in the permissive hypotension group compared to usual care, where 0.5 is considered to be medium.[52]

After the 65 trial[22] was published, the OVATION-65 Executive Committee forwarded the publication to the DSMC, which requested a meeting to discuss the results. The DSMC subsequently issued a letter on 21 February 2020 recommending termination of enrolment in OVATION-65. The DSMC "reasoned that in light of the accumulated evidence, mostly from the 65 trial[22] but also with some consideration of SEPSISPAM,[16] the posterior probability of

lower MAP targets now being better was sufficiently high that there is no longer equipoise between the interventions being compared in OVATION-65." As of 21 February 2020, 159 patients had been randomized.

Patient flow

A sample CONSORT diagram is presented in Figure 1.

Data analysis

Analyses will be performed after all follow-up is completed, data queries are resolved, and the database is locked. We will adhere to the intention-to-treat principle, and data from participants will be analyzed by allocated group, regardless of protocol adherence. All participant data will be analysed unless consent to retain data is withdrawn. Statistical testing will use a superiority framework, with two-sided $p<0.05$ interpreted as statistically significant. Estimates of effect will be reported with 95% confidence intervals. No adjustments for multiplicity will be made. All analyses will use SAS 9.4 (Cary, USA). Given the modest sample size and focus on biomarkers of organ injury, no interim analysis was planned. Continuous data will be summarised as means (SD) if normally distributed and as medians (Q1, Q3) otherwise. Categorical data will be summarised as frequencies and proportions. Baseline data will be summarised as shown in Table 3.

The primary outcome of day 3 hsTnT will be analysed adjusting for the day 1 value. We will use the original scale and analysis of covariance if the data are not skewed; if skewed we will log-transform and use robust regression to obtain more interpretable estimates. We will use pooled logistic regression to estimate the probabilities of missing values due to either death or live discharge from the ICU. Based on these models, we will compute the inverse-probability of attrition weights for each observation and use generalized estimating equation

models to test the differences in hs TnT between the permissive hypotension and usual care arm,[53] adjusting for centre using fixed effects. As a sensitivity analysis, for patients that die before day 3, we will impute the worst (highest) value and for patients discharged alive before day 3, we will impute the best (lowest) value.

For the secondary outcome of day 7 hsTnT, we will use the same approach. For patients who die before day 7, we will impute the worst (highest) value. For patients discharged alive before day 7, we will impute based on data available for other patients alive at day 7. The approach for all other biomarkers will be the same as for hsTnT.

For SOFA over the first 7 days, we will use a linear mixed effects model to account for repeated measures within patients as well as the centre effect. For patients who die before day 7, we will impute the worst (highest) value. For patients discharged alive before day 7, we will impute based on data available for patients in the same group alive at day 7. We will look for interaction between time and group as well as time trends. For TICS, we will use ordinal logistic regression with fixed effect for centre to compare the distribution of patients at 6 months in 4 categories (death and 3 cognitive status categories [non-impaired, mild impairment, and moderate-severe impairment]). If proportional odds assumption does not hold, we will use multinomial regression to compare the two groups. If there is >5% loss to follow-up for TICS, we will conduct sensitivity analyses using multiple imputation techniques for the missing values. We will also report the proportion of patients in each category by arm and test for differences in separate categories of mortality and cognitive impairment. For mortality, we will use a generalized linear mixed effect model with logit link for 90 and 365 days separately. For pre-specified adverse events, we will report the proportion of patients in each arm with the outcome and test for differences using chi-square test or Fisher's exact test, as appropriate.

In sensitivity analyses, we will also adjust for pre-specified baseline covariates: APACHE II, total dose of vasopressor administration before randomization (in norepinephrine equivalents),[54] and history of hypertension, or coronary artery disease (angina, myocardial infarction [MI], or coronary revascularisation).

No subgroup analyses are prespecified due to the small sample size. An updated IPDMA[18] including data from existing trials,[16 17] the 65 trial,[22] and the current trial is under consideration.

Registration

The trial was registered on www.clinicaltrials.gov on 13 February 2018 before enrolling the first patient in the study (NCT03431181). Initially, the primary outcome was listed as hsTnT at day 7; this error was subsequently corrected on 28 May 2020. Data will not be analyzed until trial follow-up is complete in August 2020.

Data management

The paper or electronic case report forms (CRFs) are the primary data collection tool for the study. All data requested on the CRF are recorded on paper CRFs or on the electronic CRFs within the secure REDCap EDC system. If the data are first collected on paper CRFs, site research personnel subsequently transfer all data into REDCap by direct entry.

Monitoring

Quality control measures include 1) site training of research and clinical personnel on eligibility assessment, trial procedures, and data collection; 2) standard operating procedures to guide processing, storage, and shipping of blood and urine samples; 3) ongoing assessment

of trial management metrics (monthly screening logs, monthly reports (site enrolment, protocol adherence in the permissive hypotension arm and regarding study samples), and periodic feedback to the clinical sites on performance (recruitment, protocol adherence), with benchmarking from other sites; 4) ongoing review of missing data and outliers; and 5) rapid dissemination of responses to frequently asked questions via our study website and monthly newsletter. For one site, we also conducted monitoring visits for 2 of the first 5 participants and 10% of the subsequent participants. Coordinating Centre staff and the Principal Investigators were available at all times to answer study-related questions.

Trial oversight

Executive Committee

The Executive Committee is comprised of Neill KJ Adhikari, M Elizabeth Wilcox, and François Lamontagne (co-principal investigators), Marie-Claude Battista (core laboratory), and Marie-Hélène Masse (project leader). The Executive Committee is responsible for day-to-day management.

Data Safety Monitoring Committee

The DSMC is independent of the study investigators and responsible for safeguarding the interests of study participants, assessing the safety and efficacy of study procedures, and monitoring the overall conduct of the study. DSMC members have extensive trial experience and include a senior methodologist who has served as Chair on numerous DSMCs for international RCTs, a senior biostatistician, and a clinician scientist in intensive care (online supplementary file S1). The DSMC met on an *ad hoc* basis to review reports of unanticipated serious adverse events (SAEs) not predefined as study outcomes. In accordance with a

prespecified DSMC Charter, the DSMC advised the Executive Committee of any concerns related to participant safety and trial conduct. After each meeting, the DSMC made a recommendation for study continuation as designed, continuation with major or minor modifications, temporary suspension of enrolment until some uncertainty is resolved, or termination. As noted above, the DSMC recommended termination of enrolment in response to data from the 65 trial.[22]

Ethics and Dissemination

This protocol was approved by the Comité d'éthique de la recherche du Centre intégré universitaire de santé et de services sociaux de l'Estrie – Centre hospitalier universitaire de Sherbrooke (MP-31-2018-1789). All participating clinical sites received local research ethics board (REB) approval prior to commencing participant enrolment. Before initiating the trial, each clinical site provided the Coordinating Centre with a copy of their local REB approval letter and approved informed consent form (sample in online supplementary file S4). Protocol amendments were submitted to each REB and disseminated to all investigators.

Informed consent was obtained by local research personnel, who approach eligible patients directly if they are able to consent. If the eligible patient was not capable, research personnel approached the substitute decision-maker (SDM) to obtain consent in person, or by telephone if the SDM is unavailable. Alternatively, the patient was randomized and consent was obtained subsequently under a deferred consent model, where permitted by the site REB. Consent was requested for future laboratory analyses that may arise from this protocol.

Participants may discontinue participation in the OVATION-65 trial at any time. If a participant wishes to withdraw consent, we will use the following strategies to minimize the impact on the trial, while respecting autonomy. We will seek a better understanding of the participant's wishes and offer the following alternatives to complete withdrawal, which would

include no further study intervention (only relevant for participants in the permissive hypotension arm), data deletion, and sample destruction: 1) Discontinue study intervention but allow data collection (clinical data, sample collection, telephone follow-up); 2) Discontinue study intervention, in-person follow-up, and sample collection but allow telephone follow-up; or 3) Discontinue study intervention, sample collection, and in-person and telephone follow-up, but allow access to medical records.

All personal health information collected during the study remains strictly confidential in a secure database. Participants are identified by an alphanumeric code, and the linkage from the alphanumeric code to identifying information is kept in secure storage under the supervision of the local principal investigator.

There was no compensation for harm suffered from trial participation; details on data collection for adverse events are given above. Patients enrolled in this trial were critically ill and all care was provided by intensive care clinicians. There was no provision for post-trial care other than usual clinical care for ICU patients.

Plans for end-of-grant dissemination include presentations at international critical care conferences and journal publications. In addition, building on the experience with social media during the OVATION pilot trial, we will disseminate our results via social media platforms and discussion forums managed by partner organizations.

Authorship of the trial manuscript will be based on leadership roles in trial management and at clinical sites, specific expertise (e.g. methodological, laboratory), and contributions as defined by International Committee of Medical Journal Editors criteria.

Data statement

The OVATION-65 protocol is freely accessible via this publication. The principal investigators, project leader, and study statisticians will have access to the full trial dataset; there are no contractual limitations to such access. Requests for access to the participant-level

dataset and statistical code will be considered by the Executive Committee after publication of primary results and planned secondary studies by co-investigators.

Trial status

The current protocol is version 6, dated 29 November 2019. Participant recruitment began on 17 February 2018 and was scheduled to continue until approximately June 2020. As noted, the DSMC recommended termination of enrollment on 21 February 2020. The database will be locked after the last enrolled patient completes the 6-month follow-up in August 2020, and 6 additional months will be required to address remaining data queries and to finalize the analyses.

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Authors' contributions
NA and FLam drafted the protocol for the OVATION-65 trial and drafted the manuscript; they contributed equally and co-senior authors. MHM, MCB, MEW, RPi, NM, FD'A, CS-A, MM, M-AL, HQM, BGB, YP, ECa, AJES, IW, RPo, MC, ML, FLau, AT, DB, SM, ECh, EB-C, EB, and DC contributed to protocol development and revised the manuscript. MHM, MCB, MEW, FLam, and NA on the Executive Committee. All authors read and approved the final manuscript.

Competing interests
The authors declare that they have no competing interests.

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Online supplementary files

S1 (.pdf format)
SPIRIT checklist.

S2 (.pdf format)
OVATION-65 contributors.

S3 (.pdf format)
Ancillary studies.

S4 (.pdf format)
Model informed consent form.

Figure legend

Figure 1. Progress of patients through the trial. 'Co-enrolled in another study' refers to a study for which the principal investigators of OVATION-65 or the other study had prespecified that co-enrolment would not be allowed.

Table 1 Summary of objectives and outcomes

Objectives	Outcomes
Biomarkers of organ injury	
Heart	High-sensitivity cardiac troponin T (hsTnT)
	N-terminal pro-B-type natriuretic peptide (NT-proBNP)
Brain	Glial fibrillary acidic protein (GFAP)
	Ubiquitin C-terminal hydrolase L1 (UCHL1)
	Myelin Basic Protein (MBP)
	Neuron-specific enolase (NSE)
Liver	Alanine aminotransferase (ALT)
Intestine	Intestinal-type fatty acid binding protein (FABP2)
Skeletal muscle	Creatinine kinase, muscular (CKM)
Global tissue dysoxia	Lactate
Organ function	Sequential Organ Failure Assessment (SOFA) score on days 1, 2, 3, 4, 7, 10, 14, and 28 while in the ICU
Resource utilization	Incidence and duration of mechanical ventilation
	Incidence and duration of renal replacement therapy
	Duration of vasopressor therapy
	Duration of ICU stay
	Duration of hospital stay
Adverse events	Supraventricular arrhythmia
	Stroke
	Acute kidney injury (KDIGO stage 3)
	Limb ischemia
	Intestinal ischemia
Mortality	90 days
	6 months
Cognitive impairment	Telephone Interview for Cognitive Status (TICS) at 6 months

KDIGO, Kidney Disease: Improving Global Outcomes.

All biomarkers are measured in plasma.

Table 2 OVATION-65 Trial Timeline

	Study Period												
	Days	**Days**											**Months**
	Enrolment/ Allocation	**Post-Allocation**											
TIME POINTS	**1**	**2**	**3**	**4**	**5-6**	**7**	**8-9**	**10**	**11-13**	**14**	**15-27**	**28**	**6 months**
ENROLMENT:													
Eligibility screen	x												
Informed consent	x												
Allocation	x												
INTERVENTION:													
Permissive hypotension (MAP 60-65 mmHg) vs. usual care[a]	→	→	→	→	→	→	→	→	→	→	→	▶	
ASSESSMENTS:													
Baseline variables													
Diagnosis of admission	x												
Severity of illness (APACHE II score)	x												
Pre-existing comorbidities (Clinical Frailty Score)	x												
Outcomes													
Troponin hs TnT[b]	x		x			x							
Biomarkers of organ injury[c]	x		x			x							
Global tissue dysoxia (lactate)	x		x			x							
Organ function including renal function (SOFA score)	x	x	x	x		x		x		x		x	
Resource utilization[d]										x			
Mortality at 90 days and 6 months	→	→	→	→	→	→	→	→	→	→	→	▶	x
Cognitive impairment (TICS) at 6 months													x
Stroke	→	→	→	→	→	→	→	→	→	→	→	▶	
Supraventricular arrhythmia	→	→	→	→	→	→	→	→	→	→	→	▶	
Limb or intestinal ischemia	→	→	→	→	→	→	→	→	→	→	→	▶	
Occurrence of stage 3 acute kidney injury[e]	→	→	→	→	→	→	→	→	→	→	→	▶	
Other variables													
Protocol adherence[f]	→	→	→	→	→	→	→	→	→	→	→	▶	
Co-interventions[g]	→	→	→	→	→	→	→	→	→	→	→	▶	

[a] Mean arterial pressure target while receiving vasopressor therapy up to day 28, or discontinuation for more than 24 hours.
[b] hs TnT at day 3 is the primary outcome and at day 7 is a secondary outcome

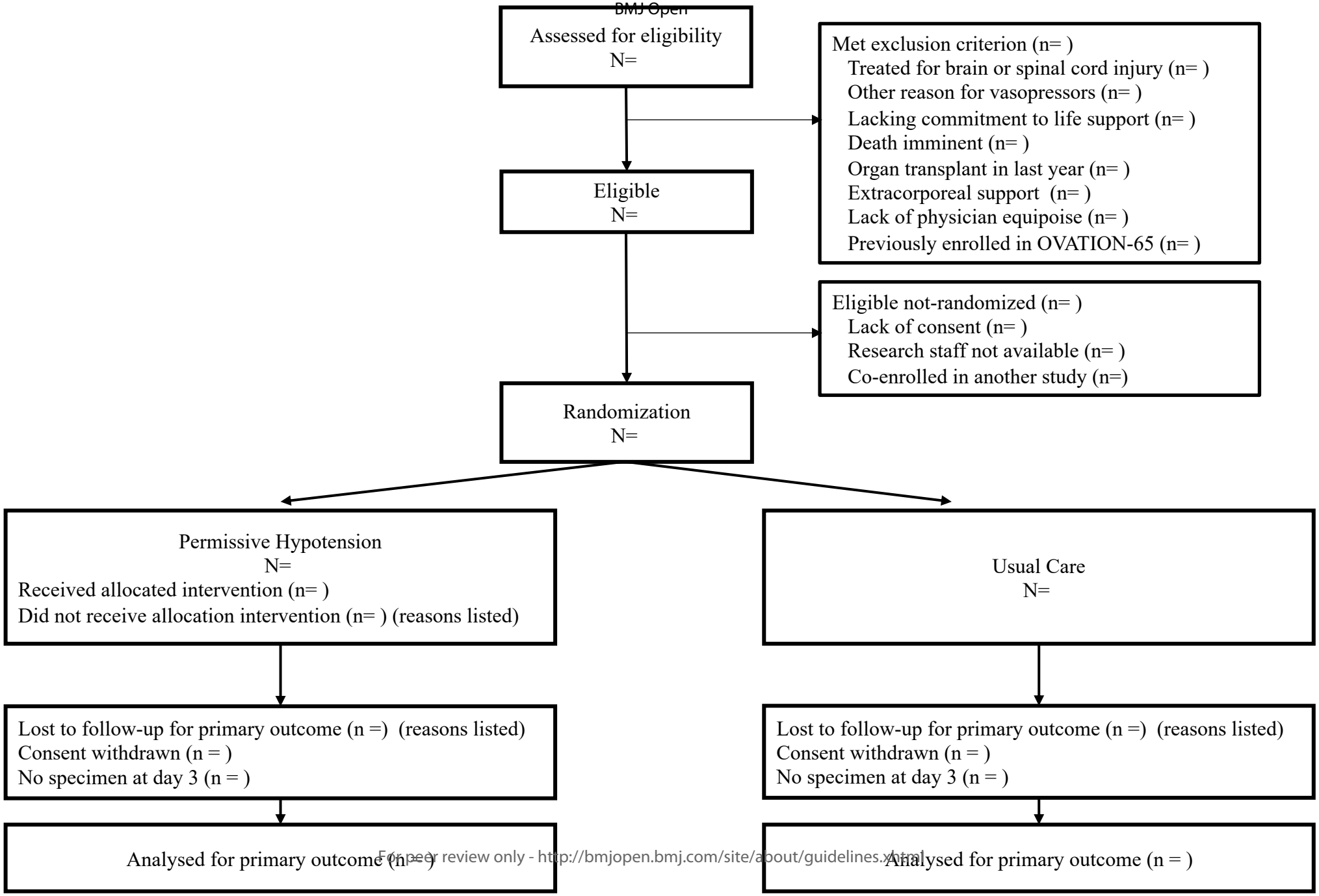
[c] NT-proBNP, GFAP, UCHL1, Myelin Basic Protein, NSE, ALT, intestinal-fatty acid binding protein, CK
[d] Mechanical ventilation, renal replacement therapy, vasopressor therapy, ICU and hospital stay
[e] As defined by KDIGO (Kidney Disease: Improving Global Outcomes) criteria
[f] Mean arterial pressure reached while on vasopressor therapy and samples collected per protocol instructions
[g] Inotropes, corticosteroids, benzodiazepines, opioids, propofol, epidural anesthesia

Table 3 Baseline characteristics

Characteristic	Permissive hypotension (n=)	Usual care (n=)
Demographics		
Age, years, mean (SD)		
Female sex, n (%)		
Weight, kg; mean (SD)		
Clinical Frailty Scale[a] >4, n (%)		
APACHE II[b], mean (SD)		
Comorbidities		
Cardiac, n (%) Supraventricular arrhythmia Ventricular arrhythmia Coronary artery disease[c] CHF class 1-3 CHF class 4 LVEF, % (mean, SD)		
Vascular, n (%) Known hypertension Peripheral vascular disease or claudication Cerebrovascular disease		
Diabetes (type 1 or 2), n (%)		
Renal, n (%) Receiving chronic dialysis Baseline creatinine[d]; mean (SD)		
Child's B or C cirrhosis, n (%)		
Chronic lung disease, n (%)		
Immunosuppression, n (%)		
Cognitive impairment or dementia, n (%)		
ICU admission data		
Primary ICU diagnosis, n (%) Medical Surgical		
Transfer from another hospital, n (%)		
Time from ICU admission to randomization, hours; mean (SD)		
Vasopressor dose, mean norepinephrine equivalents (mean µg/kg/min, [SD])		
Vasopressors, n (%) Norepinephrine Epinephrine Dopamine Phenylephrine Vasopressin		
Inotropes, n (%) Dobutamine Milrinone		
Mean arterial pressure, mmHg; mean (SD)		

APACHE II, acute physiology and chronic health evaluation II, CABG, coronary artery bypass grafting; CHF, congestive heart failure; MI, myocardial infarction; PCI, percutaneous coronary intervention

[a]The Clinical Frailty Scale [51] ranges from 1 to 7, with scores of 5-7 denoting frailty.
Scores on the APACHE II [50] range from 0 to 71, with higher scores indicating more severe disease and a higher risk of death.
[b]Scores on the SOFA [23] range from 0 to 24, with higher scores indicating more severe disease and a higher risk of death.
[c]Coronary artery disease included angina and previous MI, PCI, or CABG.
[d]The baseline creatine was determined from the outpatient creatinine within the last 12 months and closest to admission (n=) or, if not available, then the lowest inpatient creatinine before ICU admission (n=).



Page numbers refer to the Microsoft Word version of the manuscript (revision 1).

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

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	4, 21
	2b	All items from the World Health Organization Trial Registration Data Set	4, 21
Protocol version	3	Date and version identifier	24
Funding	4	Sources and types of financial, material, and other support	25
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1, 26
	5b	Name and contact information for the trial sponsor	25
	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	26
	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)	9, 22-23

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	6-8
	6b	Explanation for choice of comparators	7-8, 11-12
Objectives	7	Specific objectives or hypotheses	8
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	9
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	9, suppl S1
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	9-10
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	10-12
	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)	16-17
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	16-17
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	12-13
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	13-15
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)	33-34

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	18-19
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	21-22
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	10-11
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	10-11
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	10-11, 23
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	16
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	Not blinded
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	15-16
	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	23-24

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	21
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	19-21
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	19-21
	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)	19-21
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	22-23
	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	19
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	14-15
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	21-22
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	23
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)	23

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	23
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	23
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	24
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	25
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	24
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	24
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	24
	31b	Authorship eligibility guidelines and any intended use of professional writers	24
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	24
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Suppl S4
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	15-16

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

Online supplementary file S2 OVATION-65 team members

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Abbreviations:
Co-I – co-investigator; PI – principal investigator; PL – project leader; RA – research assistant; RC – research coordinator

Online supplementary file S3 OVATION-65 ancillary studies

Study title	Investigators	Primary objective	Secondary objective	Funding
Measuring baseline ascorbic acid levels in the OVATION-65 trial	MC Battista NK Adhikari F Lamontagne	Measure the association between baseline plasma ascorbic acid and markers of organ injury	Measure the association between baseline ascorbic acid and 1) hourly MAP to vasopressor dose ratio; 2) biomarkers of inflammation (IL-1ß, TNF-α, C-reactive protein) 3) biomarkers of endothelial injury (thrombomodulin, angiopoietin-2)	Lotte and John Hecht Memorial Foundation
Urinary biomarkers of renal injury in the OVATION-65 trial: a Nested analysis of the urinary proteome	FM Boisvert MC Battista NK Adhikari F Lamontagne	Identify peptides and proteins expressed in the urine of OVATION-65 participants using a discovery proteomic approach	Measure the association between protein clusters and renal function	Université de Sherbrooke/ Merck Sharp and Dohme
Effects of catecholamine therapy on the immune system: unsuspected consequences of routine medical interventions and opportunities for individualized care	FM Boisvert LH Tai JL Parent X Roucou MC Battista NK Adhikari F Lamontagne	Evaluate the effects of exogenous catecholamines on plasma Th1/Th2 profiles (plasma cytokines and flow cytometry)	Evaluate the effects of exogenous catecholamines on 1) Expression and activation of peripheral blood mononuclear cell adrenergic receptors; 2) Distinct proteomic signatures	Université de Sherbrooke/ Merck Sharp and Dohme

CENTRE DE RECHERCHE | CHUS

RESEARCH INFORMATION AND CONSENT FORM

Study Title: The OVATION-65- Impact of permissive hypotension on end-organ damage in the elderly

Study Number and Date: MP-31-2018-1789

Funding Agencies: Centre de recherche du CHUS
Université de Sherbrooke

Principal Investigator: Dr. François Lamontagne, Intensivist

Co-Investigators: Dr. Frédérick D'Aragon, Intensivist,
Dr. Charles St-Arnaud, Intensivist
Dr. Michaël Mayette, Intensivist,

FOR INFORMATION

Monday through Friday, from 8 am and 4 pm, you can reach:

Dr. François Lamontagne, Intensivist	Tel.: 819-346-1110, ext. 74974
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or dial "0" and ask the operator to call them on pager # 7125.

We are seeking your participation (or that of your family member) in a research study because you (or your family member) have been admitted to an intensive care unit and will need medication administered into your veins to raise your blood pressure. However, before you agree to participate, please take the time to read, understand and carefully consider the following information. If you agree to take part in this research study, you will be asked to sign the consent form at the end of this document and we will give you a signed copy for your own records.

This Information and Consent Form explains the goals, procedures, risks and inconveniences, and benefits of the study as well as providing the names of the people to reach if needed. This document may contain information or words that you do not understand. Please ask the study investigator or members of the study staff to answer your questions and explain any word or information you do not understand.

NATURE AND GOALS OF THE RESEARCH STUDY

This study aims to determine whether the target blood pressure used to adjust the dosage of the blood-pressure-increasing medication changes the evolution of participants treated in the Intensive Care Unit (ICU). Vasopressors are drugs that are given intravenously to increase the blood pressure of patients with diseases causing dangerous pressure drops that can be harmful to the organs of the body. When a doctor

prescribes a vasopressor, he asks that the dose be adjusted to achieve a specific blood pressure. However, although vasopressors have been used for nearly a century, we still do not know whether it is preferable to try and normalize the blood pressure of our patients (which requires high doses of vasopressors) or tolerate a lower pressure (which is not normal, but requires smaller doses of drugs). The current practice is quite variable, some doctors preferring to increase the blood pressure, others preferring to restrict doses of these powerful drugs and tolerate a lower blood pressure (hypotension).

The goal of this study is to determine if tolerating a lower mean blood pressure (permissive hypotension) vs. usual blood pressure targets in hypotensive patients over 65 years of age can reduce the risk of harm associated with more aggressive vasopressor therapy. The specific objectives are to evaluate: the effect of permissive hypotension on your health status after 6 months , the effects on markers of organ injury, including the heart, brain, kidneys, liver, intestine, and skeletal muscles as well as the effects on your immune system. We wish to recruit around 100 participants at the *CIUSSS de l'Estrie - CHUS* to be among the 200 participants needed for this study that will be carried out in several hospitals.

Your physician has determined that you are eligible to participate in our study and you have been selected as a participant because you are being (or will soon be) treated in the ICU and because you were prescribed vasopressor drugs.

RESEARCH STUDY PROCEDURES

If you agree to participate in this study, you (or your family member) will be assigned to one of the following two groups: The first group includes participants who are being given vasopressors for an average blood pressure of 60-65 mmHg (limiting the amount of vasopressors given); the second group includes participants who are receiving vasopressors following usual care. Your assignment to one of these two groups was determined randomly by a computer that will not retain information about you. The odds of being assigned to either group were 50% (1 in 2 chances or half-and-half). The treating team will be aware of which group you have been assigned to.

As a study participant, you will receive vasopressors to maintain your average blood pressure at the level of your assigned group. These pressure targets will remain the same throughout your treatment with this type of medication (vasopressors) until you are discharged from hospital or up to 28 days from the beginning of your participation, whichever event comes first. Also, on days 1, 3 and 7 of participation (or when you are discharged from the intensive care unit), your nurse will collect 30 ml of blood (6 teaspoons) as well as urine samples while taking the blood samples required for your medical follow-up. We will collect a little more volume than what is needed in order to compensate for unexpected losses that may arise during laboratory testing. These samples will enable us to measure certain biomarkers in your blood and in your urine that help assess the function of your heart, kidneys, muscles, brain and liver as well as your immune system. These biomarkers are already known to be useful in clinical studies and are not genetic biomarkers. During your hospital stay, we will monitor your progress to see if your organs are functioning well, if you develop other health problems and how long you will stay in the ICU and hospital. Your medical chart will be reviewed, by the investigator and the research team as long as you remain in the study. Blood test results and procedures present in your medical record will be collected for the study.

After you are discharged from the hospital, you will be contacted by phone 6 monthss after the start of your participation in the study. Your contact information will be provided to the coordinating research team.

FUTURE ANALYSES

Once the biomarker analyses have been performed as part of this study, it is possible that part of your samples may be unused. We wish to use the remainder of your samples (blood and urine) in order to answer additional questions concerning the impact of vasopressors on blood pressure targets that may arise in future. For example, we could measure a new, as yet undefined, biomarker. Only the remainder of your samples will be used and no other additional sample will be collected. At the end of the study, if some of the samples remain unused, they will be destroyed unless you agree to biobanking. A separate consent form will be presented for biobanking.

RISKS ASSOCIATED WITH PARTICIPATION IN THIS RESEARCH STUDY

Vasopressors used in this study and that you have received or may still be receiving, are approved in Canada and commonly used in the ICUs of all hospitals. The blood pressure targets we aim for in this study are also part of current medical practices.

Since your health condition required treatment with vasopressors, and continues to require treatment at this time, to our knowledge, you are exposed to the same risks, whether or not you participate in this study.

INCONVENIENCES ASSOCIATED WITH PARTICIPATION IN THE STUDY

Other than the risks described above, you (or your family member) shouldn't experience any other inconveniences.

BENEFITS ASSOCIATED WITH YOUR PARTICIPATION IN THE RESEARCH STUDY

You (or your family member) will not personally benefit from your participation in this research study. However, the findings from this study may help increase our knowledge of pressure targets, vasopressors and biomarkers. The information obtained through this study could be useful to other patients in the future.

ALTERNATIVES TO YOUR PARTICIPATION IN THIS RESEARCH STUDY

You (or to your family member) do not have to participate in this research study to be treated for your disease.

VOLUNTARY PARTICIPATION AND THE RIGHT TO WITHDRAW

Your participation in this research study is voluntary. Therefore, you may refuse to participate. You can also withdraw from the study at any time, without providing a reason, by informing the study investigator or one of his assistants.

Your decision not to participate in the study or to withdraw from it, will have no impact on the quality of care and services you (or your family member) are entitled to or on your relationship with the investigator and other stakeholders.

The study investigator, the funding agency or the Research Ethics Board may put an end your participation in the study without your consent. This may happen if new scientific developments show that participation is no longer in your interest; if the study investigator believes it is in your best interest; or if there are administrative reasons to terminate the study.

If you withdraw or are withdrawn from the study, the information and material already collected during the course of the study will be stored, analyzed or used to ensure the integrity of the study.

Any new study findings that could influence your decision to remain in the research study will be shared with you as soon as possible.

CONFIDENTIALITY

While you take part in this research study, the study investigator and study staff will collect and record information about you in a study file. Only the information needed to meet the scientific goals of the study will be collected.

This information could include data taken from your medical record concerning your past and present medical history, your lifestyle and the test results, exams and procedures you will undergo during the study.

All the information collected during the study will remain strictly confidential to the extent provided by law. To protect your identity and privacy, you will be identified by an alphanumeric code. The key linking your identity and your research file will be kept in a safe place by the study investigator.

To ensure your safety, a mention of your participation in this research project will be included in your medical file. Therefore, any person or company to whom you will give access to your medical file will have access to this information.

Your full name and your phone number will be transmitted to a qualified person of the coordinating center of the study in order to allow this person to contact you in 6 months by phone. This personal information will allow a direct identification. This information will be kept in security and confidentiality will be preserved by the qualified person and destroyed at the end of the follow-up.

Study results will be stored by the study investigator for 25 years.

Study results may be published in medical journals or discussed at scientific meetings, but it will be impossible to identify participants.

For monitoring and control purposes, your study file and medical records may be examined by a representative of the Research Ethics Board or of the institution or by a person mandated by a regulatory authority. All of these individuals and organizations adhere to confidentiality policies.

You have the right to consult your study file at any time in order to verify the information gathered and to have it corrected, if necessary, for as long as this information is available to the study investigator or the institution. However, some of this information may be made available to you only once the study has ended, in order to protect the scientific integrity of the study.

COMPENSATION

You (or your family member) will not receive any compensation for expenses and inconveniences incurred due to your participation in this research study.

SHOULD YOU SUFFER ANY HARM

Should you suffer any harm due to your participation in this research study, you will be provided with all the necessary care and services, at no cost to you.

By agreeing to take part in this study, you are not waiving any of your legal rights nor discharging the study investigators, the sponsor or the institution where this research study is being conducted of their civil liability and professional responsibilities.

FUNDING OF THE RESEARCH STUDY

The study investigator has received funding from the grant agency to carry out this study.

CONTACT PERSONS

If you have any questions regarding your participation in this research study, please refer to the box on page 1.

If you have any questions regarding your rights as a participant in this study, if you have any comments or you wish to file a complaint, you may contact the *Bureau des plaintes et de la qualité des services of the CIUSSS de l'Estrie-CHUS* at the following number: 1-866-917-7903.

MONITORING OF ETHICAL ASPECTS OF THE STUDY

The *Comité d'éthique de la recherche du CIUSSS de l'Estrie - CHUS* has approved this study and is responsible for monitoring it at all participating institutions throughout Québec's health and social service network.

If you wish to reach a member of the Research Ethics Board (REB), please contact the *Service de soutien à l'éthique de la recherche du CIUSSS de l'Estrie - CHUS* at the following number: 819-346-1110, ext. 12856.

CONSENT

I declare that I have read this Information and Consent Form. I declare that the research study has been explained to me, that my questions were answered to my satisfaction and that I was given sufficient time for consideration and to make a decision. Upon reflection, I agree to participate in this research study under the conditions stated therein.

I agree that the remainder of the samples may be used for additional analyses that may arise during the study (future analyses). ☐ YES ☐ NO

Name of participant *(please print)*	Signature of participant	Date

I have explained the research study and this Information and Consent Form and I have answered all of his/her questions.

Name of person obtaining consent *(please print)*	Signature of person obtaining consent	Date

CONSENT FROM LEGAL REPRESENTATIVE (SUDDEN INCAPACITY)

Because Mr./Mrs. _____ has suddenly become incapable of giving consent for the hereinafter mentioned reason, the Civil Code of Québec allows you to give consent for him/her as his/her _____ (indicate your relationship with the participant).

As soon as Mr./Mrs. _____has sufficiently recovered, he/she will be asked to sign his/her own consent form to indicate whether he/she wants to continue taking part in this study.

REASON FOR THE PARTICIPANT NOT BEING ABLE TO GIVE CONSENT

By signing this page, I confirm that I have read the information in this Consent Form. I acknowledge that the study has been explained to me, that all of my questions have been answered and that I was given enough time to make a decision. I voluntarily give my consent so that Mr./Mrs. _____ can participate in this study.

I also agree that the remainder of the samples may be used for additional analyses that may arise during the study (future analyses). ☐ YES ☐ NO

Name of legal representative *(please print)* | Signature of legal representative | Date

I have explained the research study and this Consent Form to the participant's legal representative. I have answered all of his/her questions.

Name of person obtaining consent *(please print)* | Signature of person obtaining consent | Date

CONSENT FROM THE LEGAL REPRESENTATIVE OR CAREGIVER SUPPORTING THE PARTICIPATION OF THE PERMANENTLY INCAPABLE PARTICIPANT (PERMANENT INCAPACITY)

I declare that I have read this Information and Consent Form. I declare that the research study has been explained to me, that my questions were answered to my satisfaction and that I was given sufficient time for consideration and to make a decision.

I agree that _____ can participate in this research study under the conditions stated therein. I will receive a signed and dated copy of this Information and Consent Form.

I also agree that the remainder of the samples may be used for additional analyses that may arise during the study (future analyses). ☐ YES ☐ NO

If the incapacitated participant is represented:

Name and signature of the legal representative (representative, curator or mandatary) Date

If the incapacitated participant is not represented by a legal representative:

Name and signature of the spouse, failing which, name of next-of-kin or name of a significant person Date

I have explained the research study and this Consent Form to the participant's legal representative. I have answered all his/her questions.

Name of person obtaining consent *(please print)* Signature of person obtaining consent Date

PHONE CONSENT
(For the participant who is suddenly or permanently incapacitated)

Because Mr./Mrs. _____ is incapable of giving consent for the hereinafter mentioned reason,

REASON FOR THE PARTICIPANT NOT BEING ABLE TO GIVE CONSENT

_____

I have explained the research study and this Consent Form to the participant's legal representative. I have answered all his/her questions.

The representative, Mr./Mrs._____
Name of the legal representative (representative, curator or mandatary)
Name of the spouse or next-of-kin or
Name of the significant person

has given consent by phone on _____ at _____
Date Hour

The representative also agrees that the remainder of the samples may be used for additional analyses that may arise during the study (future analyses).☐ YES ☐ NO

Name of person obtaining consent *(please print)*	Signature of person obtaining consent	Date

APPENDIX 1: GENETIC PHASE

(PLEASE NOTE: This part of the consent should not appear in the patient's medical file)

We invite you to participate in the genetic component of this study. This phase is optional. You may refuse this proposal and still participate in the main phase of the project.

Please note that all sections of the main consent form apply to this appendix as well.

Genetics focuses on cells in the human body that contain a type of molecule called deoxyribonucleic acid commonly referred to as "DNA". Your DNA is contained in the inherited genes that control your entire body's growth, development and functions. For instance, some genes determine the colour of your eyes or hair. DNA presents a wide array of differences or variations from one person to another. These variations may affect the risk of contracting a disease (or not) or the way individuals respond differently to a drug. The OVATION-65 project also includes a genetic sub-study focusing on the analysis of certain genes (genetics) and certain phenomena present in your environment that modify your DNA (epigenetics). These tests can be performed on the cells in your blood.

The markers of the heart, brain, kidneys, liver, intestine and skeletal muscles that we are interested in measuring as part of the OVATION-65 study as well as the molecules (receptors) that enable the vasopressors to act (beta-adrenergic receptors) on the cells of different organs are determined in part by genes. Thus, in order to better understand how to reduce organ damage related to medication (vasopressors) received during intensive care unit admissions, we propose to study the DNA as well as the variations around this DNA (called epigenetic variations) of patients included in OVATION-65. Our goal is to demonstrate that modifications in the DNA of studied markers are associated with the levels of these same blood or urine markers, which inform us on the function/involvement of the targeted organ.

If you agree to participate, we will use a portion of the samples already collected as part of the main project and an additional sample (approximately 2 teaspoons) to conduct our genetic analyses.

FUTURE ANALYSIS

Once the genetic analyses have been conducted, it is possible that a portion of the samples will remain unused. We would like to use the remainder of your samples to answer additional research questions that might arise during the course of the study. Only the remainder of your samples will be used and no other additional samples will be taken. At the end of the study, if some samples remain unused, they will be destroyed unless you agree to biobanking. Another consent form will be presented for biobanking.

SOCIO-ECONOMIC RISKS ASSOCIATED WITH PARTICIPATION IN THIS PHASE OF THE STUDY

One of the risks associated with genetic analyses is related to the disclosure of results or of your participation to third parties. Protection against genetic discrimination is not currently well defined in Canadian and Québec legislation. Thus, we cannot fully guarantee that your participation in a genetics research project will not have an impact on your chances of getting certain jobs, or of getting insurance coverage (life insurance, disability or health) for you or for members of your family.

However, as researchers, we are committed not to disclose information related to genetic results to any third party. Your results will not be made available to third parties such as an employer, a government agency, an insurer or an educational institution. This also applies to your spouse, other members of your family and your doctor. Furthermore, rest assured that no data related to any genetic results will be included in your hospital record.

VOLUNTARY PARTICIPATION AND THE RIGHT TO WITHDRAW FROM THE GENETIC PHASE OF THE PROJECT

Your participation in the genetic phase of the project is voluntary. Therefore, you may refuse to participate. You may also withdraw your consent from the genetic phase of this research project at any time. Just call the ICU research team at 346-1110 ext. 14171.

Your decision to refuse to participate in this sub-study of the project will have no impact on the quality of the care that will be provided to you or on your relationship with the healthcare team.

If you decide to terminate your participation in the genetic sub-study after providing a sample, you must notify the research team that will then destroy your sample. If your sample has already been tested and the results are already included in an analysis or publication, it will not be possible to remove this information. However, the rest of your sample will be destroyed and no further analysis will be done on your sample.

CONFIDENTIALITY

Identification:

In order to protect your identity, your samples will be identified by a unique code. Your name and your file number will not appear on the samples. The study investigator will keep a list of patients with the code numbers to identify them. This list is kept under lock and key in the research nurse's office and will not be disclosed under any circumstances.

Storage and destruction of samples:

Your samples will be kept in the principal investigator's freezers until the end of the study, unless you agree to biobanking. Another consent form will be presented to this end. The principal investigator is responsible for the destruction of samples.

COMMUNICATION OF RESULTS

Your participation and the results of the genetic analysis conducted on your samples will not be disclosed to you or to your doctor.

MARKETING POSSIBILITIES / WAIVER

Your participation in the genetic phase of this project could lead to the creation of commercial or other products that could potentially be protected by patents or other intellectual property rights. However, you will not receive any financial benefits.

CONSENT (GENETIC SUB-STUDY)

I declare that I have read this Appendix (genetic sub-study). I acknowledge that this sub-study of the project was explained to me, that all my questions were answered and that I was given the necessary time to make a decision.

I freely and willingly consent to participate in the **genetic sub-study** of this project:

I also accept that the remainder of my samples may be used for **additional genetic analyses** that may arise during the course of this study (future analysis):

☐ YES ☐ NO

Name of participant name (please print)	Signature of participant	Date

I have explained the genetic sub-study and this Consent Form to the participant, and I answered all his/her questions.

Name of person obtaining consent *(please print)*	Signature of person obtaining consent	Date

CONSENT (GENETIC SUB-STUDY)
FROM THE LEGAL REPRESENTATIVE (SUDDEN INCAPACITY)

Because Mr./Mrs. _____ has suddenly become incapable of giving consent for the hereinafter mentioned reason, the Civil Code of Québec allows you to give consent for him/her as his/her _____ (indicate your relationship with the participant) to participate in the **genetic sub-study** of the project.

As soon as Mr./Mrs. _____has sufficiently recovered, he/she will be asked to sign his/her own consent form to indicate whether he/she wants to continue taking part in this sub-study of the study.

REASON FOR THE PARTICIPANT NOT BEING ABLE TO GIVE CONSENT

By signing this page, I confirm that I have read the information in this Consent Form. I acknowledge that the **genetic sub-study** of the project has been explained to me, that all of my questions have been answered and that I was given enough time to make a decision.

I voluntarily give my consent so that Mr./Mrs. _____ can participate in the genetic sub study.

I also agree that the remainder of the samples may be used for **additional genetic analyses** that may arise during the study (future analyses). ☐ YES ☐ NO

Name of legal representative *(please print)*	Signature of legal representative	Date

I have explained all relevant aspects of the genetic sub-study of this project to the participant's legal representative and I have answered all his/her questions.

Name of person obtaining consent *(please print)*	Signature of person obtaining consent	Date

CONSENT (GENETIC SUB-STUDY)
FROM LEGAL REPRESENTATIVE OR CAREGIVER (PERMANENT INCAPACITY)

I confirm that I have read the information in this Consent Form. I acknowledge that the genetic sub-study of the project has been explained to me, that all of my questions have been answered and that I was given enough time to make a decision.

I agree that _____ can participate in this **genetic sub study** under the conditions stated therein. I will receive a signed and dated copy of this Information and Consent Form.

I also agree that the remainder of the samples may be used for **additional genetic analyses** that may arise during the study (future analyses). ☐ YES ☐ NO

If the participant is represented:

_____

Name and signature of the legal representative (representative, curator or mandatary) Date

If the incapacitated participant is not represented by a legal representative:

_____

Name and signature of the spouse, failing which, name of the next-of-kin or name of the significant person Date

I have explained the research study and this Consent Form to the participant's legal representative. I have answered all his/her questions.

Name of person obtaining consent *(please print)*	Signature of person obtaining consent	Date

PHONE CONSENT (GENETIC SUB-STUDY)
(For the participant who is suddenly or permanently incapacitated)

Because Mr./Mrs. _____ is incapable of giving consent for the hereinafter mentioned reason.

REASON FOR THE PARTICIPANT NOT BEING ABLE TO GIVE CONSENT

_____

I have explained the genetic sub study and this Consent Form to the legal representative using the phone script and I have answered all his/her questions.

The representative, Mr./Mrs._____
Name of the legal representative (representative, curator or mandatary)
Name of the spouse or of the next-of-kin or
Name of the significant person

has given consent by phone on_____ at_____
Date Time

The representative also agrees that the remainder of the samples may be used for **additional genetic analyses** that might arise during the study (future analyses). ☐ **YES** ☐ **NO**

Name of person obtaining consent *(please print)*	Signature of person obtaining consent	Date and time

BMJ Open

Optimal VAsopressor TitraTION in patients 65 years and older (OVATION-65) – protocol and statistical analysis plan for a randomized clinical trial

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Secondary Subject Heading:	Cardiovascular medicine, Pharmacology and therapeutics
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Optimal VAsopressor TitraTION in patients 65 years and older (OVATION-65) – protocol and statistical analysis plan for a randomized clinical trial

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Abstract

Introduction: Vasodilatory hypotension is common among intensive care unit (ICU) patients; vasopressors are considered standard of care. However, optimal mean arterial pressure [MAP] targets for vasopressor titration are unknown. The objective of OVATION-65 (**O**ptimal **VA**sopressor Titra**TION-65**) is to ascertain the effect of permissive hypotension (vasopressor titration to achieve MAP 60-65 mmHg) vs. usual care on biomarkers of organ injury in hypotensive patients ≥65 years old.

Methods and analysis: OVATION-65 is an allocation-concealed randomized trial in 7 Canadian hospitals. Eligible patients are ≥65 years old, in an ICU with vasodilatory hypotension, receiving vasopressors for ≤12 hours to maintain MAP ≥65 mmHg during or after adequate fluid resuscitation, and expected to receive vasopressors for ≥6 additional hours. Patients are excluded for any of the following: active treatment for spinal cord or acute brain injury; vasopressors given solely for bleeding, ventricular failure or post-cardiopulmonary bypass vasoplegia; withdrawal of life-sustaining treatments expected within 48 hours; death perceived as imminent; previous enrolment in OVATION-65; organ transplant within the last year; receiving extracorporeal life support; or lack of physician equipoise. Patients are randomized to permissive hypotension vs. usual care for up to 28 days. The primary outcome is high-sensitivity troponin T, a biomarker of cardiac injury, on day 3. Secondary outcomes include biomarkers of injury to other organs (brain, liver, intestine, skeletal muscle); lactate (a biomarker of global tissue dysoxia); resource utilization; adverse events; mortality (90 days and 6 months); and cognitive function (6 months). Assessors of biomarkers, mortality, and cognitive function are blinded to allocation.

Ethics and dissemination: This protocol has been approved at all sites. Consent is obtained from the eligible patient, the substitute decision-maker if the patient is incapable, or in a

deferred fashion where permitted. End-of-grant dissemination plans include presentations, publications, and social media platforms and discussion forums.

Trial registration: clinicaltrials.gov, NCT03431181

Keywords

vasopressors; shock; critical care; biomarkers; randomized controlled trial

Article summary

Strengths and limitations of this study

- OVATION-65 is an allocation-concealed randomized clinical trial of permissive hypotension vs. usual care in patients 65 years and older with hypotension from a vasodilatory cause, a population that may be more vulnerable to adverse effects of vasopressors
- Vasopressor titration is understudied in critically ill patients, compared to other interventions such as mechanical ventilation
- The primary and many secondary outcomes, selected with input from a patient representative, focus on biomarkers of organ injury; although these are not patient-centred outcomes, results will complement clinical outcome data from larger trials
- Because of the nature of the intervention, clinician blinding is not feasible; however, outcome assessors are blinded
- The modest sample size implies that the trial is underpowered for clinical outcomes

Introduction

Shock, a clinical syndrome of which hypotension is a cardinal feature, is common and associated with high mortality. Vasopressors are used to treat hypotension that is potentially life-threatening because they raise blood pressure by inducing vasoconstriction.[1] However, these medications are associated with adverse effects,[2-4] some of which are direct consequences of vasoconstriction-induced reduction in blood flow to vital organs. Therefore, titrating vasopressors implies balancing the risks of end-organ failure caused by hypotension and potential vasopressor-induced harm, including myocardial injury and arrhythmia, excessive vasoconstriction, hyperglycemia, and immunosuppression.[2-5] Permissive hypotension is a strategy of targeting a lower blood pressure when prescribing vasopressors, compared to usual care. Benefits have been associated with other 'permissive' therapies in critically ill patients, including hypoxia,[6] underfeeding,[7] hypercapnia,[8] red blood cell transfusion,[9] and hypotension in thoracic penetrating trauma.[10]

Clinicians in the intensive care unit (ICU) use mean arterial pressure (MAP) targets to determine the intensity of vasopressor therapy. Current international practice guidelines recommend titrating vasopressors to a MAP of 65 mmHg,[11] but because the target lacks an upper boundary, clinicians commonly put more emphasis on preventing hypotension than on minimizing vasopressor exposure. This under-appreciation of the risks associated with vasopressor overuse was apparent in a multicentre observational study[12] that reported an average MAP of 75 (standard deviation [SD] 6) mmHg in patients receiving vasopressors, approximately 10 mmHg above the recommended MAP and self-reported practice.[13] Given the relative lack of studies about vasopressor dosing, in contrast to other common ICU treatments such as mechanical ventilation, editorialists have advocated for better characterization of the lowest acceptable blood pressure target to avoid vasopressor-induced harm.[3]

Existing evidence

Observational studies have described independent associations between dose and duration of vasopressor therapy and poor outcomes, such as adverse cardiac events and increased mortality.[14 15] However, these studies are limited by indication bias, as patients who are sicker have a greater risk of unfavourable outcomes and are therefore more likely to be exposed to higher doses of vasopressor therapy.

Two randomized clinical trials (RCTs; combined n=894) published prior to the initiation of this study compared blood pressure targets in patients receiving vasopresors.[16 17] The SEPSISPAM trial compared a MAP target of 65-70 mmHg vs. 80-85 mmHg for 5 days in 776 patients with septic shock from 29 French ICUs. This study reported no difference in 28-day mortality (lower MAP 34.0% vs. higher MAP 36.6%, p=0.57), but a greater risk of atrial fibrillation in the higher MAP arm (6.7% versus 2.8%, p=0.02).[16] However, actual MAP values were 74-76 mmHg in the lower MAP arm, precluding conclusions regarding permissive hypotension. The OVATION pilot feasibility trial randomly assigned 118 patients from 1 US and 10 Canadian ICUs to a lower (60-65 mmHg) or higher (75-80 mmHg) MAP target [17]. This trial was not powered to detect differences in mortality. A subsequent individual patient data meta-analysis (IPDMA)[18] included data from both RCTs and found that higher MAP targets (75-85 mmHg) may be associated with an increased risk of 28-day mortality in older patients (p=0.1 for interaction between age and MAP).

Based on these RCTs, guidelines state that no evidence supports the use of vasopressors to achieve MAP values >65 mmHg for patients receiving vasopressors.[19] Subsequently, the 65 trial randomized 2600 patients ≥65 years old in the United Kingdom to permissive hypotension vs. usual care using a similar protocol as OVATION-65.[20 21] Patients in the permissive hypotension arm had a lower exposure to vasopressors and a lower 90-day

mortality (41.0% vs. 43.8%, p=0.15), but the difference was not statistically significant. However, an analysis adjusting for baseline covariates found lower mortality with permissive hypotension (OR 0.82, 95%CI 0.68-0.98).[22] The 65 trial collected no biological samples, precluding exploration of mechanisms underlying the effect of vasopressor dosing in that trial.

Objective and Specific Aims

The main objective of OVATION-65 is to determine whether permissive hypotension (MAP 60-65 mmHg) in patients ≥65 years old with a vasodilatory cause of hypotension and receiving vasopressors, compared to usual MAP targets, reduces organ injury as measured by biomarkers. Specific aims are to ascertain the effect of permissive hypotension vs. usual care on: 1) biomarkers of organ injury (heart [primary outcome], brain, liver, intestine, skeletal muscle); 2) biomarker of global tissue dysoxia (lactate); 3) organ function (assessed by Sequential Organ Failure Assessment [SOFA] score[23]); 4) resource utilization, 5) prespecified adverse events, 6) mortality at 90 days and 6 months; 7) cognitive impairment in survivors at 6 months (Table 1).

The primary outcome and several secondary outcomes are focused on biomarkers because of well-documented limitations of mortality in critical care trials[24] and the challenges of developing valid surrogate endpoints.[25] OVATION-65 was designed to be complementary to the 65 trial.[22] A larger version of OVATION-65 (n=800) was abandoned in 2018 after funding applications to the Canadian Institutes for Health Research and the Canadian Frailty Network were rejected. As discussed in the *Statistical Analysis* section, the Data and Safety Monitoring Committee (DSMC) recommended termination of enrollment in the current smaller version of OVATION-65 on 21 February 2020; patient follow-up is ongoing.

Methods and analysis

OVATION-65 is a multicentre, parallel-group, allocation-concealed, superiority RCT. We developed OVATION-65 on behalf of the Canadian Critical Care Trials Group (CCCTG), a 350-member organization of clinicians and researchers, incorporating feedback received since January 2012 at each of its thrice yearly scientific meetings. Table 2 shows a timeline of trial activities. The SPIRIT checklist is available in online supplementary file S1.

Study setting and management

Many study procedures for OVATION-65 are the same as those described for another trial conducted by our group.[26] OVATION-65 is conducted in adult ICUs in 7 sites in Canada. OVATION-65 team members, including research personnel at clinical sites active at the time of submission of this manuscript, are listed in online supplementary file S2. The procedures in place for OVATION-65 were piloted during the OVATION pilot RCT.[17] The Unité de Recherche Clinique et Épidémiologique (URCE) is coordinating this trial and is responsible for construction and maintenance of the randomization system and the REDCap[27 28] electronic data capture (EDC) system. The URCE also oversees the storage and analysis of blood and urine samples in the OVATION-65 core laboratory.

Inclusion criteria

Patients are included if they meet all the following criteria: 1) age ≥65 years; 2) diagnosis of vasodilatory hypotension as assessed by the treating team; 3) vasopressors started ≤12 hours ago (after or during adequate fluid resuscitation, as assessed by treating physician); and 4) vasopressors expected for ≥6 additional hours, as assessed by the treating team. Aligned with the 65 trial,[22] we do not specify a minimum volume of fluid or specific

examinations for volume status prior to the clinical (pre-randomization) decision to commence a vasopressor.

Exclusion criteria

Patients are excluded if they meet any of the following criteria: 1) actively treated for spinal cord injury or acute brain injury; 2) vasopressors given solely for bleeding, acute ventricular failure or post-cardiopulmonary bypass vasoplegia; 3) lacking commitment to life-sustaining therapies (expected withdrawal of life-sustaining treatments within the next 48 hours); 4) death perceived as imminent; 5) previously enrolled in OVATION-65; 6) organ transplant within the last year; 7) receiving extracorporeal life support at baseline; and 8) lack of treating physician equipoise regarding the overall effects of permissive hypotension vs. usual care on patient important outcomes.

Rationale for eligibility criteria

The inclusion criteria strive to identify patients most likely to benefit from permissive hypotension, namely elderly patients not already exposed to a prolonged duration of higher MAP but expected to require an additional period of vasopressor therapy. The exclusion criteria are designed to exclude patients for whom clinicians commonly apply different MAP targets (criterion 1) or whose prognosis may be dominated by factors other than the MAP target (criteria 2, 3, 4, 6, 7).

Study intervention

Treatment allocation

Using a web randomization service available 24 hours/7 days per week, patients are randomized immediately after confirming eligibility following a 1:1 sequence to permissive

hypotension or usual care. We use permuted blocks of variable and undisclosed size (4, 6 and 8) and stratify randomization by site. Stratifying by site ensures equal distribution of patients between arms at each site and decreases the probability that site-specific practices confound treatment effects.

Permissive hypotension arm

The intervention minimizes dose and duration of vasopressors. Treating teams adjust vasopressors to a target MAP range of 60 to 65 mmHg. A MAP of 60 mmHg was selected as lowest tolerable limit because it corresponds to the threshold at which Canadian intensivists usually initiate vasopressors.[13] Accordingly, it is not uncommon for patients to have MAP as low as 60 mmHg before vasopressors are instituted under usual care. The same MAP range was used in the OVATION pilot RCT.[17]

The duration of the trial intervention is determined, as it was in the pilot RCT, by the duration of the hypotensive episode, up to a maximum of 28 days. For trial purposes, the episode of hypotension ends when vasopressors are discontinued for 24 consecutive hours. As soon as patients are able to maintain the target MAP without vasopressors, the infusions are stopped. If MAP drops below 60 mmHg after this 24-hour period, and if the treating team determines that vasopressors should be reinstituted, they are titrated to the allocated target of 60 to 65 mmHg. If patients are discharged and then readmitted to the ICU, vasopressor therapy is left at the discretion of the treating team. We do not mandate resumption of the permissive hypotension strategy to enhance trial feasibility, and we anticipate relatively few readmissions overall and rare readmissions before ascertainment of our primary outcome on day 3.

Usual care arm

Patients in the control arm receive usual care, as per local practice. This constitutes an improvement to the protocol of the OVATION pilot trial, which imposed a higher target MAP range of 75 to 80 mmHg. Given preliminary evidence suggesting that this higher MAP target may increase risk of death in older patients, we believe that mandating a higher MAP would be ethically questionable. By comparing permissive hypotension to usual care, we improve acceptance from clinicians and reduce the risk that the control group will diverge widely from usual care.[29] Risks of contamination are negligible given observational data showing that MAP values of patients treated with vasopressors are much higher than the currently recommended target of 65 mmHg. Moreover, changing the behaviour of physicians and nurses is challenging even when there is consensus on the benefit of a new intervention,[30] and such a consensus does not exist for permissive hypotension.[31] To further decrease the risk of contamination (i.e. lack of separation of MAP between arms), we monitor separation of actual MAP between study arms and communicate regularly with sites.

Selection of vasopressors

We do not mandate the use of any specific vasopressor or combination of vasopressors. In OVATION-65, the term 'vasopressor' refers to the following medications given by infusion: norepinephrine, epinephrine, dopamine, phenylephrine, and vasopressin. In patients receiving multiple vasopressors, we calculate the total vasopressor dose as norepinephrine equivalent as previously reported.[32] In addition, we collect information on orally administered catecholaminergic medications (i.e., midodrine and ephedrine).

Other interventions

As per usual care of patients receiving vasopressors, we expect central venous catheters (to avoid extravasation) and arterial catheters (for close MAP monitoring) to be in

place for most patients. MAP is measured by an arterial line if present or by a non-invasive blood pressure cuff otherwise; values are taken from the nursing vital signs flowsheet. Peripheral venous lines to deliver vasopressors or non-invasive blood pressure measurements do not constitute protocol deviations, consistent with a pragmatic study design. Use of pure inotropes, intravenous fluids, and corticosteroids are recorded but left to the discretion of the treating team.

Outcomes

Primary outcome

The primary outcome of OVATION-65 is plasma high-sensitivity cardiac troponin T (hsTnT) at day 3, or before anticipated death or withdrawal of life-sustaining therapies, whichever comes first. A baseline sample (day 1) is collected before assignment to the intervention but after vasopressors have started. Cardiac troponins are consistently associated with worse outcomes in critical illness[33-37], and cardiac biomarkers may be modifiable by administration of albumin[34] and medications.[35] Given that coronary blood flow is maintained over a broad range of coronary perfusion pressures under most circumstances,[38] we hypothesize that increasing vasopressors to achieve a higher MAP will have little effect on coronary perfusion but may increase the severity of demand-related myocardial ischemia via increased heart rate (i.e. reduced coronary perfusion time) and transmural pressure (i.e. afterload). If OVATION-65 shows that permissive hypotension prevents or limits hsTnT elevation, then patients at increased risk of secondary myocardial ischemia, possibly identified by baseline hsTnT, may benefit the most from this strategy. Similarly, this biomarker could be used to identify vasopressor-induced harm earlier and modify vasopressor use accordingly.

Secondary outcomes

Secondary outcomes include high-sensitivity cardiac troponin T (hs TnT) at day 7; biomarkers associated with cardiac wall stress (N-terminal pro-B-type natriuretic peptide [NT-proBNP][34]); tissue injury to the brain[39] (glial fibrillary acidic protein [GFAP][40], myelin basic protein [MBP][41], neuron-specific enolase [NSE][42]), liver (alanine aminotransferase [ALT][43]), intestine (intestinal-type fatty acid binding protein [FABP][44]), and skeletal muscle (creatine kinase [CK][45]); and global tissue dysoxia (lactate). As for hsTnT, these biomarker outcomes are measured at day 3 and 7, along with a baseline sample; all biomarkers are measured in plasma, except for NSE, which is measured in serum. We selected lactate as a reasonable measure of tissue hypoxia in critically ill patients but recognize that hyperlactatemia may result from other factors, including aerobic glycolysis, reduced oxidative phosphorylation, and decreased clearance.[46]

We measure secondary clinical outcomes, including organ function using SOFA score (measured on days 2, 3, 4, 7, 10, 14 and 28 while in the ICU, along with a baseline [day 1] measurement). We describe healthcare utilization in terms of days of mechanical ventilation, renal replacement therapy, vasopressor therapy, and ICU and hospital stay. We report the incidence of the pre-specified adverse events of stroke, acute kidney injury (KDIGO stage 3),[47] clinically detected supraventricular arrhythmia,[5 48] and limb or intestinal ischemia as defined in the OVATION pilot trial.[17] Investigators will adjudicate these adverse events using medical records, if necessary. We ascertain mortality at 90 days and 6 months. For 6-month survivors, we assess cognition using the Telephone Interview for Cognitive Status (TICS), a validated questionnaire used in ICU cohorts.[49]

We had originally planned to measure additional secondary outcomes but lacked resources to do so for each participant. We have described these additional secondary outcomes as planned ancillary studies in online supplementary file S3.

Adverse events

OVATION-65 is testing a common intervention to treat a common problem in critically ill patients. All eligible patients are at risk of adverse events due to their underlying critical illness. Following Canadian guidelines for serious adverse event (SAE) reporting in academic drug trials in critical care,[50] expected SAEs (stroke, KDIGO stage 3 acute kidney injury, clinically detected supraventricular arrhythmia, limb or intestinal ischemia, death) are already incorporated as trial outcomes, defined *a priori*. SAEs are limited to events not already labelled as trial outcomes and that might reasonably occur as a consequence of the trial interventions. SAEs must be reported in the participant's medical notes, on the OVATION-65 dedicated case report form and to the coordinating centre within 24 hours of observing or learning of the event. Such events are promptly discussed with the DSMC.

Data collection

We collect the following data: 1) baseline data (day 1) – demographics, admitting diagnosis, etiology of hypotension, severity of illness (APACHE II score[51]), vasopressor name, dose and start time, organ dysfunction (SOFA score[23]), comorbidities (including chronic hypertension, coronary, cerebral, or peripheral vascular disease, congestive heart failure, chronic kidney disease, severe cognitive impairment, Clinical Frailty Scale,[52] co-enrolment in other prospective observational studies or RCTs; 2) daily data – protocol adherence (hourly MAP while receiving vasopressors and corresponding vasopressor names, doses, and modifications) and relevant co-interventions (fluid balance, inotropes, corticosteroids, life-support interventions, sedation); and 3) primary and secondary outcomes. We collect data on the times from hospital admission and ICU admission to the start of vasopressors. We collect data on fluid balance (total intake – total output) on the day of

randomisation, but we do not collect data on volume of intravenous fluid administered before initiation of vasopressors.

Study Samples

To minimize the treating teams' workload, study samples (blood and urine) coincide as much as possible with clinical sampling on day 1 (baseline) and on day 3 and 7 (or the day of ICU discharge or before anticipated death or withdrawal of life-sustaining therapies, whichever comes first).

To ensure consistent measurement of biomarkers, the study samples are processed on site and shipped to URCE, where they are stored at -80°C and batched for analyses at the end of the trial. Clinicians are blinded to the results of study biomarker assays but can order any laboratory tests available at their hospital. Participants are also approached for participation in a parallel Acute Care Biobank, via a separate consent form, which allows samples remaining following completion of OVATION-65 specified analyses to be stored for future projects.

Risk of bias

Randomization is concealed, with variable and undisclosed block size, thereby reducing risk of bias. Although clinical teams are not blinded to treatment arms, assessors of biomarkers, pre-specified adverse events, mortality, and TICS are blinded to treatment allocation. Specimen processing and analysis are standardized as described. Finally, we record co-interventions to detect performance bias.

A risk of bias related to the biomarker outcomes is that early death or live discharge from the ICU, which may be related to treatment allocation, are competing risks for ongoing treatment in the ICU and ascertainment of these outcomes. Our analysis plan (see *Statistical analysis* below) accounts for this possibility.

Vasopressor management and protocol adherence

In the permissive hypotension arm, a protocol deviation is defined as a failure to reduce the dose of (or discontinue) vasopressors while the MAP is >65 mm Hg for three consecutive hours. Sites report protocol deviations on study forms and are asked to specify a reason for the deviation, which may include a physician's decision to target a higher MAP because of particular clinical circumstances. Investigators will adjudicate protocol deviations using source data.

For each day on protocol, we record the MAP value recorded nearest to each hour. In the permissive hypotension arm, clinical teams are reminded to consider discontinuing vasopressor therapy if the patients are able to maintain MAP values of at least 60 mmHg. Every participating site receives on-site training, to which all ICU bedside staff are invited. We distribute standard operating procedures and protocol adherence reports generated from MAP and vasopressor data entered in the electronic case report form. Regular newsletters and trial website updates (https://www.ccctg.ca/Programs/OVATION65.aspx) keep participating sites informed of study progress, overall adherence, and answers to frequently asked questions. Research staff are available 24/7.

We will report vasopressor management in each arm in terms of duration and total dose of vasopressor therapy received, hourly MAP values and corresponding vasopressor infusion rates, and the number of episodes of vasopressor therapy. In the permissive hypotension arm, we will report the number and proportion of patients with any protocol deviation. As in the 65 trial,[22] patient-level adherence will be defined as not having experienced a protocol deviation. We will also report total time on vasopressors with recorded MAP within target range; total time on vasopressors with recorded MAP above target range; total time on vasopressors with recorded MAP >5 mmHg above upper limit of target; and

total time on vasopressors with recorded MAP below target range. These measures will be summarized with descriptive statistics.

Follow-up

Participants are followed to hospital discharge by local research teams. Either the coordinating centre or the enrolling site ascertains 90-day and 6-month mortality and 6-month cognitive status in survivors by telephone. Prior verification of known vital status with local research teams and calibrated telephone scripts mitigate the risk of emotional distress in the event that a patient has died since hospital discharge. We selected TICS to measure cognitive function in survivors because telephone administration reduces risk of bias, improves measurement consistency, reduces patient burden, and enhances feasibility.

Patient and public involvement

The protocol was developed with input from 2 ICU survivors (EB and DC), who participated in protocol development meetings, contributed to the selection of 6-month cognitive function as a secondary outcome, and are co-authors of this manuscript.

Statistical analysis

Sample size

OVATION-65 is supported by several modest operating grants, each of which required a distinct objective, sample size calculation and analysis plan. By combining funds from multiple sources, we had planned to enrol 200 participants, which provides 80% power to detect an effect size of 0.4 in the difference between day 3 hsTnT in the permissive hypotension group compared to usual care, where 0.5 is considered to be medium.[53]

After the 65 trial[22] was published, the OVATION-65 Executive Committee forwarded the publication to the DSMC, which requested a meeting to discuss the results. The DSMC subsequently issued a letter on 21 February 2020 recommending termination of enrolment in OVATION-65. The DSMC "reasoned that in light of the accumulated evidence, mostly from the 65 trial[22] but also with some consideration of SEPSISPAM,[16] the posterior probability of lower MAP targets now being better was sufficiently high that there is no longer equipoise between the interventions being compared in OVATION-65." As of 21 February 2020, 159 patients had been randomized.

Patient flow

A sample CONSORT diagram is presented in Figure 1.

Data analysis

Analyses will be performed after all follow-up is completed, data queries are resolved, and the database is locked. Analyses will follow the intention-to-treat principle, with data from participants analyzed by allocated group. All participant data will be analysed unless consent to retain data is withdrawn. Statistical testing will use a superiority framework, with two-sided $p<0.05$ interpreted as statistically significant. Estimates of effect will be reported with 95% confidence intervals. No adjustments for multiplicity will be made. All analyses will use SAS 9.4 (Cary, USA). Given the modest sample size and focus on biomarkers of organ injury, no interim analysis was planned. Continuous data will be summarised as means (SD) if normally distributed and as medians (Q1, Q3) otherwise. Categorical data will be summarised as frequencies and proportions. Baseline data will be summarised as shown in Table 3.

The primary outcome of day 3 hsTnT will be analysed adjusting for the day 1 value. We will use the original scale and analysis of covariance if the data are not skewed; if skewed we will log-transform and use robust regression to obtain more interpretable estimates. We will use pooled logistic regression to estimate the probabilities of missing values due to either death or live discharge from the ICU. Based on these models, we will compute the inverse-probability of attrition weights for each observation and use generalized estimating equation models to test the differences in hs TnT between the permissive hypotension and usual care arm,[54] adjusting for centre using fixed effects. As a sensitivity analysis, for patients that die before day 3, we will impute the worst (highest) value and for patients discharged alive before day 3, we will impute the best (lowest) value.

For the secondary outcome of day 7 hsTnT, we will use the same approach. For patients who die before day 7, we will impute the worst (highest) value. For patients discharged alive before day 7, we will impute based on data available for other patients alive at day 7. The approach for all other biomarkers will be the same as for hsTnT.

For SOFA over the first 7 days, we will use a linear mixed effects model to account for repeated measures within patients as well as the centre effect. For patients who die before day 7, we will impute the worst (highest) value. For patients discharged alive before day 7, we will impute based on data available for patients in the same group alive at day 7. We will look for interaction between time and group as well as time trends. For TICS, we will use ordinal logistic regression with fixed effect for centre to compare the distribution of patients at 6 months in 4 categories (death and 3 cognitive status categories [non-impaired, mild impairment, and moderate-severe impairment]). If proportional odds assumption does not hold, we will use multinomial regression to compare the two groups. If there is >5% loss to follow-up for TICS, we will conduct sensitivity analyses using multiple imputation techniques for the missing values. We will also report the proportion of patients in each

category by arm and test for differences in separate categories of mortality and cognitive impairment. For mortality, we will use a generalized linear mixed effect model with logit link for 90 and 365 days separately. For pre-specified adverse events, we will report the proportion of patients in each arm with the outcome and test for differences using chi-square test or Fisher's exact test, as appropriate.

In sensitivity analyses, we will also adjust for pre-specified baseline covariates: APACHE II, total dose of vasopressor administration before randomization (in norepinephrine equivalents),[55] and history of hypertension, or coronary artery disease (angina, myocardial infarction [MI], or coronary revascularisation).

No subgroup analyses are prespecified due to the small sample size. An updated IPDMA[18] including data from existing trials,[16 17] the 65 trial,[22] and the current trial is under consideration.

Registration

The trial was registered on www.clinicaltrials.gov on 13 February 2018 before enrolling the first patient in the study (NCT03431181). Initially, the primary outcome was listed as hsTnT at day 7; this error was subsequently corrected on 28 May 2020. Data will not be analyzed until trial follow-up is complete in August 2020.

Data management

Site research personnel record data on paper or electronic case report forms (CRFs) within the secure REDCap EDC system. Data collected initially on paper are re-entered into REDCap.

Monitoring

Quality control measures include 1) training of site research and clinical personnel on eligibility assessment, study procedures, and data collection; 2) standard operating procedures for processing, storage, and shipping of blood and urine samples; 3) ongoing assessment of trial conduct, with monthly review of screening logs and reports for site enrolment, protocol adherence in the permissive hypotension arm and quality of study samples), and feedback to the clinical sites on recruitment and protocol adherence, benchmarked with other sites; 4) ongoing review of missing data and outlying values; and 5) rapid responses to frequently asked questions on the study website and monthly newsletter. For one site, we also conducted monitoring visits for 2 of the first 5 participants and 10% of the subsequent participants. Coordinating Centre staff and the Principal Investigators are available to answer study-related questions.

Trial oversight

Executive Committee

The Executive Committee is comprised of Neill KJ Adhikari, M Elizabeth Wilcox, and François Lamontagne (co-principal investigators), Marie-Claude Battista (core laboratory), and Marie-Hélène Masse (project leader). The Executive Committee is responsible for day-to-day management.

Data Safety Monitoring Committee

The independent DSMC is responsible for safeguarding the interests of study participants, assessing the safety and efficacy of study procedures, and monitoring study conduct. DSMC members include a senior methodologist with DSMC Chair experience for

international RCTs, an experienced biostatistician, and a critical care clinician scientist (online supplementary file S1). The DSMC met on an *ad hoc* basis to review reports of unanticipated serious adverse events (SAEs) not predefined as study outcomes. In accordance with a prespecified DSMC Charter, the DSMC advised the Executive Committee of concerns related to participant safety and trial conduct. Following each meeting, the DSMC made a recommendation for study continuation, continuation with modifications, temporary suspension of enrolment, or termination. As noted above, the DSMC recommended termination of enrolment in response to data from the 65 trial.[22]

Ethics and Dissemination

This protocol was approved by the Comité d'éthique de la recherche du Centre intégré universitaire de santé et de services sociaux de l'Estrie – Centre hospitalier universitaire de Sherbrooke (MP-31-2018-1789). Before enrolment of the first participant, each clinical site received local research ethics board (REB) approval and provided the Coordinating Centre with their REB approval letter and informed consent form (sample in online supplementary file S4). Protocol amendments were submitted to each REB and disseminated to all investigators.

Site research personnel obtained informed consent by approaching eligible capable patients directly. For eligible incapable patients, research personnel approached the substitute decision-maker (SDM) to obtain consent in person or by telephone. Alternatively, where permitted by the site REB, the patient was randomized with consent obtained later under a deferred consent model. Consent was also requested for possible future laboratory analyses.

Participants may discontinue participation in the OVATION-65 trial at any time. If a participant wished to withdraw consent, we offered the following alternatives: 1) complete withdrawal, which included no further study intervention (only relevant for participants in the

permissive hypotension arm), data deletion, and sample destruction; 2) discontinuation of study intervention but permission for data collection (clinical data, sample collection, telephone follow-up); 3) discontinuation of study intervention, in-person follow-up, and sample collection but permission for telephone follow-up; or 4) discontinuation study intervention, sample collection, and in-person and telephone follow-up, but permission for access to medical records.

All personal health information collected remains confidential in a secure database. Participants are identified by an alphanumeric code, and the file linking the alphanumeric code to identifying information is securely stored by the local principal investigator.

There was no compensation for harm suffered from trial participation; details on data collection for adverse events are given above. Patients enrolled in this trial were critically ill, with daily care provided by intensivists. There was no provision for post-trial care.

Plans for end-of-grant dissemination include presentations at international critical care conferences and journal publications. In addition, building on the experience with social media during the OVATION pilot trial, we will disseminate our results via social media platforms and discussion forums managed by partner organizations.

Authorship of the trial manuscript will be based on leadership roles in trial management and at clinical sites, specific expertise (e.g. methodological, laboratory), and contributions as defined by International Committee of Medical Journal Editors criteria.

Data statement

The OVATION-65 protocol is freely accessible via this publication. The principal investigators, project leader, and study statisticians will have access to the full trial dataset; there are no contractual limitations to such access. Requests for access to the participant-level dataset and statistical code will be considered by the Executive Committee after publication of primary results and planned secondary studies by co-investigators.

Trial status

The current protocol is version 6, dated 29 November 2019. Participant recruitment began on 17 February 2018 and was scheduled to continue until approximately June 2020. As noted, the DSMC recommended termination of enrollment on 21 February 2020. The database will be locked after the last enrolled patient completes the 6-month follow-up in August 2020, and 6 additional months will be required to address remaining data queries and to finalize the analyses.

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Authors' contributions
NA and FLam drafted the protocol for the OVATION-65 trial and drafted the manuscript; they contributed equally and co-senior authors. MHM, MCB, MEW, RPi, NM, FD'A, CS-A, MM, M-AL, HQM, BGB, YP, ECa, AJES, IW, RPo, MC, ML, FLau, AT, DB, SM, ECh, EB-C, EB, and DC contributed to protocol development and revised the manuscript. MHM, MCB, MEW, FLam, and NA on the Executive Committee. All authors read and approved the final manuscript.

Competing interests
The authors declare that they have no competing interests.

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Online supplementary files

S1 (.pdf format)
SPIRIT checklist.

S2 (.pdf format)
OVATION-65 contributors.

S3 (.pdf format)
Ancillary studies.

S4 (.pdf format)
Model informed consent form.

Figure legend

Figure 1. Progress of patients through the trial. 'Co-enrolled in another study' refers to a study for which the principal investigators of OVATION-65 or the other study had prespecified that co-enrolment would not be allowed.

Table 1 Summary of objectives and outcomes

Objectives	Outcomes
Biomarkers of organ injury	
Heart	High-sensitivity cardiac troponin T (hsTnT) [primary outcome]
	N-terminal pro-B-type natriuretic peptide (NT-proBNP)
Brain	Glial fibrillary acidic protein (GFAP)
	Myelin basic protein (MBP)
	Neuron-specific enolase (NSE)
Liver	Alanine aminotransferase (ALT)
Intestine	Intestinal-type fatty acid binding protein (FABP)
Skeletal muscle	Creatinine kinase (CK)
Global tissue dysoxia	Lactate
Organ function	Sequential Organ Failure Assessment (SOFA) score on days 2, 3, 4, 7, 10, 14, and 28 while in the ICU (an additional measurement is taken on day 1 [baseline])
Resource utilization	Duration of mechanical ventilation
	Duration of renal replacement therapy
	Duration of vasopressor therapy
	Duration of ICU stay
	Duration of hospital stay
Adverse events	Clinically detected supraventricular arrhythmia
	Stroke
	Acute kidney injury (KDIGO stage 3)
	Limb ischemia
	Intestinal ischemia
Mortality	90 days
	6 months
Cognitive impairment	Telephone Interview for Cognitive Status (TICS) at 6 months

KDIGO, Kidney Disease: Improving Global Outcomes.

All biomarkers of organ injury and lactate are measured in plasma (except for NSE, measured in serum) at days 3 and 7, with an additional measurement at baseline (day 1).

Table 2 OVATION-65 Trial Timeline

	Study Period												
	Days	**Days**											**Months**
	Enrolment/ Allocation	**Post-Allocation**											
TIME POINTS	**1**	**2**	**3**	**4**	**5-6**	**7**	**8-9**	**10**	**11-13**	**14**	**15-27**	**28**	**6 months**
ENROLMENT:													
Eligibility screen	x												
Informed consent	x												
Allocation	x												
INTERVENTION:													
Permissive hypotension (MAP 60-65 mmHg) vs. usual care[a]	→	→	→	→	→	→	→	→	→	→	→	▶	
ASSESSMENTS:													
Baseline variables													
Diagnosis of admission	x												
Severity of illness (APACHE II score)	x												
Pre-existing comorbidities (Clinical Frailty Score)	x												
Outcomes													
hsTnT[b]	x		x			x							
Biomarkers of organ injury[c]	x		x			x							
Global tissue dysoxia (lactate)	x		x			x							
Organ function including renal function (SOFA score)	x	x	x	x		x		x		x		x	
Resource utilization[d]	→	→	→	→	→	→	→	→	→	→	→	▶	
Mortality at 90 days and 6 months	→	→	→	→	→	→	→	→	→	→	→	▶	x
Cognitive impairment (TICS) at 6 months													x
Stroke	→	→	→	→	→	→	→	→	→	→	→	▶	
Clinically detected supraventricular arrhythmia	→	→	→	→	→	→	→	→	→	→	→	▶	
Limb or intestinal ischemia	→	→	→	→	→	→	→	→	→	→	→	▶	
Stage 3 acute kidney injury[e]	→	→	→	→	→	→	→	→	→	→	→	▶	
Other variables													
Protocol adherence[f]	→	→	→	→	→	→	→	→	→	→	→	▶	
Co-interventions[g]	→	→	→	→	→	→	→	→	→	→	→	▶	

ALT, alanine aminotransferase; CK, creatinine kinase; FABP, intestinal-type fatty acid binding protein; GFAP, glial fibrillary acidic protein; hsTnT, high-sensitivity cardiac troponin T; KDIGO (Kidney Disease: Improving

Global Outcomes; MAP, mean arterial pressure; MBP, myelin basic protein; NSE, neuron-specific enolase; NT-proBNP, N-terminal pro-B-type natriuretic peptide

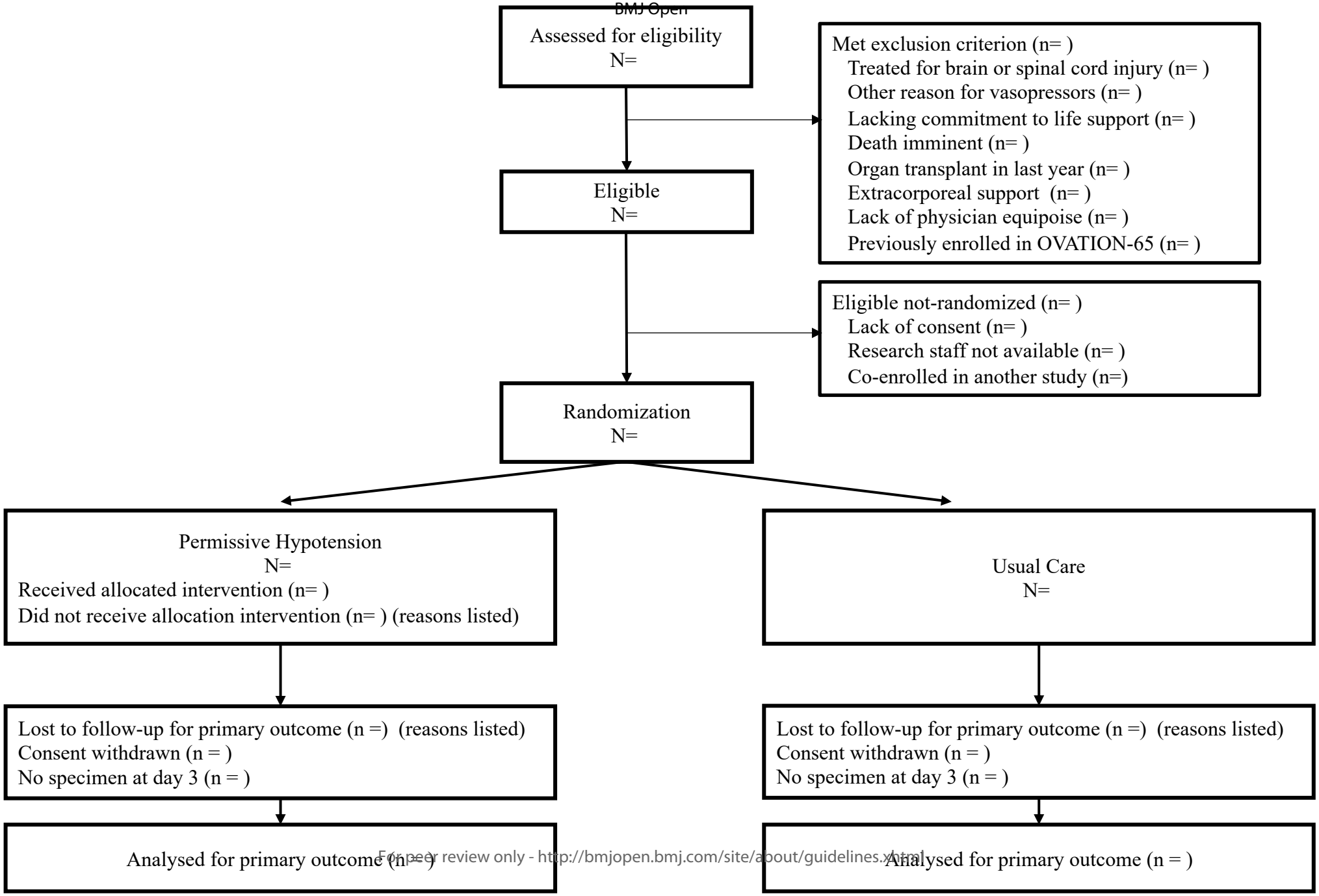
[a] MAP target while receiving vasopressor therapy up to day 28, or discontinuation for more than 24 hours.
[b] hs TnT at day 3 is the primary outcome and at day 7 is a secondary outcome
[c] NT-proBNP, GFAP, MBP, NSE, ALT, FABP, CK
[d] Duration of mechanical ventilation, renal replacement therapy, vasopressor therapy, ICU and hospital stay
[e] As defined by KDIGO criteria
[f] See text for definition
[g] See text for definition

Table 3 Baseline characteristics

Characteristic	Permissive hypotension (n=)	Usual care (n=)
Demographics		
Age, years, mean (SD)		
Female sex, n (%)		
Weight, kg; mean (SD)		
Clinical Frailty Scale[a] >4, n (%)		
APACHE II[b], mean (SD)		
SOFA[c], mean (SD)		
Comorbidities		
Cardiac Supraventricular arrhythmia, n (%) Ventricular arrhythmia, n (%) Coronary artery disease[d], n (%) Congestive Heart Failure, class 1-3, n (%) Congestive Heart Failure, class 4, n (%) Left ventricular ejection fraction, % (mean, SD)		
Vascular, n (%) Known hypertension Peripheral vascular disease or claudication Cerebrovascular disease		
Diabetes (type 1 or 2), n (%)		
Renal, n (%) Receiving chronic dialysis Baseline creatinine[e], µmol/L, mean (SD)		
Child's B or C cirrhosis, n (%)		
Chronic lung disease, n (%)		
Immunosuppression, n (%)		
Cognitive impairment or dementia, n (%)		
ICU admission data		
Primary ICU diagnosis, n (%) Medical Surgical		
Transfer from another hospital, n (%)		
Time from hospital admission to randomization, hours; mean (SD)		
Time from ICU admission to randomization, hours; mean (SD)		
Vasopressor dose, mean norepinephrine equivalents (mean µg/kg/min, [SD])		
Vasopressors, n (%) Norepinephrine Epinephrine Dopamine Phenylephrine Vasopressin		
Inotropes, n (%) Dobutamine Milrinone		
Mean arterial pressure, mmHg; mean (SD)		

APACHE II, acute physiology and chronic health evaluation II, CABG, coronary artery bypass grafting; ICU, intensive care unit; MI, myocardial infarction; PCI, percutaneous coronary intervention

[a]The Clinical Frailty Scale[52] ranges from 1 to 7, with scores of 5-7 denoting frailty.
[b]Scores on the APACHE II[51] range from 0 to 71, with higher scores indicating more severe disease and a higher risk of death.
[b]Scores on the SOFA[23] range from 0 to 24, with higher scores indicating more severe disease and a higher risk of death.
[d]Coronary artery disease included angina and previous MI, PCI, or CABG.
[e]Baseline creatinine was determined from the outpatient creatinine within the last 12 months and closest to admission (n=) or, if not available, then the lowest inpatient creatinine before ICU admission (n=).



Page numbers refer to the Microsoft Word version of the manuscript (revision 1).

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

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	4, 21
	2b	All items from the World Health Organization Trial Registration Data Set	4, 21
Protocol version	3	Date and version identifier	24
Funding	4	Sources and types of financial, material, and other support	25
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1, 26
	5b	Name and contact information for the trial sponsor	25
	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	26
	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)	9, 22-23

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	6-8
	6b	Explanation for choice of comparators	7-8, 11-12
Objectives	7	Specific objectives or hypotheses	8
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	9
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	9, suppl S1
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	9-10
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	10-12
	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)	16-17
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	16-17
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	12-13
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	13-15
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)	33-34

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	18-19
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	21-22
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	10-11
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	10-11
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	10-11, 23
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	16
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	Not blinded
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	15-16
	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	23-24

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	21
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	19-21
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	19-21
	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)	19-21
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	22-23
	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	19
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	14-15
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	21-22
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	23
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)	23

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	23
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	23
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	24
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	25
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	24
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	24
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	24
	31b	Authorship eligibility guidelines and any intended use of professional writers	24
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	24
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Suppl S4
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*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

Online supplementary file S2 OVATION-65 team members

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Bram Rochwerg (PI), Tina Millen (RC)

Abbreviations:
Co-I – co-investigator; PI – principal investigator; PL – project leader; RA – research assistant; RC – research coordinator

Online supplementary file S3 OVATION-65 ancillary studies

Study title	Investigators	Primary objective	Secondary objective	Funding
Measuring baseline ascorbic acid levels in the OVATION-65 trial	MC Battista NK Adhikari F Lamontagne	Measure the associations between baseline level of plasma ascorbic acid and peak levels of biomarkers of organ injury* (measured at day 1 [baseline], day 3, and 7) in the permissive hypotension and usual care groups. Organ injury biomarkers are specified in Table 1 of the manuscript.	Measure the association between baseline ascorbic acid and 1) total dose of vasopressors required to maintain blood pressure; 2) biomarkers of inflammation* (IL-1ß, TNF-α, C-reactive protein) 3) biomarkers of endothelial injury* (thrombomodulin, angiopoietin-2)	Lotte and John Hecht Memorial Foundation
Urinary biomarkers of renal injury in the OVATION-65 trial: a Nested analysis of the urinary proteome	FM Boisvert MC Battista NK Adhikari F Lamontagne	Identify and quantify, using a discovery proteomic approach, new peptides and proteins and their pattern of expression between baseline, day 3 and day 7 in the urine of patients in permissive hypotension and usual care groups.	Measure the association between protein clusters and renal function Validate the predictive value of biomarkers of renal injury*: TIMP2, NGAL, FABPL, CYTC, IGFBP7	Université de Sherbrooke/ Merck Sharp and Dohme
Effects of catecholamine therapy on the immune system: unsuspected consequences of routine medical interventions and opportunities for individualized care	FM Boisvert LH Tai JL Parent X Roucou MC Battista NK Adhikari F Lamontagne	Compare PBMC immune response (Th1/Th2 profiles), adrenergic receptor activity, and proteomic signature between baseline and day 7 in the permissive hypotension and usual care groups		Université de Sherbrooke/ Merck Sharp and Dohme

Abbreviations: CYTC, cytochrome C; FABPL, fatty acid-binding protein, liver-type; IGFBP7, insulin-like growth factor-binding protein 7; IL-1ß, interleukin-1ß; NGAL, neutrophil gelatinase-associated lipocalin; PBMC, peripheral blood mononuclear cell; TIMP2, issue inhibitor of metalloproteinases 2; TNF-α, tumour necrosis factor-α

*All biomarkers are assessed at baseline (day 1) and at days 3 and 7.

CENTRE DE RECHERCHE | CHUS

RESEARCH INFORMATION AND CONSENT FORM

Study Title: The OVATION-65- Impact of permissive hypotension on end-organ damage in the elderly

Study Number and Date: MP-31-2018-1789

Funding Agencies: Centre de recherche du CHUS
Université de Sherbrooke

Principal Investigator: Dr. François Lamontagne, Intensivist

Co-Investigators: Dr. Frédérick D'Aragon, Intensivist,
Dr. Charles St-Arnaud, Intensivist
Dr. Michaël Mayette, Intensivist,

FOR INFORMATION

Monday through Friday, from 8 am and 4 pm, you can reach:

Dr. François Lamontagne, Intensivist	Tel.: 819-346-1110, ext. 74974
Élaine Carbonneau, Research Coordinator	Tel.: 819-346-1110, ext. 16208
Marie-Hélène Masse, Research Coordinator	Tel.: 819-346-1110, ext. 14173
Marilène Ladouceur, Research Assistant	Tel.: 819-346-1110, ext. 14169

or dial "0" and ask the operator to call them on pager # 7125.

We are seeking your participation (or that of your family member) in a research study because you (or your family member) have been admitted to an intensive care unit and will need medication administered into your veins to raise your blood pressure. However, before you agree to participate, please take the time to read, understand and carefully consider the following information. If you agree to take part in this research study, you will be asked to sign the consent form at the end of this document and we will give you a signed copy for your own records.

This Information and Consent Form explains the goals, procedures, risks and inconveniences, and benefits of the study as well as providing the names of the people to reach if needed. This document may contain information or words that you do not understand. Please ask the study investigator or members of the study staff to answer your questions and explain any word or information you do not understand.

NATURE AND GOALS OF THE RESEARCH STUDY

This study aims to determine whether the target blood pressure used to adjust the dosage of the blood-pressure-increasing medication changes the evolution of participants treated in the Intensive Care Unit (ICU). Vasopressors are drugs that are given intravenously to increase the blood pressure of patients with diseases causing dangerous pressure drops that can be harmful to the organs of the body. When a doctor

prescribes a vasopressor, he asks that the dose be adjusted to achieve a specific blood pressure. However, although vasopressors have been used for nearly a century, we still do not know whether it is preferable to try and normalize the blood pressure of our patients (which requires high doses of vasopressors) or tolerate a lower pressure (which is not normal, but requires smaller doses of drugs). The current practice is quite variable, some doctors preferring to increase the blood pressure, others preferring to restrict doses of these powerful drugs and tolerate a lower blood pressure (hypotension).

The goal of this study is to determine if tolerating a lower mean blood pressure (permissive hypotension) vs. usual blood pressure targets in hypotensive patients over 65 years of age can reduce the risk of harm associated with more aggressive vasopressor therapy. The specific objectives are to evaluate: the effect of permissive hypotension on your health status after 6 months , the effects on markers of organ injury, including the heart, brain, kidneys, liver, intestine, and skeletal muscles as well as the effects on your immune system. We wish to recruit around 100 participants at the *CIUSSS de l'Estrie - CHUS* to be among the 200 participants needed for this study that will be carried out in several hospitals.

Your physician has determined that you are eligible to participate in our study and you have been selected as a participant because you are being (or will soon be) treated in the ICU and because you were prescribed vasopressor drugs.

RESEARCH STUDY PROCEDURES

If you agree to participate in this study, you (or your family member) will be assigned to one of the following two groups: The first group includes participants who are being given vasopressors for an average blood pressure of 60-65 mmHg (limiting the amount of vasopressors given); the second group includes participants who are receiving vasopressors following usual care. Your assignment to one of these two groups was determined randomly by a computer that will not retain information about you. The odds of being assigned to either group were 50% (1 in 2 chances or half-and-half). The treating team will be aware of which group you have been assigned to.

As a study participant, you will receive vasopressors to maintain your average blood pressure at the level of your assigned group. These pressure targets will remain the same throughout your treatment with this type of medication (vasopressors) until you are discharged from hospital or up to 28 days from the beginning of your participation, whichever event comes first. Also, on days 1, 3 and 7 of participation (or when you are discharged from the intensive care unit), your nurse will collect 30 ml of blood (6 teaspoons) as well as urine samples while taking the blood samples required for your medical follow-up. We will collect a little more volume than what is needed in order to compensate for unexpected losses that may arise during laboratory testing. These samples will enable us to measure certain biomarkers in your blood and in your urine that help assess the function of your heart, kidneys, muscles, brain and liver as well as your immune system. These biomarkers are already known to be useful in clinical studies and are not genetic biomarkers. During your hospital stay, we will monitor your progress to see if your organs are functioning well, if you develop other health problems and how long you will stay in the ICU and hospital. Your medical chart will be reviewed, by the investigator and the research team as long as you remain in the study. Blood test results and procedures present in your medical record will be collected for the study.

After you are discharged from the hospital, you will be contacted by phone 6 monthss after the start of your participation in the study. Your contact information will be provided to the coordinating research team.

FUTURE ANALYSES

Once the biomarker analyses have been performed as part of this study, it is possible that part of your samples may be unused. We wish to use the remainder of your samples (blood and urine) in order to answer additional questions concerning the impact of vasopressors on blood pressure targets that may arise in future. For example, we could measure a new, as yet undefined, biomarker. Only the remainder of your samples will be used and no other additional sample will be collected. At the end of the study, if some of the samples remain unused, they will be destroyed unless you agree to biobanking. A separate consent form will be presented for biobanking.

RISKS ASSOCIATED WITH PARTICIPATION IN THIS RESEARCH STUDY

Vasopressors used in this study and that you have received or may still be receiving, are approved in Canada and commonly used in the ICUs of all hospitals. The blood pressure targets we aim for in this study are also part of current medical practices.

Since your health condition required treatment with vasopressors, and continues to require treatment at this time, to our knowledge, you are exposed to the same risks, whether or not you participate in this study.

INCONVENIENCES ASSOCIATED WITH PARTICIPATION IN THE STUDY

Other than the risks described above, you (or your family member) shouldn't experience any other inconveniences.

BENEFITS ASSOCIATED WITH YOUR PARTICIPATION IN THE RESEARCH STUDY

You (or your family member) will not personally benefit from your participation in this research study. However, the findings from this study may help increase our knowledge of pressure targets, vasopressors and biomarkers. The information obtained through this study could be useful to other patients in the future.

ALTERNATIVES TO YOUR PARTICIPATION IN THIS RESEARCH STUDY

You (or to your family member) do not have to participate in this research study to be treated for your disease.

VOLUNTARY PARTICIPATION AND THE RIGHT TO WITHDRAW

Your participation in this research study is voluntary. Therefore, you may refuse to participate. You can also withdraw from the study at any time, without providing a reason, by informing the study investigator or one of his assistants.

Your decision not to participate in the study or to withdraw from it, will have no impact on the quality of care and services you (or your family member) are entitled to or on your relationship with the investigator and other stakeholders.

The study investigator, the funding agency or the Research Ethics Board may put an end your participation in the study without your consent. This may happen if new scientific developments show that participation is no longer in your interest; if the study investigator believes it is in your best interest; or if there are administrative reasons to terminate the study.

If you withdraw or are withdrawn from the study, the information and material already collected during the course of the study will be stored, analyzed or used to ensure the integrity of the study.

Any new study findings that could influence your decision to remain in the research study will be shared with you as soon as possible.

CONFIDENTIALITY

While you take part in this research study, the study investigator and study staff will collect and record information about you in a study file. Only the information needed to meet the scientific goals of the study will be collected.

This information could include data taken from your medical record concerning your past and present medical history, your lifestyle and the test results, exams and procedures you will undergo during the study.

All the information collected during the study will remain strictly confidential to the extent provided by law. To protect your identity and privacy, you will be identified by an alphanumeric code. The key linking your identity and your research file will be kept in a safe place by the study investigator.

To ensure your safety, a mention of your participation in this research project will be included in your medical file. Therefore, any person or company to whom you will give access to your medical file will have access to this information.

Your full name and your phone number will be transmitted to a qualified person of the coordinating center of the study in order to allow this person to contact you in 6 months by phone. This personal information will allow a direct identification. This information will be kept in security and confidentiality will be preserved by the qualified person and destroyed at the end of the follow-up.

Study results will be stored by the study investigator for 25 years.

Study results may be published in medical journals or discussed at scientific meetings, but it will be impossible to identify participants.

For monitoring and control purposes, your study file and medical records may be examined by a representative of the Research Ethics Board or of the institution or by a person mandated by a regulatory authority. All of these individuals and organizations adhere to confidentiality policies.

You have the right to consult your study file at any time in order to verify the information gathered and to have it corrected, if necessary, for as long as this information is available to the study investigator or the institution. However, some of this information may be made available to you only once the study has ended, in order to protect the scientific integrity of the study.

COMPENSATION

You (or your family member) will not receive any compensation for expenses and inconveniences incurred due to your participation in this research study.

SHOULD YOU SUFFER ANY HARM

Should you suffer any harm due to your participation in this research study, you will be provided with all the necessary care and services, at no cost to you.

By agreeing to take part in this study, you are not waiving any of your legal rights nor discharging the study investigators, the sponsor or the institution where this research study is being conducted of their civil liability and professional responsibilities.

FUNDING OF THE RESEARCH STUDY

The study investigator has received funding from the grant agency to carry out this study.

CONTACT PERSONS

If you have any questions regarding your participation in this research study, please refer to the box on page 1.

If you have any questions regarding your rights as a participant in this study, if you have any comments or you wish to file a complaint, you may contact the *Bureau des plaintes et de la qualité des services of the CIUSSS de l'Estrie-CHUS* at the following number: 1-866-917-7903.

MONITORING OF ETHICAL ASPECTS OF THE STUDY

The *Comité d'éthique de la recherche du CIUSSS de l'Estrie - CHUS* has approved this study and is responsible for monitoring it at all participating institutions throughout Québec's health and social service network.

If you wish to reach a member of the Research Ethics Board (REB), please contact the *Service de soutien à l'éthique de la recherche du CIUSSS de l'Estrie - CHUS* at the following number: 819-346-1110, ext. 12856.

CONSENT

I declare that I have read this Information and Consent Form. I declare that the research study has been explained to me, that my questions were answered to my satisfaction and that I was given sufficient time for consideration and to make a decision. Upon reflection, I agree to participate in this research study under the conditions stated therein.

I agree that the remainder of the samples may be used for additional analyses that may arise during the study (future analyses). ☐ YES ☐ NO

Name of participant *(please print)*	Signature of participant	Date

I have explained the research study and this Information and Consent Form and I have answered all of his/her questions.

Name of person obtaining consent *(please print)*	Signature of person obtaining consent	Date

CONSENT FROM LEGAL REPRESENTATIVE (SUDDEN INCAPACITY)

Because Mr./Mrs. _____ has suddenly become incapable of giving consent for the hereinafter mentioned reason, the Civil Code of Québec allows you to give consent for him/her as his/her _____ (indicate your relationship with the participant).

As soon as Mr./Mrs. _____has sufficiently recovered, he/she will be asked to sign his/her own consent form to indicate whether he/she wants to continue taking part in this study.

REASON FOR THE PARTICIPANT NOT BEING ABLE TO GIVE CONSENT

By signing this page, I confirm that I have read the information in this Consent Form. I acknowledge that the study has been explained to me, that all of my questions have been answered and that I was given enough time to make a decision. I voluntarily give my consent so that Mr./Mrs. _____ can participate in this study.

I also agree that the remainder of the samples may be used for additional analyses that may arise during the study (future analyses). ☐ YES ☐ NO

Name of legal representative *(please print)* | Signature of legal representative | Date

I have explained the research study and this Consent Form to the participant's legal representative. I have answered all of his/her questions.

Name of person obtaining consent *(please print)* | Signature of person obtaining consent | Date

CONSENT FROM THE LEGAL REPRESENTATIVE OR CAREGIVER SUPPORTING THE PARTICIPATION OF THE PERMANENTLY INCAPABLE PARTICIPANT (PERMANENT INCAPACITY)

I declare that I have read this Information and Consent Form. I declare that the research study has been explained to me, that my questions were answered to my satisfaction and that I was given sufficient time for consideration and to make a decision.

I agree that _____ can participate in this research study under the conditions stated therein. I will receive a signed and dated copy of this Information and Consent Form.

I also agree that the remainder of the samples may be used for additional analyses that may arise during the study (future analyses). ☐ YES ☐ NO

If the incapacitated participant is represented:

Name and signature of the legal representative (representative, curator or mandatary) Date

If the incapacitated participant is not represented by a legal representative:

Name and signature of the spouse, failing which, name of next-of-kin or name of a significant person Date

I have explained the research study and this Consent Form to the participant's legal representative. I have answered all his/her questions.

Name of person obtaining consent *(please print)* Signature of person obtaining consent Date

PHONE CONSENT
(For the participant who is suddenly or permanently incapacitated)

Because Mr./Mrs. _____ is incapable of giving consent for the hereinafter mentioned reason,

REASON FOR THE PARTICIPANT NOT BEING ABLE TO GIVE CONSENT

_____

I have explained the research study and this Consent Form to the participant's legal representative. I have answered all his/her questions.

The representative, Mr./Mrs._____
Name of the legal representative (representative, curator or mandatary)
Name of the spouse or next-of-kin or
Name of the significant person

has given consent by phone on _____ at _____
Date Hour

The representative also agrees that the remainder of the samples may be used for additional analyses that may arise during the study (future analyses).☐ YES ☐ NO

Name of person obtaining consent *(please print)*	Signature of person obtaining consent	Date

APPENDIX 1: GENETIC PHASE

(PLEASE NOTE: This part of the consent should not appear in the patient's medical file)

We invite you to participate in the genetic component of this study. This phase is optional. You may refuse this proposal and still participate in the main phase of the project.

Please note that all sections of the main consent form apply to this appendix as well.

Genetics focuses on cells in the human body that contain a type of molecule called deoxyribonucleic acid commonly referred to as "DNA". Your DNA is contained in the inherited genes that control your entire body's growth, development and functions. For instance, some genes determine the colour of your eyes or hair. DNA presents a wide array of differences or variations from one person to another. These variations may affect the risk of contracting a disease (or not) or the way individuals respond differently to a drug. The OVATION-65 project also includes a genetic sub-study focusing on the analysis of certain genes (genetics) and certain phenomena present in your environment that modify your DNA (epigenetics). These tests can be performed on the cells in your blood.

The markers of the heart, brain, kidneys, liver, intestine and skeletal muscles that we are interested in measuring as part of the OVATION-65 study as well as the molecules (receptors) that enable the vasopressors to act (beta-adrenergic receptors) on the cells of different organs are determined in part by genes. Thus, in order to better understand how to reduce organ damage related to medication (vasopressors) received during intensive care unit admissions, we propose to study the DNA as well as the variations around this DNA (called epigenetic variations) of patients included in OVATION-65. Our goal is to demonstrate that modifications in the DNA of studied markers are associated with the levels of these same blood or urine markers, which inform us on the function/involvement of the targeted organ.

If you agree to participate, we will use a portion of the samples already collected as part of the main project and an additional sample (approximately 2 teaspoons) to conduct our genetic analyses.

FUTURE ANALYSIS

Once the genetic analyses have been conducted, it is possible that a portion of the samples will remain unused. We would like to use the remainder of your samples to answer additional research questions that might arise during the course of the study. Only the remainder of your samples will be used and no other additional samples will be taken. At the end of the study, if some samples remain unused, they will be destroyed unless you agree to biobanking. Another consent form will be presented for biobanking.

SOCIO-ECONOMIC RISKS ASSOCIATED WITH PARTICIPATION IN THIS PHASE OF THE STUDY

One of the risks associated with genetic analyses is related to the disclosure of results or of your participation to third parties. Protection against genetic discrimination is not currently well defined in Canadian and Québec legislation. Thus, we cannot fully guarantee that your participation in a genetics research project will not have an impact on your chances of getting certain jobs, or of getting insurance coverage (life insurance, disability or health) for you or for members of your family.

However, as researchers, we are committed not to disclose information related to genetic results to any third party. Your results will not be made available to third parties such as an employer, a government agency, an insurer or an educational institution. This also applies to your spouse, other members of your family and your doctor. Furthermore, rest assured that no data related to any genetic results will be included in your hospital record.

VOLUNTARY PARTICIPATION AND THE RIGHT TO WITHDRAW FROM THE GENETIC PHASE OF THE PROJECT

Your participation in the genetic phase of the project is voluntary. Therefore, you may refuse to participate. You may also withdraw your consent from the genetic phase of this research project at any time. Just call the ICU research team at 346-1110 ext. 14171.

Your decision to refuse to participate in this sub-study of the project will have no impact on the quality of the care that will be provided to you or on your relationship with the healthcare team.

If you decide to terminate your participation in the genetic sub-study after providing a sample, you must notify the research team that will then destroy your sample. If your sample has already been tested and the results are already included in an analysis or publication, it will not be possible to remove this information. However, the rest of your sample will be destroyed and no further analysis will be done on your sample.

CONFIDENTIALITY

Identification:

In order to protect your identity, your samples will be identified by a unique code. Your name and your file number will not appear on the samples. The study investigator will keep a list of patients with the code numbers to identify them. This list is kept under lock and key in the research nurse's office and will not be disclosed under any circumstances.

Storage and destruction of samples:

Your samples will be kept in the principal investigator's freezers until the end of the study, unless you agree to biobanking. Another consent form will be presented to this end. The principal investigator is responsible for the destruction of samples.

COMMUNICATION OF RESULTS

Your participation and the results of the genetic analysis conducted on your samples will not be disclosed to you or to your doctor.

MARKETING POSSIBILITIES / WAIVER

Your participation in the genetic phase of this project could lead to the creation of commercial or other products that could potentially be protected by patents or other intellectual property rights. However, you will not receive any financial benefits.

CONSENT (GENETIC SUB-STUDY)

I declare that I have read this Appendix (genetic sub-study). I acknowledge that this sub-study of the project was explained to me, that all my questions were answered and that I was given the necessary time to make a decision.

I freely and willingly consent to participate in the **genetic sub-study** of this project:

I also accept that the remainder of my samples may be used for **additional genetic analyses** that may arise during the course of this study (future analysis):

☐ YES ☐ NO

Name of participant name (please print)	Signature of participant	Date

I have explained the genetic sub-study and this Consent Form to the participant, and I answered all his/her questions.

Name of person obtaining consent *(please print)*	Signature of person obtaining consent	Date

CONSENT (GENETIC SUB-STUDY)
FROM THE LEGAL REPRESENTATIVE (SUDDEN INCAPACITY)

Because Mr./Mrs. _____ has suddenly become incapable of giving consent for the hereinafter mentioned reason, the Civil Code of Québec allows you to give consent for him/her as his/her _____ (indicate your relationship with the participant) to participate in the **genetic sub-study** of the project.

As soon as Mr./Mrs. _____has sufficiently recovered, he/she will be asked to sign his/her own consent form to indicate whether he/she wants to continue taking part in this sub-study of the study.

REASON FOR THE PARTICIPANT NOT BEING ABLE TO GIVE CONSENT

By signing this page, I confirm that I have read the information in this Consent Form. I acknowledge that the **genetic sub-study** of the project has been explained to me, that all of my questions have been answered and that I was given enough time to make a decision.

I voluntarily give my consent so that Mr./Mrs. _____ can participate in the genetic sub study.

I also agree that the remainder of the samples may be used for **additional genetic analyses** that may arise during the study (future analyses). ☐ YES ☐ NO

Name of legal representative *(please print)*	Signature of legal representative	Date

I have explained all relevant aspects of the genetic sub-study of this project to the participant's legal representative and I have answered all his/her questions.

Name of person obtaining consent *(please print)*	Signature of person obtaining consent	Date

CONSENT (GENETIC SUB-STUDY)
FROM LEGAL REPRESENTATIVE OR CAREGIVER (PERMANENT INCAPACITY)

I confirm that I have read the information in this Consent Form. I acknowledge that the genetic sub-study of the project has been explained to me, that all of my questions have been answered and that I was given enough time to make a decision.

I agree that _____ can participate in this **genetic sub study** under the conditions stated therein. I will receive a signed and dated copy of this Information and Consent Form.

I also agree that the remainder of the samples may be used for **additional genetic analyses** that may arise during the study (future analyses). ☐ YES ☐ NO

If the participant is represented:

_____

Name and signature of the legal representative (representative, curator or mandatary) Date

If the incapacitated participant is not represented by a legal representative:

_____

Name and signature of the spouse, failing which, name of the next-of-kin or name of the significant person Date

I have explained the research study and this Consent Form to the participant's legal representative. I have answered all his/her questions.

Name of person obtaining consent *(please print)*	Signature of person obtaining consent	Date

PHONE CONSENT (GENETIC SUB-STUDY)
(For the participant who is suddenly or permanently incapacitated)

Because Mr./Mrs. _____ is incapable of giving consent for the hereinafter mentioned reason.

REASON FOR THE PARTICIPANT NOT BEING ABLE TO GIVE CONSENT

_____

I have explained the genetic sub study and this Consent Form to the legal representative using the phone script and I have answered all his/her questions.

The representative, Mr./Mrs._____
Name of the legal representative (representative, curator or mandatary)
Name of the spouse or of the next-of-kin or
Name of the significant person

has given consent by phone on_____ at_____
Date Time

The representative also agrees that the remainder of the samples may be used for **additional genetic analyses** that might arise during the study (future analyses). ☐ **YES** ☐ **NO**

Name of person obtaining consent *(please print)*	Signature of person obtaining consent	Date and time